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Early View

Original research article

Prevalence, time trends and treatment practices of asthma in India: Global Asthma Network study

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Take home message

Data from Indian centers that participated in multicentre Global Asthma Network showed a significant decline in symptoms of asthma compared to previous studies. The study highlighted under-diagnosis and under-treatment in children and adults with asthma.

Abstract

Objective

The objective of the sub-analysis of data from centers across urban areas in India of the Global Asthma Network (GAN) was to study the 1) prevalence of symptoms of asthma in children and adults, 2) change in prevalence of asthma and its trigger factors since the International Study of Asthma and Allergies in Childhood (ISAAC), and, 3) current asthma treatment practice.

Methods

In this cross–sectional, multicenter, school-based, and self-administered questionnaire, responses from children aged 6–7 years, 13–14 years, and their respective parents were analysed.

Results

The GAN phase I study included 20084 children in the 6–7-year-age group, 25887 children in the 13–14-year-age group, and 81296 parents. The prevalence of wheeze in the past 12 months was 3.16%, 3.63%, and 3.30% in the three groups respectively. In comparison to the ISAAC studies, there was a significant reduction in the prevalence of current wheeze ($p<0.001$). Bivariate analysis revealed a significant reduction in the prevalence of trigger factors. Almost 82% of current wheezers and 70% of subjects with symptoms of severe asthma were not clinically diagnosed as having asthma. The daily use of inhaled corticosteroid (ICS) was less than 2.5% in subjects with current wheeze and those with symptoms of severe asthma but less than 1% used daily ICS when asthma remained undiagnosed.

Conclusion

The prevalence of current wheeze and its causal factors showed a significant reduction compared to previous ISAAC studies. Among subjects with current wheeze and symptoms of severe asthma, the problem of under-diagnosis and under-treatment was high.

Keywords

Children, Cough, Inhaled corticosteroids, Questionnaire survey, Wheeze, Asthma epidemiology.

Main text

Introduction

The prevalence of asthma varies widely among countries/ geographical regions and also within countries with different geographies and socioeconomic stratas.[1,2] The Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults (INSEARCH) estimated the national burden of asthma at 17.23 million with an overall prevalence of 2.05%.[3] The recent Global Burden of Disease (GBD, 1990–2019) estimated the total burden of asthma in India as 34.3 million, accounting for 13.09% of the global burden.[4] It also attributed that 13.2 thousand deaths in India were due to asthma.[4] Asthma accounted for 27.9% of the disability-adjusted life years (DALYs) in Indians.[4] On the whole, India has three times higher mortality and more than two times higher DALYs compared to the global proportion of asthma burden. The disproportionate mortality and morbidity can be explained by global studies with uniform methodology.

The International Study of Asthma and Allergy in Childhood (ISAAC) phase I (1995) and III (2001-3) were the largest multicenter global studies conducted with uniform methodology worldwide.[5,6] The study showed around 6% of children in India had current wheezing and identified, several environmental factors associated with asthma globally and those included environmental tobacco smoke[7], firewood cooking[8], heavy truck traffic exposure[9], obesity[10], fast-food consumption[11], dampness in homes[12], and paracetamol/antibiotic use.[13]

Over the past two decades there has been a change in the economy, industrialisation, air pollution levels, environmental and socio-cultural factors in India. Apart from the ISAAC studies, no other worldwide multicenter study has been conducted to analyse the impact of these changes on the prevalence and severity of asthma. The ISAAC study group was

resurrected in the form of the Global Asthma Network (GAN) in 2012 to estimate the current prevalence of symptoms of asthma and allergies.[14]

The GAN study included certain aspects that were not covered in the ISAAC studies including the prevalence of asthma symptoms amongst parents of children and the medications used for control.[14] The objective of this paper was to analyse the GAN phase I data from Indian centers for 1) the prevalence of asthmatic symptoms in children (aged 6-7 years and 13-14 years) and their adult parents; 2) change in prevalence of asthmatic symptoms in children compared to previous ISAAC studies and associated environmental factors and; 4) the current use of medicines among children and adults with asthma.

Material and methods

GAN Phase-I study was a cross–sectional, multi-country, multi-centre, and questionnaire–based epidemiological research conducted in schools. The study protocol and methodology were similar to the previous ISAAC phase III study, details of which are explained in an earlier publication.[14] The GAN phase I study included seven centers that participated in ISAAC Phase III and two new centers. The new centers (Mysuru and Kolkata represented south and east India respectively) were included for better representation of all geographical areas. The survey was conducted across nine centers in India (Bikaner, Chandigarh, Delhi, Jaipur, Kolkata, Kottayam, Mysuru, Lucknow and Pune) in the 13-14-year-age group and eight centers in the 6-7-year age group of children (Kolkata did not participate in the younger age-group). The study was approved by the ethics committee from the respective local centers and was registered in the Clinical Trial Registry, India (CTRI/2018/02/011758).

Schools were randomly selected from a pool of total schools in the selected centers (Figure 1) with the help of Indian Institute of Health Management & Research (IIHMR), Jaipur. The geographic boundary was defined for each city and it was divided into four zones. A fraction

of schools were randomly selected from each zone. Invitations were sent to the principals of the schools and consenting schools were enrolled in the study. Upon refusal to participate by a school in the randomized list, the next school was approached. Passive consent was obtained from the participants. The option of refusal to participate was communicated by either a phone call to the field worker by the parents/guardians or written/verbal refusal by the child to participate.

Two age groups of school children (13–14 years, and 6–7 years) and their parents/guardians were administered with written questionnaires. On the day of administration of questionnaire height and weight of the children were recorded. The adolescent group (13–14 years) had to complete a questionnaire about themselves at school and were asked to take the adult questionnaires home for their parents/guardians to complete about their own health. The younger age group (6–7 years) took the questionnaires to their homes for parents/guardians to complete the questionnaire about the health of their wards and themselves. Codes assigned to the children and their respective parents were same.

The questionnaire used in the study was similar to the previously validated core questionnaire used in ISAAC for both age groups of children. The questionnaire had 70, 50, and 47 questions for the 6–7 years, 13–14 years, and the adult groups respectively (additional two questions for the children and five questions for the adults in the questionnaire used in Indian centers compared to the questionnaire used globally). The items in the questionnaires pertained to demography; symptoms of asthma, rhinoconjunctivitis, and atopic eczema; environment and use of medications. The adult questionnaire was derived from the questionnaire used in ISAAC and European Community Respiratory Health Survey. The questionnaire was available in different languages (English, Hindi, Bengali, Marathi, Punjabi, Kannada and Malayalam). The language translation of the questionnaire was validated by back translating the questionnaire to the English language according to standard protocol.

A meeting was convened for all principal investigators (PIs) of their respective centers at the National Data Coordinating Center (NDCC, Asthma Bhawan, Jaipur) to delineate the study pathway. Field investigators and data entry operators received training at IIHMR, Jaipur.

