

Is there a rural/urban gradient in the prevalence of eczema? A systematic review

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Summary

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Conflicts of interest

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Background Eczema affects approximately 10% of all schoolchildren in the western world and has shown an increase over the past decades in 'developing' countries. Numerous factors have been suggested that might contribute to the increasing prevalence of eczema. A plausible explanation is the role of environmental factors. As part of the 'hygiene hypothesis' it has been thought that eczema is more common in urban than in rural communities, but such a notion has never been assessed systematically.

Objective Our aim was to assess whether there is a rural/urban gradient for the prevalence of eczema and, if so, to what extent.

Methods All data sources were identified through a search in MEDLINE and EMBASE. All primary studies comparing the prevalence rate of eczema between urban and rural populations were assessed for eligibility. Included articles were reviewed for methodological quality and a relative risk was calculated to indicate the risk of eczema in urban over rural areas.

Results Twenty-six articles were included for analysis. Nineteen showed a higher risk for eczema in an urbanized area, of which 11 were significant. Six studies showed a lower risk of eczema in an urbanized area, of which one was statistically significant. One study had a relative risk of 1.00. Results were more homogeneous among studies of good methodological quality. A pooled relative risk could have been calculated but was not because of heterogeneity.

Conclusion There is some evidence of a higher risk for eczema in urban compared with rural areas, suggesting that place of residence may have a role in the pathogenesis of eczema. Future reviews on environmental circumstances should be carried out to reveal the factors associated with a higher prevalence of eczema in urban areas and the association with other allergic diseases.

Eczema affects approximately 10% of all schoolchildren in the western world and has shown a rapid increase over the past decades in 'developing' countries.¹⁻⁴ Numerous factors have been suggested that might contribute to the increasing prevalence of eczema and other atopic diseases. A genetic predisposition is likely to play an important role for both skin barrier dysfunction and inflammatory responses, but such factors cannot explain the rapid increase in disease prevalence. Changes in public and professional awareness of eczema and diagnostic labelling are also thought to have had their effect. Another plausible explanation however is the role of environmental factors.⁵ A major theory explaining the

increased prevalence and incidence of eczema and atopy in general is the 'hygiene hypothesis'.⁶⁻⁹ This view indicates that hygienic environments in modern society result in insufficient microbial stimulation in the immune system of newborns. This leads to lack of signals diverting type 2 responses to regulatory and type 1 T-cell responses and thereby induces eczema. Over the past 50 years industrialization, urbanization and improvement of housing and hygiene have been prominent in the western world, whereas 'developing' countries are currently undergoing these steps. Indications for an increasing prevalence in 'developing' countries have already been found.¹⁰

As part of the 'hygiene hypothesis' it was thought that eczema is more common in urban than in rural communities, but such a notion has never been assessed systematically.

Our aim was to assess whether there is a rural/urban gradient for the prevalence of eczema and if so, to what extent. If a strong rural/urban gradient in populations that are genetically similar is found, this suggests that area of residence has a role in the pathogenesis of eczema.

Methods

Literature search

In February 2009, a literature search in MEDLINE and EMBASE was performed (Fig. 1). As the main search strategy, 'eczema', 'atopic dermatitis', 'epidemiology', 'prevalence', 'urban', 'rural' and all their synonyms were used and combined (Table 1). References to all relevant articles found were checked for eligible articles.

Inclusion and exclusion criteria

All primary studies comparing the prevalence rate of eczema between urban and rural populations were assessed for eligi-

