 International Journal of Epidemiology 2001;**30**:173–179

The relationship of per capita gross national product to the prevalence of symptoms of asthma and other atopic diseases in children (ISAAC)

Alistair W Stewart,[a] Ed A Mitchell,[b] Neil Pearce,[c] David P Strachan[d] and Stephan K Weiland[e] on behalf of the ISAAC Steering Committee

Background	Increasing prevalence and worldwide variation in asthma and other atopic diseases suggest the influence of environmental factors, at least one possibly related to socio-economic wellbeing. This paper examines the relationship of symptoms of asthma, rhinitis and eczema with gross national product per capita (GNP per capita).
Methods	The prevalences of atopic symptoms in 6–7- and 13–14-year-old children were assessed in 91 centres (from 38 countries) and 155 centres (from 56 countries), respectively, in the International Study of Asthma and Allergy in Childhood (ISAAC). These symptoms were related to 1993 GNP per capita for each country as reported by the World Bank. The relationships between symptoms of atopic diseases and infant mortality, the human development index and 1982 GNP per capita were also considered.
Results	The countries in the lowest quartile of GNP per capita have the lowest median positive responses to all the questions on symptoms of asthma, rhinitis and eczema. There was a statistically significant positive association between wheeze in the last 12 months and GNP per capita in the 13–14-year age group, but not in the 6–7-year age group. There was also a positive association between GNP per capita and eczema in both age groups.
Conclusions	The positive associations between GNP per capita and atopic symptoms being of only moderate strength suggests that the environmental factors are not just related to the wealth of the country.

Keywords	Allergies, asthma, children, ecological, eczema, GNP per capita, rhinitis, wheeze, ISAAC
Accepted	1 March 2000

The International Study of Asthma and Allergy in Childhood (ISAAC) found marked worldwide variation in prevalence of symptoms of asthma, eczema and allergic rhinoconjunctivitis.[1–4] In general the prevalence of asthma in developing countries is lower than that in developed countries. Strachan proposed that '... social and demographic variations in allergy prevalence argue strongly for environmental influences on allergic sensitisation ...'.[5] Furthermore, the prevalence of asthma is increasing.[6] Although genetic factors are important, they cannot explain the increase in prevalence or worldwide variation. This has led to the suggestion that there must be some environmental factors producing these changes. Increasing pollution,[7,8] decreasing infection[9] and changes in diet have all been suggested.[10–12] Any environmental factor must be changing and must vary between countries. At least one environmental factor would appear to be associated with socioeconomic wellbeing, but this has only been examined at the individual level.[13–16]

This ecological study examines the association of the prevalence of symptoms of asthma and other atopic diseases with gross national product per capita (GNP per capita) at a centre

[a] Department of Community Health, University of Auckland, Auckland, New Zealand.

[b] Department of Paediatrics, University of Auckland, Auckland, New Zealand.

[c] Department of Medicine, Wellington Clinical School, University of Otago, Wellington, New Zealand.

[d] Department of Public Health Sciences, St Georges Hospital Medical School, London, UK.

[e] Institut Für Epidemiologie un Sozialmedizin, Westfälische Wilhelms Universität, Münster, Germany.

Reprint requests to: Alistair W Stewart, Department of Community Health, Faculty of Medicine and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand. E-mail: aw.stewart@auckland.ac.nz

and country level where GNP per capita is being used as a surrogate for socioeconomic status of the country.

Methods

Prevalence data for the symptoms of asthma and allergy variables were obtained from the ISAAC study. The selection of centres and children have been described in detail elsewhere.[1–4] In brief, for children 13 and 14 years of age in 155 centres from 56 countries, either all schools or a random selection of schools in a defined area were chosen. All children in classes of the appropriate age completed a short written questionnaire and in 99 of these centres the children also watched a video depicting various wheezing situations and then responded to questions. For children, aged 6 or 7 years in 91 centres in 38 countries from either all schools or a random selection of schools, a parent completed the same written questionnaire but the video option was omitted.

The questions considered here asked about the presence of symptoms of asthma and allergies. The asthma-related question asked children whether they had wheezing or whistling in the chest in the last 12 months. The question on rhinoconjunctivitis asked whether they had a problem with sneezing or a runny or blocked nose without signs of a cold in the last 12 months and whether this was accompanied by itchy-watery eyes. The eczema questions asked children if they had an itchy relapsing rash in the last 12 months that had affected the skin creases at some time. Also, the older children were asked whether they had breathed, in the last 12 months, like the wheezing young person on the video. Responses to all questions were yes or no, missing data being treated as a negative response.

To assess the severity of wheezing a question about the frequency of sleep disturbance was asked. Those responding that this occurred one or more nights a week having responded positively to the wheezing question were considered to have severe wheezing. A similar question was asked to get a measure of severity of the itchy rash. A severe itchy relapsing skin rash was one which kept the respondent awake one or more nights per week on average in the last year.