Ten percent of the data were uploaded online, and the data entry errors were kept below 2% by entering the data twice, first at the site and then the second time by the statistical team at IIHMR, Jaipur, India. The statistical team consolidated the entire data at IIHMR University, Jaipur, and sent it to the GAN global center (Auckland, New Zealand) and subsequently to the main data center (London, United Kingdom), where the data was cleaned for consistency and duplicity (Figure 1).

Coding of the data was done as per the GAN protocol. Current wheeze was defined as the presence of wheeze in the past 12 months (WHEZ12), this aforementioned variable was used to calculate the prevalence of asthma. The other variables were ever diagnosed as asthma (ASTHMAEV) and wheeze ever (WHEZEV). Dry cough in the night during the past 12 months apart from infection (COUGH12) was termed as nocturnal cough. Severe asthma was defined as a current wheeze with more than four attacks per year or wheeze affecting speech or sleep.

Data Management and Statistical Analysis

The sample size targeted for each age group was 3000 participants and potentially 6000 adults per center. This sample size could detect a 5% difference between the two centers with 99% certainty (at the 1% level of significance).[14] The missing data were not included in analysis. Statistical test such as chi square was carried out for bivariate analysis to estimate the distribution and association of current wheeze and severe asthma in different predictors. If the cell frequency was less than 5, the Fisher exact probability test was used. The quantitative data were analysed using STATA version 12 (StataCorp. 2011. Stata Statistical Software:

Release 12. College Station, TX: StataCorp LP). Prevalence of current wheeze as reported in ISAAC phase I, III and GAN phase I studies were compared using Chi-square test.

Results

In this study, questionnaires were received from 20084 children in the age group 6–7 year, 25887 children in the age group of 13–14 year and 81296 adults (Table 1). The average response rate was 83.9%, 96.6%, and 99.4% in the 6–7 years, 13–14 years, and adults respectively. There were 48%, 51.1%, and 50.2% females in the 6–7 years, 13–14 years, and adults respectively. The mean age of the adults was 37.6±6.4 years.

The prevalence of current wheeze was 3.16%, 3.63%, and 3.30% among the 6–7—years old, 13–14—year olds and adults, respectively (Table 1) with no significant difference between the age-groups ($p>0.05$). A significantly higher prevalence of current wheeze, wheeze ever, asthma ever, doctor–diagnosed asthma, and nocturnal cough in the last 12 months was noted in boys in both the age groups of children ($p<0.05$) (Table 1). However, in adults, the prevalence of asthma ever and doctor-diagnosed asthma were significantly higher in women than in men ($p<0.001$). Severe asthma was prevalent in 1.59%, 1.60%, and 1.16% in the 6–7—year olds, 13–14—year olds, and adults (parents), respectively (Table 1). The prevalence of current wheeze, nocturnal cough in the past 12 months and severe asthma varied markedly across centers (Supplementary Tables 1, 2, 3).

Across ISAAC phase III and GAN phase I, in both age groups, there was a significant decrease in the prevalence of current wheeze ($p<0.001$) and asthma ever ($p<0.001$), but there was a significant increase in the prevalence of the symptom nocturnal cough ($p<0.001$, Figure 2, Supplement Table 4). Bivariate analysis of comparison of various causal factors of current wheeze among children during GAN from ISAAC showed a significant reduction in

paracetamol use, maternal smoking, farm exposure, pets in the house and trucks passing outside house. There was significant increase in the usage of fresh fruits (Table 2).

In the 6-7-year age group absenteeism due to wheeze was noted in 66.1% and 2.5% of children with current wheeze, with and without a concomitant doctor diagnosis of asthma respectively (Table 3). In the 13-14-year age group these numbers were 52.7% and 24.0% respectively. Hospitalisations at least once in the past year because of breathing problems were noted in 44.3% of children with current wheeze with a concomitant doctor diagnosis of asthma and 1.2% of children with current wheeze without a doctor diagnosis. (Table 3). In the 13-14-year age group these numbers were 25.5% and 8.7%. respectively. Similarly, exercise-induced wheeze and visit to emergency due to breathing trouble were also higher in subjects with doctor diagnosed asthma.

In all groups both inhaled and oral medicines were used in almost equal proportion. However, in subjects in either of the three groups with current wheeze or with symptoms of severe asthma less than 2.5% subjects were using daily ICS and less than 2% subjects used inhaled beta-agonist daily (Table 4).

Among subjects with current wheeze, 75 -82% remained clinically undiagnosed (Table 5). Among subjects with severe asthma, 68-70% of subjects were never clinically diagnosed with asthma (Table 5). Among subjects with current wheeze who had undiagnosed asthma, less than 1% took daily ICS (Table 5). In subjects with current wheeze who were clinically diagnosed with asthma, use of daily ICS increased to 2-8% in different age groups; this difference was statistically significant ($p<0.001$). A similar trend was noted in subjects with symptoms of severe asthma (Table 5). Almost 40% of doctor diagnosed patients used beta agonist inhaled treatment whenever they had symptoms, but less than 7% used when asthma was clinically not confirmed by a doctor (Table 5).

Discussion

The GAN phase I study was the largest, multicenter study since the ISAAC phase III that analysed the prevalence of asthma symptoms in children and adults in India. The prevalence of current wheeze was 3.16%, 3.63% and 3.30% in the 6–7 year olds, 13–14 year olds and adults respectively. The comparison of prevalence of current wheeze across Indian centers in ISAAC phase I, III and GAN phase I showed a significantly lower prevalence in both the age groups of children in the GAN study ($p<0.001$), but a higher prevalence for nocturnal cough ($p<0.001$). Most subjects with symptoms of asthma were not diagnosed clinically with asthma. A significantly higher number of current wheezers/symptoms of severe asthma with a doctors' diagnosis of asthma were taking either inhaled medications or inhaled steroids or oral medications in all three groups ($p<0.001$) compared to those without a doctors' diagnosis of asthma.

The time trends of prevalence of asthma from our study are contrary to the widely held belief that asthma is increasing in recent decades. However, our study reveals a significant reduction in the prevalence of current wheeze which has been considered a symptom of asthma. The methodology, recruitment sites and investigators were the same in ISAAC and GAN studies, thereby allowing for a reasonable comparison of data to assess the time trends. A significant reduction was also noted in the GAN study in the prevalence of most of causal factors of current wheeze as compared to the previous ISAAC studies such as paracetamol use, maternal smoking, farm exposure, pets in house,trucks passing outside the house and antibiotic use during first year of life (Table 2). In India strict vehicle emission norms have also been implemented during this period.Conversely use of factors such as fruit consumption and child ever breast fed were increased significantly in the GAN phase-1 study as compared to the ISAAC phase III study, which are considered as protective factor for asthma.[11] National asthma guide lines were also formulated and n initiated which would

have also resulted in better outcome.[15] The change in aforementioned environmental factors may be a possible explanation for reduction in the prevalence of current wheeze.

