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Effect of Breastfeeding on Asthma, Lung function, and Bronchial Hyperreactivity in ISAAC-Phase-Two

Gabriele Nagel[1], Gisela Büchele[1], Gudrun Weinmayr[1], Bengt Björkstén[2], Yu-zhi Chen [3], Hongyu Wang [4,5] Wenche Nystad[6], Yildiz Saraclar[7], Lennart Bråbäck[8], Jose Batlles-Garrido[9], Gloria Garcia-Hernandez [10], Stephan K. Weiland† [1], and the ISAAC Phase Two Study Group*

[1] Institute of Epidemiology, Ulm University, Germany
[2] Institute of Environmental Medicine, Karolinska Institutet Stockholm, Sweden
[3] Capital Institute of Pediatrics, Beijing, P. R. China
[4] Guangzhou Institute of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical College, Guangzhou, PR China
[5] Firestone Institute for Respiratory Health, St. Joseph's Healthcare, Hamilton; and Department of Medicine, McMaster University, Hamilton, Ontario, Canada.
[6] Norwegian Institute of Public Health, Division of Epidemiology, Tromso, Norway
[7] Dept. of Pediatric Allergy and Asthma, Hacettepe University, Ankara, Turkey
[8] Department of Public Health and Research, Sundsvall Hospital, Sweden
[9] Paediatric Dept, Torrecárdenas Hospital, Almería, Spain
[10] Paediatric Allergy and Pulmonology Unit, Doce de Octubre University Children's Hospital, Madrid, Spain
* listed at the end of the paper

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Corresponding author:
Dr. Gabriele Nagel
Institute of Epidemiology
Ulm University
Helmholtzstr.22
89081 Ulm
Germany

Phone: +49 731 50 31073
Fax: +49 731 50 31069
E-Mail: gabriele.nagel@uni-ulm.de

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Abbreviations:

ISAAC	International Study of Asthma and Allergies in Childhood
SPT	Skin prick test
GNI	Gross national income
BHR	bronchial hyperreactivity
ETS	Environmental tobacco smoke at present
FEV_1%	Percent of predicted forced expiratory volume in 1 sec.
IgA	Immunoglobulin A
IgE	Immunoglobulin E
PUFA	Polyunsaturated fatty acids
SEP	socio-economic position

Abstract

Background: We evaluated the association between breastfeeding and wheezing, lung function and atopy in the International Study of Asthma and Allergy in Childhood (ISAAC) Phase Two.

Methods: Cross-sectional studies were performed in 27 centres in 20 countries. Information on disease and exposure factors was collected by parental questionnaire. We used data from 54,000 randomly selected schoolchildren (eight-12 years, 31,759 with skin prick testing) and a stratified subsample (N=4,888) for testing correlation of breastfeeding with bronchial hyperreactivity and lung function. Random effect models for meta-analysis were applied to calculate combined odds ratios (OR).

Results: Any breastfeeding was associated with less wheeze both in affluent ($OR_{adj,}$ 0.87; 95% CI, 0.78-0.97) and non-affluent countries ($OR_{adj,}$ 0.80; 95% CI, 0.68-0.94). Further analyses revealed that this was true only for non-atopic wheeze in non-affluent countries (OR_{adj}, 0.69; 95%-CI: 0.53-0.90). Breastfeeding was not associated with atopic wheeze and objective measures of allergy in both affluent and non-affluent countries. In contrast, breastfeeding was associated with higher predicted FEV_1 only in affluent countries (mean ratio, 1.11; 95% CI, 1.02-1.20).

Conclusion: Breastfeeding is associated with protection against non-atopic wheeze, which becomes particularly evident in non-affluent countries. Overall, breastfeeding was not related to any measure of allergy. These findings may explain some of the controversy regarding breastfeeding, since the direction of the association with breastfeeding depends on the predominating wheeze phenotype (e.g. atopic, non-atopic).

Introduction

Human milk contains numerous components that provide the infant both with passive protection against infections and components that enhance the maturation of the immune system [1]. Various possible biological mechanisms by which breast milk (e.g. via secretory IgA, antigens, cytokines, chemokines, PUFA, polyamines) may influence atopic disease have been reported [2]. In developing countries breastfeeding reduces the incidence of infections, particularly gastrointestinal infections, while in affluent countries the effects are less apparent [3]. Despite numerous studies over the past 45 years addressing the possible protective effects of breastfeeding against the development of allergic disease this issue is still controversial [4;5]. Van Odijk et al. reviewed the literature on breastfeeding and risk of allergic disease from 1966 to 2001 and concluded that breastfeeding seems a protective factor for the development of atopic disease [6]. The inverse association was stronger in children with atopic heredity. However, the authors excluded many of the reviewed papers due to non-informative findings and did not clearly differentiate between allergic and non-allergic origin of clinical symptoms. Gdalevich et al. also reported in a meta-analysis of 12 studies an overall protective effect of breastfeeding on asthma, especially in children with hereditary risk for atopy [7].

In a recent review, Friedman and Zeiger tried to identify reasons for heterogeneous results for the relationship between breastfeeding and the development of allergies and asthma [4]. The results of previous studies were categorized according to neutral or allergy inducing effects of breastfeeding [8-10] and a protective effect of breastfeeding [11-14]. Some of the inconsistency in the published literature may be caused by incomplete control for potential confounding, differences in the investigated age group, and outcome definition, such as the focus on atopic dermatitis [10;14]. Most of the epidemiological studies included in the reviews were from affluent countries. However, the relationship of breastfeeding to wheezing may be different in less affluent populations with a higher burden of infectious disease and low prevalence of allergies.

Our purpose was to examine associations of breastfeeding practice with asthma among children aged eight to 12 years in a large international study using data from 20 countries. By applying highly standardized methodology and objective measurements we wanted to minimize variability to differences in the way data were collected. We also explored whether atopic status or sex modifies these associations.

Material and Methods

The rationale and methods of the International Study on Allergies and Asthma in Childhood (ISAAC) Phase Two have already been described in detail elsewhere [15]. In brief, random samples of at least 10 schools in a defined geographical area were chosen and children in classes where the majority of children were aged nine-11 years ($n \geq 1000$ per centre) were invited to participate. Overall, about 63,000 schoolchildren (76.4 % of those eligible) took part. Parental questionnaires identical to those used in ISAAC Phase I [16] were used to collect data on allergies and asthma. For the present analyses 54,439 children aged eight-12 years, from 27 centres in 20 countries were included, with a complete set of parental responses on breastfeeding.

