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“Trends in worldwide asthma prevalence”.

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Summary Take home message

Worldwide asthma prevalence, measured in populations using standardised methods increased from the mid-1990s to the mid-2000s, the last global measurements. The Global Asthma Network Phase I (2017-20) will provide recent data in children and adults.

Abstract

This review of trends in worldwide asthma prevalence starts with defining how asthma prevalence s measured in populations and how it is analysed. Four population studies of asthma across at least two regions are described: European Community Respiratory Health Survey (ECRHS), The International Study of Wheezing in Infants (EISL), The International Study of Asthma and Allergies in Childhood (ISAAC) and the World Health Survey (WHS). Two of these (ISAAC and WHS) covered all the regions of the world; each using its own standardised questionnaire-based methodology with cross-sectional study design, suitable for large populations. EISL (2005 and-2012) and ISAAC (1996-1997 and 2002-2003) have undertaken a second cross sectional population survey from which trends are available: EISL in three centres in two countries; ISAAC 106 centres in 56 countries (13-14 year olds) and 66 centres in 37 countries (6-7 year olds). Key results from these studies are presented. Unfortunately, there is no new worldwide new data outside of EISL since 2003. Global Burden of Disease estimates of asthma prevalence have varied greatly. Recent reliable worldwide data on asthma prevalence and trends is needed; the Global Asthma Network Phase I will provide this in 2021.

The purpose of this article is to review trends in worldwide asthma prevalence. In doing so we have limited our review to studies of asthma prevalence which are between several countries, and thus worldwide, and used similar methodology, and thus trends are discernible. In approaching this topic, we have reviewed: what is asthma prevalence and how is it measured; standardised methodology for comparing asthma prevalence between locations around the world, and over time within locations; worldwide time trends in asthma prevalence; the Global Burden of Disease Study; and relationship of time trends in hospital admissions and mortality to time trends in asthma prevalence.

What is asthma prevalence and how is it measured?

The definition and classification of asthma has been the subject of many approaches and opinions for several decades (1), with variable airways obstruction being its key feature. The essential features of asthma are captured by the Global Initiative for Asthma (GINA) describing it as "a heterogeneous disease, usually characterised by chronic airway inflammation. Asthma is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation"(2).

Asthma symptoms most commonly first develop in early childhood. Children of pre-school age often wheeze with viral infection, but only about half of them go on to have characteristic asthma at school age. Children who have frequent or persistent wheeze are more likely to have evidence of airway inflammation and remodelling, impaired lung function, and persistently troublesome symptoms into adulthood (1, 3).

The underlying mechanisms of asthma are still not well understood. About one-half of people with asthma have underlying allergic (4) and the other half non-allergic mechanisms (5) and this latter type is more common in low- and middle-income countries (LMICs). It is unclear whether asthma is a single disease, or if it is in fact a grouping of different conditions which all result in the same clinical effect (5, 6). Despite this, most people with asthma symptoms improve with asthma medicines, and the use of the term asthma as a clinical diagnosis is still useful in most patients because it opens the door to appropriate management to reduce disease burden (7).

Asthma prevalence is simply the proportion of the population, or a subgroup of the population (e.g. 13-14 year olds) who have the condition at a particular time. This usually requires assessment of symptoms over a set period (e.g. the past year) as many asthmatics have intermittent symptoms and may not have them on the day of study.

The diagnosis of asthma involves an overall assessment of the patient's medical history, physical examination, and usually a measure of lung function and often a test of response to inhaled bronchodilator. More recently biomarkers such as exhaled nitric oxide have been added in some settings. There are no universally accepted rules for combining the information from these various sources, such that diagnosis of asthma varies between doctors, between locations, between countries, and over time, and there are pitfalls(8). There are reports of underdiagnosis (9) and overdiagnosis (10) of asthma in children and in adults (11). In young children who commonly wheeze, only about half will go on to have asthma at school age, so there is caution about using the term asthma in that age group. Nevertheless, the term preschool asthma is recommended for those who respond to essential asthma medicines (12, 13), and this term can be reviewed regularly.

Therefore, for population-based studies of asthma, these are usually done outside of the preschool age group. Where doctor diagnosis is not practicable, questionnaires are the tool of choice. Questions about more recent symptoms (in the past 12 months) are more reliable than questions about symptoms in the past, because they reduce errors of recall (14, 15).

Written questionnaires have therefore been the principal instrument for measuring asthma symptom prevalence in community surveys which must be standardised to enable valid comparisons – that is conform to a set of questions in a questionnaire format, and delivered according to a specified protocol including details about sampling frame, age and size of sample. This is especially important in examining trends over time, as changes in methodology could be the explanation for variation over time rather than it being a true change. In homogeneous populations questionnaires have been standardised, validated, and shown to be reproducible (16). A number of symptoms including wheezing, chest tightness, breathlessness, and coughing with or without sputum are recognised by physicians as indicative of

asthma. Of these the most important symptom for the identification of asthma in epidemiological studies is wheezing. A large number of such questions have been used in epidemiological surveys.

Studies within communities at different times (between1960s and early 1990s) reported increasing asthma prevalence, but each used their own methodology and very few were not high-income countries (17). A critical appraisal of repeated cross-sectional surveys of asthma in children and young adults 1983-1996 found 16 studies of interest. Only studies in United Kingdom, Australia and New Zealand reported trends in current wheeze, the remainder were dependent upon asthma diagnosis which can be influenced by fashions in diagnosis or labelling as well as the prevalence of disease (8, 18). The urgent need for standardised methodologies to estimate asthma prevalence from symptoms in a wide range of settings in the world led to the development of the International Study of Asthma and Allergies in Childhood (ISAAC).

Standardised methodology for comparing asthma prevalence between locations, and over time within locations

European Community Respiratory Health Survey (ECRHS)

In adults the European Community Respiratory Health Survey (ECRHS) (19) built on the questions developed for the International Union against Tuberculosis and Lung Diseases (IUATLD) (20). ECRHS planned to answer specific questions about the distribution of asthma and health care for adults with asthma in the European Community. In ECRHS I (1991-3) participating centres selected an area defined by pre-existing administrative boundaries with a population of at least 150,000. When possible, an up-to-date sampling frame was used to randomly select at least 1,500 males and 1,500 females, aged 20–44 yrs (21). The Screening Questionnaire was generally sent by post and self-administered. A smaller random sample of those subjects were invited to attend for a more detailed interviewer-administered questionnaire and several tests. Engagement in ECRHS extended beyond Europe; participating locations were 48 centres in 22 countries of which 17 were Europe and five elsewhere: Algeria, Australia, India, New Zealand, USA, a total of 137,619 participants (21). The standardised methodology enabled ECRHS to repeat the

survey after 10 years (ECRHS II) (22) and again after 20 years (ECRHS III) (23); each of these surveys were done in the same individuals over time, thus making it a longitudinal study. While the three phases of ECRHS are valuable in their own right, they are less suited than repeated cross-sectional studies for examining time trends in population asthma prevalence.