Nevertheless, there is a wide variation in the prevalence of wheeze in comparative studies. A questionnaire-based study in adults in India revealed the prevalence of asthma as 2.05%.[3] Another multicenter research has reported a prevalence of asthma as 2.38% in adults.[16] An ISAAC questionnaire-based study reported that the prevalence of bronchial asthma as 13.1% in children aged between 11 and 16 years (n=927). The prevalence of current subjects with asthma (defined as asthma episode/(s) in the past one year) was 10.2%.[17] Pal et al. profiled 15 epidemiological studies related to asthma in children and reported the prevalence of asthma as 2.74%.[18] Significant time has elapsed since these studies were conducted and published. These studies also had a varied methodology, time frames, and study population, which could be the possible reasons for this difference. The recently published GBD data estimated 34.3 million cases in 1330 million population of India, almost comparable to our study.[4]

The GAN phase I global data also shows significant changes as per center, age and income in prevalence of asthma across the world.[19] The world total data showed a significant decline in current wheeze, with both increase and decrease noted as per individual center. Preliminary data from few other global centers have shown mixed results regarding time trends in the prevalence of current wheeze.[20-22] Data from a single center in Mexico showed a 7.9% increase in the prevalence of current wheeze in both age groups compared with ISAAC phase III.[20] On the other hand, the GAN phase I study conducted in Bangkok suggests a similar prevalence of current wheeze in the younger age group and slightly lower prevalence in the older age group when compared with the ISAAC phase III.[21] Interestingly, lower prevalence of current wheeze was reported from the centers from low-income group countries while it did not change for high-income countries in either age group. However, prevalence of current wheeze was increased in upper middle-income countries. [19] There have been changes

in the micro-environment, and macro-environment in between the phases of studies across the centers, the exact cause of the trend would be difficult to identify.

The prevalence of current wheeze varied from center to center and was consistent with the previous ISAAC studies. Similar heterogeneity was documented in previous ISAAC studies; intercontinental, intercountry, inter–regional and intra–regional variations.[2,5,6] The various cities across India have varying geography, climate, environment, and socio-economic conditions. The lowest prevalence of current wheeze was documented in Bikaner (0.35%) and the highest in Chandigarh (8.54%) in the 6–7-year age group. Bikaner is a desert area located in the western part of India and it faces a dry and hot weather associated with dust storms. Chandigarh on the other hand has a cooler andhumid climate, situated in the northern part of the country. In the 13–14-year age group, the lowest prevalence was in New Delhi (0.89%) and highest in Jaipur (6.62%) (Supplement Tables 1 and 2, Supplement Figure 1). Among adults, New Delhi (0.88%) reported the lowest prevalence and Kottayam (6.02%) the highest prevalence (Supplement table 3). The findings are contradictory as Jaipur is located in western India and faces dry and arid desert climate while New Delhi is situated in the northern part of the country, with poor air quality. Kottayam is situated in South India with warm and tropical climate. Such variation is also observed in global data, which is difficult to explain. After ISAAC phase III, in New Delhi compressed natural gas (CNG) replaced petrol and diesel in nearly all public vehicles including truck traffic after December 2002.[23] Diesel exhaust particles have been the associated with increase in Th2 and Th17 cytokines, that are responsible for the asthmatic response.[24] Reduction in the diesel exhaust particles may in turn have been a contributing factor for a decrease in prevalence in New Delhi. The INSEARCH also reported variation in the prevalence of bronchial asthma (adults) among the 12 participating centers (from 0.4% in Secunderabad to 4.8% in Kolkata).[3]

The self-reported prevalence of wheeze was significantly more common in boys in both age groups ($p<0.001$).[25] It is unclear why this gender difference exists in the children; probable explanation could be variations in sex hormone levels,[26] bronchial lability[27], and allergen sensitivities.[28] Interestingly, among adults this difference was not noted for current wheeze and a significantly higher prevalence of asthma ever and doctor-diagnosed asthma were seen in women, which is consistent with previous reports in adults. Previous health surveys conducted from 2005–2006 in India in adults have reported a prevalence of wheeze of 1.8% (95%CI 1.6–2.0) and 1.9% (95%CI 1.8–2.0) in men and women, respectively.[29]

Nocturnal cough is a symptom of asthma that has increased in prevalence during GAN phase 1 compared to ISAAC phase I, III. However, nocturnal cough can be attributed to other causes also such as gastro-esophageal reflux disease, post-nasal drip, bronchiectasis and medication induced.[30] It is a non-specific symptom and all nocturnal cough would not be due to bronchial asthma. Nonetheless, it is worthwhile to note a significant increase in the prevalence of nocturnal cough, a similar increase was also noted in both the age-groups in the worldwide GAN phase I data, a trend which is difficult to explain.[19]

Our study reveals a gap in the diagnosis of asthma. More than 82% of the subjects with current wheeze and more than 70% of the subjects with symptoms of severe asthma were not clinically diagnosed to have asthma by a doctor. This gap in diagnosis is high compared to a similar study that reported almost a third of the subjects remained undiagnosed.[31] Under treatment is another problem, among doctor diagnosed subjects with wheeze and with symptoms of severe asthma daily ICS was used in less than 9% among different age groups of subjects (Table 5). Under-diagnosis and under-treatment may be attributed to lack of medical facilities, poverty, illiteracy, ignorance on the part of the patients, improper technique of medication intake, non-adherence and poor communication skills of medical personnel.[32,33,34] Apart from these factors an interesting aspect worth discussing is disease

terminology used by asthmatic patients and their treating doctors. When an asthmatic patient consults a doctor, only 71% of doctors refer to "Asthma" as name of their disease and 29% use other terminology. The problem is worse at patient level; only 23% asthmatic patients call their disease as asthma while rest of them use terminology like *swas, dama* or cold and cough.[35] Asthma is considered as a stigma and many parents conceal the disease and therefore avoid medications or give only when a patient is symptomatic or unable to tolerate symptoms. Incorrect notions such as inhalers are harmful and habit forming also play a role in treatment non-adherence. Regular use of ICS among undiagnosed current wheezers was thereby very low; under-treatment may account for high school absenteeism, urgent medical consultation to a doctor and emergency (Table 3). Even hospitalisation due to breathing problem was significantly high. Similarly indexes of uncontrolled asthma such as exercise related wheeze in children and restriction of usual activities were also significantly higher in current wheezers than healthy subjects (Table 3). These findings suggest high morbidity and use of hospital resources among current wheezers.

Untreated children with asthma have been found to have higher school absenteeism in similar studies.[36] Exercise induced asthma, emergency visits, hospitalisation and school absenteeism are markers of uncontrolled asthma.[37] However, all these markers were more significantly affected in subjects having a clinical diagnosis of asthma probably indicating that more severely affected persons consult a doctor more frequently and thereby have a higher chance of getting clinically diagnosed with asthma. Though earlier studies show that more than half of asthmatic subjects discontinue asthma medications once they tolerate symptoms and this tendency of symptom tolerance persists in more than 1/3rd even after education.[32,33] This issue needs to be addressed in asthma education programs as it leads to significant clinical implications in the form of non-compliance.