Exposure assessment:

Data on breastfeeding were collected retrospectively by parental questionnaire by the questions: Was your child ever breastfed? (yes, no) and If yes, for how long? (< 6 months, 6-12 months, >1 year), Duration of breastfeeding was categorized never breastfed, < 6 months, and ≥ 6 months breastfed. Exclusiveness of breastfeeding was assessed by the question, If yes, for how long was your child breastfed without adding other foods or juices? (< 2 months, 2-4 months, 5-6 months, > 6 months). Time of exclusive breastfeeding was categorized as never breastfed, < 2 months, 2-4 months, and ≥ 4 months. As potential confounders were considered: sex, age of the child

(years), exposure to environmental tobacco smoke at present (ETS) (Does anybody, at present, smoke inside your child's home? yes, no), present bedroom sharing with other persons (yes, no) and maternal atopic disease (Has the child's mother ever had any of the following diseases: asthma, hay fever or eczema? yes, no).

The ISAAC Phase Two protocol allowed objective measurements to be performed either in the full sample or in stratified subsamples of children [15]. Most centres invited all children for skin prick testing, while blood samples were collected mostly in subsamples of children stratified according to wheezing status during the past year (approx. 100 wheezers and 100 non-wheezers per centre). The stratified subsampling was applied by most centres for lung function measurements and BHR testing. Approval of the local ethics committees was obtained by all centres [15].

As a difference was suspected in the strength of any association between breastfeeding and wheezing, asthma, and allergy in affluent and non-affluent countries, we classified the study centres into two broad categories on the basis of gross national income (GNI) per capita, converted into U.S. dollars, using the World Bank Atlas method [17]. All centres from countries which were classified by the World Bank as 'high income countries' were combined in one group called 'affluent countries'. The remaining centres were combined as 'non-affluent countries' (GNI < $9200 per year per capita).

Outcome:

The question "Has your child had wheezing or whistling in the chest in the past 12 months?" was used as the indicator for childhood asthma. In addition, the lifetime prevalence of asthma was investigated using the question "Has your child ever had asthma?". Skin prick tests (SPT) were performed on 31,759 children using six common aeroallergens: *D. pteronyssinus*, *D. farinae*, cat

hair, *Alternaria tenuis*, mixed tree and grass pollen (ALK, Hørsholm, Denmark). In addition, data of locally relevant allergens tested in 15 centres were included. For this analysis at least one positive reaction (wheal size ≥ 3mm after subtraction of the negative control) was defined as a positive SPT. Atopic wheeze was defined as wheeze during the past year and a positive skin prick test [18].

Spirometry was performed according to ATS criteria [19]. At least two spirograms were recorded, and the higher of two reproducible measurements (with less than 5% variation) of forced expiratory volume in one second (FEV_1) was recorded as baseline value. The predicted values of FEV_1 in percent (FEV_1%) as descriptor of lung function were calculated based on age, weight (except Albania and the United Kingdom) and height stratified for sex and centre by linear regression models. High FEV_1% indicates good lung function.

As described elsewhere in detail [15] bronchial hyperreactivity (BHR) was assessed using de Vilbiss nebuliser by further measurements of FEV1 after inhalation of nebulised hyperosmolar saline (4.5 %) for increasing time periods (0.5, 1, 2, 4, and 8 minutes) [20]. FEV1 was measured 1 min after the end of each inhalation period and the next challenge was performed after 3 min wash-out time. If the FEV1 fell 10-15 % below the baseline value, the previous exposure time was repeated. If after two repetitions the fall of FEV1 was still between 10% and 15%, the exposure time was also doubled. Bronchial challenge was stopped if either the FEV_1 had fallen by 15% or more or the total inhalation period of 15.5 min had been reached. In children with a baseline FEV_1 of <75% of predicted value, no bronchial challenge was performed and an inhaled bronchodilator was administered.

Statistical analysis:

For stratified subsamples, weighted prevalences and risk estimates were calculated [21]. Random effect models for meta-analysis were applied to calculate crude and adjusted odds ratios (OR) or

mean ratios (MR) for FEV_1% with 95% confidence intervals (CI) combined for affluent and non-affluent countries [22]. The following potential confounders were considered: sex, age of the child in order to control for age or sex differences, exposure to environmental tobacco smoke at present (ETS) to control for respiratory symptoms due to tobacco smoke, present bedroom sharing with other persons was used to control for family size and living conditions, and maternal atopic disease to control for increased risk of atopy and potential lifestyle modifications. Heterogeneity estimated from random effects meta-analysis was tested with the Wald-statistics ($P_{heterogeneity}$). In case of heterogeneity, fixed random effect models were calculated and a statistical test on differences of the study means based on the chi^2 distribution was performed ($P_{heterogeneity\text{-}fixed}$). Interaction was investigated by including a product term in the logistic regression equation.

Depending on prevalence and completeness of the variables the numbers of subjects and sometimes the number of centres/countries in the models differ if some subjects/centres did not contribute any information and, therefore, had to be excluded.

All calculations were performed stratified by centre and the combined estimates for affluent and non-affluent countries are shown. Further stratification by maternal atopic disease, sex, atopic and non-atopic wheeze was performed. The statistical software package SAS release 9.1 (SAS Institute, Cary, N.C.; USA) and SUDAAN 9.0 (Research Triangle Institute, N.C. USA) were used to analyze the data.

Results

Table 1 shows the basic characteristics of the study populations. The prevalence of any breastfeeding ranged between 26.4% in Hong Kong (China) to 100% in Pichincha (Ecuador). The proportion of children reporting wheeze during the past year ranged from 0.8 % in Pichincha (Ecuador) to 25.6 % in Uruguaiana (Brasil). The lifetime prevalence of asthma ranged between 2.7% in Tirana, Albania to 35.6% in Hawkes Bay in New Zealand. Among breastfed children

mothers with atopic disease and bedroom sharing were more prevalent than among non-breastfed children.