World Health Survey (WHS)

The largest and widest source of information on asthma in adults in low-income countries comes from the World Health Survey (WHS) implemented by the World Health Organization in 2002-2003 (24). The WHS investigated many diseases as well as asthma. Instruments were developed and household face-to-face surveys were done in most countries, randomly selected households were contacted and a single person from each household was interviewed (25). There was a total of 178,215 adults aged 18 to 45 years from 70 countries who responded to questions about asthma and related symptoms (26). The prevalence of asthma was based on responses to questions relating to self-reported doctor diagnosed asthma, clinical/treated asthma, and wheezing in the past 12 months. This study showed that there are very wide variations in the prevalence of wheeze and asthma regardless of overall national income. Overall, the prevalence of symptoms and diagnosis showed a U-shaped pattern with the largest prevalence reported in low- and high-income countries. The global prevalence rates were 4.3% doctor diagnosed asthma, 4.5% clinical/treated asthma and 8.6% wheezing in adults, and varied by as much as 21-fold amongst the 70 countries. The authors concluded that these findings support the need for continued global respiratory illness surveillance for disease prevention, health policy and management. However there has been no repetition of the WHS despite its valuable results, standardised methodology suitable for further cross-sectional surveys, and therefore there is no time trend data.

The International Study of Asthma and Allergies in Childhood (ISAAC)

ISAAC was founded to maximize the value of epidemiological research into asthma and allergic disease, by establishing a standardized methodology and facilitating international collaboration (27). It built on previous work and established its own standardised core asthma questionnaire, along with questionnaires on rhinitis and eczema (27). From the outset one of its goals was measuring time trends, so the

methodology had to be sufficiently robust to achieve this. Its specific aims were to describe the prevalence and severity of asthma, rhinitis and eczema in children living in different centres, and to make comparisons within and between countries; to obtain baseline measures for assessment of future trends in the prevalence and severity of these diseases; and to provide a framework for aetiological research into genetic, lifestyle, environmental, and medical care factors affecting these diseases. The ISAAC design comprised three phases. Phase One (1994-95) assessed the prevalence and severity of asthma and allergic disease. Phase Two investigated possible aetiological factors, particularly those suggested by the findings of Phase One. Phase Three (2001-2003) was a repetition of Phase One to assess trends in prevalence.

Two age groups of school children participated: The compulsory age group was 13-14 year olds (adolescents), who self-completed questionnaires at school. An optional addition was 6-7 year olds (children), who took questionnaires home to be completed by their parents, and. In Phase One an international clinical asthma video questionnaire was developed for adolescents in response to address potential translation problems with the written questionnaires, as it obviated the need to describe symptoms verbally and was also used in Phase Three. The written and video questions have been compared for their prediction of bronchial hyper-responsiveness in different ethnic groups (28-32).

ISAAC Phase One involved over 700 000 adolescents and children, from 156 centres in 56 countries. Schools were the sampling units with a minimum of 10 schools randomly selected per centre (or all schools used). Students were selected either by grade/level/year, where classes with most children of the age group were selected, or by age group alone. A high response rate was required for valid estimates of population prevalence and in adolescents the use of passive consent achieved higher response rates than active consent (33)

The core ISAAC asthma questions were: “Have you (has your child) ever had wheezing or whistling in the chest at any time in the past?”; “Have you (has your child) had wheezing or whistling in the chest in the past 12 months?”; and “Have you (has your child) ever had asthma?”. Those self diagnostic questions are qualified by severity and frequency questions such as: “How many attacks of wheezing have you

(your child) had in the past 12 months?"; "How often, on average, has your (your child's) sleep been disturbed due to wheezing?"; "In the past 12 months, has wheezing ever been severe enough to limit your (your child's) speech to only one or two words at a time between breaths?" (34).

The simplicity of the ISAAC methodology, and its relatively low cost enabled it to be undertaken in most settings around the world, more than in any other epidemiological study of asthma. It was hailed as "a tremendous development in encouraging participation in research across the world…The concept of ISAAC was very simple at the outset—to develop a simple frame to undertake standard measurements and to make comparisons from one location to another, across geographic, cultural and linguistic boundaries. It operated with a decentralised structure, with partners in the venture encouraging groups in each geographic area. The base of the frame was very 'light', encompassing straightforward techniques that could be undertaken at any location and with few financial resources, enabling truly global participation." (35).

The key asthma questions (wheezing in the chest ever and in the past 12 months) have been validated against the clinical diagnosis of asthma and compared to the bronchial hyper-responsiveness (BHR) test. The Youden index (Y-index), the best statistical method for these comparisons (36), was 66% (sensitivity 85%, specificity 81%) (37), which was higher than the one achieved for the IUATLD questionnaire (53%) (20) and one of the highest in validation studies from 1971 to 2014 (38). The Y-index for the validation of the questions in Spanish (the second most commonly used language in ISAAC) was 57% (39). Compared to the BHR test (hypertonic saline) the ISAAC questionnaire showed greater sensitivity (85% vs. 54%), slightly lower specificity (81% vs. 89%) and a substantially higher Y-index (66% vs. 43%), with the gold standard being physician-diagnosed asthma (37).

ISAAC had a very strict protocol for the translation of questions, and back translation to English, and these were compared. The results of a study of ISAAC translations (40) showed that important deviations from the exact meaning of the core questions were very low, although minor deviations from literal translations of English (particularly "wheezing") were permitted in order to maintain the original meaning,.

The methodology, including power and sample size together with organisation of centres and their interaction with the data centres was carefully documented (34)

A comparison of prevalence between 17 countries that participated in both ISAAC and ECRHS showed that although there were differences in the absolute levels of prevalence observed, there was good general agreement on the patterns of asthma prevalence internationally (41). These findings support the validity of the two studies.

International Study of Wheezing in Infants (EISL)

Wheezing in young children is very common, sometimes causing considerable morbidity, and sometimes leading on to asthma. The International Study of Wheezing in Infants (Estudio Internacional de Sibilancias en Lactantes, EISL) is the largest multi-centre study of wheezing in the first year of life (12). It was based on the tools developed by ISAAC, and validated for this age group (42). The questionnaire was administered to parents in primary health centres when children attended to receive the MMR vaccination at ages 12 to 15 months (depending on countries), although questions referred to the first year of life. It has contributed new information about the prevalence of wheezing and treatment approaches of recurrent wheezing. Data from this cross-sectional study in 2005 included 30,093 children in 17 centres: 25,030 in 12 centres in Latin America and 5,063 from 5 centres in Europe and published in 2010 (43, 44).

A modified, shortened Portuguese version of the EISL wheeze questionaire in children up to 36 months of age in São Paulo, Brazil, was validated and its usefulness in diagnosing probable asthma in these children was established (45). The standardised methods have enabled, in children under three, time trends in wheezing and probable asthma to be determined. Unfortunately, only three of the centres participating in EISL phase I were able to provide data on time trends seven years later in 2012 (46). In all three centres: Sao Paulo (Brazil), Curitiba (Brazil) and Santiago (Chile) the prevalence of any wheezing, recurrent wheeze and wheezing during the first 3 months of life decreased from 2005 to 2012 (46).

