Prevalence, severity and risk factors of asthma, rhinitis and eczema symptoms in school-aged children from Oropeza Province – Bolivia

Solís Soto, María Teresa

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submitted by

Solís Soto, María Teresa

aus (Geburtsort)
born in (place of birth)

Bolivia

am (Tag an dem die Dissertation abgeschlossen wurde)
submitted on (day of finalization of the thesis)

04.29.2013

Supervisors LMU:

Habilitated Supervisor	Prof. Dr. Nowak, Dennis
Direct Supervisor	Prof. Dr. Radon, Katja
3rd LMU Supervisor	PD Dr. Rainald Fischer
4th LMU Supervisor	Dr. Eva Rehfuess

Supervisor External:

Local Supervisor	Dr. Patiño Michel, Armando

Reviewing Experts:

1st Reviewer	Prof. Dr. Nowak, Dennis
2nd Reviewer	Prof. Dr. Radon, Katja

Dean: Prof. Dr. Dr. h. c. M. Reiser, FACR, FRCR

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Affidavit

Solís Soto, María Teresa

Surname, first name

354, Urriolagoitia Street

Street

0000, Sucre

Zip code, town

Bolivia

Country

I hereby declare, that the submitted thesis entitled

Prevalence, severity and risk factors of asthma, rhinitis and

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Place, Date

Signature PhD Student

PhD Program International Health

CIHLMU Center for International Health

Ludwig-Maximilians-Universität, Munich

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iii. ABBREVIATIONS

ISAAC: International Study of Asthma and Allergies in Childhood

GINA: Global Initiative for Asthma

ARIA: Allergic Rhinitis and its Impact on Asthma

IgE: Immunoglobulin E

NICE: The National Institute for Health and Clinical Excellence

AIRLA: Asthma Insights and Reality in Latin America

POR: Prevalence odds ratio

PRR: Prevalence ratio

ABSTRACT

Background: Asthma and allergies are world-wide common chronic diseases among children and young people. Little is known about prevalence and environmental and dietary risk factors of asthma and allergies among rural and urban school children in Bolivia. The aim of this study was to describe the prevalence, severity and risk factors associated with asthma, rhinoconjunctivitis, and eczema symptoms in children of school age in Oropeza Province – Bolivia

Methods: Overall, 2584 children (response 91%) attending fifth elementary grade in Oropeza province answered the written and the video questionnaire of the International Study on Asthma and Allergies in Childhood. Lifetime, 12 months and severity prevalence were determined for asthma, rhinoconjunctivitis and eczema symptoms. The associations between: environmental and dietary factors and symptoms of asthma, rhinoconjuctivitis and eczema symptoms were analysed using logistic regression analysis with adjustment for age, sex and place of living.

Results: Median age of children was 11 years, 52% were female and 26% lived in rural areas. The prevalence of asthma symptoms was higher in the written (18%) than in the video questionnaire (6%). 22% of children reported symptoms of rhinoconjunctivitis and 9% eczema symptoms. Overall, rural children reported more frequently symptoms of asthma and allergies than urban children. Parental smoking (adjusted OR 1.3; 95%IC 1.0-1.6), presence of disease vectors at home (fourth quartile vs. first quartile: 1.5; 1.1-2.2) and farm animals (1.3; 1.0-1.6) were statistically significant predictors of asthma symptoms detected by the written questionnaire. The associations were similar for symptoms of rhinoconjunctivitis and eczema. A greater adherence to the Mediterranean Diet (MD) was inversely related with asthma symptoms in the video questionnaire (reference category: 1st quartile; second quartile 0.6; 0.3-0.9, third quartile 0.7; 0.4-1.2, fourth quartile 0.6; 0.3-1.0)

Conclusion: Our results suggest that promoting a healthy diet and reducing exposure to modifiable risk factors like environmental tobacco smoke, precarious housing conditions

and certain disease vectors would have a significant positive impact on asthma and allergies morbidity in children in this region.

KEY WORDS

Asthma, rhinoconjunctivitis, eczema, children, prevalence, Bolivia, food, mediterranean diet, environmental factors

1) INTRODUCTION

Asthma and allergies are world-wide common chronic diseases with high prevalence among children and young people and a large variation between and within countries and cities[1]. These pathologies are associated with adverse outcomes at physical, emotional, social, and professional level for both, patients and their families, interfering with normal activity and quality of life[2].

Asthma and allergies prevalence are increasing in many countries around the world[3], and in certain developing regions, prevalence has appeared to rise in conjunction with increases in urbanization. Although the reasons for this increase are not clear, studies agree that gene - environment interaction plays an important role.

Information on asthma and allergies in Bolivia is scarce. Therefore, this project aimed to estimate the prevalence of self-reported asthma, rhinoconjunctivitis and eczema symptoms among school-aged children of the ages 9 to 15 of rural and urban areas of Oropeza province, Bolivia and explore the relationships between diet and environmental factors with the reported symptoms in the study population.

Next we present some theoretical aspects, which supported this thesis.

1.1) ASTHMA

1.1.1) DEFINITION AND MECHANISMS OF ASTHMA

Global Initiative for Asthma (GINA) defines asthma as a *chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment*[4]. Asthma is a complex, coordinated, multisystem, multicellular, inflammatory disorder. The development of asthma requires an interaction between the environment and genetic susceptibility[5].

Although the clinical spectrum of asthma is highly variable, the presence of airway inflammation is a common feature. Airway inflammation is persistent affecting all airways in special medium-sized bronchi. This pattern appears to be similar in all clinical forms of asthma, whether allergic or nonallergic and at all ages, and is characterized by presence of activated mast cells, increased numbers of activated eosinophils, and increased numbers of T cell receptor invariant natural killer T cells and T helper 2 lymphocytes (Th2), which release mediators that contribute to symptoms[6].

In addition to the inflammatory response, there are characteristic structural changes, often described as airway remodeling, in the airways of asthma patients. In severe cases of the disease these changes result in relatively irreversible narrowing of the airways which is considered the final common pathway leading to symptoms and physiological changes in asthma[7].

Some special mechanisms of asthma have been described in the following situations:

Acute exacerbations: Transient worsening of asthma may occur as a result of exposure to risk factors for asthma symptoms, or "triggers," such as exercise or air pollutants viral infections (rhinovirus, respiratory syncytial virus)[8] or allergen exposure which increase inflammation in the lower airways (acute or chronic inflammation) that may persist for several days or weeks.

Nocturnal asthma: The mechanisms accounting for the worsening of asthma at night are not completely understood but may be driven by circadian rhythms of circulating hormones such as epinephrine, cortisol, and melatonin and neural mechanisms such as cholinergic tone. The occurrence of nocturnal asthma is associated with increased morbidity and inadequate asthma control, and has an important negative impact on quality of life[9].

Irreversible airflow limitation : Some patients with severe asthma develop progressive airflow limitation. They present longer disease duration, a greater inflammatory process airway abnormality suggestive of airway remodeling[10].

Difficult-to-treat asthma: The reasons why some patients develop asthma that is difficult to manage and relatively insensitive to the effects of glucocorticosteroids are not well understood. Although the pathology appears similar to other forms of asthma, difficult-to-treat asthma presents an increase in neutrophils, more small airway involvement, and more structural changes[11].

Smoking and asthma: Asthma and active cigarette smoking interact to cause more severe symptoms, asthma more difficult to control, accelerated decline in lung function, and impaired short-term therapeutic response to corticosteroids. The mechanisms of corticosteroid resistance in asthmatic smokers are unexplained, but could be as a result of alterations in airway inflammatory cell phenotypes (e.g. increased neutrophils or reduced eosinophils), changes in the glucocorticoid receptor-alpha to -beta ratio, and increased activation of pro-inflammatory transcription factors or reduced histone deacetylase activity[12].

The interaction between a patient's genetic makeup and their environment is often described in terms of "phenotypes"[13]. A better characterization of the patients enables customization of programs to manage the disease. Although several clinical phenotypes are recognized on the basis of cluster analysis of clinical and other features of asthma, we are going to mention three phenotypes have been identified in children with asthma Based in epidemiological studies [13, 14]:

Transient wheezing: This phenotype is associated with symptoms that are limited to the first 3–5 years of life, and are characterized by impaired lung function at birth, maternal smoking during pregnancy and exposure to other siblings or children at daycare centers, without association of family history of asthma or allergic sensitization.

Non-atopic wheezing (Non-atopic asthma) : Most of them have a history of viral lower respiratory tract infection early in life and are more likely to be wheezing up to 13 years of age.

IgE-mediated wheezing (atopic asthma): This phenotype is associated with high levels of atopy, bronchial responsiveness, and impaired lung function. Early allergic sensitization is a major risk factor for persistent asthma.

Late-onset childhood asthma: This phenotype occurs during or after puberty, affecting mainly women and with a low remission rate. It is characterized by a higher prevalence of bronchial hyperresponsiveness and atopy.

1.1.2) ASTHMA MANAGMENT

Managing the asthma patient involves four key components: diagnosis, pharmacotherapy, environmental control and patient education.

Diagnosis

An early and correct diagnosis is achieved on the basis of medical history, physical examination and objective measurements of lung function. The earlier the diagnosis and start of treatment, the better the outcome for the patient.

Medical History: Asthma symptoms may be intermittent and in many cases non-specific. This can lead to a misdiagnosis especially among children. However, a clinical diagnosis of asthma is often driven by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness[15] . Some aspects that can help diagnosis are related with episodic symptoms after an incidental allergen exposure, seasonal variability of symptoms and a positive family history of asthma and atopic disease. Symptoms variability; precipitation by non-specific irritants, such as smoke, fumes, strong smells, or exercise; worsening at night; and responding to appropriate asthma therapy are symptoms that strongly suggest the presence of asthma[4]. Some patients, especially children, have chronic cough (more problematic at night) as their principal symptom. Other diagnoses to be considered are cough-induced by angiotensin-converting-enzyme (ACE) inhibitors, gastroesophageal reflux, postnasal drip, chronic sinusitis, and vocal cord dysfunction[16]. Physical activity is an important cause of asthma symptoms for most asthma patients. Exercise-induced bronchoconstriction typically develops within 5-10 minutes after completing exercise and may occur in any climatic condition, but it is more common when the patient is breathing dry, cold air[17]. In this case rapid improvement of post-exertion symptoms after inhaled β2-agonist use could guide a diagnosis of asthma[4]

Physical Examination: The physical examination should include the upper respiratory tract and skin, as well as the lower respiratory tract. When physical examination is performed

during symptomatic periods it is possible to find features of hyperinflation and airflow limitation (wheezing on auscultation)[4]. Findings supporting a diagnosis of asthma include hyper-expansion of the thorax (especially in children), sounds of wheezing during normal (or deep) breathing, signs and symptoms of nasal disease (allergic rhinitis, rhinosinusitis, nasal polyps) and in some cases atopic dermatitis/eczema.

Pulmonary Function Tests: Although diagnosis of asthma is usually based on the presence of characteristic symptoms, measurements of lung function provides an assessment of the severity of airflow limitation, its reversibility and its variability, and provides confirmation of the diagnosis of asthma[4]. The evaluation of airflow limitation it is possible to perform thought spirometry, particularly the measurement of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), and peak expiratory flow (PEF) measurement. Predicted values of FEV1, FVC, and PEF based on age, sex, and height have been obtained from population studies. Among some non-invasive markers of airway inflammation are the evaluations of spontaneously produced or hypertonic saline-induced sputum for eosinophilic or neutrophilic inflammation[18]. In addition, levels of exhaled nitric oxide[19] and carbon monoxide[20], although they are not specific for asthma[4].

Once asthma is diagnosed, the patient's disease severity has to be classified in order to determine appropriate therapy. Severity is classified according to: the frequency, duration and severity of symptoms; the degree of airflow obstruction and the extent to which the disease interferes with daily activities. Asthma severity is a continuum that can change over time for any patient[4].

Pharmacotherapy

The goal of asthma treatment is to achieve and maintain clinical control. Asthma control focuses on two domains: (1) reducing impairment —the frequency and intensity of symptoms and functional limitations currently or recently experienced by a patient; and (2) reducing risk —the likelihood of future asthma attacks, progressive decline in lung function (or, for children, reduced lung growth), or medication side effects. To achieve and maintain asthma control requires providing appropriate medication, addressing environmental factors

that cause worsening symptoms, helping patients learn self-management skills, and monitoring over the long term to assess control and adjust therapy accordingly[21].

Medications to treat asthma can be classified as controllers or relievers:

Controllers: These are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. Some of these drugs are: inhaled and systemic glucocorticosteroids, longacting inhaled β2-agonists in combination with inhaled glucocorticosteroids, sustained-release theophylline, leukotriene modifiers, cromones, and anti-IgE. Inhaled glucocorticosteroids are the most effective controller medications currently available[4].

Relievers: These are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms. They include rapid-acting inhaled β2-agonists, inhaled anticholinergics, short-acting theophylline, and short-acting oral β2-agonists.

Environmental control

Environmental control measures are an important aspect to reduce symptoms in patients with mild, intermittent and persistent asthma, and even it is possible to lower medication requirements.

Education

As for any chronic disease, an educational plan allows the patient (and family) to understand and successfully manage the disease. Patient education should clarify any misperceptions about asthma and its treatment. The following aspects have to be emphasized:

• Asthma is a chronic disease;
• Asthma is physical, not emotional;
• Medication for asthma is not addictive and does not become ineffective over time;
• Asthma is best treated with prescription medications;
• Regular healthcare visits are important, even during symptom-free times

1.1.3) EPIDEMIOLOGY AND BURDEN OF ASTHMA

Epidemiology

Epidemiological studies using validated questionnaires have reported a wide variation in asthma prevalence. Studies of both children and adults revealed low prevalence rates (2%–4%) in Asian countries (especially China and India) and high rates (15%–20%) in the United Kingdom, Canada, Australia, New Zealand and other developed countries[3, 22].

Observations of Germany after reunification[23], migrating populations[24] suggested the role of local environmental factors on asthma and gene-environment interactions. This aspects are supported by family and twin studies which have shown that although a positive family history of asthma predicts an increased risk of asthma, it is neither sufficient nor necessary for the development of asthma[25].

Burden

Asthma is one of the most common chronic conditions in the world. It is estimated that 235 million people worldwide suffer from asthma[26]. Asthma is under-diagnosed and under-treated, creating a substantial burden to individuals and families and possibly restricting individuals' activities for a lifetime. It is estimated that asthma accounts for about 250.000 deaths per year worldwide, most of them preventable with optimal long-term medical care and obtaining timely help during the asthma attacks[27].

Annually, approximately 15 million disability-adjusted life years – or approximately 1% of all disability-adjusted life years – lost worldwide are due to asthma[27]. Uncontrolled or poorly controlled asthma can: disturb sleep, increase fatigue and decrease energy, produce difficulty concentrating, restrict physical activity and exercise, cause absences from work and/or school and reduce participation in normal daily activities[4].

The economic costs associated with asthma are estimated to rank as one of the highest among chronic diseases due to the significant healthcare utilization associated with this

condition. The economic cost of asthma is considerable both in terms of direct medical costs (such as hospital admissions and cost of pharmaceuticals) and indirect medical costs (such as time lost from work and premature death)[28]. Both direct and indirect costs associated with asthma increase significantly when asthma is not under control.

Among some barriers to reducing the burden of asthma are[29]:

- Generic barriers: poverty, poor education, and poor infrastructure.
- Environmental barriers: indoor and outdoor air pollution, tobacco smoking, and occupational exposures.
- Low public health priority: due the lack of data on morbidity and mortality from asthma and the prioritization of other respiratory illnesses such as tuberculosis and pneumonia
- The lack of symptom-based rather than disease-based approaches to the management of respiratory diseases.
- The lack of existence of management guidelines in developing countries, which consider the local reality.
- Inherent barriers in the organization of health care services: geography, education and training systems, respiratory specialists.
- The limited availability and use of medications: omission of basic medications from WHO or national essential drug lists, poor supply and distribution infrastructure, cost, cultural attitudes towards drug delivery systems.
- Patient barriers: cultural factors, lack of information, underuse of self-management, over-reliance on acute care, use of alternative unproven therapies.
- Inadequate government resources provided for health care including asthma.

1.2) ALLERGIC RHINITIS

1.2.1) DEFINITION AND MECHANISMS OF ALLERGIC RHINITIS

Rhinitis has been defined clinically as an inflammation of the lining of the nose and is characterized by nasal symptoms including anterior or posterior rhinorrhea, sneezing, nasal blockage and/or itching of the nose. These symptoms occur during two or more consecutive days for more than one hour on most days. Allergic rhinitis is the most common form of non-infectious rhinitis and is associated with an IgE-mediated immune response against allergens. It is often associated with ocular symptoms[30].

Allergic Rhinitis and its Impact on Asthma (ARIA), proposed a subdivision of rhinitis, considering the terms "intermittent" and "persistent". This classification consider that patients with rhinitis more than 4 days a week as persistent rhinitis[30].
Have studies different aspects mechanisms influencing the mechanism of allergic rhinitis. Some of them are described below:

Allergic inflammation: The mechanisms of Allergic rhinitis consider a complex inflammatory reaction involving cells, mediators, cytokines, chemokines, neuropeptides, as well as adhesion molecules and cells co-operate in a complex network provoking the specific symptoms and non-specific nasal hyperreactivity.

IgE-dependent mechanisms: Immunoglobulin E (IgE) plays a critical role in the allergic inflammatory process in allergic rhinitis. Allergy is generally caused by a sustained overproduction of Immunoglobulin IgE in response to common environmental antigens such as indoor and outdoor allergens, foods and other allergens[31]. IgE production is the results of complex interactions between T-cells, B-cells, mast cells and basophils, involving the presence of the cytokines IL-4, IL-13 and IL-18, as well as a physical interaction between T- and B-cells by a number of surface and adhesion molecules[32] . Has been

reported that IgE is produced in the local lymphoid tissues and locally in both the nasal and bronchial mucosa[33].

Allergen-specific IgE, synthesized in response to allergens in the environment, becomes fixed to FcepsilonRI on the membranes of mast cells and basophils. Mast cell accumulation in the airway mucosa is an important pathophysiological event in allergic rhinitis and asthma, as inhaled allergens impact the mucosal surfaces of the nose and/or lungs. The aggregation of receptor-bound IgE molecules on exposure to specific allergen results in the production of mediators (histamine, leukotrienes and others) that produce the allergic response[34]. The immediate response is characterized by itching, sneezing, rhinorrhoea and blockage in the nose.

Non-IgE-dependent mechanisms: It has been studied that allergens may induce inflammation independent of IgE, promote directly activate epithelial cells and eventually lead to a Th2-immune response, inducing cytokine and chemokine release[35].

Remodeling processes: Although epithelial damage is only minimal in the nasal mucosa of patients with allergic rhinitis, epithelial cell metaplasia has been observed in the nasal biopsies of some patients suffering from perennial rhinitis. Although the nasal and bronchial mucosa are exposed to the same noxious environment (and even more so the nose), epithelial shedding is more pronounced in the bronchi than in the nose of the same patients suffering from asthma and rhinitis[36].

Nasal hyperreactivity and non-specific triggers: Nasal hyperreactivity is an important feature of allergic and non-allergic rhinitis. This nasal hyperreactivity is a consequence of the overall hyperresponsiveness to non-specific stimuli in daily (tobacco smoke, perfume, dust and paint). This complex process involve different types of nasal tissue (vascular, glandular) and also different neuroregulatory systems (adrenergic, cholinergic, peptidergic) determining the type of reaction to nasal stimulation[37].

Links between rhinitis and asthma: The nasal and bronchial mucosa present similarities and one of the most important concepts regarding nose-lung interactions is the functional complementarity[38]. The vast majority of patients with asthma have rhinitis, moreover have been reported that the presence of allergic rhinitis commonly exacerbates asthma, increasing the risk of asthma attacks, emergency visits and hospitalizations for asthma[39].

1.2.2) ALLERGIC RHINITIS MANAGEMENT

Next are described the components for and adequate management of Allergic rhinitis:

Diagnosis

The diagnosis of allergic rhinitis is based in the typical history of allergic symptoms and diagnostic tests[40]. Clinical history is essential for an accurate diagnosis of allergic rhinitis and for the assessment of its severity as well as its response to treatment. Patients with allergic rhinitis suffer from sneezing, anterior rhinorrhea, very often from bilateral nasal obstruction. This is usually the most troublesome symptom in patients with allergic rhinitis[40].

Immediate-hypersensitivity skin tests are widely used to demonstrate an IgE-mediated allergic reaction of the skin, and provide useful confirmatory evidence for a diagnosis of specific allergy. Skin testing represents one of the primary tools for allergy diagnosis. It is a simple, painless and highly efficient method when is carefully performed and correctly interpreted including skin tests with high-quality allergen vaccines and a battery that includes all the relevant allergens of the patient's context[40].

Education

The education program should consider the following aspects[41]:

- The patient or parents of children should be informed about the nature of the disease, causes, mechanisms, symptoms, complications and available treatments in

local area. Education of allergen avoidance and drug therapy (including safety and potential side effects) should be provided.

- Appropriate training in the use of nasal sprays and nasal drops is essential for a correct allergic rhinitis management.
- Patients should be provided with realistic expectations for the results of therapy, explaining the need of long-term treatment.

Allergen avoidance

Although the evidence in controversial for a beneficial effect of allergen avoidance is recommended to avoid contact with known allergens and triggers[41].

Pharmacotherapy

Despite allergen and trigger avoidance, many rhinitis sufferers continue to have persistent symptoms, the nature of which should determine the selection of medication. For allergic rhinitis in children have been described:

First-line treatments[41]:

- Antihistamines: These drugs are useful if the main symptoms are rhinorrhea and sneezing, or if there are symptoms outside the nose such as conjunctivitis or rash. For optimal results, they should be given continuously or prophylactically
- Nasal steroids: These drugs are useful for nasal congestion and obstruction. Intermittent use may be beneficial due to the rapid vasoconstrictor effect of corticosteroids. Compliance and efficacy is improved if the child learned how to use the nasal spray properly.

Second-line treatments[41]: For relief of nasal congestion, is recommended the use of short-term use of corticosteroid nose drops (e.g. betamethasone or fluticasone) and a topical decongestant[42].

Surgical referral for submucosal resection of the inferior turbinate bones may be indicated only if extensive medical treatment fails[43].