Table 2 shows the crude and adjusted associations between breastfeeding and wheeze during the past year. In the multivariate models, breastfeeding was inversely associated with wheeze during the past year, both in affluent countries ($OR_{adj,}$ 0.87; 95% CI, 0.78-0.97; $P_{heterogeneity}$ = 0.50) and in non-affluent countries ($OR_{adj,}$ 0.80; 95% CI, 0.68-0.94; $P_{heterogeneity}$ = 0.50). Though going in the expected direction no significant effect was found for the duration of breastfeeding in affluent countries, whereas in non-affluent countries breastfeeding for at least six months was associated with less wheeze (OR_{adj}, 0.74; 95% CI, 0.62-0.88; $P_{heterogeneity}$ = 0.25). In affluent countries, duration of exclusive breastfeeding tended to be inversely associated with wheeze, but reached statistical significance only for the categories two to four months. In non-affluent countries, however, exclusive breastfeeding for at least two months (OR_{adj}, 0.77; 95% CI, 0.63-0.94); $P_{heterogeneity}$ = 0.17) and more than four months (OR_{adj}, 0.74; 95% CI, 0.61-0.90); $P_{heterogeneity}$ = 0.47) was inversely associated with wheeze. In addition, any breastfeeding was related to reduced lifetime prevalence of asthma in affluent countries (OR_{adj}, 0.87; 95% CI, 0.78-0.97) and a similar trend non-affluent countries (OR_{adj}, 0.89; 95% CI, 0.71-1.11) (Table 3).

Breastfeeding showed no significant relation with atopic wheeze for neither affluent (OR_{adj}, 0.85; 95% CI, 0.67-1.08; $P_{heterogeneity}$ = 0.13) nor non-affluent countries non-affluent countries (OR_{adj}, 0.86; 95% CI, 0.55-1.35; $P_{heterogeneity}$ = 0.27)(Table 4). For non-atopic wheeze, the inverse association with breastfeeding was stronger in non-affluent (OR_{adj}, 0.69; 95% CI, 0.53-0.90; $P_{heterogeneity\text{-}fixed}$ = 0.98) than affluent countries (OR_{adj}, 0.87; 95% CI, 0.72-1.06; $P_{heterogeneity}$ = 0.48). Moreover, no associations were found between breastfeeding practice and positive SPT or elevated specific IgE levels, neither in affluent nor non-affluent countries (please see supplemental data).

The associations between any breastfeeding and wheeze was not affected by maternal atopy in affluent (OR_{adj}, 0.93; 95% CI, 0.79-1.10; $P_{heterogeneity}$ = 0.50 and OR_{adj}, 0.82; 95% CI, 0.71-0.95; $P_{heterogeneity}$ = 0.50, respectively), nor in non-affluent countries (OR_{adj}, 0.78; 95% CI, 0.48-1.27; $P_{heterogeneity}$ = 0.23 and OR_{adj}, 0.80; 95% CI, 0.66-0.96; $P_{heterogeneity}$ = 0.50, respectively). In affluent countries, the inverse association between breastfeeding and wheeze was more pronounced for girls (OR_{adj}, 0.78; 95% CI, 0.64-0.95; $P_{heterogeneity\text{-}fixed}$ = 0.69) than for boys ($OR_{adj,}$ 0.95; 95% CI, 0.83-1.10; $P_{heterogeneity\text{-}fixed}$ = 0.91), while the opposite was true in non-affluent countries (OR_{adj}, 0.73; 95% CI, 0.56-0.95; $P_{heterogeneity}$ = 0.33 vs. $OR_{adj,}$ 0.82; 95% CI, 0.64-1.05; $P_{heterogeneity}$ = 0.49 in girls). When all countries were combined, there was no significant effect modification by gender (p-value 0.455).

Breastfeeding tended to be inversely related to BHR in affluent and non-affluent countries, but none of the associations were statistically significant (OR_{adj}, 0.92; 95% CI, 0.75-1.12; $P_{heterogeneity}$ = 0.50 and OR_{adj}, 0.66; 95% CI, 0.37-1.20; $P_{heterogeneity}$ = 0.50, respectively) (Figure 1a). Breastfed children tended to have better lung function as determined by FEV_1% in affluent countries however (means ratio, 1.11; 95% CI, 1.02-1.20; $P_{heterogeneity}$ = 0.42), but not in non-affluent countries (means ratio, 0.89; 95% CI, 0.68-1.17; $P_{heterogeneity}$ = 0.30) (Figure 1b). This interaction with affluence was not significant (p-value 0.564).

Discussion

In line with some of the previous literature [6;7;11-14;23], but in contrast to some other reports [9;10;24], we observed an inverse association between breastfeeding and wheezing. This was particularly true in non-affluent countries. Breastfeeding for at least six months and more than two months of exclusive breastfeeding were associated with less wheeze in non-affluent countries, while there was no consistent evidence that the duration of breastfeeding was

associated with asthma in affluent countries, Furthermore, the protective effect of breastfeeding against childhood wheezing was limited to non-atopic wheeze, while IgE associated wheeze and atopic sensitization were not affected. Our findings could explain at least some of the current controversy regarding the relationship between breastfeeding and wheezing later in childhood. While overall there was a protective effect of breastfeeding against wheeze, in reality it was evident only for non-atopic wheeze in non-affluent countries. In affluent countries, in which wheezing is more commonly associated with allergy, breastfeeding showed no relation with wheeze, despite the large sample size. Depending on the predominant wheeze phenotype in populations, an association between breastfeeding and wheeze may appear.

Other authors found breastfeeding for at least four months to be associated with less wheeze, as compared to children who were never breastfed [12;25]. Results from a recent randomized intervention study on prolonged and exclusive breastfeeding revealed no protective effect on symptoms of allergies, asthma, and SPT positivity among 6.5 year old children in Belarus [5]. Our results indicate no major reduction in the prevalence of prolonged breastfeeding or exclusive breastfeeding for more than four months in affluent countries in contrast to non-affluent countries where the prevalence of wheeze was lower. There is evidence for age-dependent prevalence and phenotype patterns in children [26]. Different prevalence of the wheeze phenotypes non-atopic and atopic (IgE associated) wheeze, may explain the differential associations by affluence status. We found favourable FEV1 % values among breastfed children in affluent countries. Differences in the prevalence of non-atopic and atopic (IgE associated) wheeze, may explain the differential associations by affluence status.