Worldwide comparisons of time trends in asthma prevalence

To analyse time trends in asthma prevalence it is essential that the same methodology is used to compare the two or more time points and to compare the trends in the various centres or regions under study. Here we briefly describe the methodology used to analyse time trends data in ISAAC: two cross-sectional studies 5-10 years apart using the same sampling frame and methodology (47), before proceeding to summarize the findings of these analyses.

In ISAAC, centres who conducted both ISAAC Phases Three and One conducted the both phases following the same protocol. For time trend analyses, the data for adolescents and children were analysed separately. In each centre symptom prevalences were calculated by dividing the number of positive responses to each question by the number of completed questionnaires. The annual change in symptom prevalence was calculated by taking the difference between the Phase One and Three prevalences and dividing by the number of years between the two surveys. For regional and global summaries, the data for each centre was weighted by the inverse of the variance of the change. The key findings were also presented as “ranking plots” showing the change in symptom prevalence (e.g. current wheeze) for each centre by country, with countries ordered by their average prevalence (for all centres combined) across Phases One and Three. The average prevalence was used to order countries since this is statistically independent from the change in prevalence (between Phases One and Three) whereas the Phase One prevalence was not (47).

ISAAC time trends in asthma prevalence

ISAAC Phases One and Three time trends in prevalence were estimated for 3 related conditions: asthma, rhinitis and eczema in 304 679 13-14 year olds (adolescents) from 106 centres in 56 countries and 193 404 6-7 year olds (children) from 66 centres in 37 countries (48). Replication of standardised methodology is very important; methodological comparisons between ISAAC Phase Three and Phase One were found to be good (49).

Figure 1 shows a world map of changes for asthma symptoms. Most centres showed a change in prevalence of 1 or more SE for at least one condition, with increases being twice as common as decreases, and children than in the adolescents, and at most levels of mean prevalence. An exception was asthma symptoms in the

adolescents, in which decreases were more common at high prevalence. For both age-groups, more centres showed increases in all three conditions more often than showing decreases, but most centres had mixed changes. Despite some increase in the proportion of children and adolescents with symptoms of asthma, rhinitis and eczema, the pattern between the three diseases has not changed much, suggesting that similar factors may be affecting them at a global level (50).

For asthma (47) the mean worldwide symptom prevalence of current wheeze in the last 12 months changed slightly (Figure 2) from 13.2% to 13.7% in adolescents (mean increase of 0.06% per year) and from 11.1% to 11.6% in children (mean increase of 0.13% per year). There was also little change in the mean symptom prevalence of severe asthma (Figure 3) or the symptom prevalence measured with the asthma video questionnaire (Figure 4). However asthma ever increased (Figure 5). The time trends in asthma symptom prevalence showed different regional patterns. In Western Europe, current wheeze decreased by 0.07% per year in adolescents but increased by 0.20% per year in children. The corresponding findings per year for the other regions in adolescents and children, respectively, were: Oceania (20.39% and 20.21%); Latin America (+0.32% and +0.07%); Northern and Eastern Europe (+0.26% and +0.05%); Africa (+0.16% and +0.10%); North America (+0.12% and +0.32%); Eastern Mediterranean (20.10% and +0.79%); Asia-Pacific (+0.07% and 20.06%); and the Indian subcontinent (+0.02% and +0.06%). English language countries showed a particularly marked reduction in current asthma symptom prevalence (20.5% and 20.1%), and similar patterns were observed for symptoms of severe asthma. However, the percentage of children reported to have had asthma at some time in their lives (“asthma ever”) increased by 0.28% per year in adolescents and by 0.18% per year in children.

These findings from ISAAC show increases in asthma symptom prevalence in the most populous parts of the world where prevalence was previously low (Africa, Latin America and parts of Asia), indicating that the global burden of asthma is continuing to rise. However the global asthma symptom prevalence differences are lessening because, particularly adolescents, decreases were found in prevalence in English speaking countries and Western Europe. Although there was little change in the overall global prevalence of current wheeze, the percentage of children and

adolescents reported to have had asthma increased significantly, possibly reflecting greater awareness of this condition and/or changes in diagnostic practice.

Two subsequent studies using ISAAC methodology have done a third survey: In Brazil adolescents in Curitiba, Recife and São Paulo were studied in ISAAC Phases One (1994) and Three (2003) and again in 2012 (51). Over the 18 year period the prevalence of current asthma symptoms reached a peak and then levelled off, however the prevalence of more severe and atypical forms of asthma increased. In South-Santiago, Chile, ISAAC Phases One and Three were completed, and a further survey of asthma in adolescents using ISAAC methodology in 2015 (52). The prevalence of current asthma in adolescents from the studied area continues to increase whereas severe asthma and asthma with exercise decreased.

Potential causes of variations and increase in asthma prevalence

Notwithstanding all this epidemiological research, the causes of variations and increases in prevalence and have proved largely elusive and are matter of speculation. In ISAAC Phase Three the strongest associations in children (131 924 in 25 countries) and adolescents (238 586 in 42 countries) were exposure to current paracetamol use and open fire cooking, for children early life antibiotic use and for adolescents maternal tobacco use, but the odds ratios were less than 2 (53). The explanation for decreases in asthma prevalence in English-speaking countries, and increases in low- and middle-income countries (47) have been hampered by lack of time trend data on potential risk factors.

The next trends in worldwide asthma prevalence: Global Asthma Network (GAN)

The Global Asthma Network (GAN) was established in 2012 intentionally building on the ISAAC approach and methods with its core activities including global surveillance of asthma prevalence, severity, management and risk factors. There are no research programmes other than GAN Phase I providing new data on trends in worldwide asthma prevalence. The four main hypotheses of GAN Phase I are: 1) globally, the burden of asthma is changing in adults and children; 2) there is large variation in the diagnosis of asthma; 3) in many locations, asthma is under-diagnosed and its

management is suboptimal; and 4) there are potentially remedial risk factors of asthma.

GAN Phase I, 2017-2020, uses the same cross-sectional methods as ISAAC: information on asthma, rhinitis and eczema prevalence and severity, with additional questions on diagnoses, asthma emergency room visits, hospital admissions, management and use of asthma essential medicines. The same age groups (adolescents and children) as ISAAC are used, and their parents. This is the first global monitoring of asthma in children and adults since 2003, built on the ISAAC and ECRHS questionnaires for children and adults (54), with the same core questions for asthma. The questionnaire is self-completed by adolescents and parents children and adolescents.