As an assessment of the socioeconomic status of a country we have used the gross national product per capita (GNP per capita) as reported by the World Bank.[17] Purchasing power parity adjusted GNP per capita would be the preferred measure but was not available for eight countries. The GNP per capita measures the total domestic and foreign value added income claimed by residents. We used the 1993 GNP per capita (in US dollars) and also the 1982 GNP per capita[18] as this was the approximate year of birth of the older children. As the calculation of GNP per capita can vary slightly, only the one source has been used and no estimate for Iran was available. Infant mortality and the human development index (HDI) have been suggested as measures of socioeconomic development of a country and we also considered these variables.[17,19,20] The HDI is a composite of three basic components of human development: longevity (life expectancy), knowledge (combination of adult literacy and mean years of schooling) and standard of living (gross domestic product per capita adjusted for purchasing power parity).

The GNP per capita and the other factors are reported for a country whereas the ISAAC study allows the estimation of the atopic condition at a centre level. In Figure 1 this results in countries being shown in vertical columns, each point representing a centre within that country.

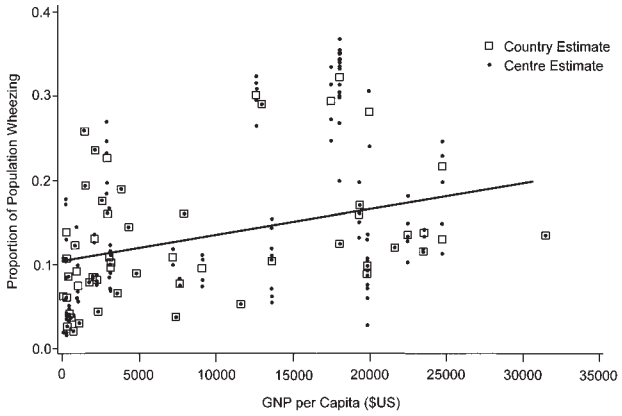

Figure 1 The association between prevalence of wheeze in the last 12 months (from the written questionnaire) among 13–14-year olds measured in centres and GNP per capita ($US) for each country

To simply display changes in the level of atopic symptoms with increasing GNP per capita, GNP per capita for each country in the age group has been divided into quartiles. Within these quartiles the centre with the median proportion of children responding positively is located and its value reported along with the values from the centres at the 10th and 90th percentiles. The numbers of centres in each quartile differ because of the varying number of centres per country. This procedure has also been used for infant mortality and HDI.

Assuming a linear relationship between the proportion of children who responded positively to the question on atopic symptoms and the GNP per capita of the country in which they went to school, the data were modelled using a generalized linear mixed model.[21] This model was used to allow each centre to be considered as if randomly selected from within its country and so account for the clustering effect. The model used a binomial error but assumed the identity link so that there was a simple linear association between the outcome measure and GNP per capita. The calculations were done using the SAS macro GLIMMIX.[22]

Results

There was a very wide range of GNP per capita values from the countries participating in the ISAAC study (Table 1). The African countries of Ethiopia, Kenya and Nigeria along with India had GNP per capita values ⩽$US300 whilst Sweden and the US had GNP per capita values >$24 000 and Japan had highest GNP per capita of $31 490. The median GNP per capita for the 55 countries for which we had values was $US3610. The GNP per capita information for Iran was not available and so two centres were excluded, leaving 153 and 89 centres for 13–14- and 6–7-year-old children, respectively.

For the children aged 13–14 years, the proportion responding positively to the wheezing variable ranged from 1.6% up to a centre with 36.7%, for rhinoconjunctivitis the range was 1.4% to 39.8%, for itchy relapsing skin rash the range was 0.3% to 20.5% and for the video question the responses ranged from 0.6% to 19.5% (Table 1). For children aged 6–7 years the

Table 1 The prevalence of atopic symptoms during the last 12 months in children from two age groups in 55 countries ordered by gross national product (GNP) per capita