The reviews by van Odijk [6] and by Gdalevich [7] et al reported an overall protective effect of breastfeeding on asthma prevalence, especially in children with a family history of atopy. Our study, comprising 54,000 children in 20 countries could not confirm this, as we observed a

slightly stronger inverse association with breastfeeding in children without maternal atopy in affluent, but not in non-affluent countries.

There is more or less consensus that breastfeeding offers protection against infections and thus also against wheezing in infancy [1;2]. Prospective studies have revealed that recurrent respiratory infections in infancy may indicate a predisposition for wheezing and BHR [27;28]. Wright et al. found that breastfeeding has a protective effect early in life, whereas it may be associated with increased risk of asthma in adolescents, especially in atopic children of asthmatic mothers [24]. Results of a cohort study from Australia suggest that the association between breastfeeding and asthma may depend on the age of manifestation, conferring protection up to the age of seven, but associated with an increased risk for asthma after this age [29]. As asthma is usually not associated with allergy during the first years of life in contrast to the situation in older children, these findings would support our observations that breastfeeding was associated with less wheezing but not less sensitization and particularly so in non-affluent countries.

Human milk contains various bioactive and immunomodulatory constituents such as antibodies, oligosaccharides, cells and cytokines [3;30]. The composition of breast milk differs between allergic and non-allergic mothers and it has been suggested that this could explain some of the controversy regarding the possible allergy-preventive effects of breastfeeding [30]. In support of this, a Swedish study has shown that the composition of PUFA in breast milk not only differed between allergic and non-allergic mothers but also affected the development of allergic disease, at least up to the age of two years [31]. Such differences could also explain the observations by Wright et al. [24] that children who were breastfed by allergic as compared to non-allergic mothers had a higher incidence of allergies.

Breastfeeding may influence the immunologic and respiratory function during early childhood [2]. A long-term immunological effect of breastfeeding is also supported by the observations that the thymus size was larger in breastfed than in non-breastfed infants [32]. The effect of breastfeeding may depend on the age of onset of asthma, with stronger protective effect for early onset of asthma [12;29]. In our data, breastfeeding had favourable effects on wheeze during the past year and particularly on non-atopic wheeze in non-affluent countries, suggesting an infection linked immune modulation. It is also possible that the composition of breast milk was affected by socio-economic factors, maternal diet, pollutants, and the nature of microbiological exposure [3;31].

After stratification by sex the protective effect of breastfeeding remained stronger in girls than in boys in affluent countries, whereas the opposite was found in non-affluent countries. This observation is in agreement with another report concerning neonatal respiratory infections [33]. Other environmental factors such as diet, infections, or hormones may further contribute to sex-specific patterns of associations between breastfeeding, asthma and allergies [34]. In our study, however, breastfeeding was unrelated to either of the primary risks/co-factors of asthma (atopy and BHR), which supports the lack of relation with atopic wheeze. In affluent societies, the protective effect of breastfeeding against non-atopic wheeze which is probably mainly due to infections is marginal while it is a major factor in developing countries. This observation is corroborated by the findings that substantially higher fractions of current wheeze are attributable to SPT reactivity in affluent as compared to non-affluent countries [18]. In addition, lower prevalence rates of SPT reactivity were found in less affluent countries [18].

Some limitations have to be kept in mind. Since we performed a cross- sectional study and the data on breastfeeding history were collected retrospectively recall biases are likely, which may have affected more the duration and exclusiveness of breastfeeding than breastfeeding per se. In

addition, no detailed information on early infections was available. Parental socioeconomic conditions varied within the centres and may have confounded our observations. However, the calculation of models adjusting for years of maternal or paternal education as indicator for socio-economic position (SEP) for the centres with available information did not substantially affect the associations. We performed multiple comparisons which need to be considered for interpretation of the results. The application of well established and standardized questionnaires and methodology in the centres would support the consistency of the findings across centres in affluent and non-affluent countries. In addition, objective markers of allergy sensitization and lung function were applied. Our study adds results from non-affluent countries.

Our results provide evidence that breastfeeding is protective against non-allergic wheeze among children aged eight-12 years in non-affluent societies. However, there was no protective relation of breastfeeding with measures of allergy. The findings may explain some of the controversy regarding the long term effects of breastfeeding on respiratory symptoms, as atopic (IgE-associated) and non-atopic wheeze were not clearly separated in most previous studies. Depending on which type of wheeze phenotype predominates (e.g. atopic or non-atopic) at a particular age breastfeeding may exert a protective or marginal effect on wheeze. Further research needs to consider differential pathways according to atopic and non-atopic wheeze phenotype.

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* The ISAAC Phase Two Study Group consists of:

ISAAC II Steering Group. B. Björkstén (Stockholm, Sweden), B. Brunekreef (Utrecht, Netherlands), W. Cookson (Oxford, U.K.), E. von Mutius (München, Germany), D. Strachan (London, U.K.), S.K. Weiland †, ISAAC II Coordinator (Ulm, Germany).

ISAAC II Coordinating and Data Centre (Institute of Epidemiology, Ulm University, Germany): G Büchele, A. Kleiner, G. Nagel, P. Rzehak, G. Weinmayr, SK. Weiland † (Director).

List of Principal Investigators and Scientific Team. *Tirana, Albania*: A. Priftanji, A. Shkurti, J. Simenati, E. Grabocka, K. Shyti, S. Agolli, A. Gurakuqi. *Uruguaiana, Brazil*: ,R.T. Stein, M. Urrutia de Pereira, M.H. Jones, P.M. Pitrez. *Pichincha province, Ecuador*: P.J Cooper, M. Chico. *Bejing, China*: Y.Z. Chen. *Guangzhou, China:* N.S Zhong. *HongKong, China:* C. Lei (National Coordinator), G. Wong. *Tallinn, Estland:* M.-A. Riikjärv, T. Annus. *Créteil, France:* I. Annesi-Maesano. *Tblisi, Georgia:* M. Gotua, M. Rukhadze, T. Abramidze, I. Kvachadze, L. Karsanidze, M. Kiladze, N. Dolidze. *Dresden, Germany*: W. Leupold, U. Keil, E von Mutius, S. Weiland †. *Munich, Germany*: E. von Mutius, U. Keil, S. Weiland † *Kintampo, Ghana*: P Arthur (deceased), EAddo-Yobo. *Athens, Greece:* C.Gratziou (National Coordinator), C.Priftis, A.Papadopoulou, C.Katsardis. *Thessaloniki, Greece:* J.Tsanakas, E.Hatziagorou, F. Kirvassilis. *Reykjavik, Iceland*: M. Clausen. *Mumbai, India*: J.R. Shah, R.S. Mathur, R.P. Khubchandani, S. Mantri. *Rome, Italy*: F. Forastiere, R. Di Domenicantonio, M. De Sario, S. Sammarro, R. Pistelli, M.G. Serra, G. Corbo, C.A. Perucci. *Riga, Latvia:* V. Svabe, D. Sebre, G. Casno, I. Novikova, L. Bagrade. *Utrecht, Netherlands*: B. Brunekreef, D. Schram, G Doekes, P.H.N. Jansen-van Vliet, N.A.H. Janssen, F.J.H. Aarts, G. de Meer. *Hawkes Bay, New Zealand*: J. Crane, K. Wickens, D. Barry. *Tromsø, Norway*: W. Nystad, R. Bolle, E. Lund. *Ramallah, West Bank*: N. El-Sharif, B. Nemery,