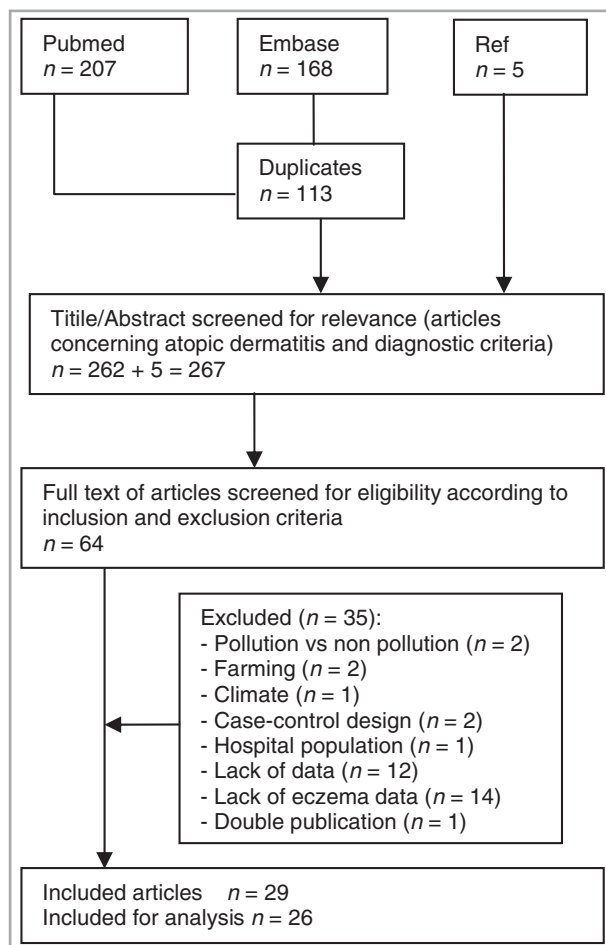


Fig 1. Flow chart of selection process.

Table 1 Search strategy for MEDLINE and EMBASE

1	exp dermatitis, atopic/
2	((atopic\$ or intrins\$ or allergic\$) adj3 (dermatit\$ or eczem\$)).tw.
3	1 or 2
4	exp animals/ not (exp animal/ and exp humans/)
5	3 not 4
6	exp Urban Rural Difference/ or exp Urban Area/ or exp Urban Population/ or exp Urban Hygiene/
7	exp Rural Health Care/ or exp Rural Population/ or exp Rural Area/ or exp Rural Hygiene/ or exp Rural Health Nursing/
8	6 or 7
9	rural.ti,ab.
10	bucolic.ti,ab.
11	country-side.ti,ab.
12	rustic.ti,ab.
13	provincial.ti,ab.
14	agrarian.ti,ab.
15	urban*.ti,ab.
16	metropolitan.ti,ab.
17	municipal.ti,ab.
18	nonagricultural.ti,ab.
19	nonfarm.ti,ab.
20	inner-city.ti,ab.
21	farming.ti,ab.
22	((rural or remote or nonmetropolitan) adj (communit\$ or area? or region? or province?)).tw.
23	11 or 21 or 9 or 17 or 12 or 20 or 15 or 14 or 22 or 18 or 19 or 10 or 13 or 16
24	8 or 23
25	24 and 5

bility. The phenotypic appearance of eczema and/or questions leading to the presence of that phenotypic appearance (e.g. in questionnaires) were considered sufficient for the diagnosis of eczema. Although the terms 'atopic dermatitis' or 'atopic eczema' are commonly used in epidemiological studies, we use the term 'eczema' throughout in accordance with the World Allergy Nomenclature Committee's recommendation.¹¹ The demonstration of allergen-specific IgE sensitization of patients with eczema was not required. Included were all definitions of 'urban' and 'rural' described in articles; if no definition was given, but the prevalence of eczema was assessed between areas with different population densities (e.g. villages vs. cities), articles were included. Most important is that the same strategies and definitions were used to assess the prevalence of eczema in both the rural (less dense populations) and the urban setting (more dense populations).

Articles comparing farming with nonfarming communities, polluted with nonpolluted areas, hospital populations, case-control studies, unpublished articles, reviews or abstracts, double publications or articles reporting only descriptive information were excluded. Articles that lacked essential data for calculating a relative risk (RR) were also excluded from analy-

sis. No restrictions were imposed regarding sample size, age, sex and skin type of the subjects and no language restriction was applied.

Study selection and data extraction

All articles with a title and abstract considering a comparison of the prevalence rate of eczema, asthma and rhinitis between urban and rural populations were selected for relevance by the reviewers M.E.S. and A.M.T. To determine eligibility, the full text of the selected articles was screened. Data were extracted independently and disagreements about the selection process and data extraction were solved by discussion between the two reviewers.

If studies reported measured prevalences in rural and urban areas, but only showed combined data, the authors were contacted with a request to provide data per group.

Assessment of methodological quality

Measuring the methodological quality of prevalence studies was done according to the guidelines for the critical appraising of studies of prevalence or incidence of a health problem as proposed by Loney *et al.* and adapted by M. Radulescu *et al.*^{12,13} Each article is scored according to seven criteria: (i) target population – this item was considered adequate if the prevalence surveys gave a definition of the target population, information on geographical area, age and sex; (ii) sampling methods – these were considered adequate if a whole or an entirely random sample of the population was used; (iii) sample size – adequate if sample size was > 810 subjects [assuming prevalence of eczema was 5% and an error rate of $\pm 1.5\%$ at the 95% confidence interval (CI) is accepted];^{12–14} (iv) response rate – a response rate of > 70% was considered adequate;^{15,16} (v) information on nonresponders – accepted if any attempt was made to obtain information about reasons for nonparticipation and characteristics of the group of nonresponders; (vi) use of valid and repeatable disease definitions – this item was considered adequate if a generally accepted disease definition was presented and diagnosis was defined by validated criteria or clinical observation;¹⁷ and (vii) efforts to reduce observer bias – considered adequate when attempts were made to reduce observer bias by training, teaching or presenting interobserver variability in case of surveys based on clinical observation or interviews; when one observer is responsible for all examinations, a conflict of interest should be excluded.

