Combined impact of healthy lifestyle factors on risk of asthma, rhinoconjunctivitis, and eczema in school children: ISAAC Phase Three

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Abstract

Background: Asthma is not the key focus of prevention strategies. A healthy lifestyle index (HLI) was developed to examine the combined effect of modifiable lifestyle factors on asthma, rhinoconjunctivitis, and eczema using data from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three.

Methods: Information on symptoms of asthma, rhinoconjunctivitis, eczema and several lifestyle factors was obtained from children aged 6–7 years through written questionnaires. The HLI combined five lifestyle factors: no parental smoking, child's adherence to Mediterranean diet, child's healthy body mass index, high physical activity and non-sedentary behaviour. The association between the HLI and risk of asthma, rhinoconjunctivitis, and eczema was evaluated using multilevel mixed-effects logistic regression models.

Findings: Data of 70795 children from 37 centres in 19 countries were analysed. Each additional healthy lifestyle factor was associated with a reduced risk of current wheeze (OR=0.87, 95% CI 0.84-0.89), asthma ever (OR=0.89, 95% CI 0.87-0.92), current symptoms of rhinoconjunctivitis (OR=0.95, 95% CI 0.92-0.97), and current symptoms of eczema (OR=0.92, 95% CI 0.92-0.98). If associations were causal, a combination of four or five healthy lifestyle factors would result into a reduction up to 16% of asthma cases (ranging from 2.7 to 26.3% according to region of the world).

Conclusions: Although causality cannot be established from this study, results suggest that interventions to improve multiple modifiable lifestyle factors should be considered and their efficacy assessed to reduce the burden asthma and allergy in childhood.

Key words: allergy, asthma, childhood, lifestyles, prevention.

Key messages

- **What is the key question?**
  What is the combined effect of common modifiable lifestyle factors on asthma, rhinoconjunctivitis, and eczema in childhood?

- **What is the bottom line?**
  This large worldwide multicentre cross-sectional study found that with each point added to a child's healthy lifestyle index (i.e. no parental smoking, child's healthy body mass index, adherence to a Mediterranean diet, physical activity, and non-sedentary behaviour) the risk of current wheeze and reported asthma ever fell by 13% and 11%, respectively. If associations were causal, adherence to a combination of four or five healthy lifestyle factors would theoretically prevent up to 16% of asthma cases.

- **Why read on?**
  Although causality cannot be established from this study, researchers should consider adapting and assessing the efficacy of public health interventions modifying multiple lifestyle factors to reduce the burden of asthma.

Introduction

Asthma is currently the most common chronic disease in childhood worldwide.[1] Higher prevalence rates of asthma have been reported in Western countries and in those that are English speaking; however, in the last two decades the prevalence of asthma there has changed little globally and even declined in some Western countries.[2] Most people affected are in low- and middle-income countries,[3] where asthma prevalence is estimated to be increasing fastest presumably because of their progressive "westernisation" of environmental and lifestyle factors.[4]

The aetiology of asthma remains largely unknown but it is likely a multifactorial and heterogeneous condition, involving combined or interacting effects of non-modifiable (i.e. heredity and sex) and modifiable (i.e. environment and behaviour) risk factors.[5] The International Study of Asthma and Allergies in Childhood (ISAAC) has revealed several modifiable parental and child lifestyle factors to be individually associated with the risk of asthma and allergy symptoms in childhood. These include second-hand tobacco smoke exposure from parental smoking,[6] some specific dietary patterns (e.g. Mediterranean diet and fast food),[7-9] child's overweight and obesity,[10,11] and child's physical activity and sedentary behaviour;[11] which are also the focus of population-wide approaches to prevention of cardiovascular disease and cancer in adults.

Although it would be pertinent to quantify the joint effect of modifiable lifestyle factors on the risk of childhood asthma and allergic conditions, only one previous small study conducted among 609 Puerto Rican children aged 6–14 years has assessed the potential synergistic effects of several risk factors (obesity, early-life second hand smoking, unhealthy diet, and gun violence exposure) on asthma risk.[12]

In this large study, we developed a healthy lifestyle index (HLI) composed of five potentially modifiable lifestyle factors – parental smoking, child's adherence to Mediterranean diet, healthy body mass index (BMI), child's physical activity and sedentary behaviour – and examined the association of this index with risk of asthma, rhinoconjunctivitis, and eczema symptoms using data from ISAAC Phase Three. We used this multidimensional lifestyle approach to estimate the impact of potential prevention strategies (mainly recommended for non-respiratory diseases) upon the population burden of asthma, rhinitis, and eczema in childhood.