1.2.3) EPIDEMIOLOGY AND BURDEN OF ALLERGIC RHINITIS

Asthma and allergic rhinitis are common health problems that cause major illness and disability worldwide[40]. The International study of asthma and Allergies in Childhood in Phase one has reported a prevalence of rhinitis with itchy-watery eyes ("rhinoconjunctivitis") from 1.4% to 39.7% in 13-14-year-olds, with significant correlation between the prevalence of asthma and rhinitis in school children[44]. Studies reporting allergic rhinitis trends showed a global increase in allergic rhinitis in countries where low, medium and high prevalence rates were found during ISAAC Phase I, although in some countries where the prevalence of allergy and rhinitis was high, a reduction in increase, a plateau or a slight reduction have been observed[3].

The prevalence of an IgE sensitization to aeroallergens measured by allergen-specific IgE in serum or skin tests is over 40% to 50% in the population of Europe, the USA and Australia-New Zealand. Most but not all sensitized subjects suffer from allergic rhinitis and or asthma. On the other hand non-allergic rhinitis was reported to account for 30 to 70% of patients with chronic perennial rhinitis[40].

Allergic rhinitis has been related with a high burden of disease. Has been reported that allergic rhinitis involves more than the classical symptoms of sneezing, rhinorrhea and nasal obstruction. It is associated with limitation in day-to-day life. Allergic rhinitis has a negative impact on sleep, mood, work or school performance, social functioning, depression, anxiety and health-related quality of life, especially in patients with moderate and severe symptoms. This impact is associated with high direct (health resource costs) and indirect cost (e.g. absenteeism and loss of productivity)[40].

1.3) ECZEMA

1.3.1) DEFINITION AND MECHANISMS OF ECZEMA

Eczema is an inflammatory, chronically relapsing and intensely pruritic skin disease. The term Eczema has been proposed to describe an aggregation of several skin diseases with certain clinical characteristics in common involving a genetically determined skin barrier defect. According to the revised nomenclature for allergy, only eczema of patients with elevated total serum IgE and specific IgE responses should be called *atopic eczema*. The classification of atopy, is based on IgE sensitization and thus cannot be reached without an IgE-antibody determination or skin test. Some studies have reported that non-atopic eczema presence during childhood is related with less risk to develop asthma as adolescents than for those who had atopic eczema during childhood. However, non-atopic eczema in children may develop into atopic eczema[45].

Have been described two forms of eczema:
IgE-mediated sensitization (extrinsic): This form involves around 70–80% of the patients[46], and is characterized increased levels of Th2 cytokines by memory T cells expressing the skin homing receptor, cutaneous lymphocyte-associated antigen (CLA). These include IL-4 and IL-13, which are known to induce isotype switching to IgE synthesis, as well as IL-5, which plays an important role in eosinophil development and survival. These CLA+ T cells also produce abnormally low levels of IFN-γ, a Th1 cytokine known to inhibit Th2 cell function[47].

Non IgE-mediated sens itization (intrinsic): This form involve around 20–30% of the patients[46], and is associated with less IL-4 and IL-13 production than extrinsic eczema[47].

Both forms have associated eosinophilia.

Next are described some key elements in the pathophysiology of eczema:

Immune responses: Patients with eczema frequently manifests increased dryness and a greater irritant skin response than healthy controls. Analyses of biopsies from clinically unaffected skin of patients with atopic eczema, as compared with normal non atopic skin, showed an increased number of Th2 cells expressing IL-4 and IL-13, but not IFN-γ, mRNA[48].

Skin barrier dysfunction: Eczema is characterized by dry skin and increased transepidermal water loss, in both lesional and nonlesional skin in eczema patients. It lead to an increased susceptibility to irritants in eczema, it therefore represent a primary defect of epidermal differentiation compounded by the presence of inflammation-induced skin damage[47].

Genetics: Eczema is a genetically complex disease with genetic factors playing an important role in the development of this disease (20). Have been identified some candidate genes involving IgE and Th2 cytokines. A particular focus on chromosome 5q31-33 has been reported, as it contains a clustered family of Th2 cytokine genes (i.e., IL-3, IL-4, IL-5, IL-13)[49]. According to hygiene hypothesis, early infections or exposure to microbial-derived material (such as lipopolysaccharide) early in life prevent the development of Th2-driven allergic disease. Have been studied that polymorphisms of genes involved in the recognition of microbial material may alter the balance between Th1- and Th2-driven immune responses and could alter an individual's susceptibility to development of allergic diseases[47].

1.3.2) MANAGEMENT OD ECZEMA

The chronic and relapsing nature of eczema causes difficulties to propose and explain long-term management strategies. Is recommended that healthcare professionals should adopt a holistic approach when assessing a child's atopic eczema considering the severity of the atopic eczema and the child's quality of life, including everyday activities and sleep, and

psychosocial wellbeing[50]. Four aspects are considered in management of eczema in children:

Diagnosis

Eczema is diagnosed clinically. The main characteristics are itchy skin plus three or more of the following[50]:

- Visible flexural dermatitis involving the skin creases, such as the bends of the elbows or behind the knees
- Personal history of flexural dermatitis
- Personal history of dry skin in the last 12 months
- Personal history of asthma or allergic rhinitis (or history of atopic disease in a first-degree relative of children aged under 4 years)
- Onset of signs and symptoms under the age of 2 years (this criterion should not be used in children aged under 4 years)

Identification and management of trigger factors

Some of the common triggers are: irritants (soaps and detergents), skin infections, contact allergens, food allergens, and inhalant allergens.

Treatment

The aims of the treatment are to reduce the symptoms, improve quality of life, and decrease the degree and frequency of flares. The National Institute for Health and Clinical Excellence (NICE) has proposed a stepped approach for managing atopic eczema in children (Table 1.1)

Table1.1 Stepped approach for managing atopic eczema in children

Mild atopic eczema	**Moderate atopic eczema**	**Severe atopic eczema**
Emollients	Emollients	Emollients
Mild potency topical corticosteroids	Mild potency topical corticosteroids	Mild potency topical corticosteroids
	Topical calcineurin inhibitors	Topical calcineurin inhibitors
	Bandages	Bandages
		Phototherapy
		Systemic therapy

Source: NICE clinical guideline for atopic eczema in children 2007[50]

Children with eczema and their families have to learn how to recognize flares of atopic eczema (increased dryness, itching, redness, swelling and general irritability), and how to manage flares according to the stepped-care plan.

Education

Patient and family education is a relevant primary intervention. Education has an important role in order to reduce disease severity and improve quality of life[51]. The education program has to emphasize: how much of the treatments to use; how often to apply treatments; when and how to step treatment up or down and how to treat infected atopic eczema[50]

1.3.3) Epidemiology and Burden of Eczema

Eczema is a common pediatric dermatosis. The incidence of this disease has increased, like asthma, since the 1950s. The International Study of Asthma and Allergies (ISAAC) have reported prevalence of eczema symptos ranging from 0.2% in China to 24.6% in Columbia with the highest values in Africa and Latin America for 13-14 years old children[52].

Management of atopic eczema in children is potentially complex and costly, often requiring a well-planned multidisciplinary approach for optimal care. Some studies have reported important cost (direct and indirect) to the patient, their family and their community. Several factors may contribute to the higher impact on family impact as: sleep deprivation, time taken to care for the child, and interruption to employment. These factors also could affect to the community due of lost productivity and sick leave, or cost the individual as loss of income. Have been studied other potential reasons for the high impact of eczema on families, including parental feelings of guilt, effects of sleep deprivation on parents and children, behavioral and socialization skills[53, 54].

1.4) THE INTERNATIONAL STUDY OF ASTHMA AND ALLERGIES IN CHILDHOOD (ISAAC)

Since 1991, the International Study of Asthma and Allergies in Childhood (ISAAC) has reported a large body of new national, regional and global information on the prevalence, severity, risk factors, trends and several other aspects related to asthma, rhinoconjunctivitis and eczema in childhood. ISAAC, by using standardized methodologies, has permitted reasonably reliable comparisons of the prevalence of asthma symptoms between and within countries.

From an early stage, it was conceived as comprising three phases[55]:

The aims of ISAAC Phase One were:

1. To describe the prevalence and severity of asthma, rhinitis and eczema in children living in different centres and to make comparisons within and between countries;
2. To obtain baseline measures for assessment of future trends in the prevalence and severity of these diseases; and
3. To provide a framework for further aetiological research into lifestyle, environmental, genetic and medical care factors affecting these diseases.

The aims of ISAAC Phase Two were:

1. To describe the prevalence of 'objective' markers of asthma and allergies in children living in different centres, and to make comparisons within and between centres.
2. To assess the relation between the prevalence of 'objective' markers of asthma and allergies and the prevalence of symptoms of these conditions in children living in different centres.
3. To estimate to what extent the variation in the prevalence and severity of asthma and allergies in children between centres can be explained by differences in known or suspected risk factors or by differences in disease management.
4. To explore new aetiological hypotheses regarding the development of asthma and allergies in children.

The aims of ISAAC Phase Three were:

1. To examine time trends in the prevalence of asthma, allergic rhinoconjunctivitis and atopic eczema in centres and countries, which participated in ISAAC Phase One.
2. To describe the prevalence and severity of asthma, allergic rhinoconjunctivitis and atopic eczema in centres and countries, which did not participate in Phase One.
3. To examine hypotheses at an individual level which have been suggested by the findings of Phase One, subsequent ecological analyses and recent advances in knowledge.

The results has allowed to estimate the burden of disease associated with these diseases and also helps to clarify risk factors and protective factors for the development of these pathologies in order to propose appropriate strategies preventing allergic disorders[56].

ISAAC Phase one reported the highest prevalence of asthma and allergic diseases in high-income populations[57] in comparison with some developing countries where the prevalence was lower especially in rural areas[58]. Large variations were reported, even in genetically similar groups[58], with differences of between 20-fold and 60-fold between centers, suggesting that environmental factors underlie the variations. From this data, many

environmental aspects were explored through ecological analysis and have provided some support for hypotheses that economic development[59], dietary factors[60], climate[61], infections[62] and pollens[63] might influence some of this variation.

ISAAC Phase three, a repetition of Phase one after an interval of at least five years, examined variations in time trends of childhood asthma, rhinoconjunctivitis and eczema around the world. It was found that in most high prevalence countries, particularly English countries, the rise in the prevalence of asthma symptoms has peaked and may even have begun to decline. In contrast, many - but not all - countries with low prevalence in Phase one had shown increases in prevalence in Phase three[3]. The causes of these changes remain unclear, therefore epidemiological studies are playing a major role in the search for new theoretical paradigms, which could explain the reasons for these changes, and could suggest developing preventive interventions.

1.5) RISK FACTORS OF ASTHMA RHINOCONJUNCTIVITIS AND ECZEMA:

It is widely accepted that eczema, rhinitis, and asthma are major allergic syndromes in childhood and that comorbidity is observed. Some studies have reported allergic rhinitis in 75% of patients with atopic asthma[40]. This comorbidity has been attributed to a common mechanism of altered immunologic mechanisms favoring a systemic response of type 2 helper T cell cytokines to environmental allergens [64]. A recent publication of the ISAAC suggested that factors underling the changing prevalence of symptoms of the three diseases; they may be similar around the world even in study centers and countries with diverse economic and cultural environments. It suggests that these diseases are mainly determined by environmental rather than genetic factors. This is of particular interest, since it is suggested that these diseases are linked not only through atopic processes but also by non-atopic processes[65].

Next is described some risk factor which their role has been studied for asthma, rhinoconjunctivitis and eczema:

1.5.1) ATOPY

Atopy is defined as *a personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema*[45].

In order to provide more evidence trying to explain the large international variations in disease prevalence, ISAAC Phase two include Clinical examinations and skin prick tests to explore the role of atopy in these diseases[66]. In this study atopy was defined as having at least 1 positive skin prick test response to any of the allergens tested: house dust mites; cat fur; mixed grass pollen; mixed tree pollen; and the outdoor mould genus *Alternaria.* Additional allergens were tested in 18 centers and included cockroach, dog, horse, olive, Parietaria officinalis, mixed weeds, Turkish tree mix, mixed molds, and Cladosporium species[67].

Although a large variability has been reported worldwide, the results showed at the individual level, the association of atopy with asthma, rhinoconjunctivitis and eczema was stronger in more affluent centers than in less affluent centers. For current asthma symptoms the fraction attributable to atopic sensitization was 40.7% in affluent countries and 20.3% in non-affluent countries[68]. For rhinoconjunctivitis, the population attributable fraction to seasonal and perennial allergens was 36 and 25%, respectively in affluent countries and 1.3 and 12.6%, respectively in non-affluent countries[69]; and for flexural eczema the population attributable fraction for atopy was 27.9% for affluent and 1.2% for non-affluent country centers[70].

In Latin America, only a small percentage of wheeze was attributable to skin prick test reactivity (11% in both Ecuador and Brazil). Although in Latin America the majority of asthma is likely to be non-atopic, a case control studied developed in the central south of

Chile reported a high prevalence of atopic asthma[71]. In other hand there is evidence that in Latin America more severe asthma disease is more likely to be associated with atopy[72, 73].

1.5.2) URBANIZATION AND MODERNIZATION

The processes of urbanization and modernization are having profound effects around the world. Both processes occur hand in hand and reflect the processes of social and economic development, and the adoption of a modern lifestyle[74].

Urban populations are growing rapidly in Latin America. In 2010, 79.4% of Latin America and Caribbean population resided in urban areas. By 2025, 6 of the 30 largest cities in the world are anticipated to be in this region: Bogota, Buenos Aires, Lima, Mexico City, Rio de Janeiro, and Sao Paulo. Urban Latin American cities tend to concentrate wealth, creativity, innovation, and opportunities on all fronts—from the artistic and cultural, to the technical and scientific, to employment and economic. Despite this, the rapid urbanization process in Latin America and in Bolivia has strained the capacity of local and national governments to provide basic services (e.g. sewage, water, electricity, etc.). Thus, is expected that, in coming years, cities will continue to be home to populations in different gradients of poverty and vulnerability[75].

Among others, ISAAC showed a higher prevalence of asthma and allergies in industrialized countries than in developing countries[52, 76, 77]. However, in Latin American countries the prevalence was shown to be even higher than in industrialized countries, becoming a new public health challenge for the region[78]. Changes in lifestyle, modernization, living conditions and dietary habits have been studied as possible explanations for such an increase[79].

One aspect frequently shown for industrialized countries is a higher prevalence of asthma and allergies in urban compared to rural areas. This association was confirmed for African and Asian countries[80, 81] but so far only few studies from Latin America exist[82, 83]. A higher exposure to microbial compounds in rural areas was discussed as one of the mechanisms

underlying the lower prevalence of asthma and allergies in rural areas. However, a high prevalence of asthma was shown in inner city environments with high microbial load[84, 85]. Some authors have speculated that these contradictory findings might be related to different asthma phenotypes and have hypothesized that rural living protects from allergy but not from asthma[68, 86, 87]. However, recent studies do not confirm this hypothesis[71, 88].

1.5.3) MIGRATION

Several studies have examined the association between migration and asthma and allergies diseases. Some results showed that birth in a low asthma prevalence country provides some protection after migration to a high prevalence country, but that the protection may decline with time of residence in the new environment[89].

Some studies in Europe[90] and Asia[91] have examined migration within a country, and have provided evidence that birth and residence in a rural environment is protective against atopic disease, but this protection may be lost or decreases after migration to a town in adulthood. These observations indicate that the protection afforded in environments of low asthma risk may not strictly limited to a time window in early life but rather may persist through adolescence and adulthood, and be dependent on the continuous presence of protective exposures.

Migration of populations from rural to urban areas within a country is likely to be associated with changes in many lifestyle and environmental exposures. In developing countries in Latin America such as Bolivia, recent rural migrants tend to settle at the periphery of a city and bring with them social behaviors and lifestyle choices from their rural environment. In the other hand, more established migrants adopt a more urban lifestyle, eat a more urban diet, live in concrete houses, and reside in asphalt and concrete neighborhoods[92]. The urban lifestyle may include changes in exposures to pets, infectious diseases and hygiene behaviors, activity levels, and smoking. The risks of asthma may

differ between recent and established migrant populations depending on the exposure to risk factors[93].

1.5.4) HYGIENE

The hygiene hypothesis, proposed for the first time in 1989 by Strachan, suggests that the increase in the prevalence of allergic diseases is linked to a decrease in exposure to germs[94]. This hypothesis appears to be related to the increase in allergic diseases in developed countries[95]. For example, the protective effect of farming observed in a number of studies conducted in Europe has been associated with endotoxin exposure in stables and barns[81, 96], and similar types of microbial exposure could explain the low prevalence of asthma in rural Latin America. However in Latin America it was shown that the prevalence of asthma and allergies in some low-resourced countries in Latin America with low hygienic standards was similar or even higher than in industrialized ones[1, 59, 97].

Various studies suggest that exposure to some infectious organisms and bacterial endotoxin may provide protect against atopy, whereas other infections appear to promote allergic diseases. What does seem to be important is the timing of exposure to infection, the properties of the infectious agent itself, and also genetic susceptibility of the host – these factors play a significant role in the future development of allergic disease[98].

There is evidence that early respiratory viral infections may be important in the development of persistent childhood asthma[73, 99]. Human infection of Toxocara canis, a dog helminth parasite, has been implicated as an important risk factor for wheeze in preschool children[100]. Although there is evidence that exposure to intestinal helminth infections may enhance bronchial hyper-reactivity and asthma severity[73] and that anthelmintic treatment of subjects with asthma may reduce both the number of exacerbations and the need for medication[101], several studies have suggested helminth infections as protective factor for allergic diseases and a more attenuated form of asthma[102]. It is possible that the effects of helminths on asthma may vary according to prevalence – temporary infections acquired in

areas of low prevalence may be associated with enhanced bronchial hyper-reactivity and asthma symptoms.

Have been studied that family size and the number and order of siblings may affect the risk of asthma. The exposure of an infant to a substantial number of infections and many types of bacteria stimulates the developing immune system toward non-asthmatic phenotypes. Thus the older siblings protect their younger siblings from asthma through a modulating effect on the still-maturing immune system[94]. I this sense some studies have reported that a large family size (more than 4 children) is associated with a decreased risk of asthma but birth order is not involved[103].

1.5.5) INDOOR AND OUTDOOR POLLUTION

Although some epidemiological, human, and animal studies suggest that air pollutants are involved in the pathogenesis of asthma, allergic rhinitis, and other allergic disorders, both in terms of their development and exacerbation[104], the evidence is still inconclusive[93].
Cooking fuel has been reported as another important source of air pollution and is associated with significant morbidity and mortality. The use of gas stoves and other combustion appliances can lead to higher indoor concentrations of NO2, which is potentially harmful to health[105]. Although several studies have reported that the use of domestic gas appliances or exposure to NO2 indoors is associated with respiratory symptoms or a diminished lung function in children and adults, the results are inconsistent[106].

Outdoor air pollution includes gaseous materials such as ozone (O_3) and nitrogen dioxide (NO_2), as well as particulate matter (PM), which is generated by automobile traffic and industry. PM and it is considered as the most serious air pollution problem in cities and towns, particularly being associated with various adverse health effects. PM is a mixture of solid and liquid particles of different origin, including pollen grains and mold spores.

Diesel exhaust particulate (DEP) accounts for most of the airborne PM (up to 90%) in the atmosphere of the world's largest cities. Acute exposure to diesel exhaust may cause irritation of the nose and eyes, headache, lung function disturbances, respiratory changes, fatigue and nausea, while chronic exposure is usually associated with chronic cough, sputum production and lung function decline. DEP are characterized by both adjuvant activity for sensitization against common allergens and enhancing effects on allergic symptoms in sensitized patients[107].

In Latin American countries, such indoor and outdoor environmental factors vary largely between urban and rural areas and by socioeconomic class[108, 109]. Some epidemiological studies in Latin America have reported controversial results in the association between asthma and air pollution. The prevalence of asthma symptoms in big Latin American cities with well-known high levels of air pollution such as Mexico, Sao Paulo and Santiago were much lower (or similar) than places with significantly lesser atmospheric pollution[109]. These results were consistent with the observation of a lower prevalence of asthma in a polluted area of East Germany compared to a cleaner area in West Germany[23]. Current evidence, therefore, does not provide strong support for a causal association between atmospheric pollution and asthma, although some pollutants may trigger asthma exacerbations[110].

Currently in Bolivia, air pollution is not perceived as a major problem[111]. Nevertheless, some reports show that air pollution is a particularly serious problem in Bolivia, especially in cities on altitudes above 2000 meters, (e.g. La Paz, El Alto and Cochabamba). The most significant sources of particles are motor vehicles, industry (particularly bricks production, metal foundries and oil refineries), burning of household and agricultural waste. In some locations concentrations of particles smaller than 10 microns amount to 106 micrograms per cubic meter, which is 2.5 times higher than the average for Latin America and the Caribbean, and similar to highly polluted cities such as Santiago (Chile) and Mexico City[112]. Regarding indoor air pollution, almost 80 percent of the rural population in Bolivia

uses firewood and other solid fuels for cooking and heating. This is a key cause of respiratory infections[111].

1.5.6) ENVIRONMENTAL TOBACCO SMOKE

Environmental tobacco smoke is often thought of as the biggest indoor air pollutant. Tobacco smoke contains more than 4,000 chemical substances, many of which are carcinogenic, mutagenic, irritating, or toxic[113]. Combustion byproducts from cigarettes have been shown to lead to higher rates of allergy and asthma[110]. Some studies have shown a dose-dependent increase in children's rates of asthma related to increasing number of household smokers, with the strongest effect detected in the youngest children. Maternal smoking has been reported to have a stronger effect than other household members' smoking[110].

There is also strong evidence to link fetal exposure to maternal active smoking with lower birth weight increased risk for sudden infant death syndrome, reduced lung function, and increased respiratory tract infections, and asthma. This negative effect has also been observed for maternal passive smoking[114], and could increase when combined with postnatal smoke exposure[115].
The mechanisms by which maternal smoking affect lung function are not fully understood, but may include direct toxic effects on the respiratory system and DNA methylation of genes[116].

1.5.7) DIET, OBESITY, AND PHYSICAL ACTIVITY

Urbanization and the urban lifestyle are likely to be associated with major changes in diet and physical activity. These factors have been proposed as risk factors for asthma. Among the dietary habits the polyunsaturated fatty acids (PUFAs) have been associated with the prevalence of asthma, especially if the diet contains a higher intake of ω-6 (e.g. margarine and vegetable oil) in relation to ω-3 (e.g. oily fish)[117]. While the presence of PUFAs could

intensify the production of IgE, the formation of arachidonic acid–derived eicosanoids, and thus it could promote the development of allergic diseases, diet rich in antioxidants (e.g. fruit and vegetables) could prevent from asthma and allergic diseases[117].