When assessing these points, special attention was given to detecting differences in data collection processes between the urban and rural areas. If such a difference was found, the particular criterion was considered inadequate.

Good methodological quality of an article was defined as not having any limitations on the above-mentioned criteria. If only 'reduction of observer bias' was lacking and/or there was no information given on nonresponders, we also considered the articles to be of good quality. Articles with limitations in

the sampling methods, sample size, response rate and use of valid and repeatable disease definition were considered to be of low quality.

Statistical analysis

We used RRs and 95% CIs to explore the risk of eczema in an urban over a rural residential area. Countries were classified as being 'developed/western' and 'developing' according to the classification of the United Nations and International Monetary Fund (<http://www.imf.org/external/pubs/ft/weo/2009/01/weodata/groups.htm>) at the time the study was performed.

The results of individual studies were compiled into The Cochrane Collaboration Review Manager 5 (<http://www.cc-ims.net/revman>) and analysed using Metaview 5. The χ^2 test was used to calculate heterogeneity between studies. The pooled RR and 95% CI were estimated using a random-effect model, as heterogeneity was evident.

Results

Literature search

Figure 1 summarizes the selection process for studies comparing urban and rural prevalences of eczema. An initial search retrieved 268 articles of which five were found during the additional reference search. After screening titles and abstracts for eligibility, 64 articles were selected. Of the initial 64 included articles, 35 were excluded after screening the full texts of the articles. Three primarily eligible studies were excluded from the analysis because they did not report essential data from which a RR could be calculated.^{18–20}

Study description

Twenty-nine articles, published between 1982 and 2009 were included in this review (Table 2).^{18–46} All articles were prospective cohort studies, with the exception of one retrospective cohort study.²² Study populations consisted primarily of children ($n = 22$); four studies included subjects of all ages and three studies only adults. Seventeen studies were conducted in 'developed/western' countries and 12 in 'developing' countries.

The definitions of 'urban' and 'rural' employed were often not reported and only predefined areas were given ($n = 17$). In most cases urban and rural residency was defined by the number of inhabitants. However, the cut-off values varied from 200 to 100 000 inhabitants between studies. Also, inhabitants per square metre,²⁵ distance from the city centre, physical features of the school building involved and water supply,³⁵ and National Health Service classification of the family practice were used.³⁰ In the study of Van der Ven *et al.*⁴¹ the level of urbanization was judged by the patients themselves. The definition of 'eczema' and diagnostic or epidemiological criteria for diag-