Methods

Study participants

ISAAC Phase Three (2000-2003) was a multi-centre, multi-country, cross-sectional study of children (aged 6-7 years) and adolescents (aged 13-14 years) chosen from a random sample of schools in each defined geographical area.[13] The present study is based on data for healthy lifestyle behaviour in 70795 children aged 6-7 years from 37 centres in 19 countries.

Child's health outcomes assessment

Information on symptoms of asthma, rhinoconjunctivitis, and eczema was obtained from parents/guardians of the child through the ISAAC Phase Three core questionnaire (http://isaac.auckland.ac.nz). Current symptoms of asthma were indicated by current wheeze defined as a positive answer to the written question *'Has your child had wheezing or whistling in the chest in the past 12 months?'*. Reported asthma ever was defined as a positive response to the question: *'Has your child ever had asthma?'*

Current symptoms of rhinoconjunctivitis were determined by positive answers to two questions: *'In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?'* If yes: *'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?'*. Hay fever ever was defined as an affirmative answer to the question *'Has your child ever had hay fever?'*.

Current symptoms of eczema were determined by positive answers to: *'Has your child ever had an itchy rash which was coming and going for at least six months?'* If yes: *'Has your child had this itchy rash at any time in the past 12 months?'* If yes: *'Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?'*. Reported eczema ever was determined by a positive answer to: *'Has your child ever had eczema?'*.

Assessment of lifestyle factors and derivation of the healthy lifestyle index (HLI)

Information on lifestyle factors was collected from parents/guardians of the child using the ISAAC Phase Three environmental questionnaire (http://isaac.auckland.ac.nz). The following questions were used to assess smoking habits by the parents of children: *1) Does your child's mother (or female guardian) smoke cigarettes?; and 2) Does your child's father (or male guardian) smoke cigarettes?*. Parents were also asked about the weight and height of their children, which was used to calculate the body mass index (BMI) in kg/m^2. Overweight and obesity were defined according to the cut-off points of child's BMI defined by Cole et al. for each age group and sex,[14] which provides cut-off points for overweight (25 kg/m^2) and obesity (30 kg/m^2) from the age of 2 years and the projection of these values at the age of 18 years.

The environmental questionnaire also included questions about the frequency of consumption over the past year (never or occasionally, one or twice per week, three or more times a week) of the following foods: meat, seafood (including fish), fruit,

vegetables, pulses, cereal, pasta, rice, butter, margarine, nuts, potatoes, milk, eggs and fast food/burgers. A score of the 'Mediterranean diet' pattern was developed according to the consumption frequency of these food items based on the score used by Psaltopoulou et al.[15] Fruit, seafood, vegetables, pulses, cereal, pasta, rice, and potatoes were considered ''pro-Mediterranean'' foods and eating each of these foods was rated 0 (never or occasionally), 1 (one or twice per week) or 2 (three or more times a week) points. Meat, milk, and fast food/burgers were considered ''anti-Mediterranean'' foods and eating each of these was rated 0 (three or more times a week), 1 (one or twice per week) or 2 (never or occasionally) points. In contrast to the score by Psaltopoulou et al.,[15] the ISAAC questionnaire did not allow adjustment of food consumption to energy intake. The points for each of the eleven items were added up to a summary score.

The amount of exercise done by the child was assessed by the question: *'How many times a week does your child engage in vigorous physical activity long enough to make him/ her breathe hard (never or occasionally, once or twice per week, three or more times per week)?'*. Television viewing was assessed by the question: *'During a normal week, how many hours a day (24 h) does your child watch television?'* Possible responses were less than an hour, 1 h but less than 3 h, 3 h but less than 5 h, or 5 h or more.

We then used a binary score for each evaluated factor to allow easy translation of findings into a potential policy context. Children were assigned one point for each of the following factors: mother and father both non-smokers, child has a healthy BMI, child undertakes vigorous physical activity (at least one time per week), child does not have a sedentary behaviour (less than one hour a week of television viewing) and adheres to a Mediterranean diet (Mediterranean diet score above the median value). Finally, the HLI was constructed by summing the binary score for each of the five modifiable lifestyle factors which ranged from 0 (least healthy) to 5 (most healthy) points.