GAN has completed data collection for Phase I in many centres and countries, and some also participated in ISAAC which will provide time trend data on asthma prevalence and risk factors. The worldwide analyses have not yet been completed but the first published findings are anticipated in 2021. There have been three GAN Phase I studies with previous ISAAC data published: In Bangkok, Thailand, there was little change between ISAAC Phase Three and GAN Phase I study (55). In a north part of Mexico City (Mexico) with high asthma prevalence GAN Phase I was undertaken 10 years after ISAAC Phase Three (56). There was a 7.9% increase in the prevalence of asthma symptom, and almost half of the adolescents and children presenting with symptoms had experienced more than four episodes per year, but less than 50% of adolescents and children with asthma symptoms had been diagnosed with this disorder, suggesting under-diagnosis. In a further study of four Mexican centres the prevalence of asthma and its symptoms increased from ISAAC Phase Three to GAN Phase I in Mexico (57).

Global Burden of Disease Study (GBD)

The GBD has reported estimates of the global asthma prevalence, deaths and disability adjusted life years (DALYs) between 1990 and 2017. In the GBD 2015 systematic analysis data were available for 121 countries (58), but, apart from ISAAC, references for these studies are not given; it is unclear how many of these other studies had undertaken time trend surveys with standardised methodology.

The GBD case definition for asthma was a reported diagnosis by a physician, with wheezing in the past 12 months.

GBD asthma prevalence trends.

The GBD estimates of the global prevalence of asthma have varied considerably between the sequential reports: 220.4 million in the year 2000 (59), 327.1 million in 2005 (60), 334.2 million in 2010 (61), 241.7 million in 2013 (62), 358.2 million in 2015 (58), 339.4 million in 2016 (63) and 272.7 million in 2017 (64). Such large variations between 2010 and 2017, of up to 109 million, are unexplained, but are likely to be due to changes in analytical methods, as there have been no new large scale standardised data on asthma prevalence during this period. Moreover it is inconceivable that the global prevalence could have swung down up and down by such large amounts. The GBD 2017 modelling (64) shows relatively smaller variations in estimated prevalence 2000-2017 than the variations in the GBD counts in separate analyses during the same time period. For an earlier period, mid-1990s to early 2000s, GBD 2017 back-extrapolates a decline in global prevalence (all ages) from ~3.5% to ~3.3% for males and from ~4.0% to ~3.6% for females. In contrast, at that time there was some standardised worldwide prevalence time-trend data from adolescents and children in ISAAC Phases One to Three (47), suggesting a rise in prevalence of asthma symptoms in most centres – see discussion earlier in this article. During a similar time period there was little increase in asthma symptoms in adults (22). The swinging GBD estimates illustrate how vital it is to have new and ongoing standardised measurements of asthma prevalence in populations in representative countries around the world.

GBD asthma mortality trends

The GBD estimates of the global asthma deaths have degrees of variation which may be explainable by differences in number of sites reporting asthma deaths and their accuracy: 380,200 to 504,300 in the year 1990 (65, 66), 218,000 in 2000 (59), 449,900 in 2005 (67), 345,700 in 2010 (66), 489,000 in 2013 (65), 397,100 in 2015 (58, 67), 420,000 in 2016 (68) and 495,100 in 2017 (69).

GBD asthma DALYs trends

DALYs are the sum of years of life lost (the years of healthy life lost due to asthma death) and years lived with disability (the prevalence multiplied by the disability weight for asthma). To calculate the disability weight for asthma, the proportions of mild, moderate and severe asthma disease need to be known as they have different disability weights. In GBD the source data for this is unclear. From 2005 to 2017 the DALYs from asthma have been relatively stable while earlier estimates fluctuated: 13.858 to 21.469 million in in 1990 (59, 70), 22.2404 to 26.8597 million in 2005 (71, 72), 22.459 million in 2010 (70), 22.1827 million in 2013 (72), 26.1688 million in 2015 (58, 71), 23.9205 million in 2016 (73), and 22.8 million in 2017 (74).

Relationship of time trends in hospital admissions and mortality to time trends in asthma prevalence

National hospital admission statistics are lacking for most LMICs. Historically, the relationship between asthma prevalence, severity and admission rates in higher-income countries has been complex, but changes in the admission rate over time correlate (albeit imperfectly) with changes in the prevalence and severity of childhood asthma.

For countries with ISAAC study centres participating in both Phase One and Three, Figure 6 plots the annual change in childhood hospital admission rates against the change in the prevalence of wheeze causing adolescents to wake at night at least once a week. Over this period (approximately 1995-2002), admission rates declined in all these countries except Hong Kong and Poland. There was a significant positive correlation between the decline in prevalence of severe asthma symptoms between Phases One and Three and the decline in the corresponding national admission rates for childhood asthma over a similar period (75).

In most, but not all, European countries, age-standardised asthma admission rates declined from 2001-2005 to 2011-2015, some countries showing more than a twofold reduction (75). The relative decline was of similar magnitude among under-20s and adults (aged 20+). The continuing decline in asthma admission rates among children and adolescents is part of a longer-term rise and fall, peaking in the early 1990s which bears no temporal relationship to two epidemics of asthma mortality (in the

1960s and the 1980s) nor to time trends for self-reported asthma prevalence (76). However, data from the United Kingdom showed a peak of primary care contacts for acute asthma, particularly among children, in the early 1990s, similar to that of asthma hospital admissions (77). This is consistent with a rise and fall in the incidence of asthma attacks in the community, rather than simply a change in patterns of referral to secondary care, or a reduction in the severity threshold for admission to the hospital ward.

Comparison of within-country changes in asthma mortality and admission rates for 24 European countries over the decade 2001-2005 through 2011-2015 shows no correlation between time trends in these two indicators of more severe asthma (78). Over this period, national age-standardised death rates for asthma reduced to a greater extent (in relative terms) than did age-standardised asthma admission rates, reflecting a global pattern in which asthma mortality rates approximately halved in most countries from 2001-2005 to 2011-2015. A similar relative decline was seen in the age group 5-34 years (78, 79), upon which attention often focuses because diagnostic confusion between asthma and other fatal respiratory diseases is least likely in this age group.

When national asthma mortality rates for children were compared with the asthma symptoms prevalence and severity data for ISAAC Phase One centres in the same countries, a significantly positive correlation was found between childhood asthma mortality and the prevalence of more severe asthma symptoms in both 6-7-year-olds (29 countries) and 13-14-year-olds (38 countries) (80). Such comparisons need to be interpreted with caution, because ISAAC centres are not necessarily representative of the countries in which they are located.

Conclusion

To address the global burden of asthma, sequential standardised studies are vital, and this data needs to be obtainable in all settings around the world. Four studies have achieved this, prospectively collecting data to make estimates of asthma prevalence, within and between populations: EISL, ECRHS, ISAAC and WHS. Only ECRHS and ISAAC have been able to repeat these standardised surveys in large

numbers of countries, with only ISAAC having a truly global reach to estimate worldwide trends. However there have been no further global field studies since 2002-3 until GAN Phase I which follows ISAAC methodology and is well underway. This is expected to contribute to our understanding of asthma.