Table 2 Overview of included articles

First author (publication year, country)	Age (years)	Diagnosis of eczema	Prev estimate	Definition of urban and rural	Prev urban (%)	Prev rural (%)
Bouayad <i>et al.</i> ²¹ (2006, Morocco)	13–14	ISAAC	1-year	None	20.3 ^a	13.3
Bråback <i>et al.</i> ²² (2004, Sweden)	17–20	Qnaire, clin exam	Point	Urban: home located in settlement with at least 200 inhabitants	3.3 ^b	2.7 ^b
Chalmers <i>et al.</i> ²³ (2007, South Africa)	3–11	U.K., clin exam	Point	None	2.1 ^b	0.3 ^b
du Prel <i>et al.</i> ²⁴ (2006, Germany)	6	Clin exam	Lifetime	None	16.1	15.4
Dutau <i>et al.</i> ¹⁸ (1997, France)	5–6	Qnaire	Lifetime	Urban: areas with industrial impact	19.4	17.1
Galassi <i>et al.</i> ²⁵ (2006, Italy)	13–14	ISAAC	1-year	Rural: areas without heavy industrial impact		
Gniazdowska and Jefimow ²⁶ (1990, Poland)	10–15	Qnaire	Unknown	Urban: > 500 000	8.6	8.4
Graif <i>et al.</i> ¹⁹ (2004, Israel)	13–14	Modified ISAAC	Point	Other areas: population density of < 1000 inhabitants km ²		
Haileamlak <i>et al.</i> ²⁷ (2005, Ethiopia)	1–5	ISAAC	Lifetime	None		
Hanfin <i>et al.</i> ²⁸ (2007, U.S.A.)	All	Qnaire	1-year	Urban: area of residence > 2000 inhabitants	2.1	0.4
Heinrich <i>et al.</i> ²⁹ (2001, Germany)	5–14	Qnaire, clin exam	Lifetime	Rural: < 2000	7.7	8.6
Iversen <i>et al.</i> ³⁰ (2005, Scotland)	> 16	Qnaire	Lifetime	Urban: < 100 000 size of population centre	3.8 ^a	4.0 ^a
Kim <i>et al.</i> ³¹ (2000, South Korea)	6–8, 10–12, 16–18	Qnaire, clin exam	Lifetime	Rural: < 100 000	6	6
Kuhlsch <i>et al.</i> ³² (2000, Germany)	5–11	ISAAC, Qnaire	1-year	Urban: 16 000–35 000 inhabitants	11.3	7.7
Laughter <i>et al.</i> ³³ (2000, U.S.A.)	5–9	Qnaire	Lifetime	Rural: < 2500 inhabitants	18.3	13.7
Lynch <i>et al.</i> ³⁴ (1984, Venezuela)	All	Interview, clin exam	Unknown	Rural: by National Health Service classification of the family practice – practice that received rural practice payment for more than one-third of the patients		
Mavale-Manuel <i>et al.</i> ³⁵ (2007, Mozambique)	6–7, 13–14	ISAAC	1-year	None. Predefined areas plus industrialized area (excluded)	7.8	6.6
Maymi <i>et al.</i> ³⁶ (2007, Puerto Rico)	6–7	Laughter	Lifetime	None. Predefined areas. Inhabitants per square meter given	17.1	9.9
Nilsson <i>et al.</i> ²⁰ (1999, Sweden)	13–14	ISAAC	Lifetime	None	18.6	13.9
Padeigimas and Dauksiene ³⁷ (1982, Lithuanian)	All	Qnaire	Unknown	None	3.2	3.6
Sacki <i>et al.</i> ³⁸ (2005, Japan)	6–7, 11–12	Clin exam	Point	Urban: physical features – building, pavement, water supply, distance town centre	4.0	4.8
				Semirural: water supply by wells, no electricity or telephone connections	10.9	10.9
				None	25.8	23.5
				Urban: area with fewer than 50 households within distance of 200 m from each other and with fewer than 200 residents in total	28.0 ^{a,c}	24.0 ^{a,c}
				Urban: > 10 000 inhabitants in total	28.5 ^{a,d}	22.5 ^{a,d}
				None	2.9 ^a	1.9
				None	10.9	11.55

Table 2 (Continued)

First author (publication year, country)	Age (years)	Diagnosis of eczema	Prev estimate	Definition of urban and rural	Prev urban (%)	Prev rural (%)
Selcuk <i>et al.</i> ³⁹ (1997, Turkey)	7–12	Qnaire	1-year	None	2.1	2.5
Solé <i>et al.</i> ⁴⁰ (2007, Brazil)	13–14	ISAAC	Lifetime	Brazilian Institute of Geography. Urban: towns, villages, isolated urban areas Rural: out of limits of urban	14.1 ^c 9.8 ^f	14.2 ^c 11.8 ^f
Van de Ven <i>et al.</i> ⁴¹ (2006, the Netherlands)	12–14	ISAAC	1-year	Urban/rural: item in questionnaire, judged by subjects	9.7	8.3
Vedanthan <i>et al.</i> ⁴² (2006, India)	6–16	Qnaire	Lifetime	None	0	20
Wolkewitz <i>et al.</i> ⁴³ (2007, Germany)	50–74	Qnaire	Lifetime	Village: < 10 000 inhabitants Small town: 10 000–100 000 inhabitants Large city: > 100 000 inhabitants	4.7	4.1
Yemaneberhan <i>et al.</i> ⁴⁴ (2004, Ethiopia)	All	Qnaire	1-year	None	0.8	0.2
Yu <i>et al.</i> ⁴⁵ (2005, Taiwan)	7–15	Qnaire	Unknown	None	3.4	3.3
Zeng <i>et al.</i> ⁴⁶ (2006, China)	0–6	ISAAC	1-year	None	3.5	2.4

^aData extracted from figure or calculated; ^bfrom personal communication with authors (L. Bråbäck, H. Williams); ^cplace of residence in first year of life; ^dplace of residence in second year of life; ^earea of Cariari; ^farea of Santa Maria. Prev, prevalence; ISAAC, International Study of Asthma and Allergic Diseases in Children; Qnaire, questionnaire; clin exam; clinical examination; laughter, laughter questionnaire.

nosis also varied considerably from study to study or was not given at all.