Statistical analysis

Each centre included in the analysis had to assess at least 1000 children and have a response rate higher than 60%. We used multilevel mixed-effects logistic regression to evaluate the effect of a HLI on the presence of asthma, rhinoconjunctivitis, and eczema at age 6-7 years, and calculated odds ratios (OR) and 95% confidence intervals (CI). The HLI was modelled as a continuous and categorical variable with four categories (0 or 1 factor, 2 factors, 3 factors, and 4 or 5 factors), using 0 or 1 factor as the reference category. In the main model, adjustment was performed for sex of the child, region of the world (Western Europe, Northern and Eastern Europe, Eastern Mediterranean, Latin-America, Asia-Pacific and Oceania), and per capita gross national income (GNI) (categorised by the World Bank as low, lower-middle, upper-middle, and high).[16] Centre was included in all models as a random intercept.

Multiple regression analyses investigated whether the associations between HLI and assessed health outcomes were confounded by other variables in the environmental questionnaire. Covariates in the multiple regression analyses were maternal education level (primary, secondary, or tertiary), ever breastfeeding (yes or no), siblings (yes or no), pets at home (yes or no), and paracetamol use for fever in the first year of life (yes or no). Covariates that were significantly associated with symptoms at $p < 0.05$ or changed the effect estimate ([OR]) $\geq$10% were included in the final models. In multiple

regression analyses, children who had a missing value for any of the covariates were removed. No imputation was done for missing data, as previous analyses had shown that little or no bias was introduced by limiting the multiple regression analyses to children with complete data.[17]

Stratified analyses were performed for child's sex, region of the world and GNI. In addition, a meta-analysis was performed to take into account the heterogeneity between the centres. Random effects models were used and heterogeneity among centres was tested by using the Cochran Q test with a significance level of 0.10 and quantified by using the I^2 statistic.

To estimate the proportion or percentage of cases in the entire study population that could be prevented had all children been following four or all five healthy lifestyle factors (i.e. lowest-risk exposure group), we derived centre-specific population-attributable risk fractions (PARFs) (unadjusted for potential confounders) by comparing the total prevalence for each health outcome in that centre with the prevalence in the lowest-risk exposure group [PARF = 100% x (total prevalence - lowest-risk group prevalence) / (total prevalence)]. Analyses were performed using the statistical package Stata 15.0 (StataCorp, College Station, TX, USA).

Results

The characteristics of the study participants are shown in Table 1. Median age of participants was 6.6 ± 0.5 years, and 35122 (49.6%) of them were male. A complete list of countries, number of centres and children per country, and prevalence of current wheeze, reported asthma ever, rhinoconjunctivitis, and eczema is shown in Supplementary Table S1. The healthy lifestyle components were distributed as follows: 57% of children had no exposure to maternal and paternal smoking during childhood, 74.1% of children had a healthy BMI, 41.1% of children adhered to a Mediterranean diet, 61.9% of children were physically active, and 16.5% of children did not have a sedentary behaviour pattern (Supplementary Table S2).

Children having a higher HLI score were more likely to be from Western Europe and Latin America, from countries with high GNI, and were more likely to have mothers with higher educational level (Table 2). Moreover, children having a higher HLI score were more likely to be male, ever breastfed, had more siblings and pets at home, and a lower use of paracetamol for fever in the first year of life (Table 2).

Compared to children with no or one healthy lifestyle factor, the multiple regression adjusted OR for current wheeze was 0.93 (95% CI 0.87-1.01) for two factors, 0.77 (95% CI 0.71-0.83) for three factors, and 0.66 (95% CI 0.60-0.72) for four or five factors; P-trend <0.001 (Table 3). The decreased risk of reported asthma ever was similar to that for current symptoms of asthma. Estimates were similar in all children and in those with complete covariate data (Table 3).

Compared to children with no or one healthy lifestyle factor, the multiple regression adjusted OR for current symptoms of rhinoconjunctivitis was 0.99 (95% CI 0.91-1.07) for two factors, 0.92 (95% CI 0.84-1.00) for three factors, and 0.86 (95% CI 0.78-0.95) for four or five factors. No significant risk reduction was observed for hay fever ever. . In addition, compared with children with no or one healthy lifestyle factor, a reduced risk of current symptoms of eczema was found among children with two factors (adjusted OR=0.89, 95% CI 0.81-0.98), three factors (adjusted OR=0.84, 95% CI 0.75-0.94), and four or five factors (adjusted OR=0.84, 95% CI 0.75-0.94). No association was found for eczema ever.