F. Barghuthy, S. Abu Huij, M. Qlebo. *Almeria, Spain*: J. Batlles Garrido, T. Rubi Ruiz, A. Bonillo Perales,Y. Gonzalez Jiménez, J. Aguirre Rodriguez, J. Momblan de Cabo, A. Losilla Maldonado, M. Daza Torres. *Cartagena, Spain*: L. Garcia-Marcos (National Coordinator), A. Martinez Torres, J.J Guillén Pérez, A. Piñana López, S. Castejon Robles. *Madrid, Spain*: G. Garcia Hernandez, A. Martinez Gimeno, A.L. Moro Rodríguez, C. Luna Paredes, I. Gonzalez Gil. *Valencia, Spain:* M.M. Morales Suarez-Varela, A. Llopis González, A. Escribano Montaner, M. Tallon Guerola. *Linköping, Sweden:* L. Bråbäck (National Coordinator), M. Kjellman, L. Nilsson, X-M. Mai. *Östersund, Sweden:* L. Bråbäck, A. Sandin. *Ankara, Turkey*: Y. Saraçlar, S. Kuyucu, A. Tuncer, C. Saçkesen, V. Sumbuloğlu, P. Geyik, C. Kocabaş. *West Sussex, U.K.*: D Strachan, B Kaur.

ISAAC Steering Committee. N. Aït-Khaled (Paris, France), H.R. Anderson (London, U.K.), I. Asher (Auckland, New Zealand), R. Beasley (Wellington, New Zealand), B. Björkstén (Stockholm, Sweden), B. Brunekreef (Utrecht, Netherlands), W. Cookson (Oxford, U.K.), J. Crane (Wellington, New Zealand), P. Ellwood (Auckland, New Zealand), S. Foliaki (Nuku'alofa, Kingdom of Tonga), L. García-Marcos (Murcia, Spain), U. Keil (Münster, Germany), C. Lai (Hong Kong, SAR China), J. Mallol (Santiago, Chile). E. Mitchell (Auckland, New Zealand), S. Montefort (Naxxar, Malta), E. von Mutius (Munich, Germany), J. Odhiambo (Nairobi, Kenia), N. Pearce (Wellington, New Zealand), C. Robertson (Parkville, Australia), A. Stewart (Auckland, New Zealand), D.P. Strachan (London, U.K.), S.K. Weiland† (Ulm, Germany), H. Williams (Nottingham, U.K), G. Wong (Hong Kong, SAR China).

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Table 1: Sample characteristics and prevalence of wheeze and lifetime asthma in children aged eight-12 years in the ISAAC-Two centres

	Centre	Study sample	Prevalence wheeze past 12 months	Lifetime Prevalence of asthma	Breastfed Yes	Breast feeding >6 months	Exclusive Breastfeeding > 4 months	Age/years	Shared bedroom present	Maternal atopy	ETS present	Positive skin prick tests	IgE>0.35 kU/L	BHR reactivity	FEV1 predicted value (%)
Affluent countries [1]		N	%	%	N (%)	%	%	%	Mean (SD)	%	%	%	%	%	%
China	Hong Kong	3011	5.5	7.9	792 (26.4)	13.5	9.9	10.2 (0,5)	89.3	6.5	33.6	45.3‡	-		-
Germany	Dresden	3032	7.9	3.6	2500 (85.6)	26.6	12.2	9.7 (0.6)	50.5	26.9	32.7	25.7	37.0	10.5	101.6
	Munich	3301	8.3	4.8	2445 (79.5)	34.6	21.4	9.5 (0.6)	67.8	27.0	42.2	22.3	37.4	17.9	102.1
Greece	Athens	985	5.6	7.5	769 (78.7)	23.0	16.4	9.8 (0.4)	65.0	28.1	58.5	14.4‡	33.6*	13.6*	99.6*
	Thessaloniki	1018	8.4	11.6	747 (74.6)	20.0	12.2	9.7 (0.5)	72.1	23.9	55.7	26.8‡	32.3*	39.9*	101.3*
Iceland	Reykjavik	937	9.2	22.9	884 (96.5)	62.5	37.1	10.4 (0.5)**	21.3	35.0	30.0	23.5	-	-	-
Italy	Rome	1354	7.9	14.3	1022 (76.4)	32.8	30.3	10.0 (0.4)	63.2	27.9	49.1	28.9‡	43.1*	33.1*	100.2*
Netherlands	Utrecht	3541	8.7	7.8	2343 (66.7)	-	-	9.5 (1.2)	85.4	52.6	56.3	30.9‡	30.1	19.8	98.9
New Zealand	Hawkes Bay	1320	21.9	35.6	1138 (86.9)	55.8	33.0	10.9 (0.5)	35.6	49.1	27.9	34.5	-	23.9	95.0
Norway	Tromso	3669	14.0	10.3	3457 (94.9)	66.6	35.8	9.9 (0.7)	25.7	38.4	37.6	32.7	36.5*	42.7*	105.0*
Spain	Almeria	1126	15.5	14.6	799 (71.7)	20.4	18.1	10.2 (0.6)	100.0	29.1	60.4	43.0‡	48.5*	29.7*	105.6*
	Cartagena	1129	11.9	10.9	1004 (71.7)	22.8	18.3	9.5 (0.6)	41.5	28.2	58.0	23.8‡	40.4*	23.7*	90.4*
	Madrid	981	11.6	11.4	760 (77.9)	27.7	25.5	9.4 (0.7)	52.4	29.6	57.0	34.5‡	40.1*	8.9*	102.1*
	Valencia	1362	9.1	9.8	905 (67.1)	18.8	14.7	9.5 (0.5)	31.4	28.0	56.3	14.3‡	32.9*	24.4*	94.2*
United Kingdom	West Sussex	1056	16.2	20.3	628 (77.0)	40.0	11.7	10.4 (1.3)	25.3	34.5	29.0	17.5	41.8*	41.4*	96.1*
Non-affluent countries [2]															
Albania	Tirana	1052	4.4	2.7	915 (92.4)	69.4	47.6	9.9 (0.6)	73.1	9.0	47.7	14.7 ‡	19.5*	2.1*	99.2*
Brazil	Uruguaiana	1971	25.6	12.7	1694 (86.5)	54.0	35.3	9.6 (0.8)	80.8	20.6	51.5	13.3	-		-