		13–14 years							6–7 years					
Country	**GNP per capita**	Centres	Wheeze	Rhino-conjunctivitis	Skin rash	Wheeze (video)	Severe wheeze	Severe skin rash	Centres	Wheeze	Rhino-conjunctivitis	Skin rash	Severe wheeze	Severe skin rash
Ethiopia	100	2	6.2	6.1	11.4		1.4	1.7	0					
Kenya	270	2	13.9	14.2	10.4	11.4	4.2	3.0	0					
India	300	14	6.0	5.6	3.8	2.9	1.1	0.4	14	5.6	3.2	2.7	1.2	0.3
Nigeria	300	1	10.7	39.8	17.7		3.7	4.3	0					
Albania	340	1	2.6	4.0	0.8	1.0	0.3	0.1	1	7.6	4.1	2.5	1.3	0.5
Pakistan	430	1	8.5	18.1	9.6	7.9	1.6	1.3	0					
China	490	5	4.2	7.2	1.2	2.0	0.3	0.2	0					
Georgia	580	2	3.6	4.4	2.5		0.7	0.5	2	7.6	3.1	4.6	1.0	0.9
Indonesia	740	1	2.1	5.3	1.2	1.3	0.8	0.4	1	4.1	3.8	0.0	0.7	0.0
Philippines	850	1	12.3	15.3	5.2	9.6	2.0	1.2	1	11.3	9.2	5.1	1.4	1.1
Uzbekistan	970	2	9.2	6.3	3.0	1.3	0.2	0.1	0					
Morocco	1040	3	7.5	12.1	8.7	7.5	2.2	2.4	0					
Romania	1140	1	3.0	5.2	6.3		0.4	0.9	0					
Peru	1490	1	26.0	19.3	8.2	18.5	3.3	0.9	0					
Paraguay	1510	1	19.4	34.5	10.8	10.1	3.0	1.3	0					
Algeria	1780	1	7.8	18.2	5.2		1.8	1.1	0					
Latvia	2010	2	8.4	5.0	4.9	1.3	0.9	0.5	1	7.3	3.1	8.0	1.0	1.3
Thailand	2110	2	13.0	15.5	8.2	6.9	1.1	0.9	2	8.2	7.3	11.9	0.8	1.4
Costa Rica	2150	1	23.7	14.3	7.2		3.5	1.4	1	32.1	11.6	8.7	4.9	1.0
Poland	2260	3	8.1	9.3	5.4	3.9	0.9	0.3	2	10.9	7.2	6.3	1.5	1.0
Russia	2340	1	4.4	6.2	3.0	1.3	0.1	0.2	0					
Panama	2600	1	17.6	9.4	7.8		2.0	1.2	1	23.5	7.1	7.9	3.3	0.7
Brazil	2930	5	22.7	16.2	5.3		3.7	0.9	3	23.3	11.3	7.3	5.8	0.8
South Africa	2980	1	16.1	15.2	8.3	6.5	3.6	2.3	0					
Estonia	3080	2	10.8	4.9	5.7	2.1	1.1	0.3	1	9.3	3.5	9.8	0.7	0.5
Malaysia	3140	5	9.6	13.7	8.0	5.9	0.8	0.6	5	6.1	3.9	8.5	0.5	1.0
Chile	3170	4	10.2	10.2	8.8	11.2	1.4	1.0	4	17.9	8.2	10.9	3.5	1.7
Mexico	3610	1	6.6	9.4	4.4		1.6	0.4	1	8.6	8.6	4.9	1.6	0.3
Uruguay	3830	1	19.0	16.0	7.2	15.0	2.6	1.1	1	18.0	6.6	8.6	3.0	1.2
Lebanon	4360	1	14.4	15.4	4.7	4.9	5.0	1.1	0					
Oman	4850	1	8.9	11.3	4.7		2.9	0.9	1	7.1	6.2	4.2	3.5	0.9
Argentina	7220	2	10.9	22.8	7.3	8.3	2.1	1.5	2	16.4	9.6	7.5	3.4	1.3
Greece	7390	1	3.7	6.3	3.1		0.7	0.3	1	7.6	3.5	4.1	1.1	0.5
Republic of Korea	7660	2	7.7	10.2	3.8	3.7	0.2	0.0	2	13.3	9.8	8.8	0.5	0.0
Malta	7970	1	16.0	28.9	7.7	8.8	2.4	1.3	1	8.8	7.2	4.2	1.5	0.4
Portugal	9130	4	9.5	7.0	4.4	6.2	1.4	0.9	3	13.2	8.7	9.6	3.4	2.0
Taiwan	11 630	1	5.2	11.3	1.4	4.6	0.4	0.2	1	9.6	14.7	3.5	0.8	0.6
New Zealand	12 600	6	30.2	18.9	12.7	18.4	3.2	2.0	6	24.5	9.7	14.7	3.5	2.0
Ireland	13 000	1	29.1	19.3	13.6		2.6	1.9	0					
Spain	13 590	8	10.3	15.1	4.4	7.8	1.1	0.5	5	6.2	5.0	3.3	0.8	0.2
Australia	17 500	4	29.4	19.6	9.7	17.6	3.0	1.2	4	24.6	12.0	10.9	2.8	0.9
Hong Kong	18 060	1	12.4	24.0	2.7	10.1	0.5	0.3	1	9.1	13.7	3.9	0.3	0.4
UK	18 060	15	32.2	18.5	15.8		3.5	2.1	1	18.4	9.8	13.0	5.6	2.0
Finland	19 300	4	16.0	16.6	15.6	5.1	0.5	0.8	0					
Kuwait	19 360	1	17.0	12.5	8.3	13.3	5.7	2.3	0					
Italy	19 840	13	8.9	13.4	5.7	5.3	0.6	0.4	9	7.3	5.2	5.8	0.6	0.1
Singapore	19 850	1	9.7	15.1	7.4	9.9	1.3	0.9	1	15.7	8.5	2.8	1.8	0.3
Canada	19 970	2	28.1	20.0	9.4	12.0	2.1	1.0	2	17.6	11.7	8.5	2.2	0.7
Belgium	21 650	1	12.0	14.8	6.7		1.5	1.1	1	7.3	4.9	7.7	1.3	0.7