The odds ratio estimates were essentially the same after stratification by child's sex (Supplementary Table S3). When stratified by region of the world the decreased risk of current wheeze, current symptoms of rhinoconjunctivitis, and eczema associated with a higher HLI was primarily observed among children of Western Europe and Latin America (Supplementary Table S4). Stratified analyses by GNI showed that the reduced risk of current wheeze, current symptoms of rhinoconjunctivitis, and eczema in relation to higher HLI was observed among regions with upper-middle and high incomes (Supplementary Table S5).

When conducting meta-analyses in order to evaluate centre-specific effects, the results obtained were nearly identical to those obtained in the pooled analyses (Figures 1 and 2). A one-point increase in the HLI score was associated with a decreased risk of current wheeze (adjusted OR= 0.87, 95% CI 0.84-0.91), reported asthma ever (adjusted OR=0.89, 95% CI 0.86-0.92), current symptoms of rhinoconjunctivitis (adjusted

OR=0.96, 95% CI 0.92-1.01), and current symptoms of eczema (adjusted OR=0.95, 95% CI 0.91-0.99). However, significant heterogeneity was detected between centres.

Table 4 shows the PARFs estimated for the lowest-risk HLI group for each assessed health outcome. Overall the percentages of preventable cases of current symptoms of asthma, reported asthma ever, current symptoms of rhinoconjunctivitsis, and current symptoms of eczema attributable to adherence to a combination of 4-5 of these healthy lifestyle factors were 20%, 16%, 6% and 5%, respectively. Overall, stronger PAFRs were found among Western Europe and Latin American children.

Discussion

This large worldwide multicentre cross-sectional study found that in 6-7 years old children an index based on five potentially modifiable lifestyle factors (i.e. no parental smoking, child's healthy body mass index, adherence to a Mediterranean diet, physical activity, and non-sedentary behaviour) was inversely associated with risk of asthma, rhinoconjunctivitis, and eczema symptoms. The associations were stronger among children from Western Europe and Latin America, and from regions with upper-middle, and higher GNIs. If these associations were causal, 20% of current wheeze and 16% of reported asthma ever cases would have been prevented had all children adhered to four or all five healthy lifestyle factors.

In the development and promotion of policies for disease prevention, the importance of the joint impact of modifiable lifestyle factors on lifespan,[18], mortality,[19], and chronic diseases such as cancer,[20,21] cardiovascular disease,[22] and diabetes has been extensively investigated and recognized. In contrast, the combined effects of recommended lifestyle changes on respiratory and allergic diseases in childhood has been rarely studied and infrequently recognized. This is the only large study, to our knowledge, examining the combined effect of five modifiable lifestyle risk factors on asthma and allergic diseases in childhood, providing novel evidence relevant to public health strategies which have been developed mainly to prevent non-respiratory disease in adults.

Our findings add strong evidence to the only previously published study that investigated the association between childhood asthma and a combination of several adverse lifestyle factors.[12] This small case-control study conducted among 609 Puerto Rican children aged 6-14 years showed that the presence of three risk factors compared with none was associated with ten-to eleven-fold increased odds of asthma. Furthermore, our results for children are in agreement with a study of adults aged 18-44 years that assessed the combined effects of BMI, smoking, drinking, and solid fuel use on wheezing symptoms and asthma, and showed that in combination these were associated with double or triple the risk of asthma.[23]

When interpreting PARFs, it should be taken into account that these measures rely on the distribution of lifestyle factors among participants in the present study population. In this sense, lack of information from some countries may influence representativeness of some regions of the world. Furthermore, PARs assume that the exposures are causal and unbiased, but studies with observational design are not sufficiently able to prove this assumption. Nevertheless, this knowledge may still be useful for tailoring interventions for lifestyle modification at target population subgroups.

The strengths of this multicentre study include its power, size and multinational nature. The study participants comprised 37 centres from 19 countries with diverse lifestyle patterns and a wide range of disease prevalence. Results obtained from meta-analyses of associations analysed within each study centre were essentially the same than those obtained from the pooled analyses, with little attenuated adjustment for possible confounding variables, and clear dose–response relationship, which supports the consistency of present results.