China	Beijing	4214	3.7	6.4	2013(48.7)	30.8	15.1	10.4 (0.5)	89.8	7.4	62.3	23.9‡	-	-
	Guangzhou	3510	3.2	4.4	2638 (75.2)	56.8	30.2	9.8 (0,5)	79.8	4.8	54.8	32.0‡	-	-
Ecuador	Pichincha	894	0.8	-	894 (100)	91.7	-	10.0 (1.6)	90.2	5.8	47.1	19.7‡	-	-
Georgia	Tbilisi	1012	9.2	3.2	718 (72.7)	31.1	22.3	10.4 (0.6)	82.2	27.5	58.7	33.0‡	30.6*	29.5*	90.1*
Ghana	Kintampo	1354	6.4	15.8	1325 (97.9)	99.4	72.7	10.3 (0.6)	100	34.6	22.3	1.7	-	30.4	94.5
India	Mumbai	1658	6.1	4.8	1607 (97.6)	87.9	84.9	9.9 (0.8)	87.5	1.9	19.8	6.4	39.7*	47.8*	83.1*
Latvia	Riga	908	6.9	3.2	813 (90.2)	38.0	14.3	10.7 (0.6)	58.1	10.5	39.2	19.3	-	13.5	107.9
West Bank	Ramallah	2304	8.8	9.4	268 (91.7)*	74.8	52.6	9.8 (0.8)	91.4*	19.2*	64.2	10.3*	-	-	80.1
Turkey	Ankara	2976	10.9	n.d.	2758 (94.2)	64.8	51.2	9.1 (0.5)	70.8	34.9	63.1	24.6‡	-	22.4	105.7*

[1] GNI ≥ $9200 per capita, in 16 centres with 29,222 children
[2] GNI < $9200 per capita in 11 centres with 21,851 children

* Stratified subsamples
** Average age of 10.4 years was used due to strict data protection rules ‡ local allergens were tested in addition to standard set of six common allergens

Table 2: Association between breastfeeding practice and wheeze past year by affluence[#]

	Affluent countries[1]				Non-Affluent countries[2]			
	Crude		Adjusted*		Crude		Adjusted*	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Breastfeeding[3]								
n/N	2807/28058				1514/18581			
No	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
Yes	0.89	0.81-0.99	0.87	0.78-0.97	0.81	0.70-0.95	0.80	0.68-0.94
Duration of breastfeeding[4]								
n/N	2445/23716				1423/17841			
Not breastfed	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
<6 months	0.91	0.8-1.03	0.88	0.78 – 1.00	0.94	0.76 – 1.16	0.95	0.73-1.23
≥6 months	0.89	0.77-1.04	0.88	0.76 -1.03	0.75	0.63 – 0.89	0.74	0.62-0.88
Exclusive breastfeeding [5]								
n/N	2352/22525				1392/16223			
Not breastfed	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
2 months	0.94	0.80- 1.09	0.91	0.78-1.06	1.00	0.75-1.33	0.98	0.70-1.37

2-4 months	0.88	0.78 - 1.01	0.85	0.74-0.98	0.80	0.67 – 0.97	0.77	0.63-0.94
≥4 months	0.93	0.80 - 1.08	0.92	0.78-1.10	0.74	0.61- 0.89	0.74	0.61-0.90

[1] GNI ≥ $9200 per capita, in 16 centres with 29,222 children
[2] GNI < $9200 per capita in 11 centres with 21,851 children
[3] Without Pichincha (Ecuador)
[4] Without Utrecht (The Netherlands), and Kintampo (Ghana)
[5] Without Utrecht (The Netherlands), Kintampo (Ghana), and Pichincha (Ecuador)

Random effect models for meta-analysis
* Adjusted for sex, age, maternal atopic disease, ETS, and present bedroom sharing

Table 3: Associations between breastfeeding practice and lifetime prevalence of asthma[§] by affluence[#]

	Affluent countries [1]				Non-Affluent countries [2]			
	Crude		Adjusted*		Crude		Adjusted*	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Breastfeeding[3]								
n/N	2723/27550				1192/15593			
No	1	(ref.)		(ref.)	1	(ref.)	1	(ref.)
Yes	0.87	0.78-0.96	0.87	0.78-0.97	0.93	0.79-1.10	0.89	0.71-1.11
Duration of breastfeeding[4]								
n/N	2369/23250				1100/14047			
Not breastfed	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
<6 months	0.89	0.77-1.03	0.90	0.77 -1.04	1.12	0.90 – 1,39	1.09	0.86-1.39
≥6 months	0.84	0.72-0.97	0.87	0.75-1.00	0.85	0,71 – 1.03	0.83	0.67-1.03
Exclusive breastfeeding [5]								
n/N	2279/22091				1154/14514			
Not breastfed	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
2 months	0.91	0.79- 1.05	0.92	0.79-1.06	1.20	0.96-1.50	1.14	0.91-1.44

2-4 months	0.87	0.76- 0.99	0.88	0.77-1.01	0.92	0.68-1.23	0.86	0.63-1.17
≥4 months	0.87	0.75 - 1.02	0.91	0.78-1.07	0.74	0.59- 0.92	0.75	0.60- 0.94