With respect to assigning the degree of urbanization to subjects, all but two articles used the current place of residence: Nilsson *et al.*²⁰ used the place of residence of subjects in their first and second year of life and Wolkewitz *et al.*⁴³ used place of residence before 18 years of age.

Methodological quality

The methodological quality varied considerably between studies (Table 3). One study did not define the target population.³⁴ The sampling methods, if employed, were adequate in most cases, except for one⁴² and the sampling method was not reported in another.³⁷ Graif *et al.*¹⁹ excluded some ethnic groups from their analysis. Two studies did not meet our criterion of > 810.^{34,42} Six studies did not report a response rate^{18,27,34,37,40,43} and three of the reported rates were not adequate.^{30,33,36} Information on nonresponders was given in only two studies.^{19,30} Valid and repeatable disease definitions were used in most of the studies, although eight studies failed to provide any definition.^{18,26,30,34,37,43–45} Two studies used invalid diagnostic criteria.^{39,41} Efforts to reduce observer bias (when clinical examination or interviewing was used to determine diagnosis) were employed in only one of the seven studies.²⁹

Thirteen studies could be indicated as good quality studies, nine of which were conducted in 'developed' countries.

Prevalence studies

Prevailing prevalence rates for urban and rural residency are shown in Table 2. In 20 studies the prevalence of eczema was higher in urban areas than in rural areas, in eight studies lower and equal in one study. Twenty-six studies were involved in the risk analysis as three studies were excluded because lack of data meant it was not possible to calculate RRs. Figure 2 shows the RR of eczema in urban vs. rural areas. Nineteen of the analysed studies showed a higher risk of having eczema in an urbanized area, 11 of which were statistically significant. Six articles showed a lower risk of having eczema in an urbanized area, of which only one was significant. One study had a RR of 1.00. When dividing the studies according to level of development of the countries, it is shown that in 'western developed' countries only two of the 14 studies yielded a lower risk of eczema in urban areas; in 'developing' countries it was four out of 12 studies. Kim *et al.*³¹ showed no statistical difference in the total group of patients; however, they did find a statistically significant result in the first-graders group.

Nilsson *et al.*²⁰ compared prevalences in 13- and 14-year-olds between place of residence in the first and second year of life and found that there was a significant ($P < 0.001$) difference between urban and rural residency. Also supported by the results of Kim *et al.*,³¹ they found a statistical difference between urban and rural residency in the first-graders group exclusively. Grouping the included studies into studies