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Captions for Figures

Figure 1

World map showing direction of change in prevalence of asthma symptoms for 6-7 year age group and 13-14 year age group. *Reprinted from the Lancet, Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733-43. (Figure 3). Copyright 2006, with permission from Elsevier.*

Figure 2

Ranking plot showing the change per year in prevalence of current wheeze (wheeze in the past 12 months) in adolescents aged 13– 14 years for each centre by country, with countries ordered by their mean prevalence (for all centres combined) across Phases One and Three, with the confidence interval about zero for a given level of prevalence (ie the mean prevalence across Phases One and Three). *Reprinted from Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62(9):758-66. (Figure 1). Copyright 2007, with permission from BMJ Journals.*

Figure 3 Ranking plot showing the change per year in prevalence of >4 attacks of wheezing in the previous 12 months in adolescents aged 13–14 years for each centre by country, with countries ordered by their average prevalence (for all centres combined) across Phases One and Three, with the confidence interval about zero for a given level of prevalence (ie the mean prevalence across Phases One and Three). *Reprinted from Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62(9):758-66. (Figure 4). Copyright 2007, with permission from BMJ Journals.*

Figure 4

Ranking plot showing the change per year in prevalence of current wheeze (wheeze in the past 12 months) using the video questionnaire in adolescents aged 13-14 years of each centre by country, with countries ordered by their mean prevalence

(for all centres combined) across Phases One and Three, with the confidence interval about zero for a given level of prevalence (ie the mean prevalence across Phases One and Three). *Reprinted from Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62(9):758-66. (Figure 2). Copyright 2007, with permission from BMJ Journals.*

Figure 5

Ranking plot showing the change per year in the lifetime prevalence of asthma ("asthma ever") in adolescents aged 13-14 years of each centre by country, with countries ordered by their mean prevalence (for all centres combined) across Phases One and Three, with the confidence interval about zero for a given level of prevalence (ie the mean prevalence across Phases One and Three). *Reprinted from Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62(9):758-66. (Figure 3). Copyright 2007, with permission from BMJ Journals.*

Figure 6

Annual change in hospital admission rates for childhood asthma (ages 5-14) by change in prevalence of nocturnal wheezing among 13-14 year olds in countries with one or more ISAAC centres providing prevalence data for both ISAAC Phase One (around 1995) and ISAAC Phase Three (around 2002).

Sources: National admissions data from Anderson HR, Gupta R, Kapetanakis V, Asher MI, Clayton T, Robertson CF, et al. International correlations between indicators of prevalence, hospital admissions and mortality for asthma in children. International Journal of Epidemiology. 2008;37(3):573-82; (updated by WHO Hospital Morbidity Database 2013). Prevalence data from Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62(9):758-66.