Our study thus, highlights an unmet need in terms of diagnosis and treatment of symptoms of asthma thereby leading to significant morbidity resulting from the disease. Lack of patient education, concerns about side effects of the medications and stigma associated with inhalation devices might also contribute to this skewed treatment approach.[32,34]

Underdiagnoses, delayed treatment, under treatment or no treatment may be responsible for increased morbidity due to asthma in terms of DALYs and disproportionately high mortality.[1,4] These findings emphasise the need for national-level health programs to address better strategies to diagnose and manage asthma. It should also emphasise the need to communicate a diagnosis of asthma to the patient.

GAN phase-I study is a self-reported questionnaire–based study; objective measures of assessment of asthma and its severity, such as spirometry were not used for the diagnosis of the disease. Conducting spirometry for every child across all centers would not have been logistically feasible and would not have allowed for comparison with earlier studies. Since it was a questionnaire-based study, answers were subject to the understanding of the children and adults. Adolescents may have a poor perception of their symptoms; thus questionnaire–based assessment tools may underestimate the actual prevalence of the illness. Cough is a common symptom in subjects with asthma, especially children. Although wheeze is more specific for a diagnosis of asthma, its sensitivity is low and may therefore underestimate the prevalence of asthma. However, the previous ISAAC studies have used this particular question for the calculation of the prevalence of asthma.[2,5,6] The validated ISAAC questionnaire is the most authentic source of collecting childhood asthma prevalence globally.[14,38] Furthermore, since the study aimed to compare the current prevalence of wheeze with the previous ISAAC data, a similar questionnaire was sought to maintain consistency. The study was limited by the fact that the centers participated voluntarily, and were not randomly selected. Though the participating centers were voluntary they represented the

various geographies including north, south, east, west and central. Further, each center was divided into four zones, a fraction of schools were randomly selected from each zone, for appropriate representation from across. This same methodology was adopted by the GAN phase 1 study worldwide and the previous ISAAC studies as well. The study population was representative of the population of school going children of the respective nine centers. Despite these steps to strive for equal representation from across centers, the prevalence of asthma varies across rural and urban, and within cities itself due to differences in socio-economic conditions, thus to generalize the results to the entire country or the world would not be appropriate. Potential bias could exist as some children may have refused to participate and all children may not be attending schools. Furthermore, all schools across the country were not covered. Recall bias could also exist, as exposures in the first year of life could have been forgotten or improperly remembered. However, the same protocol was used in the previous ISAAC studies, thereby allowing for valid comparison for time trends. Prevalence of current wheeze in adults could be obtained for only those adults (age group 31-44 years) whose children were in a particular age group and were attending the participating schools; thus, a selection bias may exist.

Conclusions

The prevalence of current wheeze in the 6–7 year olds, 13–14 year olds and adults was 3.16%. 3.63% and 3.30% respectively. There was a significant reduction in current wheeze in GAN phase I compared with the previous ISAAC phase III study. It was also associated with a significant reduction in the frequency of exposure to causal factors such as paracetamol use, maternal smoking, farm exposure, pets in the house and trucks passing outside the house. The problem of under-diagnosis and under-treatment of asthma was noted. Upto 82% of subjects with current wheeze and upto 70% of subjects with symptoms of severe asthma remain undiagnosed and less than one percent of undiagnosed subjects take the recommended daily

ICS. Even among current wheezers with a clinical diagnosis of asthma use of daily ICS was relatively low. The study provides valuable insights into the changing trends in the prevalence of current wheeze in India and highlights under-diagnosis and under-treatment. The findings would help in planning management strategies for this non–communicable disease.

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Declaration of interests

There is no conflict of interest to report by any of the authors

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Table 1: Prevalence of symptoms of asthma, severe asthma, asthma ever and doctor diagnosed asthma in the children and adults across both the genders

Symptoms	6–7- year-age group (N=20 084)				13–14-year-age group (N=25 887)				Adults (N=81 296)*			
	Male (N=10 441)	Female (N=9643)	p-value¥	Total	Male (N=12671)	Female (N=13216)	p-Value¥	Total	Male (N=40468)	Female (N=40815)	p-Value¥	Total
	N (%)	N (%)		N (%)	N (%)	N (%)		N (%)	N (%)	N (%)		N (%)
Current wheeze	380 (3.64)	254 (2.63)	<0.0001	634 (3.16)	565 (4.46)	375 (2.84)	<0.00001	940 (3.63)	1344 (3.32)	1335 (3.27)	0.689	2,680 (3.30)
Wheeze ever**	757 (7.25)	498 (5.16)	<0.0001	1255 (6.25)	1,139 (8.99)	778 (5.89)	<0.00001	1917 (7.41)	-	-	-	-
Nocturnal cough in past 12 months**	1870 (17.91)	1370 (14.21)	<0.001	3240 (16.13)	3,864 (30.49)	3520 (26.63)	<0.00001	7384 (28.52)	-	-	-	-
Asthma severe***	192 (1.83)	128 (1.33)	0.004	320 (1.59)	258 (2.04)	157 (1.19)	<0.00001	415 (1.60)	465 (1.15)	476 (1.17)	0.790	942 (1.16)
Asthma ever	174 (1.67)	109 (1.13)	0.012	283 (1.41)	630 (4.97)	426 (3.22)	<0.00001	1056 (4.08)	714 (1.76)	942 (2.31)	<0.0001	1,656 (2.04)
Doctor diagnosed asthma	138 (1.32)	88 (0.91)	0.059	226 (1.13)	354 (2.79)	246 (1.86)	<0.00001	600 (2.32)	517 (1.28)	659 (1.61)	0.000	1,176 (1.45)

*Sex not defined for 13 adults

**Questions not included in adult questionnaire

***Severe Asthma is defined as >4 attacks of wheezing in last 12 months or wheeze affecting sleep or speech in last 12 months

¥Chi square test

Table 2: Time trends in known environmental trigger factors through ISAAC phase III and GAN in the two age groups of children

	6-7-year-age group			13-14-year-age group		
	GAN (N=20084)	**ISAAC III (N=47166)**	**p-value****	**GAN (N=25887)**	**ISAAC III (N=52289)**	**p-value****
Paracetamol use in last 12 months						
Never	6639 (33.1)	8945 (19.0)	0.000	9838 (38.0)	14689 (28.1)	0.000
At least once a year	9496 (47.3)	21499 (45.6)		10283 (39.7)	18749 (35.9)	
At least once per month	2104 (10.5)	5940 (12.6)		4441 (17.2)	9530 (18.2)	
No response	1845 (9.19)	10782 (22.86)		1325 (5.1)	9321 (17.8)	
Farm animals during pregnancy*						
Yes	1307 (6.5)	3357 (7.1)	0.000	-	-	
No	18051 (89.9)	34474 (73.1)		-	-	
No response	726 (3.61)	9335 (19.79)		-	-	
Farm animals during first year of life*						
Yes	1059 (5.3)	4267 (9.0)	0.000	-	-	
No	18297 (91.1)	33585 (71.2)		-	-	
No response	728 (3.62)	9314 (19.75)		-	-	
Trucks pass through the street						
Never	9999 (49.8)	9451 (20.1)	0.374	11063 (42.7)	10978 (21.0)	0.000
Seldom (not often)	8631 (43.0)	13793 (29.2)		9573 (37.0)	15354 (29.4)	
Frequently through the day	1028 (5.1)	8276 (17.5)		2902 (11.2)	9550 (18.3)	
Almost the whole day	426 (2.1)	5808 (12.3)		1268 (4.9)	2718 (5.2)	
No response	0	9838 (20.9)		1081 (4.2)	13689 (26.1)	
Child ever breastfed*						
Yes	16569 (82.5)	35215 (74.7)	0.000	-	-	
No	2728 (13.6)	2549 (5.4)		-	-	
No response	787 (3.9)	9402 (19.9)		-	-	