continued

Table 1 Continued

		13–14 years							6–7 years					
Country	GNP per capita	Centres	Wheeze	Rhino-conjunctivitis	Skin rash	Wheeze (video)	Severe wheeze	Severe skin rash	Centres	Wheeze	Rhino-conjunctivitis	Skin rash	Severe wheeze	Severe skin rash
France	22 490	5	13.5	16.0	10.0	8.3	1.1	1.0	1	8.1	5.9	8.8	0.7	0.4
Austria	23 510	2	11.6	10.7	5.2	5.4	0.8	0.4	2	8.9	6.2	6.4	1.0	0.6
Germany	23 560	2	13.8	13.5	6.9	5.3	1.2	0.7	2	8.5	5.0	6.8	1.7	0.8
Sweden	24 740	2	12.9	11.7	14.5	5.2	0.8	1.0	1	10.4	5.9	18.4	0.9	0.8
USA	24 740	3	21.7	18.9	2.7	12.9	4.2	0.3	0					
Japan	31 490	1	13.4	14.8	10.5	10.2	0.6	1.3	1	17.3	7.8	16.9	1.2	1.3

proportion responding positively to the wheezing variable ranged from 0.8% up to 32.1%, for rhinoconjunctivitis the range was 0.8% to 16.7% and for itchy relapsing skin rash the range was 0.0% to 18.4%. The centre proportions of severe wheezing varied from 0.1% to 6.3% in the older children and from 0.3% to 10.0% in the younger children.

Table 2 shows that as GNP per capita increased there was a general increase in the median proportion of children responding positively. In particular, the lowest quartile has, for all variables at both ages, the smallest median prevalence. For 13–14-year-old children there was no clear trend in the other three quartiles but the 6–7-year-old children show, for all the questions, the largest quartile decreased compared with the second to largest GNP per capita quartile.

Assuming a linear relationship between GNP per capita and the atopic disease symptom measures, the changes in the percentage responding positively for each change of US$1000 of GNP per capita, as given by the generalized linear mixed model, are shown in Table 3. The percentage changes and the associated 95% CI are given. For children aged 13–14 years the

Table 2 The median prevalence (with 10th and 90th percentiles) of atopic symptoms during the last 12 months in children from two age groups by centre grouped into four approximately equally sized groups based on the country gross national product (GNP) per capita

	Quartiles of GNP			
Children aged 13–14 years	$100–$1140	$1490–$3170	$3610–$17 500	$18 060–$31 490
No. of countries	13	14	14	14
No. of centres	36	30	34	53
Wheeze	5.3 (1.9, 13.0)	11.6 (7.0, 24.2)	11.9 (6.1, 31.4)	14.8 (8.6, 34.1)
Rhinoconjunctivitis	6.3 (2.3, 16.1)	12.6 (5.3, 18.8)	15.7 (7.7, 22.6)	15.3 (11.3, 22.5)
Itchy relapsing skin rash	3.2 (0.8, 12.0)	6.5 (3.8, 10.2)	5.6 (3.1, 12.8)	9.4 (3.9, 16.7)
Wheeze (video)	2.6 (1.0, 9.6)	6.0 (1.3, 13.0)	8.9 (4.9, 19.5)	5.7 (4.5, 11.6)
Severe wheeze	0.8 (0.2, 2.7)	1.3 (0.5, 3.6)	1.9 (0.5, 3.3)	1.2 (0.4, 3.7)
Severe skin rash	0.4 (0.1, 2.9)	0.6 (0.3, 1.5)	1.1 (0.2, 1.9)	0.9 (0.3, 2.3)
	Quartiles of GNP			
Children aged 6–7 years	$300–$2260	$2600–$7220	$7390–$18 060	$19 840–$31 490
No. of countries	9	9	10	9
No. of centres	25	19	25	20
Wheeze	5.9 (1.8, 14.3)	16.5 (5.6, 23.5)	14.7 (6.2, 27.0)	7.9 (6.5, 16.5)
Rhinoconjunctivitis	3.5 (1.6, 10.0)	7.7 (3.5, 12.5)	9.3 (3.8, 14.5)	5.6 (4.4, 8.3)
Itchy relapsing skin rash	3.1 (0.7, 11.4)	8.6 (4.9, 11.3)	10.7 (3.1, 14.4)	6.6 (4.8, 12.9)
Severe wheeze	1.0 (0.6, 2.2)	2.9 (0.4, 5.8)	2.1 (0.4, 3.9)	0.8 (0.5, 1.9)
Severe skin rash	0.5 (0.0, 1.3)	0.9 (0.5, 2.2)	0.7 (0.1, 2.6)	0.5 (0.0, 0.9)

Table 3 The relationship between gross national product (GNP) per capita and symptoms of atopic disease by age group