Findings of ISAAC suggested the Mediterranean diet (MD) as protector from asthma and allergies due the lower prevalence of asthma symptoms in the Mediterranean countries[118]. This was confirmed by several studies[119-123]. Although there are quite a few variants of this diet, there are common components like high monounsaturated/saturated fat ratio; high consumption of vegetables, fruit, legumes, and grains; moderate consumption of milk and low consumption of meat and meat products[124].

The studies carried out so far on the potential link between diet and asthma are conflicting, inconsistent, and inconclusive[119, 125-127]. Very few of these studies were conducted in developing countries.

Although there have been reports of positive associations between body mass index and asthma, the mechanism is not clear. Has been suggested that children spending increasing periods of time indoors because of changes in leisure habits (e.g. television and video games), and because of the risk of physical violence outdoors are likely to be associated with increased exposure to indoor allergens and irritants, reduced physical activity, and increased obesity[93].

Some studies have reported that maternal obesity or underweight, insufficient dietary intake, or placental dysfunction could affect fetal nutrition, fetal growth and lung development, and subsequently to an increased risk of asthma in childhood[128]. Have been study that Vitamin E, folate, vitamin B12, maternal Mediterranean and Western dietary patterns during pregnancy are related to fetal lung growth development, although the mechanisms are not fully understood[129].

Studies addressing the link between modifiable environmental factors with asthma and allergies are so far scarce in Latin America. It could help to implement prevention strategies, which are urgently needed to help reducing the burden of disease around the world.

1.6) LATIN AMERICAN SITUATION OF ASTHMA, RHINOCONJUNCTIVITIS AND ECZEMA

Latin America comprises 20 countries and 10 dependencies, with around 541 million inhabitants[130]. Race and ethnicity are complex issues in Latin America and Caribe (LAC). Most of LAC's 540 million residents descend from three major racial or ethnic groups: 1) I*ndigenous peoples*, of whom there are some 400 distinct groups; 2) *Europeans*, largely of Spanish and Portuguese heritage; and 3) Africans, descendants of slaves brought to the region during the colonial era. The term *Mestizo* generally refers to people of mixed European and indigenous lineage, while the term *Mulatto* refers to people of mixed African and European background. Currently, there are numerous racial variations in Latin America, making it one of the most – if not the most – diverse regions in the world[131].

In the past 30 years, Latin America and the Caribbean region faced marked demographic changes, with a substantial decline of mortality and fertility rates, which dropped from 8.72 to 6.06 per 1000 people and from 4.47 to 2.09, respectively, increase in life expectancy in around 9 years (from 65 to 74 years) and the region reported a fast shift in populations from rural to urban settings, contributing, as a result, to the formation of mega cities such as Mexico City, Sao Paulo and Buenos Aires. On the other hand, information on indigenous people indicates that they have higher rates of mortality, morbidity, infant mortality rates and maternal mortality ratios than the non-indigenous population. The region has also experienced fast and complex epidemiological changes in the past decades, combining increasing rates of non-communicable diseases (NCDs) and injuries, while keeping uncontrolled many existing endemic and emerging diseases[75].

ISAAC showed that the worldwide variability of asthma, rhinitis, and atopic eczema is not exclusively associated with racial or ethnic factors, moreover other factors such modifiable environmental factors could be more important explaining the differences observed in this region[130]. A global analysis of this region showed a high prevalence of asthma and allergic symptoms in children living in areas with low socioeconomic development, low hygiene and poverty conditions[97].

1.6.1) EPIDEMIOLOGY OF ASTHMA IN LATIN AMERICA

The results of ISAAC Phase I reported that the prevalence of asthma symptoms in children from South America was as high as that reported from industrialized countries. Overall, the prevalence of recent wheeze, exercise-induced bronchospasm, and severe episodes of wheezing were 16.9%, 19.3%, and 4.6%, respectively, for children aged 13– 14 years with marked differences in asthma symptom prevalence between different countries[132]. There was a trend for asthma prevalence to be lower in centers located at the south latitudes (Punta Arenas, Chile and Buenos Aires, Argentina) with higher rates at tropical latitudes (Lima, Peru and Recife and Salvador, Brazil); however, these findings were not always consistent. In Latin America – in contrast to other countries - no significant difference for asthma symptoms was found between boys and girls[132].

After a period of 5–10 years, ISAAC Phase III showed a particular scenario for this region. On the one hand, similar or even lower prevalence in asthma symptom was reported in centers with high prevalence. It suggests that the prevalence of asthma has reached a plateau. On the other hand the increases in low and intermediate prevalence centers suggest that asthma prevalence and morbidity might continue to increase in these areas[133].

Asthma in Latin America is associated with significant morbidity. The Asthma Insights and Reality in Latin America (AIRLA) survey assessed asthma treatment and control among a large sample of asthma patients in seven Latin American countries[72]. The survey provided evidence for a high level of patient morbidity and a high reliance on the use of emergency

health services. Overall, only 2.4% of patients met all GINA (the Global Initiative for Asthma) criteria for optimal asthma control, and the reasons for this were: poor recognition of uncontrolled asthma, under-use of appropriate medications, inadequate patient education and lung function monitoring, and low patient expectations.

1.6.2) EPIDEMIOLOGY OF RHINOCONJUNCTIVITIS IN LATIN AMERICA

In ISAAC Phase I, the prevalence of rhinoconjunctivitis symptoms in South American centers varied from 10% in Chile to 35% in Paraguay, with three countries in the top 10 list of most prevalent worldwide[58]. Trends study of rhinoconjunctivitis symptoms among South American children reported that the symptoms remained high (18.5% for the adolescents and 12.7% for the 6-7years old children) and the percentage of change varied widely between centers in different countries and also within a same country[77].

No correlation was observed for rhinitis symptoms prevalence with respect to latitude, altitude, humid/dry climate or other geographical aspects, suggesting that meteorological and geographic factors, individually, would not be able to explain the large variability of rhinitis prevalence found by both ISAAC phases in South America[78]. Comparison of most important markers of country development (GNP, infant mortality rate, annual proportion of registered deaths under 5 years of age due to infectious diseases, percentage of children younger than 1year of age immunized against: poliomyelitis; measles; diphtheria, tetanus, and pertussis; and tuberculosis, percentage of population with potable drinkable water service, percentage of population with sewage disposal services) and the prevalence of rhinitis-related symptoms did not show any significant correlation[134].

The ethnic differences, which might be invoked to explain the variability of rhinitis symptoms prevalence in South America, are also unlikely to be a reasonable explanation[78].

1.6.3) EPIDEMIOLOGY OF ECZEMA IN LATIN AMERICA

ISAAC Phase I showed that atopic eczema is a common health problem for children and adolescents throughout the world. In Latin America, was reported a variation in the prevalence of symptoms of eczema for 6-7 years old children from 4.8% in Mexico to 10.9% in Chile and from 4.4% in Mexico to 10.8% in Paraguay for the 13-14 years old. Compared with global values, these would be considered in the middle range[78].

As with asthma and rhinitis, the prevalence of symptoms of eczema varies widely, both within and between countries inhabited by similar ethnic groups. ISAAC Phase III showed an increase in the prevalence of eczema symptoms. This is particularly evident in Central America and the Northern part of South America, where new centers such as La Habana (Cuba), San Pedro Sula (Honduras), Managua (Nicaragua), Barranquilla (Colombia), and Quito (Ecuador) show prevalence values of more than 15%[52].

Some studies reported a lack of association between the mean prevalence of current symptoms of eczema and severe eczema in each country and the following: infant mortality rate; percentage of children younger than 1 year of age immunized against poliomyelitis, measles, diphtheria, tetanus, pertussis, and tuberculosis; percentage of population with potable water; percentage of population with sewage disposal services; annual proportion of registered deaths under 5 years of age due to intestinal infectious disease; and incidence of tuberculosis[130].

1.7) HEALTH CONDITION IN BOLIVIA

Bolivia, located in the center of South America (Figure 1.1), has nine departments, 112 provinces and 339 municipalities, a land area measuring 1,098,581 km, and a population in 2012 of more than 10 million inhabitants, as estimated by the National Statistics Institute (INE)[135].

Figure 1.1 Bolivian Map

Source: Adapted from: http://new.ops.org.bo

Bolivia is characterized by a large number of different cultures. According to the last 2001 census, roughly 60 per cent of the population self-identified as indigenous belonging to 37 recognized ethnic groups. Aymaras and Quechuas make up the majority of the Bolivian population. More than 37 per cent of the general population continue to live in rural areas and 61 per cent of the Spanish-speaking people live in urban areas[136].

Bolivia can be divided into three distinct regions: the highlands (La Paz), the valley region (Chuquisaca), and the lowlands (Santa Cruz). These three regions have very different

climates and vegetation and they attract different types of people. From pre-Columbian times till now, Aymara people have dominated the highlands, while the Quechua-speaking Incas dominate the valley region. The lowland region was originally sparsely inhabited by a number of smaller rainforest tribes, but now has a relatively large population of European descent with the low mobility of people from the highlands to the lowlands. This region has been growing faster than any other city in Bolivia during the last 50 years[111].

Bolivia is the poorest country in the Latin American region with 31% of the population living in extreme poverty[137]. According to socioeconomic indicators, poverty is also more severe and extreme among the rural areas[92] and indigenous groups[136]. The main reason for the high rural poverty levels is the low level of productivity, which is associated with a lack of basic services, such as health services, education, electricity, piped water, and road access. One of the reasons that these basic services are lacking in rural Bolivia is that the rural population is scattered over vast areas of mountainous or forested terrain. Bolivia's population density is only about 8 persons per square kilometer, which is among the lowest in the world. This makes it very expensive to extend basic services to everybody[111]. It keeps the disparities between urban and rural areas.

Although the GINI coefficient of income distribution declined from 0.59 in 2006 to 0.51 in 2009, which indicates that there is less inequality in general, urban/rural inequalities persist, reflecting the greater vulnerability of the indigenous population[138].

Bolivia is facing the double burden of nutrition: under-nutrition and Overweight. This process has been associated with various factors. Progress in improving community infra-structure and development of sound public health systems has been slow, thwarting efforts to reduce under-nutrition; while rapid urbanization and the adoption of Western diets high in refined carbohydrates, saturated fats and sugars, combined with a more sedentary lifestyle are commonly cited as the major contributors to the increase in overweight and chronic diseases[139].

Non-communicable diseases and a variety of communicable diseases coexist in a complex scenario resulting from exposure to both natural disasters and social inequities, which makes for major differences in health between population groups. The last Demographic Health Surveys (DHS), shown that Bolivia still has the second worst health indicators in Latin America. Maternal and infant mortality remain the highest in the region after Haiti (Table 1.2). Communicable diseases such as malaria, Chagas disease (American trypanosomiasis) and tuberculosis are endemic and, along with HIV-AIDS and emerging diseases like dengue, constitute significant social and economic burdens[140].

Table 1.2 Bolivia: Health Profile

Indicators	**Country**	**Latin America average**
Life expectancy at birth (years)	68	76
Under five Mortality rate (per 1000 live births)	54	18
Adult Mortality rate (probably of dying between 15 and 60 years per 1000 population)	167	125
Maternal mortality rate (per 100 000 live births	190	63
Prevalence of HIV (per 1000 adults aged 15 to 49)	2	5
Prevalence of tuberculosis (per 100 000 population)	209	36
Percentage of years of life lost by communicable diseases	55	20
Percentage of years of life lost by non-communicable diseases	34	59
Raised blood pressure (aged 25+), 2008 Female	23.5	19.7
Raised blood pressure (aged 25+), 2008 Male	30.7	26.3
Obesity (aged 20+), 2008 Female	27.1	29.7
Obesity (aged 20+), 2008 Male	10.0	23.5
Tobacco use (aged 15+) Female	18.0	16.0
Tobacco use (aged 15+) Male	42.0	26.0

Source: WHO. Bolivia, country health profile[141]

1.7.1) HEALTH CONDITION IN CHUQUISACA

Chuquisaca, located in the center south part of Bolivia, is subdivided into 10 provinces and 28 municipalities. The estimated population for 2011 was 660.813 distributed in a surface area of 51,524 square kilometers[136].

Chuquisaca, also present high percentage of people living in poverty (62%), and 66% of the population identify themselves with some ethnic group (Aymara, Quechua, Guaraní, among others) (Table 1.3), facing the same health challenges than the country [142, 143].

Table 1.3 Sociodemographic indicators of Chuquisaca, Bolivia

Indicators	**Urban**	**Rural**
Poverty (unsatisfied basic needs) (%)	40,0	89.9
Adult illiteracy (%)	12,2	37.6
Infant mortality rate (per 1000 live births)	53,0	79.8
Education (years)	9,1	3.2
People who speak Spanish as a first language (%)	63,4	46.3

Source : National Institute of Statistics, 2005[136]

Chuquisaca as well as Bolivia is experiencing an epidemiological transition where chronic diseases are increasingly becoming more prevalent and straining an already weak health-care system.

1.7.2) ASTHMA AND ALLERGIES IN BOLIVIA AND CHUQUISACA

There is a very little information about asthma and allergies in Bolivia using standardized methodologies. The results of one study in Cochabamba (in the valley region) used Peak Flow (FPE) measured by Peak Flow Meter (PFM) and Vitalograph Pulmonary Monitor (VPM) to detect asthmatics children. Additionally a questionnaire was implemented. The study reported a prevalence of 0.91% by objective test and 5.6% by questionnaire. No significative difference was found in the history of personal atopy, family history of atopy or tobacco at home in this population[144]. Another study in Cochabamba aimed to identify the relationship between toxocariasis, a common zoonotic infection, and asthma in children aged 2-13 years old. The results did not show a significant association between asthma and toxocariasis, but it found as risk factors family history of asthma, history of previous allergies and frequent play with dogs at home[145].

Within the ISAAC study, the prevalence of asthma and allergies in 13-14 years old in Bolivia has only been assessed for Santa Cruz, Bolivia's richest city[146]. The study has shown a high prevalence of current rhinoconjunctivitis (22.4%)[77, 78] and eczema symptoms (22.5%)[130] as compared to other Latin American countries (17.3 and 9.5%, respectively) but a moderate prevalence of current asthma symptoms (13.5 Vs. 15.9 % in Latin American countries)[76, 78]. So far, data on the prevalence of asthma and allergies neither exist from lower income urban areas nor from rural areas of Bolivia.

There is a need of studies exploring prevalence and risk factors for asthma and rhinitis with standardized methodologies in order to compare and clarify the different factors, which lead the high prevalence of these diseases in Latin America and around the world.

2) RATIONALE AND OBJECTIVES

Bolivia - one of the poorest countries in Latin America with a large difference between rural and urban areas - offers a unique opportunity to study the prevalence of asthma and allergies as well as the environmental and nutritional factors associated with these diseases in a multiethnic population.

The aim of this study was therefore to describe the prevalence, severity and risk factors associated with asthma, rhinoconjunctivitis, and eczema symptoms in children of school age (9 – 15 years old) in Oropeza Province – Bolivia

SPECIFICS OBJECTIVES

1. Explore prevalence and severity of asthma, allergic rhino conjunctivitis, and atopic eczema
2. Explore the association between environmental factors and asthma, rhinoconjunctivitis, and eczema symptoms
3. Explore the association between diet and current asthma symptoms

The results of this cross-sectional study will provide us a baseline for epidemiological surveillance of these diseases. The demographic, cultural and epidemiological transition observed in Bolivia offer an opportunity to explore the role of risk and protective factors, in particular modifiable environmental factors that have been associated with the presence of these diseases. The use of standardized methodologies enabled us to compare the results with other countries with similar or, even more, with different characteristics in order to

clarify which of the assessed factors are leading the wide variability reported for these diseases.

Dissemination of this information will provide evidence of the impact of asthma and allergies in the local context, supporting the design and implementation of primary health care strategies in order to prevent further disease burden.

3) METHODS

3.1) DESIGN

A population-based prevalence study was conducted in the Oropeza Province, located in the northwestern part of Chuquisaca, from July 2011 to December 2011.

3.2) SETTING

The estimated population of Oropeza province is around 336.218 inhabitants with 19.7% living in the rural area (Figure 3.1). Communities with less than 2000 inhabitants were considered rural according to the Bolivian National Statistical Institute [147].

Figure 3.1 Map of Oropeza Province. Chuquisaca, Bolivia

Source: Adapted from: http://www.sucreturistico.gob.bo

Oropeza`s population lives at altitudes between 2000 and 4000 meters above sea level. Its climate is warm and dry, with temperatures between 15.0°C and 20.0°C, relative humidity

mean annual value around 60%. Rainfall occurs predominantly in summer (average annual rainfall of 500 to 1000 cubic millimeters)[148].

3.3) STUDY POPULATION AND FIELD WORK

Study population: The study population is children attending the fifth grade at schools (public, public with private infrastructure and private) in Oropeza province, Chuquisaca – Bolivia.

In 2010 there 185 schools with fifth grade were registered in the Regional Education Service (SEDUCA- Chuquisaca), with a total of 7206 students in the respective grade.

In contrast to the International Study of Asthma and Allergies in Childhood recommendation[56], fifth grade was selected due the high drop-out rate in the following grades, especially in Bolivian public schools [149], and the difficult to implement the International Study of Asthma and Allergies in Childhood parental questionnaire due the low adult literacy level in this region[136]. Children in this grade are able to understand and respond in a proper way, therefore all the study instruments were completed by the children themselves.

Sample selection: sampling was conducted in two stages: In the first stage 43 schools were selected randomly, from which 7 schools (6 urban and 1 rural schools) did not accept to participate due to time constraints or because of parental concern. In each sampled school, the whole fifth grade student population was studied. From the 36 participating schools, 2584 children attending the fifth grade were invited to participate, 30 of these schools were located in urban areas.

Exclusion criteria: Schools with less than 20 pupils of this grade were excluded from the sampling frame for feasibility reasons, especially the geographical inaccessibility. Around 10% (710) of the children attending these schools were excluded from the sampling frame.

Sample size: The sample size was determined following the International Study of Asthma and Allergies in Childhood project recommendations considering 1% of significance level and 80% of statistical power[56]. The calculation for the minimum sample required to compare the lowest proportions (severity of wheezing 3% Vs. 5%) are shown in table 3.1.

Table 3.1 Sample size estimated*

	Significance (%)		
Power (%)		**5**	**1**
	80	1251	**2241**
	90	2016	2855

*Comparison two proportion (two sides test) in severity of wheezing (0.03 Vs. 0.05)
Calculated by: www.stat.ubc.ca

Field work: The schools were contacted to agree upon the date of the visit and to organize the written and video questionnaire ensuring a place to implement both questionnaires properly (see appendix 10.1).

After the written questionnaire, the International Study of Asthma and Allergies in Childhood video questionnaire (AVQ 3.0) was implemented according the International Study of Asthma and Allergies in Childhood standard recommendations[150]. Finally, weight and height of the participants were measured according World Health Organization recommendations[151]. The terms: asthma, allergy, rhinitis or eczema were not used in any moment.

The main researcher (MTSS) and three previously trained health professionals submitted the questionnaires (Figure 3.2-3.5).

Figure 3.2 Entrance of rural school (La Palma)

Figure 3.3 Implementation of the International Study of Asthma and Allergies in Childhood written questionnaire

Figure 3.4 Lunch time in rural school (after questionnaires)

Figure 3.5 Course picture after survey implementation

3.4) STUDY INSTRUMENTS

The International Study of Asthma and Allergies in Childhood aimed to evaluate, by a standardized methodology, the prevalence and risk factors of asthma and allergic diseases in children. For this study, the Spanish version of the International Study of Asthma and Allergies in Childhood instruments for 13/14 year were implemented[56] (see appendix 10.2).

The ISAAC core questionnaire (asthma, rhinitis and eczema modules) was used[152]. This questionnaire assesses lifetime (ever) and 12 months prevalence (current symptoms) of asthma, rhinitis and eczema symptoms. In addition, severity of symptoms is assessed.

Asthma Module: This module comprises eight questions. These questions were designed as a minimum set for inclusion in self-completed questionnaires used in population surveys of respiratory disease in children. The enquiry about symptoms proceeds from the relatively mild to the relatively severe[153].

Rhinitis module comprises sex questions and try to distinguish between rhinitis and non-rhinitis individuals in the general population, predict which subjects with rhinitis are likely to be atopic; and give some indication of the severity of rhinitis among affected individuals[153].

Eczema module comprises six questions. These questions were designed as a minimum set for inclusion in self-completed questionnaires used in population surveys of allergic or skin disease in children[153].

The ISAAC video questionnaire AVQ3.0 designed to assess asthma symptoms [150] was implemented according the ISAAC standard recommendations[56]. The video questionnaire comprised five video sequences of young people from different ethnic origins with various asthmatic symptoms. The first three sequences showed various scenes of wheezing (moderate wheezing at rest, wheezing after exercise, waking at night with wheezing), and

the final two displayed other asthmatic symptoms (waking at night with coughing, a severe attack of asthma with wheezing and breathlessness at rest).

After each video sequence, students recorded whether their breathing had ever been like that shown in the video, and if so, the frequency of such symptoms (past month, past year, ever), using a one-page printed answers sheet (See appendix 10.3).

The video questionnaire took about 10 minutes to administer, and the term "asthma" was not mentioned in any time.

Diet and environmental risk factors were assessed with an adapted version of *The ISAAC environmental questionnaire*[56]. This questionnaire was designed to address overweight, diet, exercise, gas cooking, paracetamol, parity, migration, socioeconomic status, traffic, allergen and tobacco smoke hypothesis.

In order to further explore socio-economic and hygiene conditions, questions regarding presence of disease vectors at home, number of precarious household characteristics and items ownership were added.

This module comprises 27 multi-choice and short answer questions.

3.5) DATA HANDLING

Double-entry of data and congruence checking was performed using the statistical analysis software EpiInfo V. 3.5.3 for Windows to avoid possible mistakes. Data was exported to SPSS v.17 for statistical analysis.

3.6) VARIABLE DEFINITION AND STATISTICAL ANALYSIS

According with the specific objectives proposed, we describe the main analyzes done for the PhD research project. In the first analysis we describe the prevalence of asthma, rhinoconjuctivitis and eczema symptoms (lifetime, 12 months and severity symptoms prevalence); in the second analysis we explore the association between environmental factors and current symptoms of asthma, rhinoconjunctivitis and eczema; in the third and final analysis we explored the association between diet and current asthma symptoms.

We present the following variables and statistical analysis performed for each of the analysis described above.