Cat in the home during first year of life*						
Yes	991 (4.9)	3756 (8.0)	0.000	-	-	
No	18360 (91.4)	34107 (72.3)		-	-	
No response	733 (3.7)	9303 (19.7)		-	-	
Cat in home in last 12 months						
Yes	985 (4.9)	3632 (7.7)	0.000	3221 (12.4)	8491 (16.2)	0.000
No	17875 (89.0)	34277 (72.7)		22041 (85.1)	35480 (67.9)	
No response	1224 (6.09)	9257 (19.63)		625 (2.5)	8318 (15.9)	
Dog in the home during first year of life*						
Yes	1102 (5.5)	4102 (8.7)	0.000	-	-	
No	18280 (91.0)	33836 (71.7)		-	-	
No response	702 (3.5)	9228 (19.6)		-	-	
Dog in home in last 12 months						
Yes	1200 (6.0)	3779 (8.0)	0.000	3930 (15.2)	7934 (15.2)	0.000
No	18150 (90.4)	34183 (72.5)		21394 (82.6)	36000 (68.8)	
No response	734 (3.6)	9204 (19.5)		563 (2.2)	8355 (16.0)	
Fastfood						
Never or only occasionally	13286 (66.2)	10754 (22.8)	0.000	16535 (63.9)	12553 (24.0)	0.000
Once or twice per week	3445 (17.2)	7383 (15.7)		5200 (20.1)	12018 (23.0)	
Most or all days	462 (2.3)	9865 (20.9)		1690 (6.5)	10236 (19.6)	
No response	2891 (13.3)	19164 (40.3)		2462 (9.5)	17482 (33.4)	
Antibiotic in first year of life*						
Yes	3350 (16.7)	17706 (37.5)	0.373	-	-	
No	16734 (83.3)	17711 (37.6)		-	-	
No response	0	11749 (24.9)		-	-	
Fresh fruit						
Never or only occasionally	4590 (22.9)	11179 (23.7)	0.000	7698 (29.7)	12031 (23.0)	0.000
Once or twice per week	6841 (34.1)	12503 (26.5)		6106 (23.6)	14409 (27.6)	
Most or all days	6341 (31.6)	11511 (24.4)		9255 (35.8)	15061 (28.8)	
No response	2312 (11.4)	11973 (25.4)		2828 (10.9)	10788 (20.6)	

Vegetable						
Never or only occasionally	5565 (27.7)	12291 (26.1)	0.000	13150 (50.8)	12721 (24.3)	0.000
Once or twice per week	5792 (28.8)	9395 (19.9)		4666 (18.0)	11230 (21.5)	
Most or all days	5842 (29.1)	13726 (29.1)		5193 (20.1)	17681 (33.8)	
No response	2885 (14.4)	11754 (24.9)		2878 (11.1)	10657 (20.4)	
Mother Smoking during first year of life						
Yes	209 (1.0)	385 (0.8)	0.000	-	-	
No	19194 (95.6)	37637 (79.8)		-	-	
No response	681 (3.4)	9144 (19.4)		-	-	

*Questions included in the 6-7-year age group children questionnaire only

**Chi square test

Table 3: School absenteeism, exercise induced wheeze and medical assistance required among children and adults with current wheeze with or without doctor diagnosed asthma, and healthy subjects

	6-7-year-age group				13-14-year-age group				Adults			
In the past 12 months	**Current wheezers with Doctor diagnosed Asthma (N=115)**	**Current wheezers without Doctor diagnosed Asthma (N=519)**	**Subjects without Current wheeze (N=19450)**	**p-value ***	**Current wheezers with Doctor diagnosed Asthma (N=239)**	**Current wheezers without Doctor diagnosed Asthma (N=701)**	**Subjects without Current wheeze (N=24947)**	**p-value ***	**Current wheezers with Doctor diagnosed Asthma (N=603)**	**Current wheeze without Doctor diagnosed Asthma (N=2077)**	**Subjects without Current wheeze (N=78616)**	**p-value ***
Missed school due to breathing problem ≥1 day	76 (66.09)	13 (2.50)	53 (0.27)	0.000	126 (52.72)	168 (23.96)	1499 (6.01)	0.000	-	-	-	
Wheezy chest with exercise	39 (33.91)	117 (22.54)	399 (2.05)	0.000	103 (43.10)	237 (33.81)	1943 (7.79)	0.000	-	-	-	
Urgent visit to doctor due to breathing problem (≥1 time/12 m)	81 (70.43)	16 (3.08)	54 (0.28)	0.000	119 (49.79)	208 (29.67)	1606 (6.44)	0.000	391 (64.84)	74 (3.56)	244 (0.31)	0.000
Urgent visit to Emergency department due to breathing problem (≥1 time/12 m)	42 (36.52)	5 (0.96)	18 (0.09)	0.000	53 (22.17)	73 (10.41)	598 (2.40)	0.000	180 (29.85)	32 (1.54)	106 (0.13)	0.000
Admitted to hospital due to breathing problem (≥1 time/12 m)	51 (44.35)	6(1.16)	22 (0.11)	0.000	61 (25.52)	61 (8.70)	679 (2.72)	0.000	165 (27.36)	32 (1.54)	101 (0.13)	0.000
Limited usual activity (at work or in the home) due to breathing problem	-	-	-		-	-	-		216 (35.82)	366 (17.62)	932 (1.19)	0.000

***Chi square test**

Table 4: Treatment undertaken for current wheeze and severe asthma in children and adults