Limitations of this study should also be considered. First, in order to construct the HLI, we dichotomized each lifestyle factor according to pre-defined cut-off points. Different

threshold values would have resulted in different risk estimates. The choice of cut-off points was mostly based on public health recommendations and was generalized rather than risk specific. The likely influence of the dichotomization of the variables in the index is underestimating the true effect of the observed associations. Measurement error in self-reported variables cannot be ruled out; however, such error would likely lead to a non-differential bias potentially leading to underestimating the true effects. We used a simplified diet quality index that may not sufficiently account for the complexity of diets. Second, reverse causation cannot be ruled out because of the cross-sectional design of the study (e.g. asthma could reduce vigorous physical exercise and increase sedentary behaviour; or allergic symptoms could modify some dietary patterns). Third, we relied on parental report for both the outcomes and the lifestyle factors; however, recognition of symptoms of asthma, rhinoconjunctivitis, and eczema in children was based on validated symptom-based written questionnaires.[13,24] Fourth, information on lifestyle factors was obtained retrospectively, which may be subject to underreporting, recall, and reporting bias, which could have either attenuated or accentuated the observed associations. Finally, selection bias is also a potential limitation. It is probable that parents who did not respond to the ISAAC questionnaire differed in terms of their family lifestyle from those who did respond, but we consider it less likely that the strength of the association between the HLI and asthma or allergic disease among children would be seriously affected by this type of selection bias.

In summary, these findings emphasise the potential importance of the combined impact of modifiable lifestyle factors as preventable influences on childhood asthma and related allergic conditions. Although causality cannot be established from a study with this design, our findings suggest that public health interventions which are commonly justified for prevention of cardiovascular disease and cancer are unlikely to jeopardise asthma prevention and may be required if the burden of common allergic diseases in childhood is to be reduced. Further strategies for asthma prevention in childhood scrutinized in randomised controlled trials should evaluate the impact of interventions on multiple modifiable lifestyle factors to provide sufficient evidence to lead to widespread implementation for public health primary prevention.

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Author's contributions

EM and LGM conceived the study. EM and DS conducted the statistical analyses. EM, DS and LGM prepared the first draft. All other authors provided data, reviewed results, and reviewed and contributed to the article.

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Disclosure

There are no potential or perceived conflicts of interest to disclose.

Table 1. Healthy Lifestyle Index, child and family characteristics, ISAAC Phase Three (n=70795).

Healthy Lifestyle Index components	
No parental smoking	40357 (57.0)
Child's healthy weight	52481 (74.1)
Child's adherence to Mediterranean diet	29084 (41.1)
Child's physical activity	43836 (61.9)
Child's no sedentary behavior	11691 (16.5)
Child's health outcomes	
Current wheeze, yes	7343 (10.5)
Missing data	808
Asthma ever, yes	6990 (10.1)
Missing data	1426
Current symptoms of rhino-conjunctivitis	6438 (10.9)
Missing data	11704
Hay fever ever, yes	7031 (10.5)
Missing data	3965
Current symptoms of eczema	5612 (8.5)
Missing data	4 648
Eczema ever, yes	12352 (18.6)
Missing data	4288
Region of the world	
Western Europe	21002 (29.6)
Northern and Eastern Europe	8478 (12.0)
Eastern Mediterranean	9474 (13.4)
Latin-America	19825 (28.0)
Asia-Pacific	8615 (12.2)
Oceania	3401 (4.8)
Gross national income	
Low income	1438 (2.0)
Low-middle income	11742 (16.6)
Upper-middle income	28383 (40.1)
High income	29232 (41.3)
Maternal education level	
Primary	13246 (20.6)
Secondary	28390 (44.1)
Terciary	22716 (35.3)
Missing data	6443
Sex of the child	
Male	35122 (49.6)
Female	35673 (50.4)
Child's age (years)	6.6 (0.5)
Ever breastfed	53496 (79.7)
Missing data	3645
Siblings, yes	54369 (83.6)
Missing data	5803
Pets at home, yes	23765 (35.9)
Missing data	4663
Paracetamol use for fever, yes	44464 (64.9)
Missing data	2315

Data are n (%) or mean (SD).

Table 2. Characteristics of study participants by Healthy Lifestyle Index score, ISAAC Phase Three.