Table 3 Methodological quality of included articles

First author (publication year, country)	Target population	Sampling methods	Sample size	Response rate	Information on nonresponders	Valid disease definitions	Observer bias	Overall quality
Bouayad <i>et al.</i> ²¹ (2006, Morocco)	+	+	+	+	—	+	na	Good
Bråbäck <i>et al.</i> ²² (2004, Sweden)	+	+	+	+	—	+	—	Good
Chalmers <i>et al.</i> ²³ (2007, South Africa)	+	+	+	+	—	+	—	Good
du Prel <i>et al.</i> ²⁴ (2006, Germany)	+	+	+	+	—	+	—	Good
Dutau <i>et al.</i> ¹⁸ (1997, France)	+	—	+	unk	—	—	na	Low
Galassi <i>et al.</i> ²⁵ (2006, Italy)	+	+	+	+	—	+	na	Good
Gniazdowska and Jefimow ²⁶ (1990, Poland)	+	+	+	+	—	—	na	Low
Graif <i>et al.</i> ¹⁹ (2004, Israel)	+	—	+	+	+	+	na	Low
Haileamlak <i>et al.</i> ²⁷ (2005, Ethiopia)	+	+	+	unk	—	+	na	Low
Hanifin <i>et al.</i> ²⁸ (2007, U.S.A.)	+	+	+	+	—	+	na	Good
Heinrich <i>et al.</i> ²⁹ (2001, Germany)	+	+	+	+	—	+	+	Good
Iversen <i>et al.</i> ³⁰ (2005, Scotland)	+	+	+	—	+	—	na	Low
Kim <i>et al.</i> ³¹ (2000, South Korea)	+	+	+	+	—	+	—	Good
Kuhlisch <i>et al.</i> ³² (2000, Germany)	+	+	+	+	—	+	na	Good
Laughter <i>et al.</i> ³³ (2000, U.S.A.)	+	+	+	—	—	+	na	Low
Lynch <i>et al.</i> ³⁴ (1984, Venezuela)	—	—	—	unk	—	—	—	Low
Mavale-Manuel <i>et al.</i> ³⁵ (2007, Mozambique)	+	+	+	+	—	+	na	Good
Maymi <i>et al.</i> ³⁶ (2007, Puerto Rico)	+	—	+	—	—	+	na	Low
Nilsson <i>et al.</i> ²⁰ (1999, Sweden)	+	+	+	+	—	+	na	Good
Padegimas and Dauksiene ³⁷ (1982, Lithuanian)	+	unk	+	unk	—	—	na	Low
Saeki <i>et al.</i> ³⁸ (2005, Japan)	+	+	+	+	—	+	—	Good
Selcuk <i>et al.</i> ³⁹ (1997, Turkey)	+	+	+	+	—	—	na	Low
Solé <i>et al.</i> ⁴⁰ (2007, Brazil)	+	+	+	unk	—	+	na	Low
Van de Ven <i>et al.</i> ⁴¹ (2006, the Netherlands)	+	+	+	+	—	—	na	Low
Vedanthan <i>et al.</i> ⁴² (2006, India)	+	—	—	+	—	+	na	Low
Wolkewitz <i>et al.</i> ⁴³ (2007, Germany)	+	+	+	unk	—	—	na	Low
Yemaneberhan <i>et al.</i> ⁴⁴ (2004, Ethiopia)	+	+	+	+	—	—	na	Low
Yu <i>et al.</i> ⁴⁵ (2005, Taiwan)	+	+	+	+	—	—	na	Low
Zeng <i>et al.</i> ⁴⁶ (2006, China)	+	+	+	+	—	+	na	Good

na, not applicable; unk, unknown; +, adequate; —, not adequate. See Methods for details on the criteria.

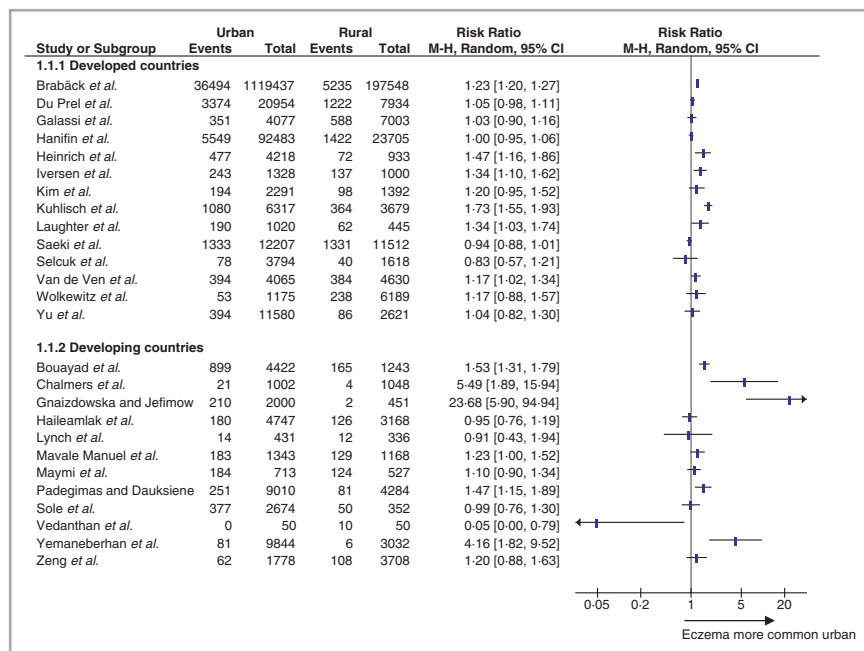


Fig 2. Relative risks for eczema in an urban area compared with a rural area. CI, confidence interval.

conducted with children or adults did not show a difference in overall RRs.