	13–14 years		6–7 years	
	Percentage increase in children responding positively for an increase of $1000 in GNP per capita (95%CI)	*P*	Percentage increase in children responding positively for an increase of $1000 in GNP per capita (95%CI)	*P*
Wheeze	0.31% (0.09%, 0.53%)	0.007	0.03% (–0.22%, 0.28%)	0.84
Rhinoconjunctivitis	0.16% (–0.04%, 0.36%)	0.12	0.06% (–0.06%, 0.17%)	0.32
Itchy relapsing skin rash	0.12% (0.00%, 0.24%)	0.05	0.16% (0.03%, 0.30%)	0.02
Wheeze (video)	0.14% (–0.01%, 0.29%)	0.08		
Severe wheeze	0.00% (–0.04%, 0.04%)	0.88	–0.02% (–0.08%, 0.03%)	0.37
Severe skin rash	0.00% (–0.02%, 0.02%)	0.70	–0.00% (–0.02%, 0.02%)	0.72

proportion in a centre wheezing had an estimated increase of 0.31% with a US$1000 increase in GNP per capita (Figure 1). Increases of 0.16%, 0.12% and 0.14% were estimated for rhinoconjunctivitis, itchy relapsing skin rash and wheezing as measured by the video, respectively, while for the younger children an increase of 0.16% with a US$1000 increase in GNP per capita was estimated for itchy relapsing skin rash. The use of purchasing power parity adjusted GNP per capita in the subset of countries in which data were available showed similar results with most of the relationships being slightly stronger.

As GNP per capita may measure different characteristics of countries when viewed across the large range of countries involved in ISAAC, we have performed the same analyses using the much more homogeneous European countries only. In these 12 countries, all members of the European Union, there was no indication of a significant (5% level) association and the parameter estimates are, in some cases, of the opposite sign to those from the analysis based on all centres (Table 4).

Alternative measures of socioeconomic status are infant mortality and HDI. In the 44 countries for which we had infant mortality data, it showed no relationship with the wheezing and other questions. For example, for each of the quartiles of infant mortality, in increasing order, the median centre had 10.4%, 8.3%, 10.2% and 16.1% of its 13–14-year-old children wheezing in the last 12 months. The HDI generally showed a stronger association with symptoms than did infant mortality. However, in the 13–14-year age group little relationship with HDI was seen with the exception being wheeze in the last 12 months where there was a positive relationship ($P = 0.007$). The median centre percentage of 13–14-year-old children wheezing in the last 12 months were 6.4%, 9.7%, 9.9% and 26.7% for the quartiles of HDI. In the 6–7-year age group, where there was no information from the African countries in particular, there was a positive relationship for wheeze, rhinoconjunctivitis and itchy relapsing skin rash. Both infant mortality and HDI range widely for countries with GNP per capita less than US$6000 but very little for countries above this level. Rank correlations between GNP per capita, HDI and infant mortality were all over 0.85 as was the rank correlation between HDI and infant mortality in countries with GNP per capita under US$6000. Despite the high correlations these variables showed different associations with the atopic symptom variables.

The GNP per capita at the time of birth of the older children, taken as 1982, was available in 45 of the ISAAC countries as the constituent republics of the Soviet Union were not listed separately at that time. This variable showed a greater effect size for wheezing in the last 12 months than the 1993 GNP per capita and, when modelled together, the 1982 GNP per capita measure showed some tendency to contribute to the explanation of current wheeze over the effect of the 1993 GNP per capita ($P = 0.075$). For the rhinoconjunctivitis and itchy rash conditions, the 1982 GNP per capita did not show any better relationship than the 1993 GNP per capita.

Discussion

This ecological study examined the relationship of GNP per capita to asthma and other atopic diseases in children of two age groups. This is in contrast to many epidemiological study designs where information is available at the individual level. It is emphasized that a correlation between variables based on group (ecological) characteristics may not necessarily be reproduced between variables based on individual characteristics. This may result in inappropriate inferences from ecological data, referred to as the 'ecological fallacy'.[23] However, 'if the environment is important, then appropriate analysis should be at the environmental level'.[19] The increasing prevalence and worldwide variation of asthma and other atopic diseases are most likely to be caused by environmental factors and hence 'ecological analyses ... are the most useful way to examine the effect of social environment on health'.[19]

Gross national product comprises gross domestic product (GDP) plus the income residents receive from abroad less similar payments made to non-residents who contributed to the domestic economy. The GDP measures the total output of goods and services for final use produced by residents and non-residents and includes an allowance for non-money income (e.g. people who grow their own fruit and vegetables). The figures for GNP per capita are GNP in US dollar values converted from domestic currencies using single-year official exchange rates divided by the population of the country in that year. The GNP/GDP statistics suffer from known defects such as the quality and quantity of the raw data and the exclusion of some activities like the black market and domestic work the extent of which also varies between countries. The importance of the correction for purchasing power parity may also vary from country to country. Nevertheless, we believe there is no evidence that these statistics are so biased as to distort their use

Table 4 The relationship between gross national product (GNP) per capita and symptoms of atopic disease by age group in countries of the European Union only[a]