		Healthy lifestyle index points				
	All	**0 or 1**	**2**	**3**	**4 or 5**	**p value**
Participants	70795	11789 (16.6)	23565 (33.3)	23504 (33.2)	11937 (16.9)	
Current wheeze	69987	1363 (11.7)	2643 (11.4)	2306 (9.9)	1031 (8.7)	<0.001
Asthma ever	69369	1199 (10.4)	2336 (10.1)	2319 (10.0)	1136 (9.7)	0.303
Current symptoms of rhinoconjunctivitis	59091	1072 (11.1)	2183 (11.2)	2150 (10.8)	1033 (10.3)	0.102
Hay fever ever	66830	1131 (10.2)	2377 (10.7)	2353 (10.6)	1170 (10.4)	0.542
Current symptoms of eczema	66147	976 (8.9)	1846 (8.4)	1863 (8.4)	927 (8.2)	0.200
Eczema ever	66507	1942 (17.7)	4035 (18.3)	4008 (18.1)	2367 (20.9)	<0.001
Region of the world	70795					
Western Europe		2916 (24.7)	6594 (28.0)	7104 (30.2)	4388 (36.8)	<0.001
Northern and Eastern Europe		1939 (16.5)	2958 (12.6)	2437 (10.4)	1144 (9.6)	
Eastern Mediterranean		1624 (13.8)	3409 (14.5)	3112 (13.2)	1329 (11.1)	
Latin-America		3320 (28.2)	6632 (28.1)	6895 (29.3)	2978 (24.9)	
Asia-Pacific		1668 (14.1)	3062 (13.0)	2609 (11.1)	1276 (10.7)	
Oceania		322 (2.7)	910 (3.9)	1347 (5.7)	822 (6.9)	
Gross national income per capita	70795					
Low income		57 (0.50)	353 (1.50)	630 (2.7)	398 (3.3)	<0.001
Low-middle income		2456 (20.8)	4580 (19.4)	3582 (15.2)	1124 (9.4)	
Upper-middle income		5144 (43.6)	9534 (40.5)	9318 (39.6)	4387 (36.8)	
High income		4132 (35.1)	9098 (38.6)	9974 (42.4)	6028 (50.5)	
Child's sex, male	70795	5672 (48.1)	11535 (48.9)	11912 (50.7)	6003 (50.3)	<0.001
Maternal education level	64352					
Primary		2806 (25.6)	4681 (21.8)	4077 (19.2)	1682 (15.8)	<0.001
Secondary		5077 (46.4)	9841 (45.8)	9286 (43.7)	4186 (39.3)	
Terciary		3055 (27.9)	6987 (32.5)	7889 (37.1)	4785 (44.9)	
Ever breastfed	67150	8411 (76.3)	17494 (78.7)	18075 (80.7)	9516 (82.8)	<0.001
Siblings, yes	64992	8781 (80.9)	17904 (82.8)	18300 (84.8)	9384 (85.8)	<0.001
Pets at home	66132	4419 (39.3)	8106 (36.5)	7630 (34.9)	3610 (33.2)	<0.001
Paracetamol use for fever	68480	7562 (66.6)	15054 (66.2)	14634 (64.3)	7214 (62.2)	<0.001

Data are n (%). P value derived from chi2 test.

Table 3. Associations* (odds ratio and 95% CI) between Healthy Lifestyle Index and symptoms of asthma, rhino-conjunctivitis, and eczema at 6–7 years of age, ISAAC Phase Three.