Some studies were not consistent with an overall tendency favouring urban increased prevalence over rural areas. A clear example of this was the study by Vedanthan *et al.*⁴² with a RR of 0.05 (95% CI 0.00–0.79). This was probably due to sampling variation from the very small and inconclusive sample size. Lynch *et al.*³⁴ and Haileamlak *et al.*²⁷ also showed a lower prevalence (although statistically not significant) in urban over rural areas, of which the first study was characterized by a very low overall methodological quality. Of the 'developed' countries, two studies also showed an increased prevalence in rural areas, but this was less prominent and not significant.^{38,39} Of these two studies, one used no valid criteria, so methodological quality was doubtful.³⁹ An outlier in favour of an increased urban prevalence was the study of Gnaizdowska and Jefimow²⁶ with a RR of 23.68 (95% CI 5.90–94.94). This study was prone to bias because disease definition was not given and criteria were not validated. Two other (less prominent) outliers were by Chalmers *et al.*²³ and Yemaneberhan *et al.*⁴⁴ In contrast with the other study, Chalmers *et al.* was a methodologically sound study.

When stratifying the studies by study quality, a slightly more stable outcome can be seen among the studies of good quality.

When using a random-effect model to estimate the cumulative magnitude of the urban/rural gradient over the developed countries, developing countries and the total group, a high statistical heterogeneity was found ($I^2 > 60$) for all groups. This was due to the richness of the data and precluded us showing a cumulative RR. When focusing on the high-quality articles exclusively, the statistical heterogeneity was still too high for data pooling. Also, grouping a selection of studies, for instance by country or age of the subjects, did not result in an acceptable heterogeneity for pooling. A factor that has led to a high statistical heterogeneity was the small coincidence intervals due to large patient populations used. Clinical and methodological heterogeneity were also contributing factors.

Discussion

This systematic review provides some evidence for a higher risk of eczema in urban over rural residential areas. This effect was even more evident in the 'western/developed' countries compared with 'developing' countries.

Overall this might indicate that exposure to environmental factors is of importance and adds to the idea that early sensitization is associated with later atopic manifestations.^{47,48}

The methodological quality of the included studies was good in approximately 50% of the articles. The older studies were more frequently among those of poor quality. None of the included studies was without limitations. In a substantial number of studies, a valid and repeatable disease definition was lacking. Most often, data on response rate and non-responders of surveys were not reported. Noticeable is that in cases of clinical diagnosis or interviews to determine

diagnosis, only one of the seven studies made efforts to reduce observer bias by training, briefings, etc.

The two largest outliers in this study (Vedanthan *et al.*⁴² and Gnaizdowska and Jefimow²⁶) scored particularly disappointing on methodological quality. Results of both studies are therefore also likely to be biased and their results might be questioned. Stratification by study quality showed slightly less heterogeneous results among the studies of good methodological quality.

The awareness among researchers of the need for sound methodological design of studies is increasing but we still want to emphasize the importance of adequate design and reporting. Radulescu *et al.*¹³ offer clear guidelines for assessing methodological quality in prevalence studies.

There are several factors that vary between rural and urban areas that might contribute to the differences found in prevalence. Examples of possible factors that contribute to the effect are differences in family size, exposure to animals, maternal age, overcrowding (in a house), differences in food (e.g. processed vs. fresh) and water intake (spring vs. chlorinated water), socioeconomic factors and time spent indoors.^{22,48–50} In addition the amount of traffic in urban areas is notably higher than in rural areas. In contrast rural areas are prone to have harsher climatic conditions, and these could also play a role in prevalence or severity of eczema.⁵¹

Pollution, which is usually higher in urban areas, could also be of influence. Dotterud *et al.*⁵² found a significantly higher prevalence of eczema in polluted vs. nonpolluted areas: RR 3.0 (2.5–3.5) and also Sriyraj *et al.*⁵³ found a significantly higher prevalence of eczema in air-polluted areas when comparing urban and semiurban areas selected for their degree of air pollution. Nilsson *et al.*²⁰ found that the largest confounding factor was the presence of bronchial asthma followed by parental history of allergy, passive smoking, indoor pets and dampness in the home.

In addition, another explanatory factor that might have contributed is whether the participants were truly atopic or not, as it is possible that IgE sensitization is the predominant factor in explaining the urban/rural gradient for atopic eczema.⁵⁴ In none of the included studies was IgE sensitization mandatory for the diagnosis of eczema and the percentage of patients with eczema with IgE sensitization was not given in any study.

A possible explanation for the more profound effect found in 'western/developed' countries compared with developing countries could lie in the differences in urban city life. In 'developed' cities, there is a lower exposure to animals, better housing and/or less crowding compared with cities in 'developing' countries and urban living is therefore more in contrast with rural living. This is also in agreement with the 'hygiene hypothesis'.

Overall, it is difficult to differentiate between factors that contribute to the differences found in prevalences and factors that are confounding.

This review was performed following methodologically sound guidelines for systematic reviews made by the Cochrane collaboration. We performed a thorough search and the

selection and data-extraction process was done objectively and by two researchers independently.