Medications used	Current Wheeze						Severe Asthma*					
	6-7-year-age group (N=634)		13-14-year-age group (N=940)		Adult (N=2680)		6-7-year-age group (N=320)		13-14-year-age group (N=562)		Adult (N=1499)	
	N	%	N	%	N	%	N	%	N	%	N	%
Inhaler medicines	97	15.3	270	28.72	487	18.17	72	22.50	208	37.01	389	25.95
Nebulizer	115	18.14	115	12.23	309	11.53	85	26.56	89	15.84	231	15.41
Oral medications	76	11.99	238	25.32	392	14.63	61	19.06	183	32.56	324	21.61
Inhaled beta agonists												
Only when need	51	8.04	140	14.89	239	8.92	36	11.25	120	21.35	188	12.54
In short courses	23	3.63	27	2.87	37	1.38	16	5.00	26	4.63	34	2.27
Every day	5	0.79	9	0.96	33	1.23	3	0.94	9	1.60	29	1.93
Inhaled corticosteroids												
Only when need	24	3.79	43	4.57	67	2.5	14	4.38	34	6.05	56	3.74
In short courses	13	2.05	52	5.53	24	0.9	11	3.44	47	8.36	22	1.47
Every day	5	0.79	8	0.85	13	0.49	3	0.94	5	0.89	11	0.73
Combined (ICS+LABA)												
Only when need	18	2.84	81	8.62	112	4.18	10	3.13	71	12.63	81	5.40
In short courses	9	1.42	10	1.06	22	0.82	4	1.25	8	1.42	18	1.20
Every day	10	1.58	7	0.74	37	1.38	8	2.50	7	1.25	32	2.13

ICS (Inhaled corticosteroid), LABA (long acting beta agonist)

*Severe Asthma is defined as current wheeze with more than 4 attacks per year or wheeze affecting speech or activity

Table 5: Use of various types of medicines in subjects with current wheeze and severe asthma with or without doctor diagnosed asthma

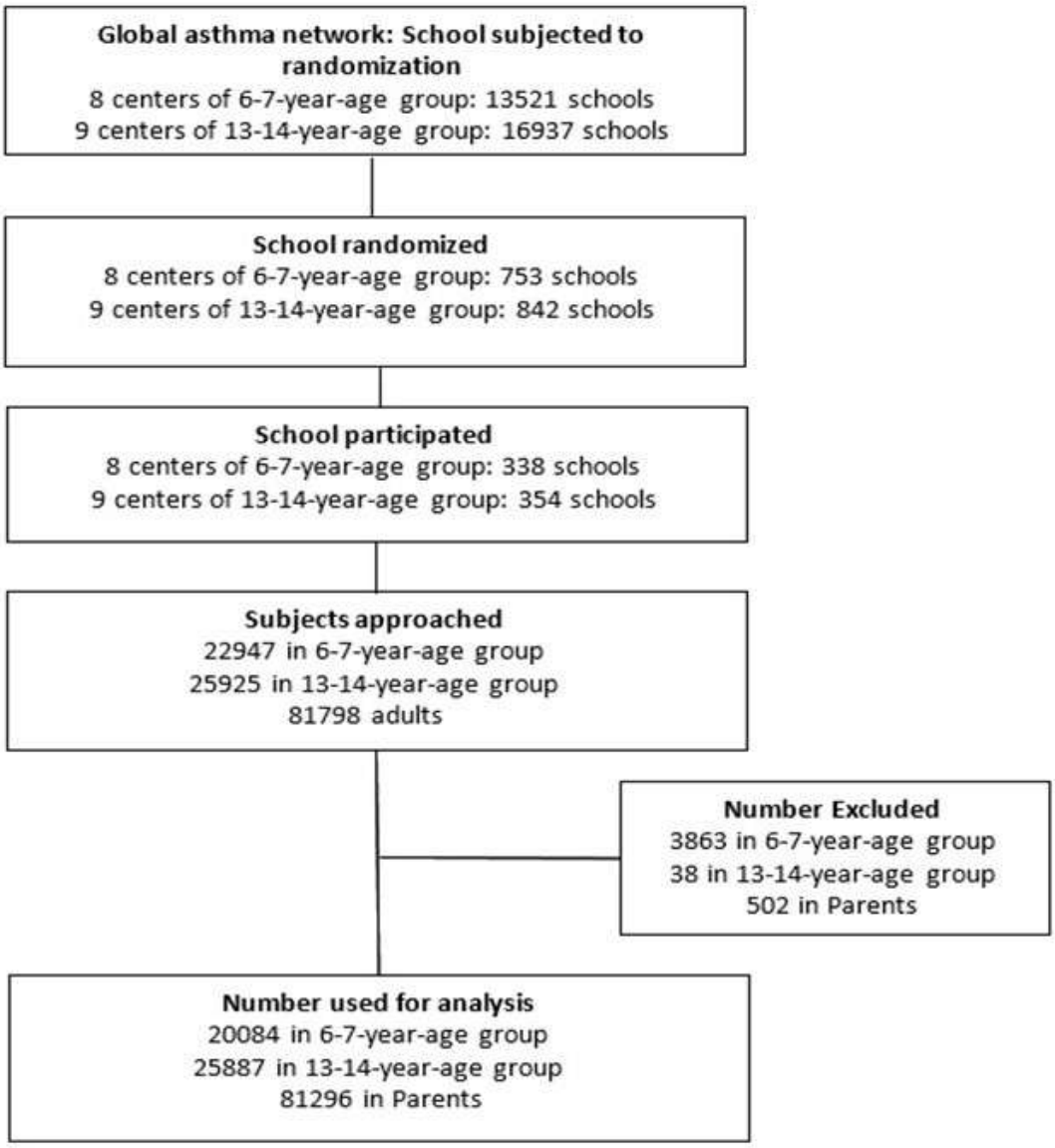
	Current Wheezers with Doctor diagnosed asthma	Current Wheezers without Doctor diagnosed asthma	p-value*	Severe Asthma with Doctor diagnosed asthma**	Severe Asthma without Doctor diagnosed asthma**	p-value*
6-7-year-age group	**N= 115**	**N= 519**		**N= 95**	**N= 225**	
Inhaled beta agonists						
Only when need	41 (35.65)	10 (1.93)	0.000	33 (34.74)	3 (1.33)	0.000
In short courses	18 (15.65)	5 (0.96)		15 (15.79)	1 (0.44)	
Every day	5 (4.35)	0 (0.0)		3 (3.16)	0 (0.0)	
Not using any Medicine	51(44.35)	504(97.11)		44(46.31)	221(98.23)	
Inhaled corticosteroids						
Only when need	16 (13.91)	8 (1.54)	0.000	11 (11.58)	3 (1.33)	0.000
In short courses	12 (10.43)	1 (0.19)		11 (11.58)	0 (0.0)	
Every day	4 (3.48)	1 (0.19)		3 (3.16)	0 (0.0)	
Not using any Medicine	83 (72.18)	509(98.08		70(73.68)	222(98.67)	
Combined (ICS+LABA)						
Only when need	14 (12.17)	4 (0.77)	0.000	9 (9.47)	1 (0.44)	0.000
In short courses	6 (5.22)	3 (0.58)		4 (4.21)	0 (0.0)	
Every day	9 (7.83)	1(0.19)		8 (8.42)	0 (0.0)	
Not using any Medicine	86(74.78)	511(98.47)		74(77.90)	224(99.56)	
13-14-year-age group	**N= 239**	**N= 701**		**N= 182**	**N= 380**	
Inhaled beta agonists						
Only when need	107 (44.77)	41 (5.85)	0.000	97 (53.30)	26 (6.84)	0.000
In short courses	18 (7.53)	22 (3.14)		17 (9.34)	7 (1.84)	
Every day	8 (3.35)	1 (0.14)		7 (3.85)	1 (0.26)	
Not using any Medicine	106(44.35)	637(90.87)		61(33.52	346(91.06	
Inhaled corticosteroids						
Only when need	30 (12.55)	13 (1.85)	0.000	23 (12.64)	11 (2.89)	0.000
In short courses	46 (19.25)	6 (0.86)		42 (23.07)	5 (1.32)	
Every day	8 (3.35)	0 (0.0)		5 (2.75)	0 (0.0)	
Not using any Medicine	155(64.85)	682(97.29)		112(61.54)	364(95.79)	
Combined (ICS+LABA)						
Only when need	65 (27.20)	16 (2.28)	0.000	58 (31.86)	13 (3.42)	0.000
In short courses	6 (2.51)	4 (0.57)	0.012	4 (2.20)	4 (1.05)	