		Healthy Lifestyle Index points					
	N	**0-1**	**2**	**3**	**4-5**	**p trend**	**Per 1-point increase**
Current wheeze							
Unadjusted	69987	1	0.95 (0.89, 1.02)	0.79 (0.73, 0.85)	0.67 (0.62, 0.73)	<0.001	0.88 (0.86, 0.90)
Adjusted[1]	69987	1	0.95 (0.88, 1.02)	0.78 (0.73, 0.84)	0.67 (0.61, 0.73)	<0.001	0.88 (0.86, 0.90)
Adjusted[2]	61122	1	0.93 (0.86, 1.00)	0.76 (0.70, 0.82)	0.63 (0.58, 0.70)	<0.001	0.86 (0.84, 0.89)
Adjusted[3]	61122	1	0.93 (0.87, 1.01)	0.77 (0.71, 0.83)	0.66 (0.60, 0.72)	<0.001	0.87 (0.85, 0.89)
Asthma ever							
Unadjusted	69369	1	0.92 (0.85, 0.99)	0.83 (0.77, 0.90)	0.73 (0.67, 0.80)	<0.001	0.91 (0.89, 0.93)
Adjusted[1]	69369	1	0.91 (0.84, 0.98)	0.82 (0.76, 0.89)	0.72 (0.66, 0.79)	<0.001	0.91 (0.88, 0.93)
Adjusted[2]	55494	1	0.88 (0.81, 0.96)	0.77 (0.70, 0.84)	0.64 (0.58, 0.71)	<0.001	0.88 (0.85, 0.90)
Adjusted[4]	55494	1	0.89 (0.81, 0.97)	0.79 (0.72, 0.86)	0.67 (0.60, 0.74)	<0.001	0.89 (0.86, 0.92)
Current symptoms of rhinoconjunctivitis							
Unadjusted	59091	1	0.98 (0.91, 1.07)	0.91 (0.84, 0.99)	0.86 (0.79, 0.95)	<0.001	0.96 (0.93, 0.98)
Adjusted[1]	59091	1	0.98 (0.91, 1.06)	0.91 (0.84, 0.98)	0.86 (0.78, 0.94)	<0.001	0.95 (0.93, 0.98)
Adjusted[2]	53366	1	0.98 (0.90, 1.07)	0.90 (0.83, 0.98)	0.84 (0.76, 0.92)	<0.001	0.95 (0.92, 0.97)
Adjusted[5]	53366	1	0.99 (0.91, 1.07)	0.92 (0.84, 1.00)	0.86 (0.78, 0.95)	0.001	0.96 (0.93, 0.98)
Hay fever ever							
Unadjusted	66830	1	1.03 (0.95, 1.11)	1.00 (0.92, 1.08)	0.96 (0.87, 1.05)	0.189	0.98 (0.96, 1.01)
Adjusted[1]	66830	1	1.02 (0.95, 1.11)	0.99 (0.91, 1.07)	0.95 (0.87, 1.04)	0.140	0.98 (0.96, 1.01)
Adjusted[2]	53747	1	1.03 (0.95, 1.13)	0.99 (0.90, 1.08)	0.93 (0.83, 1.03)	0.060	0.97 (0.95, 1.00)
Adjusted[6]	53747	1	1.03 (0.94, 1.13)	0.99 (0.90, 1.08)	0.92 (0.83, 1.02)	0.049	0.97 (0.94, 1.00)
Current symptoms of eczema							
Unadjusted	66147	1	0.91 (0.84, 0.99)	0.89 (0.82, 0.96)	0.86 (0.78, 0.94)	0.002	0.96 (0.93, 0.99)
Adjusted[1]	66147	1	0.91 (0.84, 0.99)	0.89 (0.82, 0.97)	0.86 (0.78, 0.95)	0.003	0.96 (0.94, 0.99)
Adjusted[2]	52689	1	0.90 (0.82, 0.99)	0.87 (0.79, 0.96)	0.86 (0.77, 0.96)	0.005	0.96 (0.93, 0.99)
Adjusted[6]	52689	1	0.89 (0.81, 0.98)	0.86 (0.78, 0.95)	0.84 (0.75, 0.94)	0.002	0.96 (0.93, 0.99)
Eczema ever							
Unadjusted	66507	1	1.01 (0.95, 1.08)	0.99 (0.93, 1.06)	1.10 (1.02, 1.18)	0.039	1.03 (1.01, 1.05)
Adjusted[1]	66507	1	1.01 (0.95, 1.08)	0.99 (0.93, 1.06)	1.10 (1.02, 1.18)	0.041	1.03 (1.01, 1.05)

Adjusted[2]	58164	1	1.02 (0.95, 1.09)	1.02 (0.96, 1.10)	1.15 (1.07, 1.25)	<0.001	1.04 (1.02, 1.07)
Adjusted[7]	58164	1	0.98 (0.92, 1.05)	0.97 (0.90, 1.04)	1.05 (0.97, 1.13)	0.346	1.01 (0.99, 1.04)