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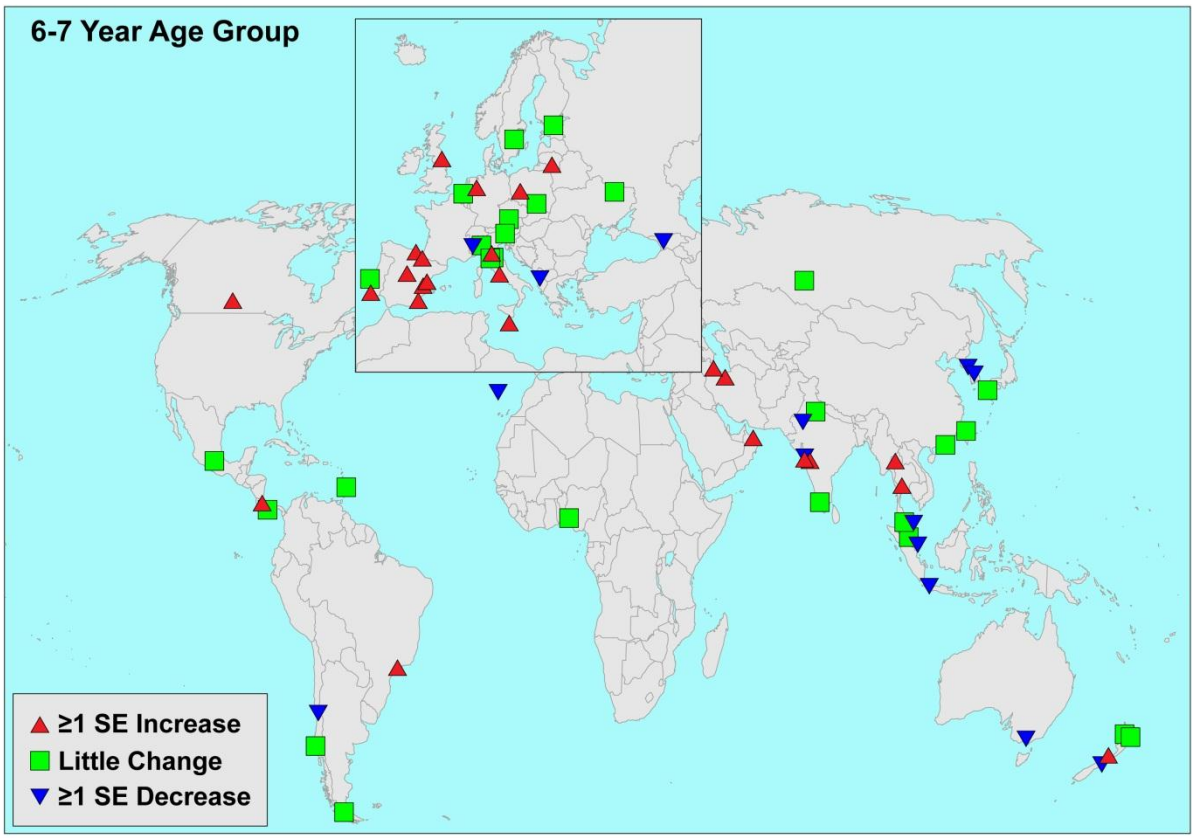
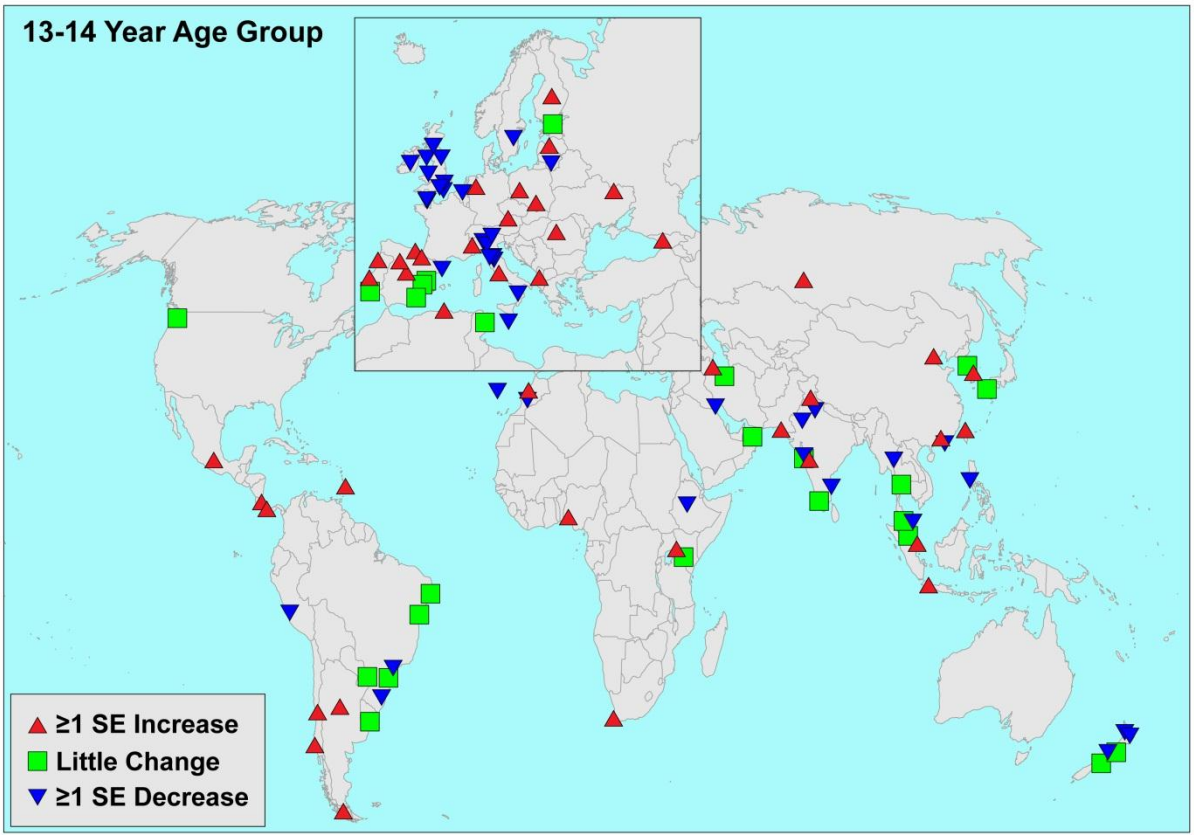
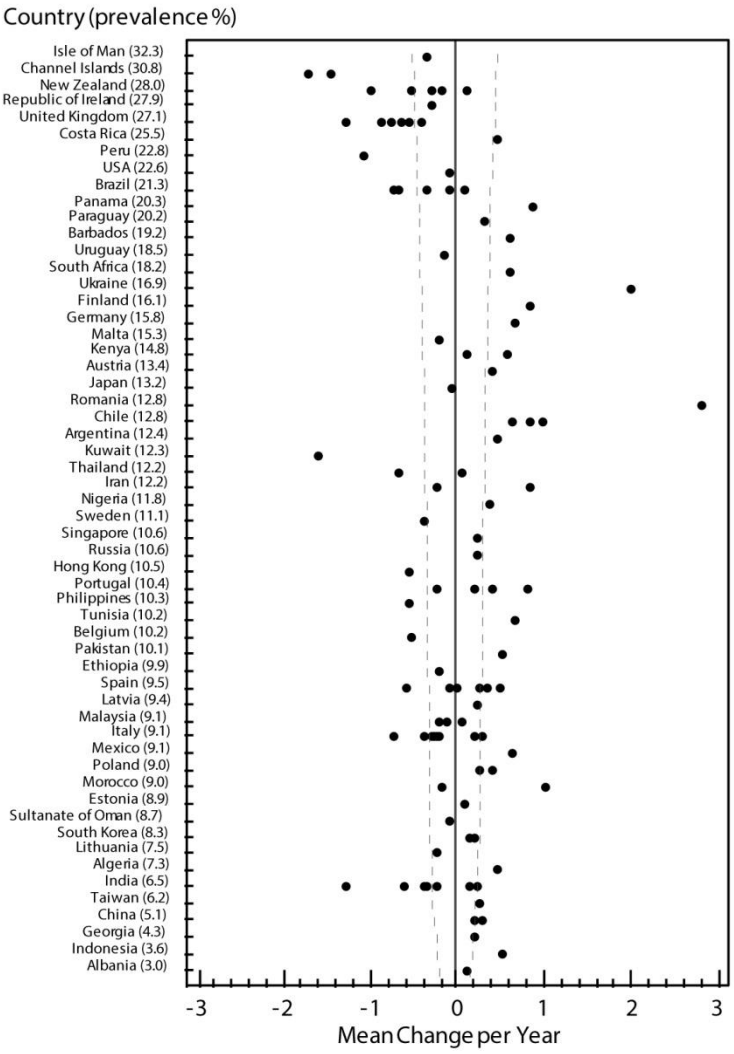