3.6.1) SPECIFIC OBJECTIVE 1: PREVALENCE OF ASTHMA, RHINITIS AND ECZEMA SYMPTOMS

The following definitions based on the International Study of Asthma and Allergies in Childhood protocol were used:

- *Asthma symptoms ever :* were defined as self-reported symptoms of wheezing or whistling in the chest at any time in the past.

- *Current asthma symptoms:* were defined as self-reported symptoms of wheezing or whistling in the chest in the last 12 months.

- *Severe asthma:* was considered present if children with current asthma symptoms reported: 4 or more attacks of wheeze, being woken by wheeze at one or more nights per week or wheezing severe enough to limit speech to only one or two words at a time between two breaths.

- Considering the video questionnaire, *wheezing, exercise-induced wheeze and dyspnea at rest* occurrence were considered by affirmative response to the respective video sequences.

- *Rhinitis symptoms ever* were defined as self-reported problems of sneezing, runny or blocked nose, without having a cold or influenza.

- *Current rhinitis s ymptoms* were defined as self-reported problems of sneezing, runny or blocked nose, without having a cold or influenza in the last 12 months.

- *Current rhino conjunctivitis symptoms* were considered present if participants reported current rhinitis symptoms accompanied by itchy watery eyes.

- *Severe allergic rhinitis* was defined as rhinoconjunctivitis symptoms interfering with daily activities[56, 77].

- *Itchy Rash ever* was considered if the participant reported an itchy rash which was coming and going for at least six months.

- *Current itchy Rash* was considered if the participant reported an itchy rash which was coming and going for at least six months in the last 12 months .

- *Current symptoms of eczema* were defined as presence of an itchy rash in the last 12 months that 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.

- *Severe eczema* was considered present if eczema symptoms affected sleep (1 or more nights per week) [52, 56].

Absolute and relative frequencies were calculated. The chi-square test was used to assess differences between rural and urban areas. Crude and adjusted odds ratios as well as their corresponding 95% confidence intervals were calculated using logistic regression analysis. Adjustment was done for age, sex and type of school.

3.6.2) Specific Objective 2: Association between Environmental factors and asthma, rhinoconjunctivitis and eczema symptoms

In the present analysis, the following variables were used as outcome:

- *Current asthma symptoms:* were defined as self-reported symptoms of wheezing or whistling in the chest in the last 12 months.
- Considering the video questionnaire current asthma symptoms were defined as a positive answer to the scene showing "moderate wheeze at rest". Both the video scene selected and the question from the written questionnaire used in for this paper, have shown to have the highest degree of agreement evaluating current wheezing[150, 154, 155].

- *Current rhinitis s ymptoms* were defined as self-reported problems of sneezing, runny or blocked nose, without having a cold or influenza accompanied by itchy watery eyes in the last 12 months.

- *Current Eczema Symptoms:* were defined as presence of an itchy rash in the last 12 months that 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.

The following definitions were used to assess the exposure variables (Table 3.2):

- Current exposure to dogs, cats or farm animals (cows, goats, sheep, pigs, hens, chickens or turkeys) were defined if children had dog or cat at home, or regular contact (at least once a week) with farm animals in the last 12 months.

- Environmental tobacco smoke exposure was defined present if participants reported that their mother, father or guardian smoked at home.

- Outdoor air pollution was assessed considering the frequency of truck traffic on the street where children lived (never, seldom, frequently through the day, and almost the

whole day). Intense truck traffic was considered present when truck traffic was reported almost the whole day, in agreement with other studies[156-158].

- The use of wood or coal as cooking fuel was considered a risk factor for the outcomes under study.

- Household conditions precarity was assessed by classifying household by the number of precarious household characteristics (none, one and two or more) according to the Bolivian National Statistical Institute precarious household characteristic definition[159] (precarious floor: soil; precarious walls: cane, palm or trunk; precarious source of water for cooking: river, lake, pump or water tank car; precarious sewage system: surface or septic tank).

- Presence of disease vectors at home (fleas, ticks, kissing bugs, mice, bedbugs and flies) was assessed as a proxy of hygiene conditions. For the analysis, the number of types of disease vectors was categorized into quartiles (25^{th} percentile = 1 vector; 50^{th} percentile 2 vectors; 75^{th} percentile $\geq$ 3 vector).

- The number of items ownership was explored according to the Bolivian National Statistical Institute classification (radio, TV, bicycle, motorbike, car, refrigerator and telephone). For the analysis, the number of item ownership was categorized into quartiles (25^{th} percentile $\leq$ 3 items; 50^{th} percentile 4 items; 75^{th} percentile 5-6 items).

Table 3.2 Exposure variables used to explore the association between environmental factors and asthma, rhinoconjunctivitis and eczema symptoms

Variable	Question	Used in the analysis
Current exposure to dog	In the past 12 months, have you had a dog in your home?	Binary (yes=1, no=0)
Current exposure to cat	In the past 12 months, have you had a cat in your home?	Binary (yes=1, no=0)
Current exposure to farm animals	In the past 12 months, have you had a regular contact (at least once a week) with farm animals (cows, goats, sheep, pigs, hens, chickens or turkeys)?	Binary (yes=1, no=0)
Intense truck traffic	How often do trucks pass through the street where you live?	Binary: intense truck traffic (almost the whole day) and no intense truck traffic (never, seldom, frequently through the day)
Environmental tobacco smoke exposure	Does your mother (or guardian) smoke cigarettes? Or Does your father (or guardian) smoke cigarettes?	Binary (yes=1, no=0)
Cooking fuel	In your house, what fuel is usually used for cooking?	Binary: wood or coal and other (gas or electricity)
Disease vectors presence at home	What vectors are present in your home? Binary (yes=1, no=0) for presence of 6 diseases vectors: fleas, ticks, kissing bugs, mice, bedbugs and flies	Quartiles calculated of the number of disease at home
Precarious household conditions	Binary (yes=1, no=0) for the following household conditions: precarious floor (soil), precarious walls (cane, palm or trunk), precarious source of water for cooking (river, lake, pump or water tank car), precarious sewage system (surface or septic tank)	Grouped into three categories: None, one and $\geq$ 2 precarious household conditions
Number of item ownership	What items do you have in your home? Binary (yes=1, no=0) for 7 items: radio, TV, bicycle, motorbike, car, refrigerator and telephone	Quartiles calculated of the number of items ownership at home

Absolute and relative frequencies were calculated to describe the study population.

Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated using univariate and multivariate logistic regression analyses to estimate the likelihood of

having asthma, rhinoconjuctivitis and eczema symptoms, given the presence of a potential risk factor. The adjusted models included variables which were statistically significant (P value ≤ 0.05) in any of the bivariate analysis. In addition, age (three categories: ≤ 10, 11 and ≥12 years), place of living (two categories: urban and rural), and sex were a-priori included in all analyses.

3.6.3) SPECIFIC OBJECTIVE 3: ASSOCIATION BETWEEN DIET AND ASTHMA SYMPTOMS

From a total of 2340 children, 685 children were excluded due incomplete data in the food questionnaire, or due to missing data in the outcome variable (in written or video questionnaire), giving a final sample of 1655 (70.7% of the participating children) for the complete data analysis.

For the purpose of this study only current asthma symptom was used as an outcome using both written and video questionnaire: as previously described, current asthma symptoms was defined by the written questionnaire as a positive answer to the question: ‘‘Have you had wheezing or whistling in the chest during the last 12 months?’’. In addition current asthma symptoms were defined as a positive answer to the first scene of the video questionnaire: “Moderate wheezing at rest” during the last 12 months.

Both the video scene selected and the question from the written questionnaire used in this study have shown to have the highest degree of agreement evaluating current wheezing[150, 154, 155].

The ISAAC environmental questionnaire for 13-14 years old children was used to obtain information about nutrition[56]. The definition of exposure variables is summarized in table 3.3. The average frequency of consumption for 16 food groups during the past 12 months was assessed on a 3 point Likert scale (never or occasionally, 1 or 2 times per week, and 3 or more times per week). Using this information, the MD score was calculated as described in previous studies[120]. In brief, the consumption of 11 food groups was scored and summed up according the following scale:

- Those considered "pro- Mediterranean" foods (fruit, fish, vegetables, legumes, cereals, pasta, rice, and potatoes) were rated according to the frequency of intake (0 points = never or occasionally; 1 point = 1 or 2 times/week; 2 points = 3 times/week).
- Those considered "anti-Mediterranean" foods (meat, milk, and fast food) were rated inversely (0 points = 3 times/week; 1 point = 1 or 2 times/week; 2 points = never or occasionally)

The MD score was the sum of the points of each food, which could take a value from 0 to 22. The higher the score, the greater the adherence to MD.

In addition, the following potential confounders assessed in the environmental questionnaire were analyzed:

- Intense exercise: "How many times a week do you engage in vigorous physical activity long enough to make you breathe hard (never or occasionally, once or twice per week, three or more times per week)?''.
- Presence of sedentary behavior was assessed using two different questions: a) "During a normal week, how many hour a day (24hrs) do you watch television?", and b) "During a normal week, how many hour a day (24hrs) do you play videogames?". These two questions were considered different variables and dichotomized by using a cut-off of 3 hours/day.

BMI was calculated using WHO AnthroPlus software for children between the ages of 5 and 19 years according to the BMI for age and sex. Finally, BMI was categorized as follow[160]:

- Normal weight children: children up to +1 standard deviation (SD) of the WHO definition. Due a very low number of children with ≤ – 1SD (14 children), the category "thin" was included in this category.
- Overweight children: Children > 1 and ≤+2SDs
- Obese children: children > +2SDs.

Table 3.3 Exposure variables used to explore the association between diet and current asthma symptoms

Variable	Question	Used in the analysis
Food Intake	In the past 12 months, how often, did you eat or drink the following? (meat, fish, fruit, vegetables, legumes, cereals, pasta, rice, butter, margarine, nuts, potatoes, milk, eggs, corn and fast food)	Three categories for each food: never or occasionally, once or twice per week, three or more times a week.
Mediterranean diet		22 points score based on: Pro- Mediterranean foods (fruit, fish, vegetables, legumes, cereals, pasta, rice, and potatoes) rated according to the frequency of intake (0 points = never or occasionally; 1 point = 1 or 2 times/week; 2 points = 3 times/week). Anti-Mediterranean foods (meat, milk, and fast food) rated according to the frequency of intake (0 points = 3 times/week; 1 point = 1 or 2 times/week; 2 points = never or occasionally)
Intense exercise:	How many times a week do you engage in vigorous physical activity long enough to make you breathe hard?	Three categories: never or occasionally, once or twice per week, three or more times per week
Sedentary behavior	During a normal week, how many hours a day (24 hours) do you watch television? (Less than 1 hour, 1 hour but less than 3 hours, 3 hours but less than 5 hours and 5 hours or more)	Binary: ≤ 2 hours per day and ≥ 3 hours per day
	During a normal week, how many hours a day (24 hours) do you play videogames? (Less than 1 hour, 1 hour but less than 3 hours, 3 hours but less than 5 hours and 5 hours or more)	Binary: ≤ 2 hours per day and ≥ 3 hours per day
Body mass index	Measurements of height and weight	Three categories: normal weight, overweight and obese children

Absolute and relative frequencies were calculated to describe the study population. Selection bias was assessed comparing children with and without complete data using Chi^2-test. Median and range were calculated for the MD score.

Logistic regression analyses were done to predict current asthma symptoms for the written and video questionnaire calculating crude and adjusted odds ratios as well as their corresponding 95% confidence intervals.

In a first approach two models (for WQ and VQ) were built to assess the relation between consumption of each food type (1 to 2 times/week or 3 or more times/week compared with never or occasionally) and current asthma symptoms, adjusting by variables which were statistically significant (P value ≤ 0.05) in the bivariate analysis (age; three categories: ≤ 10, 11 and ≥12 years), place of living (two categories: urban and rural), and sex which has been reported as confounders in the literature[121, 161].

Afterwards in a second approach two models (for WQ and VQ) were built to assess the relation between quartiles of MD and current asthma symptoms adjusting for the same variables described above.

3.7) ETHICS

The study was approved by the National Research Ethics Committee from San Andres University at La Paz – Bolivia (see appendix 10.4-10.5); also a permission to apply the questionnaire was obtained from the Regional Education Service (SEDUCA- Chuquisaca). International ethical research guidelines were considered at all research steps. A written informed consent form as well as a letter explaining the importance of the study was sent to parents or legal guardians of the children one week before the visit to the school (see appendix 10.6 and 10.7). Voluntary participation from children was respected.

4) RESULTS

In the participating schools, response was 91% (2340 children). The median age of participating students was 11 years (range from 9 to 15 years) with children from urban schools being younger and more likely to attend public schools than children from rural schools (Table 4.1).

Table 4.1 Descriptive data by for place of living (N=2340)

		Urban (N=1727)		**Rural (N=613)**		**p value***
		n	%	n	%	
Sex	Female	917	53.2	300	48.9	0.07
Age	≤ 10 years	822	48.0	175	28.6	< 0.01
	11 years	672	39.3	303	49.4	
	≥ 12 years	218	12.7	135	22.0	
Type of school	Public	1400	81.1	351	57.3	< 0.01
	Public with private Infrastructure	278	16.1	262	42.7	
	Private	49	2.8	-	-	

*Chi square test

4.1) PREVALENCE OF SYMPTOMS

4.1.1) ASTHMA SYMPTOMS

Based on the written questionnaire, the 12-months prevalence of asthma symptoms was 16.4% in urban vs. 21.7% in rural areas, while in the video questionnaire asthma symptoms were reported by only 7.3% of urban and 3.9% of rural participants (Table 4.2). Adjusting for age, sex and type of school these differences were confirmed (urban vs. rural schools: written questionnaire OR 0.7; 95% CI 0.5-0.8; video questionnaire 1.7; 1.1-2.7).

4.1.2) RHINITIS SYMPTOMS

The prevalence of rhinitis symptoms was high with a 12-months prevalence of rhinoconjunctivitis symptoms of 22% in children from urban and 24% in children from rural schools. Only for severe rhinoconjunctivitis symptoms the 12-months prevalence differed between urban and rural schools (2.5; 1.0-6.1; table 4.2).

4.1.3) ECZEMA SYMPTOMS

The 12-months prevalence of current itchy rash was higher in urban than in rural schools (12% vs. 9%; Table 4.2). The 12-months prevalence of severe eczema was very low (1.6% in children from urban schools, 0.5% in children from rural schools). After adjustment, only the 12-months prevalence of itchy rash was statically significantly higher in children from urban compared with children from rural schools (1.4; 1.0-2.0).

Table 4.2 Self-reported asthma, rhinitis and eczema symptoms in school aged children in urban and rural areas of Chuquisaca Bolivia Prevalence and results of the unadjusted and adjusted logistic regression analyses comparing urban and rural areas.

	Urban		**Rural**		**Crude OR** **95%CI[b]**	**Adj. OR** **95% CI[b,c]**
	n	%	n	%		
ASTHMA						
Written questionnaire (N=2340)						
Asthma symptoms ever	470	27.4	214	34.9	0.7 (0.6-0.9)	0.7 (0.6-0.8)
Current Asthma symptoms (12 months prevalence)	281	16.4	133	21.7	0.7 (0.6-0.9)	0.7 (0.5-0.8)
Severe asthma[a] (12 months prevalence)	158	9.2	76	12.4	0.7 (0.5 -1.0)	0.7 (0.5-0.9)
Video Questionnaire (N=2300)						
Wheezing (12 months prevalence)	124	7.3	24	3.9	1.9 (1.2-3.0)	1.7 (1.1-2.7)
Exercise-induced wheeze (12 months prevalence)	323	19.2	80	13.1	1.6 (1.2-2.1)	1.4 (1.0-1.8)
Dyspnea at rest (12 months prevalence)	68	4	17	2.8	1.5 (0.9-2.5)	1.2 (0.7-2.2)
RHINITIS (N=2327)						
Rhinitis (ever)	715	41.7	255	41.6	1.0 (0.8-1.2)	1.1 (0.9-1.3)
Rhinitis (12 months prevalence)	490	28.6	175	28.5	1.0 (0.8-1.2)	1.0 (0.8-1.3)
Rhinoconjunctivitis[d] (12 months prevalence)	369	21.5	147	24.0	0.9 (0.7-1.1)	0.9 (0.7-1.1)
Severe Rhinoconjunctivitis[e] (12 months prevalence)	43	2.5	6	1.0	2.6 (1.1-6.1)	2.5 (1.0-6.1)

Table 4.2 *(continued)*

	Urban		**Rural**		**Crude OR** **95%CI[b]**	**Adj. OR** **95% CI[b,c]**
	n	%	n	%		
ECZEMA (N=2303)						
Itchy rash (ever)	339	20	123	20.1	1.0 (0.8-1.3)	1.0 (0.8-1.3)
Itchy rash (12 months prevalence)	203	12.0	56	9.2	1.4 (1.0-1.8)	1.4 (1.0-2.0)
Eczema[f] (12 months prevalence)	161	9.5	52	8.5	1.1 (0.8-1.6)	1.2 (0.8-1.7)
Severe Eczema[g] (12 months prevalence)	27	1.6	3	0.5	3.3 (1.0-10.9)	2.9 (0.8-9.8)

[a] ≥ 4 attacks of wheeze or woken by wheeze on one or more nights per week or wheezing severe enough to limit speech to only one or two words at a time, between breaths.

[b] Reference category: rural

[c] Adjusted by age, sex and type of school

[d] Presence of sneezing or a runny or blocked nose, accompanied by itchy watery eyes without a cold or the flu.

[e] Rhinoconjunctivitis symptoms interfering with daily activities (a lot).

[f] Presence of an itchy rash at any time in the past 12 months affecting 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)

[g] Sleep disturbed by rash in the last 12 months in children with eczema symptoms (one or more nights per week)

4.2) ASSOCIATION BETWEEN ENVIRONMENTAL FACTORS AND ASTHMA, RHINOCONJUNCTIVITIS AND ECZEMA SYMPTOMS

37% of children reported that at least one of their parents smoked at home. Wood or coal was used at cooking fuel in 19% of the homes. About one third of the study population reported intense truck traffic on the street where they lived (29%).

The hygiene condition results showed that exposure to dogs (86%) and cats (59%) was common. Regular contact to farm animals was reported by more than one third of the study population (36%). More than one precarious household condition was reported by 8% of children.

The prevalence of current asthma symptoms based on the written questionnaire was 18%, 6% reported asthma symptoms according to the video questionnaire. Prevalence of rhinoconjunctivitis was highest (22%), 9% reported eczema symptoms (Table 4.3).

Table 4.3 Environmental factors and symptoms distribution (N= 2340)

Variables		**% (n)**
Place of living	Rural	26.2 (613)
Current exposure to dog		86.2 (2003)
Current exposure to cat		59.2 (1375)
Current exposure to farm animals		36.1 (837)
Intense truck traffic[1]		28.6 (655)
Environmental tobacco smoke exposure		37.1 (868)
Cooking fuel	Wood or coal	18.5 (431)
Disease vectors presence at home [2] (Median 2; Range 0 to 6)	None	8.4 (197)
	1 Vector	39.3 (920)
	2 Vectors	23.9 (559)
	3 Vectors	16.5 (385)
	≥ 4 Vectors	12.0 (279)
Precarious household conditions [3]	None	70.6 (1615)
	1	21.2 (484)
	≥ 2	8.2 (188)
Number of item ownership[4] (Median 4; Range 0 to 7)	None	0.6 (13)
	1 item	6.4 (149)
	2 items	7.4 (173)
	3 items	16.4 (383)
	4 items	22.3 (522)
	5 items	22.3 (521)
	≥ 6 items	24.8 (579)

Table 4.3 *(continued)*

Variables		**% (n)**
Symptoms		
Current asthma symptoms WQ[5]		17.8 (414)
Current asthma symptoms VQ[6]		6.4 (148)
Current rhinoconjunctivitis symptoms[7]		22.2 (516)
Current eczema symptoms[8]		9.2 (213)

[1]Intense truck traffic: Almost the whole day

[2]Disease vectors: fleas, ticks, kissing bugs, mice, bedbugs, flies

[3] Precarious floor: soil; Precarious walls: cane, palm or trunk; Precarious source of water for cooking: river, lake, pump or water tank car; Precarious sewage system: to the surface or to a septic tank

[4] Item ownership: Radio, TV, bicycle, motorbike, car, refrigerator, telephone

[5] Positive answer to the question: ''Have you had wheezing or whistling in the chest during the last 12 months?''in the written questionnaire.

[6] Positive answer to the first scene of the video questionnaire: Moderate wheezing at rest

[7] Presence of sneezing or a runny or blocked nose, accompanied by itchy watery eyes without a cold or the flu.

[8] Presence of an itchy rash at any time in the past 12 months affecting 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).

The unadjusted and adjusted models showed that current exposure to animals (dog, cat or farm animals), intense truck traffic, exposure to tobacco smoke, wood or coal as cooking fuel, two or more precarious household conditions were associated with an increase in asthma symptoms either in the written or video questionnaire. Presence of disease vectors at home showed a dose-response effect, with the highest quartile having the highest risk for asthma symptoms (Table 4.4). The associations were similar for all three conditions (asthma, rhinoconjunctivitis and eczema symptoms), however, not reaching the level of statistical significance for all items.