*Mixed-effects logistic regression including a random intercept for centre.
[1]Adjusted for child's sex, gross national income per capita (GNI) and region of the world.
[2]Children with complete covariate data, adjusted for child's sex, GNI and region of the world
[3]Multivariate analysis (children with complete covariate data), adjusted for child's sex, gross national income, region of the world, breastfeeding, pets at home, and paracetamol use for fever in the first year.
[4]Multivariate analysis (children with complete covariate data), adjusted for child's sex, GNI, region of the world, maternal education, siblings, pets at home, and paracetamol use for fever in the first year.
[5]Multivariable analysis (children with complete covariate data), adjusted for child's sex, GNI, region of the world, pets at home, and paracetamol use for fever in the first year.
[6]Multivariable analysis (children with complete covariate data), adjusted for child's sex, GNI, region of the world, maternal education, breastfeeding, siblings, and paracetamol use for fever in the first year.
[7]Multivariable analysis (children with complete covariate data), adjusted for child's sex, GNI, region of the world, maternal education, breastfeeding, and paracetamol use for fever in the first year.

Table 4. Population attributable risk fractions* for 4 or 5 Healthy Lifestyle Index factors, ISAAC Phase Three.

	Current wheeze	Asthma ever	Current symptoms of rhinoconjunctivitis	Current symptoms of eczema
All regions	20.2 (12.8 to 27.6)	16.4 (10.2 to 22.6)	6.0 (-2.8 to 14.8)	4.8 (0.2 to 9.3)
Region of the world				
Western Europe	25.5 (18.5 to 32.6)	16.4 (7.4 to 25.3)	10.8 (2.3 to 19.3)	3.1 (-2.6 to 8.9)
Northern and Eastern Europe	10.5 (-7.5 to 28.6)	26.3 (6.8 to 45.7)	-20.2 (-33.5 to -6.9)	-7.0 (-20.1 to 6.1)
Eastern Mediterranean	8.3 (-25.9 to 42.6)	2.7 (-29.5 to 34.9)	-7.8 (-49.8 to 34.2)	-0.9 (-54.9 to 53.1)
Latin American	25.8 (4.0 to 47.5)	17.6 (0.3 to 35.0)	17.7 (-1.1 to 36.5)	11.8 (-0.2 to 23.8)
Asia-Pacific	16.6 (-1.1 to 34.4)	19.8 (-8.9 to 48.5)	11.6 (-2.7 to 25.9)	15.5 (-4.5 to 35.4)
Oceania	6.58 (-0.08 to 13.2)	10.2 (4.8 to 15.6)	-15.9 (-53.6 to 21.8)	2.8 (-4.5 to 10.1)

*Data represents the proportion (95% confidence intervals) of the cases attributable to not being in the lowest risk exposure group (i.e. 4 or 5 healthy lifestyle factors). Negative values indicate no benefit from HLI.

Figure legends

Figure 1. Associations[*] (odds ratio and 95% CI) between 1-point increase in Healthy Lifestyle Index (HLI) during childhood and current wheeze[1] (A), current symptoms of rhino-conjunctivitis[2] (B), and current symptoms of eczema[3] (C), ISAAC Phase Three.

[*]Centre-specific odds ratios and 95% confidence intervals from meta-analysis using random effects. For each centre, the mean HLI score is stated in brackets.
[1]Models adjusted for child's sex, breastfeeding and pets at home. Punta Arenas and Caracas centers not included because of incomplete data.
[2]Models adjusted for child's sex and pets at home. Poznan, Ciudad Victoria and Caracas centers not included because of incomplete data.
[3]Models adjusted for child's sex, maternal education level, breastfeeding and siblings. Punta Arenas, Caracas, Fukuoka, Singapore, and Al-Khod centers not included because of incomplete data.

Figure 2. Associations[*] (odds ratio and 95% CI) between 1-point increase in Healthy Lifestyle Index (HLI) during childhood and asthma ever[1] (A), hay fever ever[2] (B), and ever eczema[3] (C) in children aged 6-7 years, the ISAAC Phase Three.

[*]Centre-specific odds ratios and 95% confidence intervals from meta-analysis using random effects. For each centre, the mean HLI score is stated in brackets.
[1]Models adjusted for child's sex, maternal education level, siblings and pets at home. Singapore, Al-Khod and Caracas centers not included because of incomplete data.
[2]Models adjusted for child's sex, maternal education level, breastfeeding and siblings. Punta Arenas, Caracas, Singapore and Al-Khod centers not included because of incomplete data.
[3]Models adjusted for child's sex, maternal education level and breastfeeding. Punta Arenas, Caracas, Fukuoka and Al-Khod centers not included because of incomplete data.

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