	13–14 years		6–7 years	
	Percentage increase in children responding positively for an increase of $1000 in GNP per capita (95%CI)	*P*	Percentage increase in children responding positively for an increase of $1000 in GNP per capita (95%CI)	*P*
Wheeze	0.15% (–0.71%, 1.01%)	0.73	–0.06% (–0.33%, 0.44%)	0.78
Rhinoconjunctivitis	0.23% (–0.17%, 0.64%)	0.28	–0.02% (–0.20%, 0.16%)	0.83
Itchy relapsing skin rash	0.29% (–0.19%, 0.77%)	0.27	0.30% (–0.14%, 0.73%)	0.22
Wheeze (video)	–0.08% (–0.28%, 0.11%)	0.44		
Severe wheeze	–0.02% (–0.12%, 0.07%)	0.64	–0.06% (–0.21%, 0.10%)	0.49
Severe skin rash	–0.01% (–0.05%, 0.06%)	0.87	–0.02% (–0.08%, 0.04%)	0.55

[a] Austria, Belgium, Finland, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden, UK.

as an index of the relative underlying socioeconomic state of the countries. We have used just one source for our statistics, the World Development Report, produced by the World Bank, to reduce some of the potential error. Previous studies have shown that GNP per capita correlates with mortality.[24,25]

We found a statistically significant positive association between wheeze in the last 12 months and GNP per capita in the 13–14-year age group, but not in the 6–7-year age group. We also found a significant association between GNP per capita and eczema that was consistent in both age groups. There was no association between GNP per capita and rhinoconjunctivitis in either age group. However, these linear regression models may not be representing the relationship correctly given that the simple tabulations show a positive association at the lower GNP per capita levels but not at the higher levels.

The EU countries give a different picture when compared with the results from all centres. It could be that there is too little data to give a clear picture. It may be that the production giving rise to the GNP per capita represents a different ratio of characteristics (e.g. health, manufacturing, etc.) in the EU countries compared with the other countries under study. A third option is that the relationship between GNP per capita and symptoms of atopic disease is not linear and the positive associations shown in Table 3 arise from an association in underdeveloped countries only.

As the socioeconomic influence may have occurred at the time the child was born we also considered the GNP per capita at that time. For the 13- and 14-year-old children there was some indication that, for the wheezing questions only, the relationship with the GNP per capita at the time of their birth may have been stronger than for the recent GNP per capita. However, this was not reflected in the consideration of rhinoconjunctivitis or the eczema measure. The relationship between the year in which GNP per capita was recorded and the year of birth of the child could reflect different aspects of the society. The GNP per capita could be a surrogate for the current health situation but it could also be a reflection of the health infrastructure in which case the GNP per capita in the past or even better a GNP per capita history may be more relevant.

An alternative measure of the social status of a country, HDI, is an attractive variable, in that it includes three measures of wellbeing of the community. We found, however, that developed countries tended to cluster at the top of the scale with little heterogeneity, which limited its usefulness. Infant mortality could also reflect the socioeconomic status of a country but, like HDI, it does not have a desirable distribution and we could not show a relationship with the wheezing and other allergic variables.

The option that the relationship is not linear fits with Table 2 which shows the countries in the lowest GNP per capita quartile consistently having the lowest median while the order of the medians in the other quartiles are less consistent. This could occur if there was a threshold effect. As GNP per capita increases towards a certain level there are changes in society which are common to most countries and result in increasing symptoms of atopic diseases. Countries with GNP per capita above the threshold however, may differ in the type of goods and services produced as the GNP per capita increases such that symptoms may or may not be affected. For example, the proportion of GNP per capita used on health care expenditure has little association in a group of countries with GNP per capita over $US 12 000.[25] Unfortunately neither HDI nor infant mortality discriminate between these wealthier countries and so do not shed further light on associations between symptoms of atopic disease and the socioeconomic status of the countries.

We considered GNP per capita as a measure of socioeconomic status of a country similarly to considering income as a measure of socioeconomic status at the individual level. The relatively weak association between socioeconomic wellbeing and atopic diseases is important, as it indicates that any environmental factor is not just related to the wealth of the country. However, as we have demonstrated an association, we recommend that GNP per capita should be included as a potential confounder for many of the subsequent ecological analyses on the ISAAC Phase One data.

Acknowledgements

The authors are indebted to the collaborators in the participating centres and all parents, children, teachers, and other school staff who participated in the surveys. We also thank Prof. Conrad Blyth, Professor of Economics at the University of Auckland, for his helpful advice on the interpretation of gross national product. The ISAAC prevalence data were collated by the ISAAC International Data Centre, Auckland, New Zealand, with financial support from HRCNZ, ARFNZ, NCHRF, HBMRF, WMRF, GWNZ and Astra NZ. Glaxo-Wellcome IMA contributed funding for regional co-ordination in ISAAC. Weiland and Strachan are members of the ISAAC Europe collaboration, supported in part by the European Union Biomed 2 programme (BMH4 CT98 3670).

References

[1] ISAAC Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;**12:**315–35.

[2] Strachan D, Sibbald B, Weiland S *et al*. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997;**8:**161–76.

[3] Beasley R, Keil U, von Mutius E *et al*. World-wide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;**351:**1225–32.

[4] Williams HC, Robertson CF, Stewart AW *et al*. Worldwide variations in the prevalence of atopic eczema in children from the international study of asthma and allergies in childhood (ISAAC). *J Allergy Clin Immunol* 1999;**103:**125–38.