Table 4.4 Association between environmental factors and asthma, rhinoconjunctivitis and eczema symptoms during the past 12 months (unadjusted and adjusted Odds Ratios with 95% Confidence Intervals) (N=2340)

Variables		**Current asthma symptoms WQ[1]**		**Current asthma symptoms VQ[2]**		**Current Rhinoconjunctivitis symptoms[3]**		**Current eczema symptoms[4]**	
		Crude OR (95%CI)	**a OR[5] (95%CI)**	**Crude OR (95%CI)**	**a OR[5] (95%CI)**	**Crude OR (95%CI)**	**a OR[5] (95%CI)**	**Crude OR (95%CI)**	**a OR[5] (95%CI)**
Current dog contact	Yes[6]	1.33 (0.96-1.86)	1.28 (0.89-1.85)	1.33 (0.78-2.27)	1.16 (0.63-2.14)	1.55 (1.13-2.12)	1.32 (0.94-1.87)	1.06 (0.70-1.61)	0.83 (0.53-1.31)
Current cat contact	Yes[6]	1.16 (0.94-1.45)	1.05 (0.83-1.33)	1.47 (1.02-2.10)	1.41 (0.96-2.07)	1.33 (1.08-1.62)	1.19 (0.96-1.48)	1.45 (1.08-1.96)	1.38 (1.00-1.90)
Current contact to farm animals	Yes[6]	1.42 (1.14-1.76)	1.25 (0.99-1.58)	1.11 (0.78-1.56)	1.00 (0.68-1.46)	1.79 (1.47-2.18)	1.52 (1.23-1.89)	1.47 (1.10-1.96)	1.31 (0.97-1.79)
Intense truck traffic7	Yes[6]	1.18 (0.93-1.48)	1.17 (0.92-1.49)	1.48 (1.04-2.11)	1.48 (1.02-2.14)	1.26 (1.02-1.56)	1.23 (0.99-1.54)	1.43 (1.06-1.92)	1.43 (1.05-1.95)
Environmental tobacco smoke exposure	Yes[6]	1.43 (1.16-1.78)	1.29 (1.03-1.63)	1.07 (0.76-1.50)	1.16 (0.80-1.68)	1.40 (1.15-1.70)	1.26 (1.02-1.56)	1.33 (1.00-1.77)	1.29 (0.95-1.75)
Cooking Fuel	Gas or electricity	1	1	1	1	1	1	1	1
	Wood or coal	1.21 (0.93-1.57)	0.89 (0.65-1.21)	1.44 (0.97-2.13)	1.87 (1.16-3.01)	1.10 (0.86-1.41)	0.84 (0.63-1.13)	0.95 (0.66-1.37)	0.83 (0.54-1.28)
Presence of disease vectors at home[8]	Quartile 1	1	1	1	1	1	1	1	1
	Quartile 2	1.20 (0.91-1.57)	1.15 (0.87-1.53)	1.08 (0.70-1.66)	1.18 (0.75-1.86)	0.96 (0.74-1.24)	0.90 (0.69-1.17)	0.92 (0.62-1.35)	0.89 (0.60-1.33)
	Quartile 3	1.35 (1.00-1.83)	1.21 (0.88-1.65)	1.18 (0.73-1.90)	1.19 (0.71-2.00)	1.37 (1.04-1.80)	1.29 (0.97-1.72)	1.55 (1.06-2.27)	1.57 (1.05-2.33)
	Quartile 4	1.85 (1.35-2.54)	1.52 (1.07-2.16)	1.89 (1.18-3.01)	2.38 (1.41-4.01)	1.96 (1.46-2.62)	1.72 (1.24-2.38)	1.89 (1.26-2.82)	1.89 (1.20-2.96)

Table 4.4 *(continued)*

		Current asthma symptoms WQ[1]		Current asthma symptoms VQ[2]		Current Rhinoconjunctivitis symptoms[3]		Current eczema symptoms[4]	
Precarious household conditions[9]	None	1	1	1	1	1	1	1	1
	1	1.27 (0.98-1.64)	1.23 (0.93-1.61)	0.97 (0.64-1.48)	0.90 (0.56-1.43)	1.04 (0.81-1.33)	1.00 (0.77-1.30)	0.96 (0.67-1.38)	0.92 (0.63-1.35)
	≥ 2	1.59 (1.11-2.27)	1.41 (0.94-2.10)	1.09 (0.60-1.99)	1.04 (0.54-2.00)	1.70 (1.22-2.37)	1.57 (1.08-2.27)	1.28 (0.79-2.08)	1.16 (0.67-1.99)
Number of item ownership[10]	Quartile 1	1	-	1	-	1	-	1	-
	Quartile 2	0.87 (0.65-1.16)	-	0.99 (0.62-1.58)	-	0.79 (0.60-1.03)	-	1.29 (0.87-1.90)	-
	Quartile 3	0.79 (0.59-1.06)	-	1.12 (0.71-1.77)	-	0.78 (0.59-1.02)	-	1.14 (0.76-1.70)	-
	Quartile 4	0.86 (0.64-1.14)	-	1.02 (0.64-1.60)	-	0.82 (0.63-1.06)	-	1.14 (0.77-1.68)	-

[1] Positive answer to the question: ‘‘Have you had wheezing or whistling in the chest during the last 12 months?’ ’in the written questionnaire.

[2] Positive answers to the first scene of the video questionnaire: Moderate wheezing at rest

[3] Presence of sneezing or a runny or blocked nose, accompanied by itchy watery eyes without a cold or the flu.

[4] Presence of an itchy rash at any time in the past 12 months affecting 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

[5]Adjusted by sex, age and place of living

[6] Comparison group: no contact / exposure

[7]Intense truck traffic: Almost the whole day

[8]Disease vectors: fleas, ticks, kissing bugs, mice, bedbugs, flies

[9] Precarious floor: soil; Precarious walls: cane, palm or trunk; Precarious source of water for cooking: river, lake, pump or water tank car; Precarious sewage system: to the surface or to a septic tank

[10] Item ownership: Radio, TV, bicycle, motorbike, car, refrigerator, telephone.

4.3) ASSOCIATION BETWEEN DIET AND ASTHMA SYMPTOMS

Comparing the 685 children with missing data to those with complete data showed that they were statistically significantly older. In addition, they tended to watch less TV (p_{Chi}^2=0.08). No other major differences could be found between the two groups (Table 4.5).

Table 4.5 Comparison between children included and excluded (N=2340)

		Included[1] (n=1655)	**Excluded[2] (n=685)**	**P value[3]**
Sex	Female	862 (52.1)	355 (52.0)	0.94
	Male	791 (47.9)	328 (48.0)	
Age	≤ 10 years	737 (44.7)	260 (38.5)	0.02
	11 years	669 (40.6)	306 (45.3)	
	≥ 12 years	243 (14.7)	110 (16.3)	
Place of living	Rural	420 (25.4)	193 (28.3)	0.16
	Urban	1235 (74.6)	492 (71.8)	
Asthma symptoms (12 m onths prevalence)	Written Questionnaire[4]	281 (17.0)	133 (19.7)	0.12
	Video Questionnaire[5]	105 (6.3)	43 (6.7)	0.78
Body mass index	Normal weight	1071 (65.0)	452 (67.2)	0.39
	Overweight	451 (27.4)	180 (26.7)	
	Obesity	125 (7.6)	41 (6.1)	
Intense exercise	Never/ Occasionally	278 (16.9)	129 (19.6)	0.28
	1-2 times per week	845 (51.4)	321 (48.7)	
	≥ 3 times per week	520 (31.6)	209 (31.7)	
Time watching television	≤ 2 hours per week	1024 (63.1)	438 (67.1)	0.08
	>3 hours per week	598 (36.9)	215 (32.9)	
Time playing video games	≤ 2 hours per day	1309 (87.7)	514 (86.0)	0.27
	>3 hours per day	183 (12.3)	84 (14.0)	
Mediterranean Diet Score	Median (range)	13 (3-22)	-	-

[1] All the food questions are completed; [2] One or more food questions are missing; [3] Chi square Test; [4] Positive answer to the question: ''Have you had wheezing or whistling in the chest during the last 12 months?'' in the written questionnaire.

[5]Positive answer to the first scene of the video questionnaire: Moderate wheezing at rest

The median age of children with complete data was 11 years (range 9 to 15 years), and 52% were female. The prevalence of current asthma symptoms was 17% in the WQ and 6% in the VQ. Around 35% of the children were overweight or obese. The study population showed low to medium adherence to the MD, with a median score of 13 points (range 3 to 22 points) (Table 4.5). The consumption of fruits, vegetables, cereals, rice, and potatoes three or more times a week was higher (>50%) than the other food types (Table 4.6).

Table 4.6 Intake frequencies of different foods (N=1655)

Food	**Never or occasionally**		**Once or twice a week**		**Three or more times a week**	
	n	%	n	%	n	%
Meat	189	11.4	868	52.4	598	36.1
Fish	804	48.6	679	41.0	172	10.4
Fruit	111	6.7	506	30.6	1038	62.7
Vegetables	156	9.4	519	31.4	980	59.2
Pulses	555	33.5	743	44.9	357	21.6
Cereal	205	12.4	458	27.7	992	59.9
Pasta	251	15.2	720	43.5	684	41.3
Rice	114	6.9	609	36.8	932	56.3
Butter	692	41.8	670	41.2	265	16.3
Margarine	921	58.1	458	28.9	207	13.1
Nuts	523	32.2	742	45.7	357	22.0
Potatoes	99	6.0	384	23.2	1172	70.8
Milk	209	12.6	770	46.5	676	40.8
Eggs	186	11.4	874	53.7	567	34.8
Corn	493	30.8	742	46.4	364	22.8
Fast food	380	23.0	784	47.4	491	29.7

4.3.1) FOOD INTAKE AND ASTHMA SYMPTOMS

Overall, no statistically significant association was shown between food consumption and asthma symptoms. For both asthma definitions there was a tendency that corn and fast food consumption increased the risk of asthma symptoms while fruit, vegetables, cereal, rice, butter, milk consumption decreased the risk of asthma symptoms (Table 4.7).

While margarine and nuts seemed to be a risk factor for asthma based on the WQ there was a tendency for a protective effect of both in the VQ. Finally, pasta consumption was not statistically significantly inversely related with asthma symptoms only in the VQ. Adjusted models basically confirmed the results of the crude models.

Table 4.7 Association between the frequency of food groups intake and current asthma symptoms during last year (Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals). Comparison group: never or occasionally (N=1655).

	Written questionnaire				Video questionnaire			
Food	**Crude OR (95% CI)**		**aOR[1] (95% CI)**		**Crude OR (95% CI)**		**aOR[1] (95% CI)**	
	Frequency of intake[2]		**Frequency of intake[2]**		**Frequency of intake[2]**		**Frequency of intake[2]**	
	1-2/week	**3+/week**	**1-2/week**	**3+/week**	**1-2/week**	**3+/week**	**1-2/week**	**3+/week**
Meat	1.16 (0.8-1.8)	1.08 (0.7-1.7)	1.19 (0.8-1.8)	1.11 (0.7-1.8)	0.73 (0.4-1.4)	1.00 (0.5-1.9)	0.76 (0.4-1.4)	1.00 (0.5-2.0)
Fish	0.97 (0.7-1.3)	1.28 (0.8-1.9)	0.98 (0.7-1.3)	1.37 (0.9-2.1)	0.94 (0.6-1.4)	0.76 (0.4-1.6)	0.94 (0.6-1.4)	0.75 (0.4-1.6)
Fruit	0.63 (0.4-1.0)	0.76 (0.5-1.2)	0.71 (0.4-1.2)	0.84 (0.5-1.4)	0.55 (0.3-1.1)	0.54 (0.3-1.0)	0.55 (0.3-1.1)	0.53 (0.3-1.0)
Vegetables	0.98 (0.6-1.5)	0.83 (0.5-1.3)	1.01 (0.6-1.6)	0.85 (0.5-1.3)	0.91 (0.4-1.8)	0.76 (0.5-1.7)	0.90 (0.4-1.9)	0.94 (0.5-1.9)
Pulses	1.10 (0.8-1.5)	1.27 (0.9-1.8)	1.08 (0.8-1.5)	1.22 (0.9-1.7)	0.99 (0.6-1.5)	0.83 (0.5-1.5)	1.01 (0.6-1.6)	0.91 (0.5-1.6)
Cereal	0.74 (0.5-1.1)	0.85 (0.6-1.2)	0.76 (0.5-1.2)	0.87 (0.6-1.3)	0.66 (0.3-1.3)	0.84 (0.5-1.5)	0.69 (0.4-1.4)	0.86 (0.5-1.5)
Pasta	0.98 (0.7-1.4)	1.14 (0.8-1.7)	1.01 (0.7-1.6)	1.18 (0.8-1.7)	0.49 (0.3-0.9)	0.77 (0.5-1.3)	0.51 (0.3-0.9)	0.85 (0.5-1.5)
Rice	0.86 (0.5-1.5)	0.99(0.6-1.6)	0.94 (0.5-1.6)	1.07 (0.3-1.8)	0.56 (0.3-1.1)	0.66 (0.3-1.3)	0.58 (0.3-1.2)	0.73 (0.4-1.5)
Butter	0.95 (0.7-1.2)	0.80 (0.5-1.2)	0.93 (0.7-1.2)	0.83 (0.6-1.2)	0.80 (0.5-1.2)	0.70 (0.4-1.3)	0.81 (0.5-1.3)	0.68 (0.4-1.3)
Margarine	1.05 (0.8-1.4)	1.48 (1.0-2.1)	1.07 (0.8-1.5)	1.45 (1.0-2.1)	0.85 (0.5-1.3)	0.52 (0.2-1.1)	0.83 (0.5-1.3)	0.52 (0.2-1.1)
Nuts	1.16 (0.9-1.6)	1.59 (1.1-2.3)	1.12 (0.8-1.5)	1.58 (1.1-2.2)	0.94 (0.6-1.5)	0.91 (0.5-1.6)	0.99 (0.6-1.6)	1.00 (0.6-1.7)
Potatoes	0.84 (0.5-1.5)	0.91 (0.5-1.5)	0.94 (0.5-1.7)	1.00 (0.6-2.1)	1.29 (0.6-3.0)	0.78 (0.3-1.7)	1.45 (0.6-3.6)	0.91 (0.4-2.2)
Milk	0.79 (0.5-1.2)	0.92 (0.6-1.4)	0.82 (0.5-1.2)	0.96 (0.6-1.4)	0.96 (0.5-1.7)	0.78 (0.4-1.4)	1.11 (0.6-2.1)	0.83 (0.4-1.6)
Eggs	0.90 (0.6-1.4)	1.14 (0.7-1.8)	1.97 (0.6-1.5)	1.16 (0.7-1.8)	0.74 (0.4-1.3)	0.73 (0.4-1.4)	0.78 (0.4-1.4)	0.82 (0.4-1.6)
Corn	1.19 (0.9-1.6)	1.60 (1.1-2.3)	1.18 (0.9-1.6)	1.50 (1.0-2.2)	0.85 (0.5-1.3)	0.95 (0.6-1.6)	0.91 (0.6-1.5)	1.10 (0.6-1.9)
Fast food	1.00 (0.7-1.4)	1.35 (1.0-1.9)	1.07 (0.8-1.5)	1.40 (1.0-2.0)	0.78 (0.5-1.3)	1.01 (0.6-1.7)	0.79 (0.5-1.3)	1.03 (0.6-1.7)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; [1]Adjusted for sex, age, place of living, [2]Reference category: Never/Occasionally

4.3.2) MD SCORE AND ASTHMA SYMPTOMS

Overall the lowest quartile of the MD score seemed to be at highest risk for asthma symptoms. This association was stronger in the VQ (adjusted OR; 95%CI: second quartile 0.6; 0.3-0.9, third quartile 0.7; 0.4-1.2, fourth quartile 0.6; 0.3-1.0) than in the WQ (second quartile 0.99; 0.7-1.4, third quartile 0.7; 0.5-1.1, fourth quartile 0.8; 0.6-1.2) (Table 4.8).

Table 4.8 Association between different risk factors under study and current asthma symptoms during the past 12 months (unadjusted and adjusted Odds Ratios with 95% Confidence Intervals) (N=1655)

		Current asthma symptoms Written questionnaire		**Current asthma symptoms Video questionnaire**	
Variables		**Crude OR (95%CI)**	**a OR (95%CI)**	**Crude OR (95%CI)**	**a OR (95%CI)**
Sex	Female	1	1	1	1
	Male	0.99 (0.8-1.3)	0.98 (0.8-1.3)	0.87 (0.6-1.3)	0.91 (0.6-1.4)
Age	≤ 10 years	1	1	1	1
	11 years	1.20 (0.9-1.6)	1.14 (0.9-1.5)	0.56 (0.4-0.9)	0.62 (0.4-1.0)
	≥ 12 years	0.96 (0.6-1.4)	0.86 (0.6-1.3)	0.76 (0.4-1.4)	0.86 (0.5-1.6)
Place of living	Rural	1	1	1	1
	Urban	0.68 (0.5-0.9)	0.69 (0.5-0.9)	2.32 (1.3-4.1)	2.24 (1.3-4.0)
Body mass index	Normal weight	1	-	1	-
	Overweight	0.95 (0.7-1.3)	-	0.95 (0.6-1.5)	-
	Obesity	1.12 (0.7-1.8)	-	1.45 (0.7-2.8)	-
Intense exercise	Never/ Occasionally	1	-	1	-
	1-2 times per week	0.90 (0.6-1.3)	-	0.68 (0.4-1.1)	-
	≥ 3 times per week	0.83 (0.6-1.2)	-	0.73 (0.4-1.3)	-
Time watching television	≤ 2 hours per week	1	-	1	-
	>3 hours per week	1.05 (0.8-1.4)	-	1.07 (0.7-1.6)	-
Time playing video games	≤ 2 hours per day	1	-	1	-
	>3 hours per day	1.41 (0.9-2.0)	-	1.40 (0.8-2.5)	-
Mediterranean diet score	Quartile 1	1	1	1	1
	Quartile 2	0.98 (0.7-1.4)	0.99 (0.7-1.4)	0.57 (0.3-1.0)	0.56 (0.3-0.9)
	Quartile 3	0.71 (0.5-1.0)	0.72 (0.5-1.1)	0.73 (0.4-1.3)	0.70 (0.4-1.2)
	Quartile 4	0.84 (0.6-1.2)	0.84 (0.6-1.2)	0.63 (0.4-1.1)	0.59 (0.3-1.0)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

5) DISCUSSION

This is the first study in Bolivia exploring the prevalence and risk factors of asthma and allergies in a representative sample of children from urban and rural areas using standardized methods.

Our results showed a similar pattern of asthma and allergies diseases as reported in Latin America. It seems that modifiable environmental factors such as diet, outdoor or indoor environmental factors and hygiene conditions at home were associated with an increased risk of asthma and allergies in children living in this region.

Next we are going to discuss different aspects related with methods and results of our study.

5.1) METHODS

5.1.1) DESIGN

A limitation of our study is related to the cross-sectional design, with the exposure and outcome being measured simultaneously, thus it is not possible to determine the temporality of the association and then causality. Although this design is prone to induce recall bias, we assume that blinding the participants to the hypothesis under investigation minimized this concern.

5.1.2) STUDY POPULATION

The participation was similar to the one reported from other studies following the ISAAC protocol in Latin America[78]. Although the participation was over 90%, 7 out of the selected 43 schools did not agree to participate (16%). Most of these schools were from urban areas. The main reason for non-participation was the frequent implementation of different governmental programs, which interrupt the education schedule. It is not assumed that this might have resulted in selection bias.

Our study population differed from the one suggested by the International Study of Asthma and Allergies in Childhood [56]. We included children in the 5th grade (age range 9-15 years) as the selection of 8th grade might have affected the generalizability of the results because in

Bolivia drop-out rate in following grades is high especially in public schools[149]. We considered that these children are able to understand and adequately respond the questionnaire. The alternative to select 1st grade pupils and use the International Study of Asthma and Allergies in Childhood parental questionnaire was omitted due the overall adults low literacy level in this region[136].

5.1.3) QUESTIONNAIRES

Given the sociocultural and educational background differences in our study population, we considered necessary to include the video questionnaire to explore prevalence of asthma symptoms and its association with diet and environmental risk factors as it has been described as being sensitive to language, culture, or literacy differences[154, 162].

Although the written questionnaire has been proven to be valid for eczema and rhinitis symptoms[163, 164] it is possible that the results were also affected by interpretation problems related to cultural and educational background differences especially in rural areas. However, the prevalence of rhinitis and eczema symptoms was comparable to previous Latin American studies[77].

In our analysis to explore risk factors, we used a symptom based definition of asthma, rhinoconjunctivitis and eczema in order to avoid major diagnostic differences related to access to medical care, language and medical practice. We preferred to use the 12-months prevalence of symptoms over lifetime prevalence as previous studies have shown that this definition is less prone to recall bias[165].

The ISAAC environmental questionnaire was chosen to explore diet and environmental factors, since it is a standardized instrument which has been used successfully in different contexts[166]. Nevertheless, this instrument has certain limitations to explore diet: it only assesses current information on food consumption; it does not assess the amount, combination or cooking process of food which varies widely between different countries and cultures[167].

5.1.4) FIELD WORK

Field work of our study included several recommendations by the ISAAC project. These recommendations are related to the approach to schools, parents and children (e.g. avoid mentioning the terms "asthma," "rhinitis" and “”eczema” at any stage of the field work), information management (e.g. double data entry, no change questionnaire responses)[56]. Adherence to ISAAC methodology and field work, allowed us to perform the comparison of our results with similar ones in a reliable way including international reports.

5.1.5) STATISTICAL ANALYSIS

Although cross sectional design is appropriate mainly for descriptive research, it is also used in some etiological studies, considering its limitation to establish causality. Two ratio measures of effect are suggested for analysis of cross sectional data with a dichotomous outcome variable: the prevalence odds ratio (POR) and the prevalence ratio (PRR). The choice between these two has been the source of ongoing debate in the epidemiological literature over the past few years[168]. Although PRR appears to be a more meaningful statistic for cross sectional data, epidemiological studies reported more frequently POR than PRR, possible due to the routine use of logistic regression. But several studies have showed that if the condition under study (outcome) is of low prevalence, then POR would be numerically similar to PRR[169].

In our study POR were calculated due to the widespread use of this measure in International Studies on this topic and therefore the increased possibility to compare our results. Moreover, given that we analyzed chronic diseases, we could assume that both measures (PRR and POR) may not be very different.

One of the statistical challenges when computing scores such as Mediterranean diet score is related to dealing with missing data. Although have been reported that multiple imputation method is a good alternative to manage missing data[170, 171], not many studies have used this method to calculate the Mediterranean diet score and then the association with diet and asthma symptoms. For such reason, we decided to develop case-analysis in order to keep international comparability.

5.2) RESULTS

5.2.1) PREVALENCE OF SYMPTOMS

The prevalence of asthma, rhinoconjunctivitis and eczema symptoms found in this study was within the range reported for South America[77, 78, 130]. Difference between rural and urban areas indicated higher prevalences for urban areas, although this difference was not significant and it was smaller in comparison with previous studies[85].

In accordance with previous studies, we have found a low agreement between written and video questionnaire for asthma with much higher prevalence in the written than in the video questionnaire[154]. Given the extremely high prevalence in the written asthma questionnaire as compared to the video questionnaire and to other studies in Latin America[133] one might assume that the results reported by video questionnaire could be more reliable than those from written questionnaire. Overall, the prevalence of current asthma symptoms (6.4%) were lower than the Latin American average (10.3%), especially those reported from the neighboring countries (17.1% in Peru, 12.1% in Chile, 10.4% in Paraguay and 8.1% in Argentina)[133]. It is likely that in our study, the unfamiliarity with the terms used in the written questionnaire could cause over reporting of symptoms especially in the rural population[172].