6-7 Year Age Group
≥1 SE Increase
Little Change
≥1 SE Decrease


13-14 Year Age Group
≥1 SE Increase
Little Change
≥1 SE Decrease


Country (prevalence %)
Isle of Man (32.3)
Channel Islands (30.8)
New Zealand (28.0)
Republic of Ireland (27.9)
United Kingdom (27.1)
Costa Rica (25.5)
Peru (22.8)
USA (22.6)
Brazil (21.3)
Panama (20.3)
Paraguay (20.2)
Barbados (19.2)
Uruguay (18.5)
South Africa (18.2)
Ukraine (16.9)
Finland (16.1)
Germany (15.8)
Malta (15.3)
Kenya (14.8)
Austria (13.4)
Japan (13.2)
Romania (12.8)
Chile (12.8)
Argentina (12.4)
Kuwait (12.3)
Thailand (12.2)
Iran (12.2)
Nigeria (11.8)
Sweden (11.1)
Singapore (10.6)
Russia (10.6)
Hong Kong (10.5)
Portugal (10.4)
Philippines (10.3)
Tunisia (10.2)
Belgium (10.2)
Pakistan (10.1)
Ethiopia (9.9)
Spain (9.5)
Latvia (9.4)
Malaysia (9.1)
Italy (9.1)
Mexico (9.1)
Poland (9.0)
Morocco (9.0)
Estonia (8.9)
Sultanate of Oman (8.7)
South Korea (8.3)
Lithuania (7.5)
Algeria (7.3)
India (6.5)
Taiwan (6.2)
China (5.1)
Georgia (4.3)
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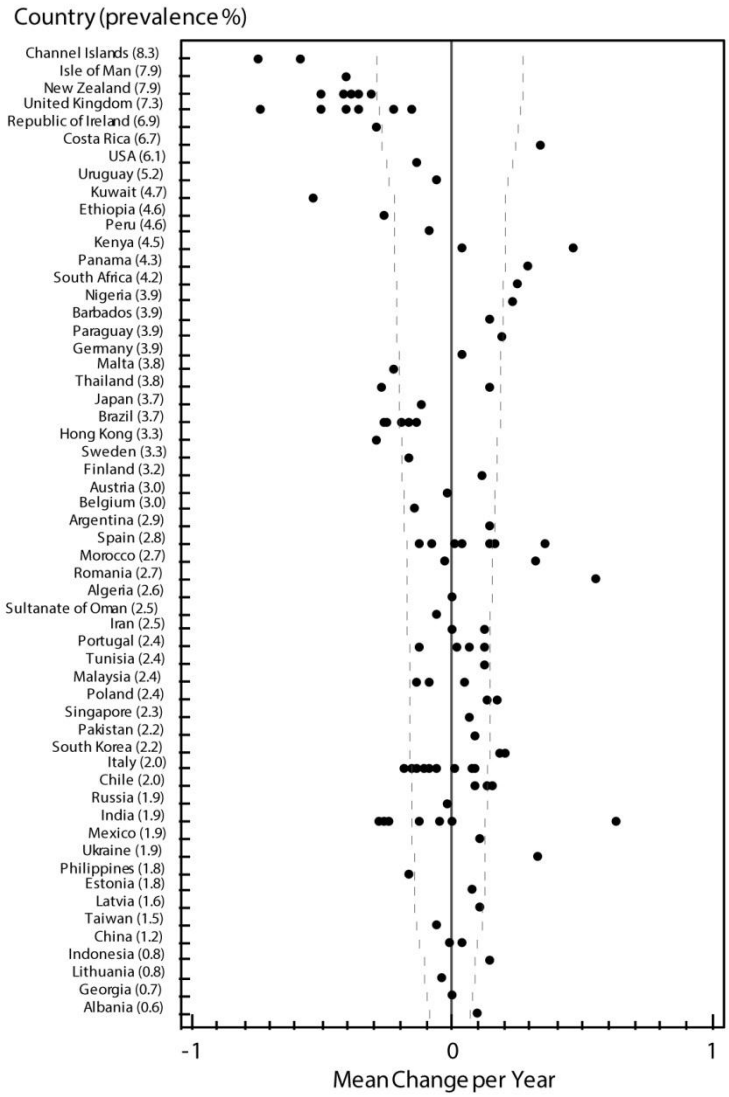
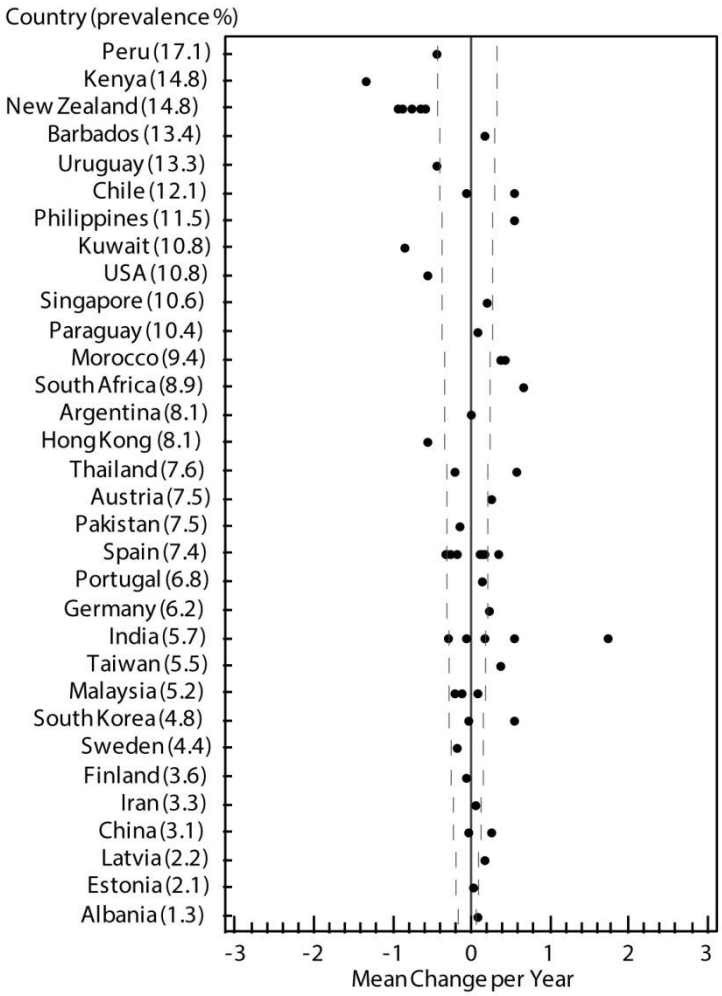
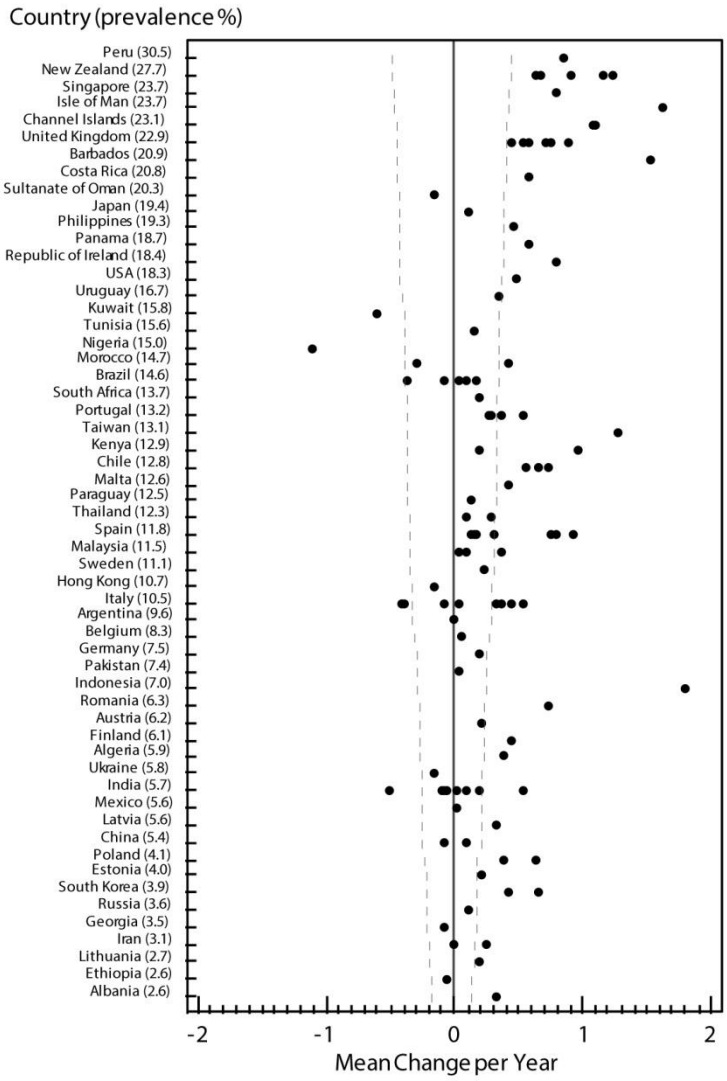
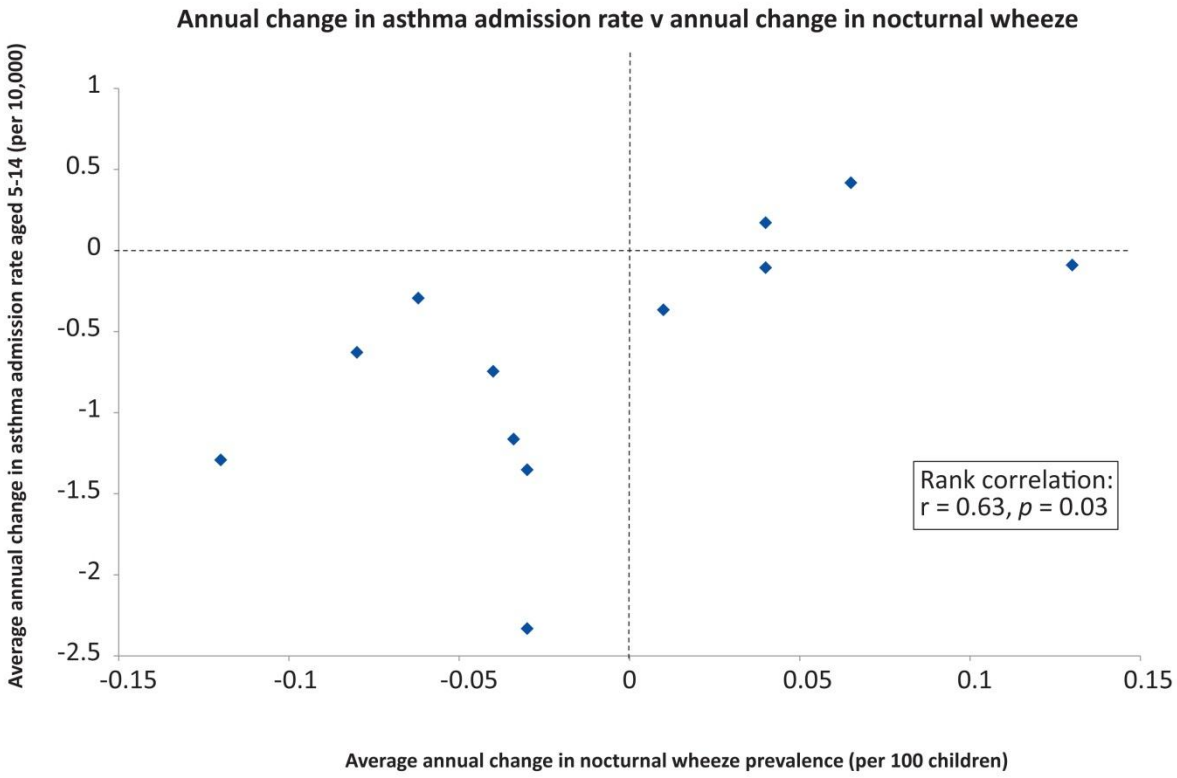
2
3
Mean Change per Year