We assigned countries a label of being 'developed/western' or 'developing'. We think this division is appropriate as environmental conditions between rural and urban areas vary considerably depending on the standard of living in a country. The primary differences between the two groups were that the study populations in 'developed/western' countries were bigger and the RRs more consistent.

We have made the broad assumption that genetic backgrounds will be more or less the same in a given country. As urban locations may be subject to a large influx of migrants and rural locations in some countries may include tribal peoples who are not often found in cities, it is unlikely that the genetic composition of the rural and urban populations within each country is the same.

As some study populations were not just divided into urban and rural areas, but also into semiurban, semirural or industrialized, we had to exclude some comparative areas. In two studies semiurban groups were excluded.^{23,43} Padegimas and Dauksiene³⁷ divided their urban population into two groups: a recently built district and a residential district built 25–30 years ago. We combined both groups into one urban group. In the study of Mavale-Manuel *et al.*,³⁵ the semirural area was considered rural. The industrialized area of Ulsan was excluded in the analysis of the study by Kim *et al.*³¹

Several relevant studies were excluded for lack of quantitative data, although they did report information on urban vs. rural prevalences of eczema. Kramer *et al.*⁵⁵ showed an odds ratio of 0.85 (0.3–2.0) in favour of a lower ratio of eczema in rural communities in Germany, which was in contrast with another study conducted in Germany that stated that there was no significant association between the frequency of eczema and density of urbanization.⁵⁶ Poysa *et al.*⁵⁷ did not show any comparative data but noted a lower prevalence of eczema in the rural communities of Finland. Also in Finland, Kilpeläinen *et al.*⁵⁸ compared urban, rural farming and rural nonfarming residency in childhood and stated that there were no significant differences. Furthermore, Aberg *et al.*⁵⁹ showed that there was no significant variation in the presence of eczema between urban and rural Swedish areas.

During this review we encountered data heterogeneity on different levels. Clinical heterogeneity was caused by differences in the characteristics of the populations, age and sample sizes (ranging from 100 to 1 316 985), the definition of eczema employed, diagnostics and prevalence estimates used. The definitions of 'atopic dermatitis/eczema', 'urban' and 'rural' regarded as acceptable for inclusion in the study were very flexible. For instance, what would be defined as being 'urban' according to the definition in one article could be defined as 'rural' in another. Thereby, over the years the differences between urban and rural circumstances have changed. All together, this leads to a considerable degree of heterogeneity. However, by ensuring that comparisons between rural and urban centres in the same study were done using the same method of disease ascertainment this will not lead to distortion of the results.

This was the subject of attention while assessing methodological quality. Studies that do not score well on the selection of subjects, response rate or criteria employed are prone to this form of bias.

Only two studies used place of residence at a certain age. All the other studies used current place of residence. As there are indications that exposure to environmental factors early in life is of importance, studies using current place of residence of older subjects could show bias in results to some extent. Patients could have moved from urban to rural areas or vice versa.

Analysis of data was further challenged by statistical heterogeneity. Although 'eye-balling' the outcomes of the studies conducted in 'developed/western' countries suggests low statistical heterogeneity, heterogeneity was high (> 60%). This was primarily due to the large populations involved and thereby small 95% CIs.

For all these reasons, we were not able to pool the collected data and give sum scores or an urban/rural gradient. However, although a cumulative gradient could not be measured, this study does support the idea that urbanization might be a key risk factor for eczema.

We are aware of the presence of new and as yet unpublished data on this matter and we encourage those authors to send us the unpublished work, when it becomes available. The same accounts for any future work or data we missed. This would enable us to maintain an accurate overview in an online database.

Future, methodologically sound reviews on environmental circumstances should be done to reveal the factors associated with a higher prevalence of eczema in urban areas and the association with other allergic diseases. Associating factors could be microbial load, exposure to endotoxins and timing of allergen exposure. If an explanation for the rural/urban gradient could be found, this would help us to unravel the complex aetiology of eczema and enable us to make evidence-based public health decisions on the prevention and even treatment of eczema.

What's already known about this topic?

- Many primary studies (e.g. the studies included in this review) have been conducted to evaluate if there is an urban/rural gradient in eczema prevalence.
- This question has never been answered by a systematic review.

What does this study add?

- Our review suggests that place of residence has a role in the pathogenesis of eczema.
- This is relevant for adding weight to supporting or refuting the hygiene hypothesis.
- This also justifies further analyses to explain the gradient and why it differs in different parts of the world.

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