[5] Strachan DP. Socioeconomic factors and the development of allergy. *Toxicol Let* 1996;**86:**199–203.

[6] Magnus P, Jaakkola JJ. Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross sectional surveys. *BMJ* 1997;**314:**1795–99.

[7] Wjst M, Reitmeir P, Dold S *et al*. Road traffic and adverse effects on respiratory health in children. *BMJ* 1993;**307:**596–600.

[8] von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;**149:**358–64.

[9] Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;**299:** 1259–60.

[10] Seaton A, Godden DJ, Brown K. Increase in asthma: a more toxic environment or a more susceptible population? *Thorax* 1994;**49:**171–74.

[11] Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990;**323:** 502–07.

[12] Black PN, Sharpe S. Dietary fat and asthma: is there a connection? *Eur Respir J* 1997;**10:**6–12.

[13] Mitchell EA, Stewart AW, Pattemore PK, Asher MI, Harrison AC, Rea HH. Socioeconomic status in childhood asthma. *Int J Epidemiol* 1989; **18:**888–90.

[14] Ernst P, Demissie K, Joseph L, Locher U, Becklake MR. Socioeconomic status and indicators of asthma in children. *Am J Respir Critical Care Med* 1995;**152:**570–75.

[15] Mielck A, Reitmeir P, Wjst M. Severity of childhood asthma by socio-economic status. *Int J Epidemiol* 1996;**25:**388–93.

[16] Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? *BMJ* 1994;**308:**1132–35.

[17] World Bank. *World Development Report, 1995*. Oxford: Oxford University Press.

[18] World Bank. *World Development Report, 1984*. Oxford: Oxford University Press.

[19] Marmot MG. Improvement of social environment to improve health. *Lancet* 1998;**351:**57–60.

[20] United Nations Development Program. *Human Development Report, 1994*. Oxford: Oxford University Press.

[21] Breslow NE, Clayton DC. Approximate inference in generalized linear mixed models. *J Am Statist Assoc* 1993;**88:**9–25.

[22] Wolfinger R, O'Connell M. Generalized linear mixed models: a pseudo-likelihood approach. *J Statist Comp Simulation* 1993;**48:**233–43.

[23] Greenland S, Morgenstern H. Ecological bias, confounding, and effect modification. *Int J Epidemiol* 1989;**18:**269–74.

[24] Hertz E, Hebert JR, Landon J. Social and environmental factors and life expectancy, infant mortality, and maternal mortality rates: results of a cross-national comparison. *Soc Sci Med* 1994;**39:**105–14.

[25] Kjellstrand CM, Kovithavongs C, Szabo E. On the success, cost and efficiency of modern medicine: an international comparison. *J Internal Med* 1998;**243:**3–14.

 International Journal of Epidemiology 2001;**30**:179–180

Commentary: Geographical heterogeneity of asthma

Guy B Marks

The marked regional variation in the prevalence of asthma and other atopic diseases,[1,2] together with increases in the prevalence of asthma over time (e.g.[3]), strongly imply that environmental factors are important in the aetiology of allergic disease.

In this issue of the *International Journal of Epidemiology* Stewart *et al.*[4] have investigated the observed geographical heterogeneity to gain insights into the aetiology of these diseases. They used data on the prevalence of reported wheeze, symptoms of rhino-conjunctivitis and symptoms of eczema among school-age children in 155 centres in 56 countries. Their most consistent finding was that the prevalence of each of these symptoms was lower in the countries in the lowest quartile of the distribution of per capita gross national product (GNP) than in the remaining countries.

The strengths of this investigation include the use of data collected from five continents spanning a wide range of environmental and socioeconomic conditions. Although many local investigators were involved, the steering committee went to great lengths to standardize the study methods, including the use of a videotaped depiction of wheezing in an attempt to overcome cultural and linguistic variation in the description of this symptom. The use of ecological analysis may reveal associations which are not apparent in studies of relatively homogeneous populations of individuals in single communities.[5] However, there are limitations to the interpretation of these data. The information on the exposure of interest, per capita GNP, is only available at a national level, whereas the prevalence data are based on the study of one or more communities within each of the 56 countries. These communities may not be representative of the country as a whole. This is particularly the case in countries in economic transition where urban-rural and other regional differences may be extreme.

High per capita income cannot directly cause atopic disease. The findings of this analysis, which are broadly consistent with other, more limited comparisons of atopic disease prevalence between economically disparate, but geographically and ethnically close, communities (e.g.[6,7]), should lead to the exposition of hypotheses about the origins of this variation. What is it about living in poorer countries that protects against the expression of atopic disease? Or conversely, what are people who live in countries with higher per capita GNP exposed to which causes atopic disease? Expressing the problem in this way highlights the difficulty in solving it. There are so many differences between these countries. However, some factors have biological plausibility and/or are supported by cross-sectional and cohort studies conducted in individuals. These include diet and obesity, allergen exposures in the home environment, and infections in early childhood.