Every day	5 (2.09)	2 (0.29)	0.005	5 (2.75)	2 (0.53)	
Not using any Medicine	163(68.20)	679(96.86)		115(63.19)	361(95.0)	
Adults	**N= 603**	**N= 2077**		**N= 467**	**N= 1032**	
Inhaled beta agonists						
Only when need	218 (36.15)	24 (1.16)	0.000	171 (36.62)	16 (1.55)	0.000
In short courses	33 (5.47)	4(0.19)		31(6.64)	3(0.29)	
Every day	30(4.98)	3(0.14)		26(5.57)	3(0.29)	
Not using any Medicine	322(53.40)	2046(98.51)		239(51.17)	1010(97.87)	
Inhaled corticosteroids						
Only when need	58 (9.62)	9(0.43)	0.000	49 (10.49)	7(0.68)	0.000
In short courses	21 (3.48)	3(0.14)		19(4.07)	3(0.29)	
Every day	13(2.16)	0(0.0)		11(2.36)	0(0.0)	
Not using any Medicine	511(84.74)	2065(99.43)		388(83.08)	1022(99.03)	
Combined (ICS+LABA)						
Only when need	101 (16.75)	11(0.53)	0.000	73(15.63)	8(0.78)	0.000
In short courses	18(2.99)	4(0.19)		14(3.00)	4(0.39)	
Every day	37(6.14)	0(0.0)		32(6.85)	0(0.0)	
Not using any Medicine	447(74.12)	2062(99.28)		348(74.52)	1020(98.83)	

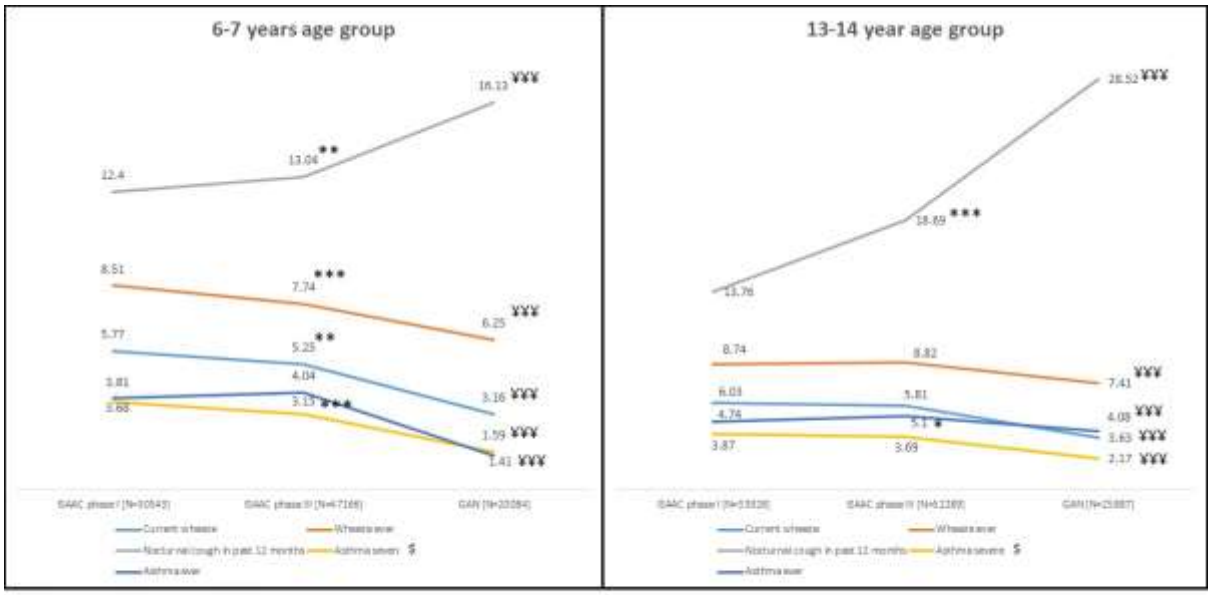
ICS (Inhaled corticosteroid), LABA (long acting beta agonist)

* Chi-square test is used when all expected cell frequencies are equal to or greater than 5. If expected cell frequency was <5 the Fisher Exact Probability Test was used

**Severe Asthma is defined as current wheeze with more than 4 attacks per year or wheeze affecting speech or activity



Flow chart depicting the recruitment in GAN study



*p<0.05, ** p<0.01, *** p<0.001 when ISAAC Phase I compared to ISAAC phase III

‡ p<0.05, ‡‡ p<0.01, ‡‡‡ p<0.001 when ISAAC Phase III compared to GAN Phase I

$ Severe Asthma is defined as >4 attacks of wheezing in last 12 months or wheeze affecting sleep or speech in last 12 months

Time trends in various aspects of asthma including current wheeze, wheeze ever, nocturnal cough, severe asthma, and asthma ever through ISAAC phase I, III, and GAN phase I in the two age groups of children.

Supplement

Title: **Prevalence, time trends and treatment practices of asthma in India: Global Asthma Network study**

Running head: Prevalence, time trends and treatment practices of asthma

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Table 1: Prevalence of current wheeze, current cough and severe asthma according to the region in **6-7 years** old children

S.No.	Center	N	Response rate	Current wheeze			Nocturnal cough in past 12 months			Severe asthma*		
				n	%	95% C.I.	n	%	95% C.I.	n	%	95% CI

1	Kottayam	2,099	69.97	115	5.48	4.58	6.54	439	20.91	19.23	22.71	60	2.86	2.23	3.66
2	New Delhi	2,516	83.87	87	3.46	2.81	4.25	575	22.85	21.25	24.54	19	0.76	0.48	1.18
3	Chandigarh	2,471	82.37	211	8.54	7.5	9.71	780	31.57	29.76	33.43	29	1.17	0.82	1.68
4	Bikaner	2,600	86.67	9	0.35	0.18	0.66	32	1.23	0.87	1.74	1	0.04	0.01	0.27
5	Jaipur	2,295	76.50	54	2.35	1.81	3.06	456	19.87	18.29	21.55	18	0.78	0.49	1.24
6	Lucknow	2,969	98.97	33	1.11	0.79	1.56	200	6.74	5.89	7.7	14	0.47	0.28	0.79
7	Pune	2,404	80.13	50	2.08	1.58	2.73	476	19.8	18.26	21.44	17	0.71	0.44	1.13
8	Mysuru	2,730	91.00	75	2.75	2.2	3.43	282	10.33	9.24	11.53	38	1.39	1.01	1.91
9	Kolkata	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Total	**20,084**	**74.39**	**634**	**3.16**	**2.92**	**3.41**	**3,240**	**16.13**	**15.63**	**16.65**	**196**	**0.98**	**0.85**	**1.12**