[1] GNI ≥ $9200 per capita, in 16 centres with 29,222 children
[2] GNI < $9200 per capita in 11 centres with 21,851 children
[3] Without Pichincha (Ecuador)
[4] Without Utrecht (The Netherlands), Pichincha (Ecuador), Ankara (Turkey), and Kintampo (Ghana)
[5] Without Utrecht (The Netherlands), Pichincha (Ecuador), and Ankara (Turkey)

§ Defined by patrental report on asthma diagnosis
# Random effect models for meta-analysis
* Adjusted for sex, age, maternal atopic disease, ETS, and present bedroom sharing

Table 4: Association of breastfeeding practice with atopic and non-atopic wheeze[§] during past year by affluence[#]

	Affluent countries [1]				Non-affluent countries [2]			
	Crude		Adjusted*		Crude		Adjusted*	
Atopic wheeze	OR	95% CI	OR	95%CI			OR	95%CI
Breastfeeding[3]								
n/N	1676 /15610				907/8503			
No	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
Yes	0.87	0.68-1.11	0.85	0.67-1.08	0.84	0.57-1.25	0.85	0.54-1.34
Duration of breastfeeding [4]								
n/N	1514/ 13646				805 / 6882			
Not breastfed	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
<6 months	0.90	0.70-1.16	0.89	0.70-1.13	1.02	0.81-1.30	1.01	0.64-1.57
>=6 months	0.88	0.68-1.13	0.87	0.68-1.11	0.78	0.50-1.23	0.78	0.46-1.33
Exclusive breastfeeding [5]								
n/N	1532/ 13894				906 / 7952			
Not breastfed	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
2 months	0.93	0.66-1.31	0.92	0.65-1.29	1.01	0.94-1.09	1.08	0.74-1.58

2-4 months	0.88	0.71-1.08	0.85	0.69-1.05	1.00	0.94-1.06	0.92	0.68-1.24
>=4 months	0.90	0.68-1.21	0.92	0.69-1.24	0.66	0.44-0.98	0.68	0.44-1.05
Non-atopic wheeze			OR	95%CI			OR	95%CI
Breastfeeding [6]								
n/N	1676/ 15610				1004/ 9741			
No	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
Yes	0.88	0.73-1.05	0.87	0.72-1.06	0.71	0.55-0.92	0.69	0.53-0.90
Duration of breastfeeding								
n/N	1606/ 14580				1027/ 10723			
Not breastfed	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
<6 months	0.87	0.71-1.07	0.88	0.69-1.11	0.32	0.03-3.23	0.82	0.61-1.11
>=6 months	0.98	0.78-1.22	1.00	0.79-1.26	0.68	0.52-0.89	0.64	0.49-0.85
Exclusive breastfeeding[7]								
n/N	1429/ 12776				818/ 7173			
Not breastfed	1	(ref.)	1	(ref.)	1	(ref.)	1	(ref.)
2 months	0.92	0.72-1.17	0.93	0.71-1.21	0.77	0.56-1.06	0.72	0.51-1.02
2-4 months	0.91	0.74-1.13	0.90	0.72-1.13	0.71	0.53-0.95	0.68	0.50-0.90

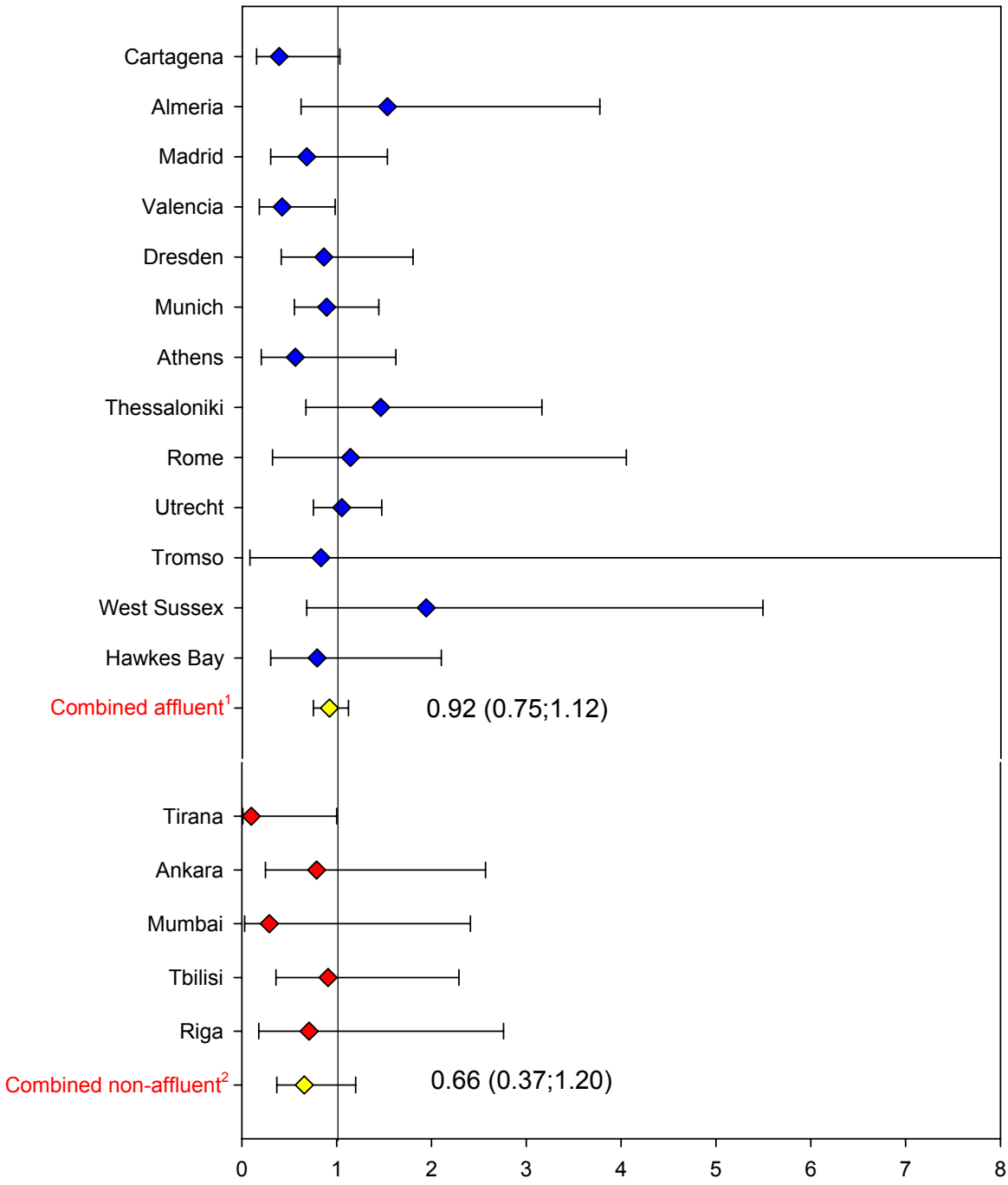
>=4 months	0.96	0.72-1.27	0.98	0.73-1.31	0.73	0.55-0.98	0.75	0.55-1.00