Current and severe rhinoconjunctivitis prevalence were higher than those reported in Latin America (17.3% and 1.1% respectively), but are quite similar with prevalence in urban areas in Santa Cruz, Bolivia (22.4% and 1.8% respectively) [77]. In addition, atopic eczema prevalence is similar than the average prevalence value for Latin America (9.5%) [130].

Several studies explored the possible relation between ethnicity, poverty, environmental pollution, level of industrialization, health conditions or genetic factors and the prevalence of asthma and allergies symptoms. The real impact of such factors remains unclear since large differences have been described specially in Latin America[109], but there is common agreement about the importance of environmental factors for the development of asthma and allergic diseases[173]. Although no significant differences were found in current symptoms of asthma, rhinoconjunctivitis and eczema between urban and rural areas, our study found a lower prevalence of severe symptoms of asthma and allergy prevalence in rural areas where extreme

poverty is above 70%, with more than 40% of the population engaged in agricultural activities and more than 90% of the population identifying themselves with native Quechua ethnicity[147].

5.2.2) Association between Environmental factors and asthma, rhinoconjunctivitis and eczema symptoms

In this analysis, outdoor as well as indoor environmental factors and hygiene conditions at home were associated with an increased risk of asthma and allergies in children living in Oropeza province in Bolivia. This contributes to our understanding of the importance of modifiable environmental factors in the development of asthma and allergies in children in Bolivia.

Some studies have stressed the importance of early exposure (first year of life) of some environmental factors on the development of asthma and allergies[174, 175]. In our study it was not possible to reliably explore this information. One might assume that most of these exposures have not changed over time especially in the Bolivian setting. Therefore, in our study current exposure might well reflect early life exposure.

The ISAAC video questionnaire was described as a sensitive tool for language, culture, or literacy differences to assess asthma symptoms[154, 162]. As our study population presents a large range of sociocultural and educational background we implemented both – the video as well as the written questionnaire. The consistency of our results indicates the validity of the findings.

The results of this study have pointed out several sources of indoor and outdoor air pollution as risk factors of asthma and allergies in children. It is well known that environmental tobacco smoke is associated with asthma symptoms. A recent systematic review and meta-analysis of 79 prospective studies found that exposure to pre- or postnatal environmental tobacco smoke exposure was associated with a 30% to 70% increased risk of incident wheezing[165, 176]. Although the evidence is not too strong for rhinoconjunctivitis and eczema symptoms[177], our results support this association.

Even though the associations between outdoor air pollution with asthma and allergy symptoms have shown paradoxical results in Latin America[109], our results agree with those

reported by the International Study of Asthma and Allergies in Childhood phase 3 showing a positive association between intense truck traffic and asthma, rhinoconjuntivitis and eczema symptoms[178]. It could be explained by the interaction of air pollutants with the immune system, increasing the allergenicity of these pathologies.

Our results support previous findings reported for Latin America[86, 93, 109], showing that asthma and allergies are associated with poverty and inequality. Poverty is a complex social and economic condition and it is not easy to identify the effects of the many associated environmental and lifestyle factors contributing on the development of asthma and allergies[86, 93]. Poverty is associated with a number of known risk factors for asthma at individual and neighbourhood level as smoking[113, 177], high indoor and outdoor pollution[179-182], diet[166, 183], ethnicity[184-186], lack of good quality potable water[187], sewer systems[188], and waste collection and disposal[189].
In the same way poverty is linked with poor hygienic conditions. This might explain why our as well as other Latin American studies[73, 86, 109] have shown lack of hygiene as risk factor for asthma and allergies while other – mainly European studies[190-192] – have indicated an inverse relationship between low level of hygiene and such diseases. Our findings are consistent for asthma, allergic rhinoconjuntivitis and - to some extend – eczema. This indicates that differences in phenotype of asthma, as discussed in earlier studies[93, 193], are not the main reason for the contradicting findings between Europe and Latin America.

5.2.3) DIET AND ASTHMA SYMPTOMS

The respective analysis suggests that Mediterranean diet may be a protective factor for current asthma symptoms in school-age children from a culturally diverse, mainly rural region of Bolivia. In contrast, results for single food groups were weak and inconsistent.

Two approaches were used to assess diet: individual food groups and the Mediterranean diet score, the latter has been suggested as a good approach in epidemiological studies[120, 194] and a good alternative to explore diet food behavior in different contexts improving statistical power[122].

The video scene chosen to define asthmas symptoms might reflect more severe asthma than the written questionnaire as it demonstrates a child having wheezing symptoms at rest [155, 195].

This, as well as the difference in the validity of both instruments in the population under study might explain why the association between Mediterranean diet and asthma symptoms was stronger for the video questionnaire than for the written questionnaire.

In agreement with other studies, our results showed an association between fast food consumption[166] and corn consumption and asthma symptoms, these association were only statistically significant in the written questionnaire. Some of the fast food components have been linked with modulation of immune reactions and consequently asthma[117, 196]. Although there are no studies addressing the corn influence on asthma symptoms, such relationship needs to be assessed in the region considering corn consumption as a marker of different style of diet in the region.

Although not statistically significant in the multivariate models, our results support the other studies findings showing a protective effect of fruit, vegetables, cereal, rice, butter and milk consumption on current asthma symptoms[121, 161, 166].

Margarine, nuts and pasta showed inconsistences between written questionnaire and video questionnaire, such results might be explained as a chance finding; nevertheless, it is possible that children did not identify properly margarine and butter, being margarine the food with the highest number of missing values (11%). In addition, nuts have been suggested as protective factor for asthma symptoms in previous studies[197], but our study showed nuts as a risk factor. One might assume the consumption of salty nuts snacks competes with the consumption of fruits and other healthy snacks and salty snacks have shown a positive association with asthma symptoms[198].

Our results assessing dietary patterns support the hypothesis that the effect of food on asthma symptoms is achieved by the interaction or mixture of several components in the diet[117, 121, 122].

Some studies have proposed that the Mediterranean diet could explain its inverse association with asthma symptoms through some mechanisms proposed previously. First, this diet is characterized by high consumption of foods rich in antioxidants which improve host resistence[117, 199], and second, a higher consumption of ω-3 PUFAs in comparison with ω-6, which decrease susceptibility to allergies by inhibiting synthesis of prostaglandin E2 (PGE2) and promoting the differentiation into helper-inducer T-lymphocytes (Th1) cells, and suppressing the Th2-cell phenotype by decreasing class switching to IgE[117].

Our populations showed to have a medium adherence to Mediterranean diet compared to other population in Spain[200] and a particular low consumption of one of the main components of the Mediterranean diet pattern: fish and oil fish with high concentration of ω-3 PUFAs. The

low availability and high cost of fish in Bolivia result in a high consumption of beef, chicken and pork. Additionally, the regional food cooking process is characterized by high salt content, condiments and fried food, not corresponding to the traditional cooking process of the Mediterranean diet.

6) CONCLUSION

This is the first report of childhood asthma and allergy symptoms in rural and urban areas of Bolivia using a standardized methodology. The prevalence for asthma, rhinoconjunctivitis and eczema symptoms was within the range reported for South America. It shows that asthma and allergies are an important public health problem in Latin America, and also in this region of Bolivia.

The overall results of prevalence showed that children living in urban areas of Bolivia seem to have a higher prevalence only in severe symptoms of asthma and allergies compared to children living in the country side.

The results regarding association between environmental factors and asthma and allergies support previous findings reported for Latin America, showing that asthma and allergies are associated with poverty. Therefore health policies that promote the reduction of harmful environmental factors such as environmental tobacco smoke or precarious housing conditions are needed in order to reduce the important disease burden of these pathologies.

Our results on the relationship of diet and asthma suggest a protective association between Mediterranean diet and current asthma symptoms. For individual foods the results are inconsistent and less clear, suggesting the importance of the interaction of several components in the diet. However, there is not enough evidence to suggest Mediterranean diet as public health police. Our results suggest the need of promotion of healthy dietary habits among children in order to avoid the rapid increase of non-communicable diseases in this region.

The implementation of prospective and multidisciplinary studies in this region comparing high and low risk populations could offer an advantage since Bolivia and other Latin American countries are currently coursing an epidemiological transition process, with recent lifestyle changes and cultural diverse backgrounds, which could be better addressed in the long term. Performing such studies, may provide important clues to identify potential protective factors and avoidable risk factors that could be used to design new interventions.

More research is needed to identify causes of asthma and allergies, considering phenotype, timing of exposure, genetic and environmental factors interaction that help us to understand

the complex mechanism for the development of asthma and allergies in children and support the need for public health measures according the local context.

Bolivia offers important research opportunities to deepen in this topic because the enormous diversity in social, environmental, genetic factors and current step of epidemiological transition. It could help to understand the large differences in prevalence of asthma and allergy symptoms observed around the world.

7) REFERENCES

1. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: A global synthesis. *Allergol Immunopathol (Madr)* 2012.
2. Lobo F, Lobo B. Quality of Life in Asthmatic Outpatients. *J Asthma* 2008;**45**:27-32.
3. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733-43.
4. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2012. Available from: http://www.ginasthma.org/.
5. Murphy DM, O'Byrne PM. Recent advances in the pathophysiology of asthma. *Chest* 2010;**137**:1417-26.
6. Cohn L, Elias JA, Chupp GL. Asthma: mechanisms of disease persistence and progression. *Annu Rev Immunol* 2004;**22**:789-815.
7. James A. Airway remodeling in asthma. *Curr Opin Pulm Med* 2005;**11**:1-6.
8. Tan WC. Viruses in asthma exacerbations. *Curr Opin Pulm Med* 2005;**11**:21-6.
9. Calhoun WJ. Nocturnal asthma. *Chest* 2003;**123**:399S-405S.
10. Bumbacea D, Campbell D, Nguyen L, Carr D, Barnes PJ, Robinson D, et al. Parameters associated with persistent airflow obstruction in chronic severe asthma. *Eur Respir J* 2004;**24**:122-8.
11. Adams A, Saglani S. Difficult-to-Treat Asthma in Childhood. *Paediatr Drugs* 2013.
12. Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. *Eur Respir J* 2004;**24**:822-33.
13. Bel EH. Clinical phenotypes of asthma. *Curr Opin Pulm Med* 2004;**10**:44-50.
14. Stein RT, Martinez FD. Asthma phenotypes in childhood: lessons from an epidemiological approach. *Paediatric respiratory reviews* 2004;**5**:155-61.
15. Levy ML, Fletcher M, Price DB, Hausen T, Halbert RJ, Yawn BP. International Primary Care Respiratory Group (IPCRG) Guidelines: diagnosis of respiratory diseases in primary care. *Prim Care Respir J* 2006;**15**:20-34.
16. Irwin RS, Boulet LP, Cloutier MM, Fuller R, Gold PM, Hoffstein V, et al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. *Chest* 1998;**114**:133S-81S.
17. Tan WC, Tan CH, Teoh PC. The role of climatic conditions and histamine release in exercise-induced bronchoconstriction. *Ann Acad Med Singapore* 1985;**14**:465-9.
18. Pizzichini MM, Popov TA, Efthimiadis A, Hussack P, Evans S, Pizzichini E, et al. Spontaneous and induced sputum to measure indices of airway inflammation in asthma. *Am J Respir Crit Care Med* 1996;**154**:866-9.
19. Kharitonov S, Alving K, Barnes PJ. Exhaled and nasal nitric oxide measurements: recommendations. The European Respiratory Society Task Force. *Eur Respir J* 1997;**10**:1683-93.
20. Horvath I, Hunt J, Barnes PJ, Alving K, Antczak A, Baraldi E, et al. Exhaled breath condensate: methodological recommendations and unresolved questions. *Eur Respir J* 2005;**26**:523-48.
21. Urbano FL. Review of the NAEPP 2007 Expert Panel Report (EPR-3) on Asthma Diagnosis and Treatment Guidelines. *Journal of managed care pharmacy: JMCP* 2008;**14**:41.
22. Janson C, Anto J, Burney P, Chinn S, de Marco R, Heinrich J, et al. The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. *Eur Respir J* 2001;**18**:598-611.
23. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;**149**:358-64.

24. Cohen RT, Canino GJ, Bird HR, Shen S, Rosner BA, Celedon JC. Area of residence, birthplace, and asthma in Puerto Rican children. *Chest* 2007;**131**:1331-8.
25. Burke W, Fesinmeyer M, Reed K, Hampson L, Carlsten C. Family history as a predictor of asthma risk. *Am J Prev Med* 2003;**24**:160-9.
26. World Health Organization. Asthma. *Chronic respiratory diseases* 2013; Available at http://www.who.int/respiratory/asthma/en/index.html. Accessed.
27. Bousquet J, Bousquet PJ, Godard P, Daures J-P. The public health implications of asthma. *Bull World Health Organ* 2005;**83**:548-54.
28. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;**9**:24.
29. Masoli M, Fabian D, Holt S, Beasley R, Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;**59**:469-78.
30. International Consensus Report on the diagnosis and management of rhinitis. International Rhinitis Management Working Group. *Allergy* 1994;**49**:1-34.
31. Poole JA, Rosenwasser LJ. The role of immunoglobulin E and immune inflammation: implications in allergic rhinitis. *Curr Allergy Asthma Rep* 2005;**5**:252-8.
32. Punnonen J, Aversa GG, Vandekerckhove B, Roncarolo MG, de Vries JE. Induction of isotype switching and Ig production by CD5+ and CD10+ human fetal B cells. *J Immunol* 1992;**148**:3398-404.
33. Smurthwaite L, Durham SR. Local IgE synthesis in allergic rhinitis and asthma. *Curr Allergy Asthma Rep* 2002;**2**:231-8.
34. Prussin C, Metcalfe DD. 5. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol* 2006;**117**:S450-6.
35. Roche N, Chinet TC, Huchon GJ. Allergic and nonallergic interactions between house dust mite allergens and airway mucosa. *Eur Respir J* 1997;**10**:719-26.
36. Gluck U, Gebbers J. Epithelial changes in seasonal allergic rhinitis throughout the year: evidence of coexistent air pollution and local secretory IgA deficiency? *ORL J Otorhinolaryngol Relat Spec* 2000;**62**:68-75.
37. Gerth van Wijk RG, de Graaf-in 't Veld C, Garrelds IM. Nasal hyperreactivity. *Rhinology* 1999;**37**:50-5.
38. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003;**111**:1171-83; quiz 84.
39. Bachert C, Vignola AM, Gevaert P, Leynaert B, Van Cauwenberge P, Bousquet J. Allergic rhinitis, rhinosinusitis, and asthma: one airway disease. *Immunol Allergy Clin North Am* 2004;**24**:19-43.
40. Bousquet J, Khaltaev N, Cruz A, Denburg J, Fokkens W, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008*. *Allergy* 2008;**63**:8-160.
41. Scadding GK, Durham SR, Mirakian R, Jones NS, Leech SC, Farooque S, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy* 2008;**38**:19-42.
42. Serra HA, Alves O, Rizzo LF, Devoto FM, Ascierto H. Loratadine-pseudoephedrine in children with allergic rhinitis, a controlled double-blind trial. *Br J Clin Pharmacol* 1998;**45**:147-50.
43. Passali D, Passali FM, Damiani V, Passali GC, Bellussi L. Treatment of inferior turbinate hypertrophy: a randomized clinical trial. *Ann Otol Rhinol Laryngol* 2003;**112**:683-8.
44. Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson HR, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997;**8**:161-76.
45. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;**113**:832-6.
46. Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol* 2003;**112**:252-62.

47. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest* 2004;**113**:651-7.
48. Hamid Q, Boguniewicz M, Leung DY. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest* 1994;**94**:870-6.
49. Liu X, Beaty TH, Deindl P, Huang SK, Lau S, Sommerfeld C, et al. Associations between total serum IgE levels and the 6 potentially functional variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. *J Allergy Clin Immunol* 2003;**112**:382-8.
50. Lewis-Jones S, Mugglestone MA. Guidelines: Management of atopic eczema in children aged up to 12 years: summary of NICE guidance. *BMJ: British Medical Journal* 2007;**335**:1263.
51. Ersser SJ, Latter S, Sibley A, Satherley PA, Welbourne S. Psychological and educational interventions for atopic eczema in children. *Cochrane Database Syst Rev* 2007:CD004054.
52. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *Journal of Allergy and Clinical Immunology* 2009;**124**:1251-8. e23.
53. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. *Arch Dis Child* 1997;**76**:159-62.
54. Carroll CL, Balkrishnan R, Feldman SR, Fleischer AB, Manuel JC. The burden of atopic dermatitis: impact on the patient, family, and society. *Pediatric dermatology* 2005;**22**:192-9.
55. Asher I. The ISAAC Story. *20 Anos em Portugal* 2011;**42**:27.
56. Ellwood P, Asher M, Beasley R, Clayton T, Stewart A. The International Study of Asthma and Allergies in Childhood (ISAAC): Phase Three rationale and methods Research Methods. *The International Journal of Tuberculosis and Lung Disease* 2005;**9**:10-6.
57. Asher M, Keil U, Anderson H, al e. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483-91.
58. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998;**351**:1225-32.
59. Stewart AW, Mitchell EA, Pearce N, Strachan DP, Weiland SK. The relationship of per capita gross national product to the prevalence of symptoms of asthma and other atopic diseases in children (ISAAC). *Int J Epidemiol* 2001;**30**:173-9.
60. Ellwood P, Asher MI, Bjorksten B, Burr M, Pearce N, Robertson CF. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. ISAAC Phase One Study Group. *Eur Respir J* 2001;**17**:436-43.
61. Weiland SK, Husing A, Strachan DP, Rzehak P, Pearce N. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 2004;**61**:609-15.
62. von Mutius E, Pearce N, Beasley R, Cheng S, von Ehrenstein O, Bjorksten B, et al. International patterns of tuberculosis and the prevalence of symptoms of asthma, rhinitis, and eczema. *Thorax* 2000;**55**:449-53.
63. Burr ML, Emberlin JC, Treu R, Cheng S, Pearce NE. Pollen counts in relation to the prevalence of allergic rhinoconjunctivitis, asthma and atopic eczema in the International Study of Asthma and Allergies in Childhood (ISAAC). *Clin Exp Allergy* 2003;**33**:1675-80.
64. Casale TB, Dykewicz MS. Clinical implications of the allergic rhinitis-asthma link. *Am J Med Sci* 2004;**327**:127-38.
65. Asher MI, Stewart AW, Wong G, Strachan DP, Garcia-Marcos L, Anderson HR. Changes over time in the relationship between symptoms of asthma, rhinoconjunctivitis and eczema: a global perspective from the International Study of Asthma and Allergies in Childhood (ISAAC). *Allergol Immunopathol (Madr)* 2012;**40**:267-74.
66. Weiland SK, Bjorksten B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J* 2004;**24**:406-12.

67. Anderson HR, Ruggles R, Pandey KD, Kapetanakis V, Brunekreef B, Lai CK, et al. Ambient particulate pollution and the world-wide prevalence of asthma, rhinoconjunctivitis and eczema in children: Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC). *Occup Environ Med* 2010;**67**:293-300.
68. Weinmayr G, Weiland SK, Bjorksten B, Brunekreef B, Buchele G, Cookson WO, et al. Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Crit Care Med* 2007;**176**:565-74.
69. Weinmayr G, Forastiere F, Weiland SK, Rzehak P, Abramidze T, Annesi-Maesano I, et al. International variation in prevalence of rhinitis and its relationship with sensitisation to perennial and seasonal allergens. *Eur Respir J* 2008;**32**:1250-61.
70. Flohr C, Weiland SK, Weinmayr G, Bjorksten B, Braback L, Brunekreef B, et al. The role of atopic sensitization in flexural eczema: findings from the International Study of Asthma and Allergies in Childhood Phase Two. *J Allergy Clin Immunol* 2008;**121**:141-7 e4.
71. Boneberger A, Haider D, Baer J, Kausel L, Von Kries R, Kabesch M, et al. Environmental risk factors in the first year of life and childhood asthma in the Central South of Chile. *J Asthma* 2011;**48**:464-9.
72. Neffen H, Fritscher C, Schacht FC, Levy G, Chiarella P, Soriano JB, et al. Asthma control in Latin America: the Asthma Insights and Reality in Latin America (AIRLA) survey. *Rev Panam Salud Publica* 2005;**17**:191-7.
73. Pereira MU, Sly PD, Pitrez PM, Jones MH, Escouto D, Dias AC, et al. Nonatopic asthma is associated with helminth infections and bronchiolitis in poor children. *Eur Respir J* 2007;**29**:1154-60.
74. Weinberg EG. Urbanization and childhood asthma: an African perspective. *J Allergy Clin Immunol* 2000;**105**:224-31.
75. Pan American Health Organization. Health in the Americas: 2012 Edition. Regional Outlook and Country Profiles. Washington, DC: PAHO, 2012

76. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;**64**:476-83.
77. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009;**64**:123-48.
78. Chong Neto HJ, Rosario NA, Sole D. Asthma and Rhinitis in South America: How Different They are From Other Parts of the World. *Allergy Asthma Immunol Res* 2012;**4**:62-7.
79. Wehrmeister FC, Menezes AM, Cascaes AM, Martinez-Mesa J, Barros AJ. Time trend of asthma in children and adolescents in Brazil, 1998-2008. *Rev Saude Publica* 2012;**46**:242-50.
80. Morcos MM, Morcos WM, Ibrahim MA, Shaheen MA. Environmental exposure to endotoxin in rural and urban Egyptian school children and its relation to asthma and atopy. *Minerva Pediatr* 2011;**63**:19-26.
81. Lee SY, Kwon JW, Seo JH, Song YH, Kim BJ, Yu J, et al. Prevalence of atopy and allergic diseases in Korean children: associations with a farming environment and rural lifestyle. *Int Arch Allergy Immunol* 2012;**158**:168-74.
82. Rodriguez A, Vaca M, Oviedo G, Erazo S, Chico ME, Teles C, et al. Urbanisation is associated with prevalence of childhood asthma in diverse, small rural communities in Ecuador. *Thorax* 2011;**66**:1043-50.
83. Robinson CL, Baumann LM, Gilman RH, Romero K, Combe JM, Cabrera L, et al. The Peru Urban versus Rural Asthma (PURA) Study: methods and baseline quality control data from a cross-sectional investigation into the prevalence, severity, genetics, immunology and environmental factors affecting asthma in adolescence in Peru. *BMJ Open* 2012;**2**:e000421.

84. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. *NCHS Data Brief* 2012:1-8.
85. Robinson CL, Baumann LM, Romero K, Combe JM, Gomez A, Gilman RH, et al. Effect of urbanisation on asthma, allergy and airways inflammation in a developing country setting. *Thorax* 2011;**66**:1051-7.
86. Cooper PJ, Rodrigues LC, Barreto ML. Influence of poverty and infection on asthma in Latin America. *Curr Opin Allergy Clin Immunol* 2012;**12**:171-8.
87. Moncayo AL, Vaca M, Oviedo G, Erazo S, Quinzo I, Fiaccone RL, et al. Risk factors for atopic and non-atopic asthma in a rural area of Ecuador. *Thorax* 2010;**65**:409-16.
88. Fuchs O, Genuneit J, Latzin P, Buchele G, Horak E, Loss G, et al. Farming environments and childhood atopy, wheeze, lung function, and exhaled nitric oxide. *J Allergy Clin Immunol* 2012;**130**:382-8 e6.
89. Gold DR, Acevedo-Garcia D. Immigration to the United States and acculturation as risk factors for asthma and allergy. *J Allergy Clin Immunol* 2005;**116**:38-41.
90. Aberg N, Engstrom I, Lindberg U. Allergic diseases in Swedish school children. *Acta Paediatr Scand* 1989;**78**:246-52.
91. Viinanen A, Munhbayarlah S, Zevgee T, Narantsetseg L, Naidansuren T, Koskenvuo M, et al. The protective effect of rural living against atopy in Mongolia. *Allergy* 2007;**62**:272-80.
92. Lifestyles, inequality and urban social mobility strategies In: United Nations Development Programme (PNUD), editor. *National Report on Human Development in Bolivia "The changes behind the change, inequality and social mobility in Bolivia" (In spanish)*. Bolivia2010.
93. Cooper P, Rodrigues L, Cruz A, Barreto M. Asthma in Latin America: a public heath challenge and research opportunity. *Allergy* 2009;**64**:5-17.
94. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;**299**:1259-60.
95. Asher MI, Stewart AW, Mallol J, Montefort S, Lai CK, Ait-Khaled N, et al. Which population level environmental factors are associated with asthma, rhinoconjunctivitis and eczema? Review of the ecological analyses of ISAAC Phase One. *Respir Res* 2010;**11**:8.
96. Braun-Fahrlander C, Lauener R. Farming and protective agents against allergy and asthma. *Clin Exp Allergy* 2003;**33**:409-11.
97. Mallol J, Sole D, Baeza-Bacab M, Aguirre-Camposano V, Soto-Quiros M, Baena-Cagnani C. Regional variation in asthma symptom prevalence in Latin American children. *J Asthma* 2010;**47**:644-50.
98. Fishbein AB, Fuleihan RL. The hygiene hypothesis revisited: does exposure to infectious agents protect us from allergy? *Curr Opin Pediatr* 2012;**24**:98-102.
99. Mallol J, Castro-Rodriguez JA, Cortez E, Aguirre V, Aguilar P, Barrueto L. Heightened bronchial hyperresponsiveness in the absence of heightened atopy in children with current wheezing and low income status. *Thorax* 2008;**63**:167-71.
100. Ferreira MU, Rubinsky-Elefant G, de Castro TG, Hoffmann EH, da Silva-Nunes M, Cardoso MA, et al. Bottle feeding and exposure to Toxocara as risk factors for wheezing illness among under-five Amazonian children: a population-based cross-sectional study. *J Trop Pediatr* 2007;**53**:119-24.
101. Lynch NR, Palenque M, Hagel I, DiPrisco MC. Clinical improvement of asthma after anthelminthic treatment in a tropical situation. *Am J Respir Crit Care Med* 1997;**156**:50-4.
102. Medeiros M, Jr., Figueiredo JP, Almeida MC, Matos MA, Araujo MI, Cruz AA, et al. Schistosoma mansoni infection is associated with a reduced course of asthma. *J Allergy Clin Immunol* 2003;**111**:947-51.
103. Goldberg S, Israeli E, Schwartz S, Shochat T, Izbicki G, Toker-Maimon O, et al. Asthma prevalence, family size, and birth order. *Chest* 2007;**131**:1747-52.
104. Takizawa H. Impact of air pollution on allergic diseases. *Korean J Intern Med* 2011;**26**:262-73.
105. Behera D, Chakrabarti T, Khanduja KL. Effect of exposure to domestic cooking fuels on bronchial asthma. *Indian J Chest Dis Allied Sci* 2001;**43**:27-31.

106. Willers SM, Brunekreef B, Oldenwening M, Smit HA, Kerkhof M, De Vries H, et al. Gas cooking, kitchen ventilation, and asthma, allergic symptoms and sensitization in young children--the PIAMA study. *Allergy* 2006;**61**:563-8.
107. Jenerowicz D, Silny W, Danczak-Pazdrowska A, Polanska A, Osmola-Mankowska A, Olek-Hrab K. Environmental factors and allergic diseases. *Ann Agric Environ Med* 2012;**19**:475-81.
108. Barreto SM, Miranda JJ, Figueroa JP, Schmidt MI, Munoz S, Kuri-Morales PP, et al. Epidemiology in Latin America and the Caribbean: current situation and challenges. *Int J Epidemiol* 2012;**41**:557-71.
109. Mallol J. Asthma in Latin America: where the asthma causative/protective hypotheses fail. *Allergol Immunopathol (Madr)* 2008;**36**:150-3.
110. Gilmour MI, Jaakkola MS, London SJ, Nel AE, Rogers CA. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environ Health Perspect* 2006;**114**:627-33.
111. Andersen L. Rural-Urban Migration in Bolivia: Advantages and Disadvantages. La Paz, Bolivia: Institute for Socio-Economic Research. Universidad Católica Boliviana; 2002.
112. Unit EE. Bolivia environmental policy brief: Environmental sustainability, poverty and the National Development Plan. 2007.
113. Lubick N. Global estimate of SHS burden. *Environ Health Perspect* 2011;**119**:A66-7.
114. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta GA2006.
115. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ* 2009;**181**:E181-90.
116. Breton CV, Byun HM, Wenten M, Pan F, Yang A, Gilliland FD. Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. *Am J Respir Crit Care Med* 2009;**180**:462-7.
117. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 2005;**115**:1109-17; quiz 18.
118. International Study of Asthma and Allergies in Childhood (ISAAC): Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;**12**:315-35.
119. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *J Allergy Clin Immunol* 2011;**127**:724-33 e1-30.
120. Castro-Rodriguez JA, Garcia-Marcos L, Alfonseda Rojas JD, Valverde-Molina J, Sanchez-Solis M. Mediterranean diet as a protective factor for wheezing in preschool children. *J Pediatr* 2008;**152**:823-8, 8 e1-2.
121. Chatzi L, Apostolaki G, Bibakis I, Skypala I, Bibaki-Liakou V, Tzanakis N, et al. Protective effect of fruits, vegetables and the Mediterranean diet on asthma and allergies among children in Crete. *Thorax* 2007;**62**:677-83.
122. de Batlle J, Garcia-Aymerich J, Barraza-Villarreal A, Anto JM, Romieu I. Mediterranean diet is associated with reduced asthma and rhinitis in Mexican children. *Allergy* 2008;**63**:1310-6.
123. Romieu I, Barraza-Villarreal A, Escamilla-Nunez C, Texcalac-Sangrador JL, Hernandez-Cadena L, Diaz-Sanchez D, et al. Dietary intake, lung function and airway inflammation in Mexico City school children exposed to air pollutants. *Respir Res* 2009;**10**:122.
124. Trichopoulou A, Lagiou P. Healthy traditional Mediterranean diet: an expression of culture, history, and lifestyle. *Nutr Rev* 1997;**55**:383-9.
125. Gonzalez Barcala FJ, Pertega S, Bamonde L, Garnelo L, Perez Castro T, Sampedro M, et al. Mediterranean diet and asthma in Spanish schoolchildren. *Pediatr Allergy Immunol* 2010;**21**:1021-7.
126. Kim JH, Ellwood PE, Asher MI. Diet and asthma: looking back, moving forward. *Respir Res* 2009;**10**:49.

127. Torres-Borrego J, Moreno-Solis G, Molina-Teran AB. Diet for the prevention of asthma and allergies in early childhood: much ado about something? *Allergol Immunopathol (Madr)* 2012;**40**:244-52.
128. Lowe A, Braback L, Ekeus C, Hjern A, Forsberg B. Maternal obesity during pregnancy as a risk for early-life asthma. *J Allergy Clin Immunol* 2011;**128**:1107-9 e1-2.
129. Duijts L. Fetal and infant origins of asthma. *Eur J Epidemiol* 2012;**27**:5-14.
130. Solé D, Mallol J, Wandalsen G, Aguirre V, Latin American ISAAC Phase 3 Study Group. Prevalence of symptoms of eczema in Latin America: results of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3. *J Investig Allergol Clin Immunol* 2010;**20**:311-23.
131. Giuffrida A, Bernal R, Cárdenas M, Handa A, Trujillo AJ, Vernon JA, et al. *Racial and Ethnic Disparities in Health in Latin America and the Caribbean*. Social Protection and Health Division, Country Department Andean Group, Inter-American Development Bank; 2007.
132. Mallol J, Sole D, Asher I, Clayton T, Stein R, Soto-Quiroz M. Prevalence of asthma symptoms in Latin America: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Pulmonol* 2000;**30**:439-44.
133. Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007;**62**:758.
134. Sole D, Mallol J, Camelo-Nunes IC, Wandalsen GF. Prevalence of rhinitis-related symptoms in Latin American children - results of the International Study of Asthma and Allergies in Childhood (ISAAC) phase three. *Pediatr Allergy Immunol* 2010;**21**:e127-36.
135. National Institute of Statistics of Bolivia (INE). Newsletter: National Census of Population and Housing (in Spanich). La Paz, Bolivia2012.
136. National Institute of Statistics. Chuquisaca: Statistics and sociodemographic, productive and financial indicators by Municipalities (in Spanish). La Paz, Bolivia2005.
137. Economic Comission for Latin America and the Caribbean (ECLAC). Statistical Yearbook for Latin America and the Caribbean. Santiago, Chile: United Nations; 2011.
138. Analysis Unit of Social and Economic Policy (UDAPE), Interinstitutional Committee on Millennium Development Goals (CIMDM). Sixth progress report on the Millennium Development Goals in Bolivia (in Spanish). La Paz, Bolivia2010.
139. Popkin BM, Richards MK, Montiero CA. Stunting is associated with overweight in children of four nations that are undergoing the nutrition transition. *The Journal of nutrition* 1996;**126**:3009-16.
140. Pan American Health Organization. Health in the Americas: Bolivia. In: Volume C, editor. 2012.
141. World Health Organization. Bolivia (Plurinational State of): health profile. 2009; Available at http://www.who.int/gho/countries/bol.pdf. Accessed 04/07/2013.
142. Aramayo J. Atlas of Health: Department of Chuquisaca, Bolivia (In Spanish). Chuquisaca, Bolivia: Chuquisaca Department of Health Services, Pan American Health organization, World health organization; 2007.
143. United Nations Development Programme, Social and Economic Policies Analysis unit. Human Development in Chuquisaca (In Spanish). 2010.
144. Granado Md, Ortiz de Robles D. Estudio preliminar de la prevalencia del asma en niños de 9 a 13 años en la ciudad de Cochabamba-Bolivia; Preliminary study of asthma prevalence in children from 9 to 13 years old in Cochabamba city, Bolivia. *Carta med AIS Boliv* 1994;**8**:8-12.
145. Lozano Beltran DF, Suarez Barrientos E, Ortuño E. Relación entre asma y toxocariasis en pacientes pediátricos en Cochabamba, Bolivia. *Gac Med Bol* 2011;**34**:76-9.
146. United Nations Development Programme. Santa Cruz: current status, evaluation and perspectives. *Millennium Development Goals (In Spanish)*. La Paz, Bolivia2007.
147. National Statistical Institute. Population and Housing Census (In Spanish). 2001.
148. National Statistical Institute. Bolivia: relative humidity by Seasons 1999 - 2008 (In Spanish). 2012; Available at http://www.ine.gob.bo. Accessed 08/14/2012.

149. Ministry of Education. Education in Bolivia: Indicators, numbers and results (in Spanish). Bolivia2004.
150. Gibson PG, Henry R, Shah S, Toneguzzi R, Francis JL, Norzila MZ, et al. Validation of the ISAAC video questionnaire (AVQ3.0) in adolescents from a mixed ethnic background. *Clin Exp Allergy* 2000;**30**:1181-7.
151. World Health Organization. Growth reference 5-19 years. 2007; Available at http://www.who.int/growthref/en/. Accessed 01/22/2013.
152. Mata Fernandez C, Fernandez-Benitez M, Perez Miranda M, Guillen Grima F. Validation of the Spanish version of the Phase III ISAAC questionnaire on asthma. *J Investig Allergol Clin Immunol* 2005;**15**:201-10.
153. International Study of Asthma and Allergies (ISAAC). Manual (Phase One). 2 ed. Auckland (NZ)/ Münster (FRG)1993.
154. Crane J, Mallol J, Beasley R, Stewart A, Asher MI. Agreement between written and video questions for comparing asthma symptoms in ISAAC. *Eur Respir J* 2003;**21**:455-61.
155. Hong SJ, Kim SW, Oh JW, Rah YH, Ahn YM, Kim KE, et al. The validity of the ISAAC written questionnaire and the ISAAC video questionnaire (AVQ 3.0) for predicting asthma associated with bronchial hyperreactivity in a group of 13-14 year old Korean schoolchildren. *J Korean Med Sci* 2003;**18**:48-52.
156. Awasthi S, Gupta S, Maurya N, Tripathi P, Dixit P, Sharma N. Environmental risk factors for persistent asthma in Lucknow. *Indian J Pediatr* 2012;**79**:1311-7.
157. Villamizar LA, Lopez AB, Ortiz HC, Velazquez JN, Cala LM. [Incidence of respiratory symptoms and the association with air pollution in preschoolers: a multilevel analysis]. *Cad Saude Publica* 2010;**26**:1411-8.
158. Kasznia-Kocot J, Kowalska M, Gorny RL, Niesler A, Wypych-Slusarska A. Environmental risk factors for respiratory symptoms and childhood asthma. *Ann Agric Environ Med* 2010;**17**:221-9.
159. National Institute of Statistics (INE). Unmet basic needs indicator. Bolivia 1992 and 2001 (in spanish).
160. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 2007;**85**:660-7.
161. Nagel G, Weinmayr G, Kleiner A, Garcia-Marcos L, Strachan DP. Effect of diet on asthma and allergic sensitisation in the International Study on Allergies and Asthma in Childhood (ISAAC) Phase Two. *Thorax* 2010;**65**:516-22.
162. Rahimi Rad MH, Hejazi ME. Agreement between written and video asthma symptoms questionnaires in school children in Urmia, Iran. *Iran J Allergy Asthma Immunol* 2007;**6**:21-5.
163. Flohr C, Weinmayr G, Addo-Yobo E, Annesi-Maesano I, Björkstén B, Bråbäck L, et al. How well do questionnaires perform compared with physical examination in detecting flexural eczema? Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. *British Journal of Dermatology* 2009;**161**:846-53.
164. Asher M, Keil U, Anderson H, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *European Respiratory Journal* 1995;**8**:483-91.
165. Mitchell EA, Beasley R, Keil U, Montefort S, Odhiambo J. The association between tobacco and the risk of asthma, rhinoconjunctivitis and eczema in children and adolescents: analyses from Phase Three of the ISAAC programme. *Thorax* 2012;**67**:941-9.
166. Ellwood P, Innes Asher M, Garcia-Marcos L, Williams H, Keil U, Robertson C, et al. Do fast foods cause asthma, rhinoconjunctivitis and eczema? Global findings from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Thorax* 2013.
167. Lipski E. Traditional non-Western diets. *Nutr Clin Pract* 2010;**25**:585-93.
168. Lee J. Odds ratio or relative risk for cross-sectional data? *Int J Epidemiol* 1994;**23**:201-3.
169. Thompson ML, Myers J, Kriebel D. Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: what is to be done? *Occup Environ Med* 1998;**55**:272-7.

170. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ: British Medical Journal* 2009;**338**.
171. Barzi F, Woodward M, Marfisi RM, Tognoni G, Marchioli R. Analysis of the benefits of a Mediterranean diet in the GISSI-Prevenzione study: a case study in imputation of missing values from repeated measurements. *Eur J Epidemiol* 2006;**21**:15-24.
172. Koffi N, Kouassi B, Ngom A, Aka-Dangui E. [Value of a video questionnaire in the evaluation of the prevalence of asthma in Africa]. *Med Trop (Mars)* 2000;**60**:412-3.
173. Mallol J. Satellite symposium: Asthma in the World. Asthma among children in Latin America. *Allergol Immunopathol (Madr)* 2004;**32**:100-3.
174. Peters JL, Boynton-Jarrett R, Sandel M. Prenatal environmental factors influencing IgE levels, atopy and early asthma. *Curr Opin Allergy Clin Immunol* 2013;**13**:187-92.
175. Dotterud CK, Storro O, Simpson MR, Johnsen R, Oien T. The impact of pre- and postnatal exposures on allergy related diseases in childhood: a controlled multicentre intervention study in primary health care. *BMC Public Health* 2013;**13**:123.
176. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012;**129**:735-44.
177. Morales Suarez-Varela M, Garcia-Marcos L, Kogan MD, Llopis Gonzalez A, Martinez Gimeno A, Aguinaga Ontoso I, et al. Parents' smoking habit and prevalence of atopic eczema in 6-7 and 13-14 year-old schoolchildren in Spain. ISAAC phase III. *Allergol Immunopathol (Madr)* 2008;**36**:336-42.
178. Brunekreef B, Stewart AW, Anderson HR, Lai CK, Strachan DP, Pearce N. Self-reported truck traffic on the street of residence and symptoms of asthma and allergic disease: a global relationship in ISAAC phase 3. *Environ Health Perspect* 2009;**117**:1791-8.
179. Migliore E, Berti G, Galassi C, Pearce N, Forastiere F, Calabrese R, et al. Respiratory symptoms in children living near busy roads and their relationship to vehicular traffic: results of an Italian multicenter study (SIDRIA 2). *Environ Health* 2009;**8**:27.
180. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Gehring U, Koletzko S, et al. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. *Occup Environ Med* 2007;**64**:8-16.
181. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Kramer U, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med* 2008;**177**:1331-7.
182. Braback L, Forsberg B. Does traffic exhaust contribute to the development of asthma and allergic sensitization in children: findings from recent cohort studies. *Environ Health* 2009;**8**:17.
183. Willers SM, Wijga AH, Brunekreef B, Scholtens S, Postma DS, Kerkhof M, et al. Childhood diet and asthma and atopy at 8 years of age: the PIAMA birth cohort study. *Eur Respir J* 2011;**37**:1060-7.
184. Hunninghake GM, Weiss ST, Celedon JC. Asthma in Hispanics. *Am J Respir Crit Care Med* 2006;**173**:143-63.
185. Zahran HS, Bailey C. Factors associated with asthma prevalence among racial and ethnic groups-United States, 2009-2010 Behavioral Risk Factor Surveillance System. *J Asthma* 2013.
186. Oraka E, Iqbal S, Flanders WD, Brinker K, Garbe P. Racial and Ethnic Disparities in Current Asthma and Emergency Department Visits: Findings from the National Health Interview Survey, 2001-2010. *J Asthma* 2013.
187. Hsu NY, Wang JY, Wu PC, Su HJ. Paternal heredity and housing characteristics affect childhood asthma and allergy morbidity. *Arch Environ Occup Health* 2012;**67**:155-62.
188. Brugge D, Rice PW, Terry P, Howard L, Best J. Housing conditions and respiratory health in a Boston public housing community. *New Solut* 2001;**11**:149-64.
189. Cureton S. Environmental victims: environmental injustice issues that threaten the health of children living in poverty. *Rev Environ Health* 2011;**26**:141-7.
190. von Mutius E. Maternal farm exposure/ingestion of unpasteurized cow's milk and allergic disease. *Curr Opin Gastroenterol* 2012;**28**:570-6.

191. Wlasiuk G, Vercelli D. The farm effect, or: when, what and how a farming environment protects from asthma and allergic disease. *Curr Opin Allergy Clin Immunol* 2012;**12**:461-6.
192. Lodge CJ, Lowe AJ, Gurrin LC, Matheson MC, Balloch A, Axelrad C, et al. Pets at birth do not increase allergic disease in at-risk children. *Clin Exp Allergy* 2012;**42**:1377-85.
193. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999;**54**:268-72.
194. Jacobs DR, Tapsell LC. Food synergy: the key to a healthy diet. *Proc Nutr Soc* 2013:1-7.
195. Pizzichini MM, Rennie D, Senthilselvan A, Taylor B, Habbick BF, Sears MR. Limited agreement between written and video asthma symptom questionnaires. *Pediatr Pulmonol* 2000;**30**:307-12.
196. Mickleborough TD, Gotshall RW, Cordain L, Lindley M. Dietary salt alters pulmonary function during exercise in exercise-induced asthmatics. *J Sports Sci* 2001;**19**:865-73.
197. Maslova E, Granstrom C, Hansen S, Petersen SB, Strom M, Willett WC, et al. Peanut and tree nut consumption during pregnancy and allergic disease in children-should mothers decrease their intake? Longitudinal evidence from the Danish National Birth Cohort. *J Allergy Clin Immunol* 2012;**130**:724-32.
198. Arvaniti F, Priftis KN, Papadimitriou A, Yiallouros P, Kapsokefalou M, Anthracopoulos MB, et al. Salty-snack eating, television or video-game viewing, and asthma symptoms among 10- to 12-year-old children: the PANACEA study. *J Am Diet Assoc* 2011;**111**:251-7.
199. Seaton A, Godden DJ, Brown K. Increase in asthma: a more toxic environment or a more susceptible population? *Thorax* 1994;**49**:171-4.
200. Suarez-Varela MM, Alvarez LG, Kogan MD, Ferreira JC, Martinez Gimeno A, Aguinaga Ontoso I, et al. Diet and prevalence of atopic eczema in 6 to 7-year-old schoolchildren in Spain: ISAAC phase III. *J Investig Allergol Clin Immunol* 2010;**20**:469-75.