Some features of nutrition and diet have been linked to asthma and atopic disorders. Reduced *in utero* nutrition, manifest as a lower birthweight or lower ponderal index (birthweight in proportion to birth length), has been shown to be protective against asthma and eczema.[8,9] The biological mechanism underlying this association remains unknown. While this hypothesis would be consistent with the observed reduced risk of atopic disease in low GNP countries, other proposed dietary risk factors such as lack of fish intake[10] are not consistent with the observed ecological association.

Institute of Respiratory Medicine, University of Sydney, Australia. E-mail: g.marks@unsw.edu.au

The extent of early life exposure to inhalant allergens influences the subsequent acquisition of sensitization to those allergens.[11] However, it remains unclear to what extent the presence of any atopy, as opposed to specific sensitization, is explained by the level of allergen exposure. Furthermore, it is unlikely that there is any strong relation between national wealth and the level of domestic allergen exposure.

The relation between childhood infections and subsequent atopy and asthma is complex. Parents of schoolchildren with asthma recall that their children had respiratory infections in infancy more commonly than other parents. However, this is likely to represent recall and unmasking bias[12] rather than an aetiological association. Indeed, there is evidence to suggest that respiratory and non-respiratory viral infections and other systemic infections in early life may actually protect against the development of atopy.[13–16] The observation that children who are born into large sibships[17] or who attend child care centres from an early age[18] are relatively protected against the development of atopy is consistent with this hypothesis. It may also be consistent with the finding that children who live on farms with livestock in early life are less likely to develop atopy.[19] The proposed mechanism for this protective effect of early life infections is immune deviation: infectious agents induce the establishment of clones of antigen-specific memory T lymphocytes which secrete anti-allergic cytokines.[20] It is at least plausible that children living in countries with low per capita GNP are exposed to more of these atopy-protecting infections than children in wealthier countries.

Stewart *et al.*'s observations pose a challenge. No-one would wish to solve the problem of allergic disease by reducing national wealth. The challenge is to identify what consequence of increased national wealth increases the risk of expression of allergic disease and to establish whether this can be modified while retaining the other economic, social and health benefits of national development.

References

[1] European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;**9:**687–95.

[2] International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;**351:**1225–32.

[3] Peat JK, van den Berg RH, Green WF, Mellis CM, Leeder SR, Woolcock AJ. Changing prevalence of asthma in Australian children. *BMJ* 1994;**308:**1591–96.

[4] Stewart AW, Mitchell EA, Pearce N, Strachan DP, Weiland SK. The relationship of per capita gross national product to the prevalence of symptoms of asthma and other atopic diseases in children (ISAAC). *Int J Epidemiol* 2001;**30:**173–80.

[5] Rose G. Sick individuals and sick populations. *Int J Epidemiol* 1985; **14:**32–38.

[6] Leung R, Ho P. Asthma, allergy, and atopy in three south-east Asian populations. *Thorax* 1994;**49:**1205–10.

[7] von Mutius E, Martinez F, Fritzsch C, Nicolai T, Roell G, Thiemann H-H. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;**149:**358–64.

[8] Rasanen M, Kaprio J, Laitinen T, Winter T, Koskenvuo M, Laitinen LA. Perinatal risk factors for asthma in Finnish adolescent twins. *Thorax* 2000;**55:**25–31.

[9] Olesen A, Ellingsen A, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: historical follow up by record linkage. *BMJ* 1997;**314:**1003–08.

[10] Hodge L, Salome C, Peat J, Haby M, Xuan W, Woolcock A. Consumption of oily fish and childhood asthma risk. *Med J Aust* 1996;**164:**137–40.

[11] Wahn U, Lau S, Bergmann R *et al*. Indoor allergen exposure is a risk factor for sensization during the first three years of life. *J Allergy Clin Immunol* 1997;**99:**763–69.

[12] Martinez F, Morgan W, Wright A, Holberg C, Taussig L. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988;**319:**1112–17.

[13] Martinez F, Stern D, Wright A, Taussig L, Halonen M, and the Group Health Medical Associates. Association of non-wheezing lower respiratory tract illnesses in early life with persistently diminished serum IgE levels. *Thorax* 1995;**50:**1067–72.

[14] Matricardi P, Rosmini F, Riondino S *et al*. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000;**320:**412–17.

[15] Shaheen S, Aaby P, Hall A *et al*. Measles and atopy in Guinea-Bissau. *Lancet* 1996;**347:**1792–96.

[16] Aaby P, Shaheen S, Heyes C *et al*. Early BCG vaccination and reduction in atopy in Guinea-Bissau. *Clin Exp Allergy* 2000;**30:**644–50.

[17] Jarvis D, Chinn S, Luczynska C, Burney P. The association of family size with atopy and atopic disease. *Clin Exp Allergy* 1997;**27:**240–45.

[18] Krämer U, Heinrich J, Wjst M, Wichmann H-E. Age of entry to day nursery and allergy in later childhood. *Lancet* 1999;**353:**450–54.

[19] Braun-Fahrländer C, Gassner M, Grize L *et al*. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. *Clin Exp Allergy* 1999;**29:**28–34.

[20] Hogg C. T-helper polarization in atopic disease—how early does it occur? *Clin Exp Allergy* 1997;**27:**1237–39.