NA-data not available

*Severe Asthma is defined as more than 4 wheezing attacks in last 12 months or sleep disturbed in last 12 months or wheeze affecting speech (nwhez12 or awake12 or speech12)

Table 2: Prevalence of current wheeze, current cough, and severe asthma according to the region in **13-14 years** old children

S.No.	Center	N	Response rate	Current wheeze				Nocturnal cough in past 12 months				Severe asthma*			
				n	%	95% CI		n	%	95% CI		n	%	95% CI	
1	Kottayam	2,091	69.70	93	4.45	3.64	5.42	362	17.31	15.75	18.99	32	1.53	1.08	2.16
2	New Delhi	3,024	100.00	27	0.89	0.61	1.30	825	27.28	25.72	28.90	15	0.5	0.30	0.82
3	Chandigarh	3,000	100.00	75	2.50	2.00	3.12	1,174	39.13	37.40	40.89	22	0.73	0.48	1.11

4	Bikaner	2,702	90.07	65	2.41	1.89	3.06	609	22.54	21.00	24.15	42	1.55	1.15	2.10
5	Jaipur	3,022	97.12	200	6.62	5.78	7.56	1,383	45.76	43.99	47.55	61	2.02	1.57	2.59
6	Lucknow	2,969	98.97	48	1.62	1.22	2.14	673	22.67	21.20	24.21	25	0.84	0.57	1.24
7	Pune	3,030	100.00	139	4.59	3.90	5.39	1,001	33.04	31.38	34.73	60	1.98	1.54	2.54
8	Mysuru	3,051	100.00	100	3.28	2.70	3.97	371	12.16	11.05	13.37	59	1.93	1.50	2.49
9	Kolkata	2,998	99.93	193	6.44	5.61	7.37	986	32.89	31.23	34.59	99	3.30	2.72	4.01
	Total	**25,887**	**95.43**	**940**	**3.63**	**3.41**	**3.87**	**7,384**	**28.52**	**27.98**	**29.08**	**415**	**1.38**	**1.24**	**1.54**

*Severe Asthma is defined as more than 4 wheezing attacks in last 12 months or sleep disturbed in last 12 months or wheeze affecting speech (nwhez12 or awake12 or speech12)

Note: Total sample size for 13-14 children is 27127 and 25887 children interviewed among them.

Table 3: Prevalence of current wheeze, and severe asthma according to the region in **parents** (adults)

S.No.	Center	N	Response rate	Current wheeze				Severe asthma*			
				n	%	95% CI		N	%	95% CI	
1	Kottayam	6,940	57.83	418	6.02	5.49	6.61	174	2.51	2.16	2.9
2	New Delhi	9,449	78.74	83	0.88	0.71	1.09	27	0.29	0.2	0.42
3	Chandigarh	10,386	86.55	407	3.92	3.56	4.31	118	1.14	0.95	1.36
4	Bikaner	10,495	87.46	167	1.59	1.37	1.85	25	0.24	0.16	0.35
5	Jaipur	8,933	74.44	522	5.84	5.38	6.35	173	1.94	1.67	2.24
6	Lucknow	11,820	98.50	183	1.55	1.34	1.79	67	0.57	0.45	0.72
7	Pune	7,999	66.66	311	3.89	3.49	4.33	93	1.16	0.95	1.42
8	Mysuru	11,178	93.15	383	3.43	3.1	3.78	180	1.61	1.39	1.86
9	Kolkata	4,096	34.13	206	5.03	4.40	5.74	85	2.08	1.68	2.56
	Total	**81,296**	**75.27**	**2,680**	**3.30**	**3.18**	**3.42**	**942**	**1.16**	**1.09**	**1.23**

*Severe Asthma is defined as wheezing with more than 4 attacks in last 12 months or sleep disturbed in last 12 months or wheeze affecting speech (nwhez12 or awake12 or speech12)

Table 4: Time trends in various aspects of asthma across India through ISAAC phase I, III and GAN in the two age groups of children

	6-7 year age group					13-14 year age group				
Symptoms	**ISAAC phase I**	**ISAAC phase III**	**GAN**	**p-value (CI)**		**ISAAC phase I**	**ISAAC phase III**	**GAN**	**p-value (CI)**	
	N=30543	N=47166	N=20084 (%)	ISAAC I vs ISAAC III	ISAAC III vs GAN	N=33928	N=52289	N=25887 (%)	ISAAC I vs ISAAC III	ISAAC III vs GAN
Current wheeze	1763 (5.77)	2475 (5.25)	634 (3.16)	0.001 (0.19-0.85)	0.000 (1.77-2.40)	2046 (6.03)	3040 (5.81)	940 (3.63)	0.180 (-0.101-0.545)	0.000 (1.87-2.48)
Wheeze ever	2600 (8.51)	3653 (7.74)	1255 (6.25)	0.000 (0.38-1.17)	0.000 (1.07-1.89)	2966 (8.74)	4611 (8.82)	1917 (7.41)	0.68 (-0.31-0.46)	0.000 (1.00-1.80)
Nocturnal cough in past 12 months	3789 (12.40)	6151 (13.04)	3240 (16.13)	0.009 (0.16-1.12)	0.000 (2.50-3.69)	4670 (13.76)	9776 (18.69)	7384 (28.52)	0.000 (4.43-5.42)	0.000 (8.99-10.27)
Asthma severe*	1124 (3.68)	1484 (3.15)	320 (1.59)	0.000 (0.27-0.79)	0.000 (1.32-1.79)	1315 (3.87)	1933 (3.69)	562 (2.17)	0.17 (-0.07-0.44)	0.000 (1.28-1.76)
Asthma ever	1164 (3.81)	1907 (4.04)	283 (1.41)	0.108 (-0.05-0.51)	0.000 (2.67-3.13)	1609 (4.74)	2669 (5.10)	1056 (4.08)	0.017 (0.064-0.65)	0.000 (0.79-1.40)

*Severe Asthma is defined as >4 attacks of wheezing attacks in last 12 months or wheeze affecting sleep or speech in last 12 months

Figure 1: Map of India depicting the 9 participating centres, with the data being consolidated at the national data coordinating centre (Asthma Bhawan, Jaipur) subsequently verified and consolidated at GAN global centre (GGC, Auckland, New Zealand) and Main data centre (MDC, London, UK)


Chandigarh
New
Delhi
Bikaner
Jaipur
Lucknow
Kolkata
Pune
Mysuru
Kottayam