§ Defined as wheeze with (atopic) and without SPT positvity (non-atopic)
# Random effect models for meta-analysis
* Adjusted for sex, age, maternal atopic disease, ETS, and present bedroom sharing

1 GNI ≥ $9200 per capita, in 16 centres with 29,222 children
2 GNI < $9200 per capita in 11 centres with 21,851 children

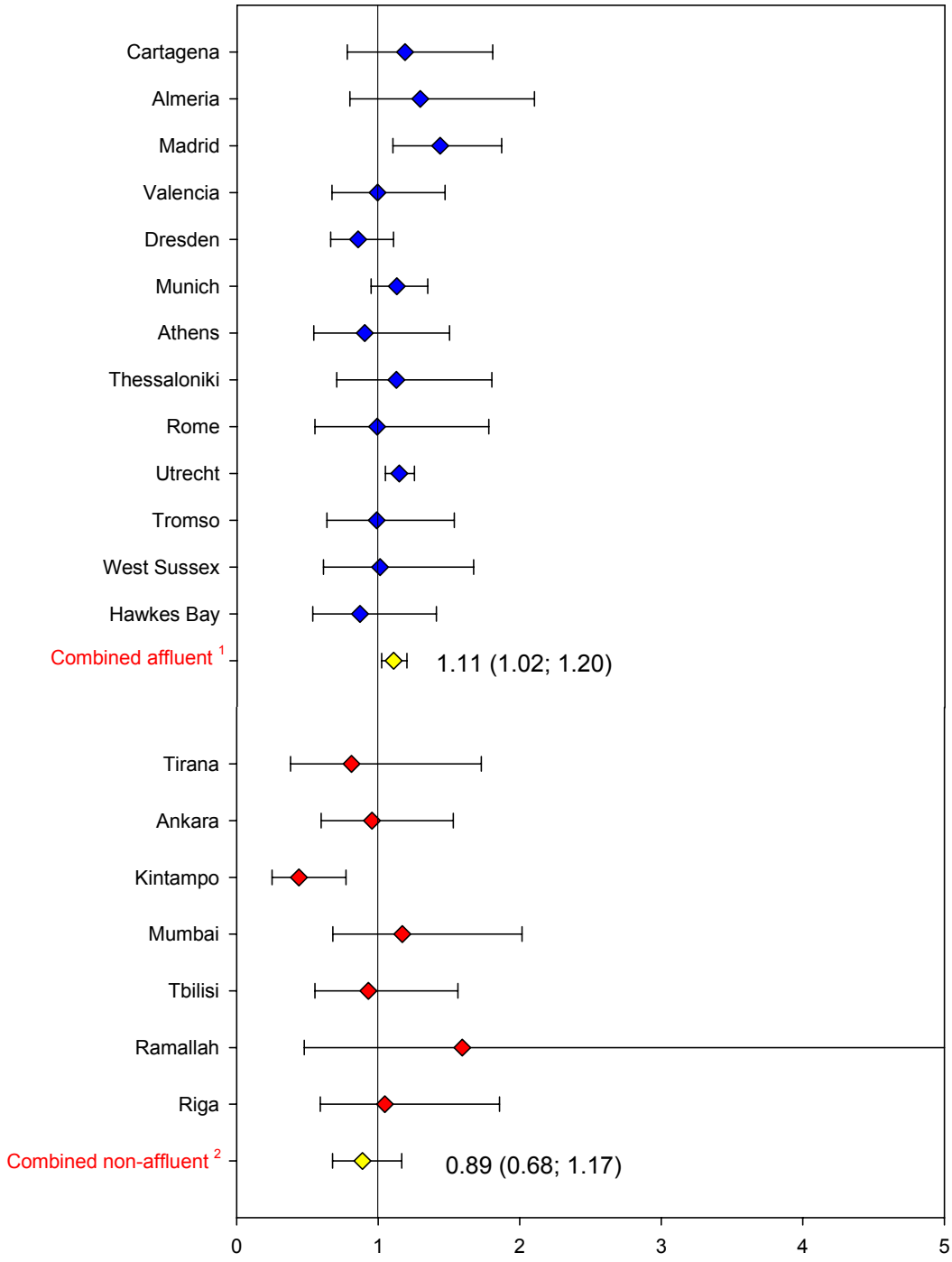
3 Without Pichincha (Ecuador)
4 Without Utrecht (The Netherlands), Pichincha (Ecuador), Kintampo (Ghana), and Ramallah (West Bank)
5 Without Utrecht (The Netherlands) and Pichincha (Ecuador)
6 Without Reykjavik (Iceland) and Pichincha (Ecuador)
7 Without Reykjavik (Iceland), Utrecht (The Netherlands), Pichincha (Ecuador), and Kintampo (Ghana),

Figures 1a: Associations between breastfeeding and Bronchial hyperreactivity * (Odds ratio and 95% CI) #



1 GNI ≥ $9200 per capita, in 13 centres with 4,028 children
2 GNI < $9200 per capita in 5 centres with 860 children
Random effect models for meta-analysis
* Adjusted for sex, age, maternal atopic disease, ETS, present bedroom sharing

Figures 1b: Associations between breastfeeding and predicted FEV_1 * (means odds ratio and 95% CI) #



1 GNI ≥ $9200 per capita, in 13 centres with 6348 children

2 GNI < $9200 per capita in 7 centres with 1376 children

Random effect models for meta-analysis

* Adjusted for sex, age, maternal atopic disease, ETS, present bedroom sharing