Country (prevalence %)
Channel Islands (8.3)
Isle of Man (7.9)
New Zealand (7.9)
United Kingdom (7.3)
Republic of Ireland (6.9)
Costa Rica (6.7)
USA (6.1)
Uruguay (5.2)
Kuwait (4.7)
Ethiopia (4.6)
Peru (4.6)
Kenya (4.5)
Panama (4.3)
South Africa (4.2)
Nigeria (3.9)
Barbados (3.9)
Paraguay (3.9)
Germany (3.9)
Malta (3.8)
Thailand (3.8)
Japan (3.7)
Brazil (3.7)
Hong Kong (3.3)
Sweden (3.3)
Finland (3.2)
Austria (3.0)
Belgium (3.0)
Argentina (2.9)
Spain (2.8)
Morocco (2.7)
Romania (2.7)
Algeria (2.6)
Sultanate of Oman (2.5)
Iran (2.5)
Portugal (2.4)
Tunisia (2.4)
Malaysia (2.4)
Poland (2.4)
Singapore (2.3)
Pakistan (2.2)
South Korea (2.2)
Italy (2.0)
Chile (2.0)
Russia (1.9)
India (1.9)
Mexico (1.9)
Ukraine (1.9)
Philippines (1.8)
Estonia (1.8)
Latvia (1.6)
Taiwan (1.5)
China (1.2)
Indonesia (0.8)
Lithuania (0.8)
Georgia (0.7)
Albania (0.6)
-1
0
1
Mean Change per Year


Country (prevalence %)
Peru (17.1)
Kenya (14.8)
New Zealand (14.8)
Barbados (13.4)
Uruguay (13.3)
Chile (12.1)
Philippines (11.5)
Kuwait (10.8)
USA (10.8)
Singapore (10.6)
Paraguay (10.4)
Morocco (9.4)
South Africa (8.9)
Argentina (8.1)
Hong Kong (8.1)
Thailand (7.6)
Austria (7.5)
Pakistan (7.5)
Spain (7.4)
Portugal (6.8)
Germany (6.2)
India (5.7)
Taiwan (5.5)
Malaysia (5.2)
South Korea (4.8)
Sweden (4.4)
Finland (3.6)
Iran (3.3)
China (3.1)
Latvia (2.2)
Estonia (2.1)
Albania (1.3)
-3
-2
-1
0
1
2
3
Mean Change per Year


Country (prevalence %)
Peru (30.5)
New Zealand (27.7)
Singapore (23.7)
Isle of Man (23.7)
Channel Islands (23.1)
United Kingdom (22.9)
Barbados (20.9)
Costa Rica (20.8)
Sultanate of Oman (20.3)
Japan (19.4)
Philippines (19.3)
Panama (18.7)
Republic of Ireland (18.4)
USA (18.3)
Uruguay (16.7)
Kuwait (15.8)
Tunisia (15.6)
Nigeria (15.0)
Morocco (14.7)
Brazil (14.6)
South Africa (13.7)
Portugal (13.2)
Taiwan (13.1)
Kenya (12.9)
Chile (12.8)
Malta (12.6)
Paraguay (12.5)
Thailand (12.3)
Spain (11.8)
Malaysia (11.5)
Sweden (11.1)
Hong Kong (10.7)
Italy (10.5)
Argentina (9.6)
Belgium (8.3)
Germany (7.5)
Pakistan (7.4)
Indonesia (7.0)
Romania (6.3)
Austria (6.2)
Finland (6.1)
Algeria (5.9)
Ukraine (5.8)
India (5.7)
Mexico (5.6)
Latvia (5.6)
China (5.4)
Poland (4.1)
Estonia (4.0)
South Korea (3.9)
Russia (3.6)
Georgia (3.5)
Iran (3.1)
Lithuania (2.7)
Ethiopia (2.6)
Albania (2.6)
-2
-1
0
1
2
Mean Change per Year


Annual change in asthma admission rate v annual change in nocturnal wheeze
Average annual change in asthma admission rate aged 5-14 (per 10,000)
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-0.15
-0.1
-0.05
0
0.05
0.1
0.15
Rank correlation:
r = 0.63, p = 0.03
Average annual change in nocturnal wheeze prevalence (per 100 children)