8) CURRICULUM VITAE

Solís Soto, María Teresa
354 Urriolagoitia Street, Sucre, Bolivia
Telephone: (591-4)6435859; (591)73463935
Email: maritesolissoto@gmail.com;

Education

2010-present	**PhD in International Health**: Center for International Health, Ludwig Maximilians University - Munich, Germany
2012-2013	**Diploma: Teaching in Higher Education:** Universidad Mayor Real y Pontificia de San Francisco Xavier de Chuquisaca
2007 - 2009	**Master in Epidemiology:** Universidad Católica – Santiago, Chile
2006 - 2008	**Master in Public Health. Specialization area: Epidemiology:** Public Health School - Universidad de Chile, Santiago de Chile
1999 - 2005	**Medical Doctor:** Universidad Mayor Real y Pontificia de San Francisco Xavier de Chuquisaca, Bolivia

Professional experience

➢ **Centre for Postgraduate Studies and Research (CEPI) - Universidad San Francisco Xavier de Chuquisaca.** Teacher for the following courses:

- Research Module III for the Master of Occupational Medicine and Occupational Health program, Version III. Santa Cruz – Bolivia (09/07/2012 – 10/21/2012).
- Computing and Communication for Field Epidemiology, for the Diploma in Field Epidemiology Program. Online course (08/06/2012 – 08/18/2012).
- General and Applied Epidemiology for the Diploma Program in Field Epidemiology Program. Online course (06/25/2012 – 07/07/2012).
- Epidemiology for the Master of Public Health program (Version III). Sucre – Bolivia (11/25/2011 – 12/11/2011).

- Epidemiology for the Master of Public Health program (Version III). Potosí – Bolivia (09/23/2011 – 10/23/2011).
- Informatics in Health Systems for the Master of Public Health Program. Santa Cruz – Bolivia (01/29/2010 – 02/28/2010).

➢ **Observatorio de Salud Pública, Escuela de Salud Pública de la Universidad de Chile** (02-05/2009)

Reserchер in Project: "Barómetro comunal" Santaigo – Chile. Analysis of information to monitor social determinants and equity.

➢ **Centro de Modelamiento Matemático and Escuela de Salud Pública de la Universidad de Chile** (11/2008-05/2009)

Reserchер in Project (Health component): "Optimal and Productive Restructuring Camp Division El Salvador, Codelco – Chile". Analysis of information and projection of health indicators during the reconversion of a mining camp.

➢ **Universidad Católica de Chile** (05/2007-03/2008)

Researcher in Project: "Burden of disease for selected risk factors in Chilean population. Chile". Study to prioritize disease prevention and health in public health policies of Chile. Study performed for the Chilean Ministry of Health.

➢ **IMCC (International Medical Cooperation Committee)–Bolivia** (01/2006-02/2006)

Consulting firm team member: Knowledge, attitudes and practices in health assessment, Azurduy region, rural area with indigenous communities.

➢ **Neurological Diagnostic Ce nter - D r Alberto Solis Padilla, Sucre - Bolivia** (04/2005 – 02/2006). General practitioner

Key competences and skills

Professional skills

- Teaching experience
- Design, implementation (field work), analysis and reporting of quantitative and qualitative research projectship experience
- Research projects tutor

- Advertising, marketing, graphic design and web development
- Graphic design
- Commercial packages management

Personal skills

- Enthusiasm and positive Attitude
- Team work
- Critical Thinking
- Adaptability

References

Centre for Postgraduate Studies and Research (CEPI) - Universidad San Francisco Xavier de Chuquisaca

Dra. Mary Flores de Gonzalez, PhD: gonzalezmary01@hotmail.com

Sucre – Bolivia

Escuela de Salud Pública de la Universidad de Chile

Nella Marchetti: mmarchet@med.uchile.cl

Santiago – Chile

Departamento de Salud Pública de la Universidad Católica de Chile

Catterina Ferreccio: catferre@gmail.com

Santiago – Chile

Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Hospital of the Ludwig-Maximilians-University Munich

Katja Radon: katja.radon@gmail.com

Munich- Germany

9) LIST OF PUBLICATIONS

1. Solís M., Aillon D. *Differential diagnosis between osteosarcoma and Giant Cell Tumor. Case Report* (in Spanish). Ciencia y Medicina, ABOLCEM. Nº 3, Sucre-Bolivia, 2002.

2. Solís M., Basagoitia A., et al. *Diagnosis of Neurological Disorders by EEG in the Psychiatric Institute: Gregorio Pacheco* (in Spanish). Arte y Ciencia Médica, V Edition, Sucre-Bolivia, 2003.

3. Solís M, et al. *Risk Factors of Cervical Cytological Alterations in Chilean women: a case-control study.* Santiago-Chile 2009 (in Spanish). Rev. méd. Chile v.138 n.2 Santiago feb. 2010. Available in: http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0034-98872010000200005

4. Flores C, Solís M, Fortt A, Valdivia G. *Respiratory Symptoms and Chronic Obstructive Pulmonary Disease associated with indoor air pollution in the metropolitan area of Santiago: Studio Platinum* (in Spanish). Rev. chil. enferm. respir. v.26 n.2 Santiago jun. 2010. Available in: http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0717-73482010000200002

5. Paudel D, Abera M, Kyeyune R, Solis-Soto MT, Lohani A, Wandiga S, Nji A, Froschel G. *Inequalities in Health : Realities, Efforts and Way Forward.* Word Medical and Health Policy, Volume 4, Issue 2, 2012. Article 13. Available in: http://onlinelibrary.wiley.com/doi/10.1515/1948-4682.1237/abstract

6. Solis M, Patiño A, Nowak D, Radon K. Prevalence of asthma, rhinitis and eczema symptoms in rural and urban school-aged children from Oropeza Province - Bolivia: A Cross-sectional Study (submitted)

7. Solis M, Patiño A, Nowak D, Radon K. Association between diet and current asthma symptoms in school-aged children from Oropeza Province–Bolivia (submitted)

8. Solis M, Patiño A, Nowak D, Radon K. Association between environmental factors and current asthma, rhinoconjunctivitis and eczema symptoms in school-aged children from Oropeza Province – Bolivia (submitted).

10) APPENDIX

10.1) INFORMATION LETTER FOR SCHOOL (IN SPANISH)

Sucre, ……. de 2011

Sr (a).

Director (a) de Unidad Educativa ……

Ref: Participación en encuesta sobre problemas de salud en niños

Estimado (a) Director (a):

A tiempo de saludarle y desearle éxito en sus funciones, me permito comunicarle que la Universidad Alemana Ludwig Maximilian Universitet junto a mi persona estamos llevando adelante un estudio con el objetivo de conocer la situación de algunos problemas en la función respiratoria, en la nariz y en la piel de niños de edad escolar. La información obtenida en este estudio podrá guiar la implementación de programas de salud de manera adecuada a la realidad del departamento.

Por tal motivo estamos solicitando la participación de los niños de quinto año de enseñanza básica, previa autorización de los padres, en varias escuelas del departamento de Chuquisaca seleccionadas al azar, y dentro de las cuales se encuentra su establecimiento educativo.

Para la realización de la investigación solicitamos gentilmente la colaboración de su escuela en las siguientes actividades:

1. Durante el período de coordinación, un miembro del equipo de investigación traerá a su escuela hojas de información para los padres, para que sean distribuidas una semana antes del estudio.

2. El día de la visita a la escuela, le pediremos a los niños que completen dos cuestionarios escritos, también se les mostrará un video de 10 minutos sobre ejercicio y respiración y finalmente se les medirá el peso y talla.

En total necesitaremos alrededor de 2 horas de clases para terminar todas las actividades.

3.- Al finalizar el proyecto, el investigador se compromete hacer llegar a su establecimiento los resultados generales de la investigación haciendo énfasis en su establecimiento, pero sin identificar a ningún niño en particular.

Consideramos pertinente informarle que este estudio ha sido evaluado y aprobado por la *Comisión Nacional de Ética en la investigación* y es de conocimiento del Servicio Departamental de Educación de Chuquisaca. Todo esto se ha realizado en procura de brindarle la mayor seguridad y confianza para que los niños participen en el estudio.

Si usted necesita mayor información, puede ponerse en contacto con la persona responsable a los teléfonos que figuran abajo.

Agradeciendo de antemano su colaboración, se despide atentamente,

Dra. María Teresa Solís Soto
Investigador Responsable
Fono: 64- 35869 - Celular: 734 63935
e-mail: maritesolissoto@yahoo.es
c. Manuel Durán #17. Sucre-Bolivia

10.2) WRITTEN QUESTIONNAIRE (IN SPANISH)

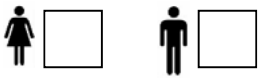
ENCUESTA SOBRE PROBLEMAS DE SALUD EN LA NARIZ, PIEL Y RESPIRACIÓN

Por favor escribe tus respuestas en el espacio proporcionado para cada una de ellas. Esta información será estrictamente confidencial (nadie mencionará tu nombre).

Nombre y apellido: ……..…….

Escuela/Colegio: ……..… Curso: …… Fecha de hoy: ____/____/_____
Día Mes Año

¿Qué edad tienes?: ..... años ¿En qué fecha naciste?:____/_____/_____
Día Mes Año

Sexo:  ☐ ☐

1. ¿Alguna vez en tu vida tuviste silbido al pecho?

SI ☐ NO ☐ SI CONTESTASTE "NO" SALTATE A LA PREGUNTA 

2. ¿Has tenido silbido al pecho en estos últimos 12 meses (último año)?

SI ☐ NO ☐

3. ¿Cuántos ataques o crisis de silbido al pecho has tenido en estos últimos 12 meses (último año)?

NINGUNO ☐ 1 a 3 ☐ 4 a 12 ☐ Más de 12 ☐

4. ¿En estos últimos 12 meses (último año) cuántas veces te has despertado en la noche debido a silbido al pecho?

Nunca he despertado con silbido al pecho ☐
Menos de una noche por semana ☐
Una o más noches por semana ☐

5. ¿En estos últimos 12 meses (último año) has tenido silbido al pecho tan fuerte como para no dejarte hablar más de una o dos palabras entre cada respiración?

SI ☐ NO ☐

¿Has tenido asma alguna vez en tu vida?

SI ☐ NO ☐

7. ¿En estos últimos 12 meses (último año) has tenido silbido al pecho durante o después de hacer ejercicios (correr, etc.)?

SI ☐ NO ☐

8. ¿En estos últimos 12 meses (último año) has tenido tos seca en la noche? (Cuando **NO** estabas resfriado ni con infecciones respiratorias).

SI ☐ NO ☐

Todas las preguntas a continuación se refieren a problemas de la nariz que ocurren cuando **NO ESTAS CON GRIPE NI CON RESFRIO**.

9. ¿Alguna vez en tu vida has tenido problemas de estornudos, de que te corra (moco), o se te tape la nariz? (cuando **NO TENÍAS RESFRÍO COMÚN NI GRIPE**).

SI ☐ NO ☐ SI CONTESTASTE "NO" SALTATE A LA PREGUNTA 

10. ¿En los últimos 12 meses tuviste problemas de estornudos, de que te corriera (moco), o se te tapara la nariz? (**CUANDO NO TENÍAS RESFRÍO COMÚN NI GRIPE**).

SI ☐ NO ☐

11. En los últimos 12 meses junto con el problema de la nariz ¿te picaban y lloraban los ojos?

SI ☐ NO ☐

12. ¿En qué meses del año ocurrían estos problemas en la nariz? (**MARCA TODAS LAS OPCIONES QUE SEAN NECESARIAS**)

Enero	☐	Febrero	☐	Marzo	☐	Abril	☐
Mayo	☐	Junio	☐	Julio	☐	Agosto	☐
Septiembre	☐	Octubre	☐	Noviembre	☐	Diciembre	☐

13. ¿En los últimos 12 meses en qué cantidad interfirieron estos problemas de tu nariz con tus actividades diarias?

En nada ☐ Un poco ☐ Moderadamente M☐ ☐

¿Has tenido usted alguna vez Rinitis Alérgica?

SI ☐ NO ☐

15. ¿Has tenido alguna vez en la vida granos o ronchas acompañado de picazón que estén yéndose y volviendo durante por lo menos 6 meses?

SI ☐ NO ☐ SI CONTESTASTE "NO" SALTATE A LA PREGUNTA 

16. ¿Ha tenido estas ronchas o granos con picazón en algún momento de estos últimos 12 meses (último año)?

SI ☐ NO ☐

17. ¿Los granos o ronchas con picazón te han salido en alguno de los siguientes lugares del cuerpo? (**MARCA TODAS LAS OPCIONES QUE SEAN NECESARIAS**)

Pliegues de los codos	☐	Detrás de las rodillas	☐	Alrededor de los ojos	☐
Cuello	☐	Tobillos	☐	Orejas	☐
Nalgas	☐	Otro lugar	☐		

18. ¿Has estado completamente sano de este problema de la piel (granos o ronchas con picazón) en algún momento en los últimos 12 meses (último año)?

SI ☐ NO ☐

19. ¿Cuántas veces en estos últimos 12 meses (en promedio) te has mantenido despierto en la noche debido a ésta picazón con granos o ronchas?

Ninguna vez en los últimos 12 meses	☐
Menos de una noche por semana	☐
Una o más noches por semana	☐

¿Has tenido eczema o dermatitis alérgica alguna vez en tu vida?

SI ☐ NO ☐

21.- En los pasados 12 meses, en promedio, ¿qué tan frecuentemente comiste o bebiste los siguientes alimentos? (**MARQUE UNA OPCIÓN PARA CADA ALIMENTO**)

	Ocasionalmente o nunca	Una o dos veces a la semana	Tres o más veces a la semana
 Carne (res, cerdo, pollo, cordero)			
 Pescados			
 Fruta (cualquier tipo)			
 Vegetales frescos (lechugas, tomates, etc.)			
 Porotos, lentejas, garbanzos, otros			
 Cereal (incluyendo pan)			
 Pasta (fideos, coditos, tallarines, etc.)			
 Arroz			
 Mantequilla			
 Margarina			
 Nueces, maní			
 Papas			
 Leche			
 Huevo			
 Maiz			
 Hamburguesas, Hot Dogs, Pollo frito (u otras "comidas rápidas")			

22.- ¿Cuántas veces a la semana realizas EJERCICIO FÍSICO lo suficientemente intenso como para agitar tu respiración?

Ocasionalmente o nunca	☐
Una o dos veces a la semana	☐
Tres o más veces a la semana	☐

23.- Durante una semana normal, ¿cuántas horas al día VES TELEVISIÓN?

NO veo Televisión	☐
Menos de una hora	☐
De una a dos horas	☐
De tres a cuatro horas	☐
Cinco horas o más	☐

24.- Durante una semana normal, ¿cuántas horas al día JUEGAS TILINES O ALGÚN VIDEOJUEGO?

NO juego Tilines ni videojuegos	☐
Menos de una hora	☐
De una a dos horas	☐
De tres a cuatro horas	☐
Cinco horas o más	☐

25.- ¿Cuántos hermanos y hermanas MAYORES tienes?

N° de hermanos y hermanas MAYORES (en total):…….. No tengo hermanos(as) MAYORES ☐

26.- ¿Cuántos hermanos y hermanas MENORES tienes?

N° de hermanos y hermanas MENORES (en total):…….. No tengo hermanos(as) MENORES ☐

27.- ¿Has tenido algún GATO en tu casa en los últimos 12 meses (último año)?

SI ☐ NO ☐

28.- ¿Has tenido algún PERRO en tu casa en los últimos 12 meses?

SI ☐ NO ☐

29.- ¿Has tenido contacto regular (por lo menos una vez por semana) con ANIMALES DE GRANJA (vacas, cabras, ovejas, cerdos, gallinas, pollos o pavos) en los últimos 12 meses?

SI ☐ NO ☐

30.- ¿Fuma cigarrillos tu MAMÁ o la persona que te cuida?

SI ☐ NO ☐

31.- ¿Fuma cigarrillos tu PAPÁ o la persona que te cuida?

SI ☐ NO ☐

32.- ¿TÚ has fumado alguna vez cigarrillos?

SI ☐ NO ☐

33.- ¿Cuántas personas de las que habitan en tu casa (incluyendo tus papás) FUMAN CIGARRILLOS?

Número de personas:……..... Ninguna Fuma ☐

34.- ¿Durante cuántos años has vivido en este lugar (en esta ciudad o comunidad)?

Número de años:…….. No recuerdo ☐

35.- ¿Dónde viviste en tu primer año de vida (cuando tenías 1 año de edad)?

Nombre del lugar (Ciudad o comunidad): ……. No recuerdo ☐

36.- ¿Qué tan frecuentemente durante el día pasan camiones o autos por la calle en dónde vives?

Nunca	☐
Ocasionalmente	☐
Frecuentemente durante el día	☐
Durante la mayor parte del día	☐

37.- ¿Qué tipo de combustible se utiliza habitualmente en tu casa para cocinar? **(MARCA LA OPCIÓN MÁS IMPORTANTE)**

 Gas (garrafas o tubería) ☐	 Leña ☐	 Electricidad ☐	Otro ☐

38.- ¿Qué tipo de combustible se utiliza habitualmente para calentar tu casa? **(MARCA LA OPCIÓN MÁS IMPORTANTE)**

NO SE CALIENTA LA CASA							
NINGUNO		Gas (calentador de gas)		Leña, carbón o petróleo		Electricidad (calentador eléctrico)	Otro

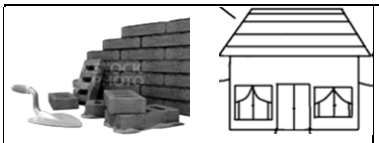
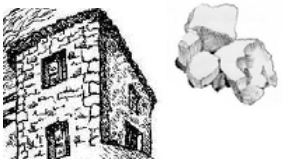
39.- ¿Que bichos existen en tu casa?






Pulgas ☐ Garrapatas ☐ Vinchucas ☐ Chinches ☐ Ratones ☐ Moscas ☐

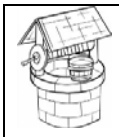
40.- ¿Cuál es el material más importante de las paredes de tu casa? **(UNA SOLA OPCIÓN)**

			
Ladrillo, cemento u hormigón	Madera	Adobe	
			
Caña, Palma o Tronco	caña con barro	Piedra	Otro

41.- ¿Cuál es el material más importante del piso de tu casa? (UNA SOLA OPCIÓN)

			
Tabl as de madera ☐	Machimbre o Parquet ☐	Mosaico, Baldosa o cerámica ☐	Tierra ☐
			
Ladrillo ☐	Alfombra o Tapizón ☐	Cemento ☐	Otro material ☐

42.- ¿De dónde obtienen el **AGUA PARA BEBER O COCINAR** en tu casa?

			
Pileta dentro de tu casa ☐	Pileta pública ☐	Río, vertiente, lago o laguna ☐	Pozo con Bomba ☐
			
Pozo sin bomba ☐	Carro repartidor ☐	Otro lugar ☐	

43.- ¿Cómo es el BAÑO de tu casa?

			
Alcantarillado ☐	Cámara séptica ☐	Fosa de tierra ☐	En la superficie (calle/quebrada/río) ☐

44.- ¿Tienen un **CUARTO EXCLUSIVO PARA COCINAR** (la cocina está en un cuarto separado)?

SI ☐ NO ☐

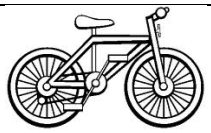
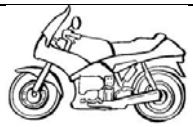
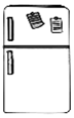
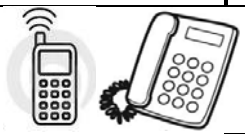
45.- ¿Cuántas personas viven en tu casa (incluyéndote)?

Número de personas:…….

46.- ¿Cuantos cuartos o habitaciones se ocupan para dormir?

Número de cuartos:…….

47.- En tu casa tienen: (Marca TODAS las opciones que correspondan)

 Radio o equipo de sonido ☐	 Televisor ☐	 Bicicleta ☐	 Motocicleta ☐
 Vehículo automotor ☐	 Refrigerador ☐	 Teléfono o celular ☐	

10.3) ISAAC INTERNATIONAL VIDEO QUESTIONNAIRE ANSWER SHEET (IN SPANISH)

Nombre y apellido: …….

Curso:……

ESCENA 1

La primera escena es de un joven descansando.

→ ¿Tu respiración ha sido así, en algún momento de tu vida? **SI** ☐ **NO** ☐

Si contestas SI:

¿Ha pasado esto en el último año? **SI** ☐ **NO** ☐

Si contestas SI:

¿Ha pasado esto una o más veces en un mes? **SI** ☐ **NO** ☐

ESCENA 2

La segunda escena es de dos jóvenes haciendo ejercicio. Uno de ellos tiene una camisa oscura, y la otra persona tiene una camisa blanca.

→ ¿Alguna vez tu respiración ha sido como la del niño con camisa oscura durante o después del ejercicio? **SI** ☐ **NO** ☐

Si contestas SI:

¿Ha pasado esto en el último año? **SI** ☐ **NO** ☐

Si contestas SI:

¿Ha pasado esto una o más veces en un mes? **SI** ☐ **NO** ☐

ESCENA 3

La tercera escena es de un joven que despierta en la noche.

→ ¿Alguna vez en tu vida tú has despertado de esa manera? **SI** ☐ **NO** ☐

Si contestas SI:

¿Ha pasado esto en el último año? **SI** ☐ **NO** ☐

Si contestas SI:

¿Ha pasado esto una o más veces en un mes? **SI** ☐ **NO** ☐

ESCENA 4

La cuarta escena también es de un joven despierto por la noche.

→ ¿Alguna vez en tu vida tú has despertado de esa manera? **SI** ☐ **NO** ☐

Si contestas SI:

¿Ha pasado esto en el último año? **SI** ☐ **NO** ☐

Si contestas SI:

¿Ha pasado esto una o más veces en un mes? **SI** ☐ **NO** ☐

ESCENA 5

La escena final es de otra persona en reposo.

→ ¿Tu respiración ha sido así, en algún momento de tu vida? **SI** ☐ **NO** ☐

Si contestas SI:

¿Ha pasado esto en el último año? **SI** ☐ **NO** ☐

Si contestas SI:

¿Ha pasado esto una o más veces en un mes? **SI** ☐ **NO** ☐

10.4) EHICS APPROVAL GIVEN BY THE NATIONAL RESEARCH ETHICS COMMITTEE (IN SPANISH)

COMITE NACIONAL DE BIOETICA

COMISIÓN DE ÉTICA DE LA INVESTIGACIÓN

CERTIFICADO DE AVAL ÉTICO

A quien corresponda.

La Comisión de Ética de la Investigación del Comité Nacional de Bioética (CEI-CNB), tiene a bien informar que fue presentado a la CEI-CNB, para su revisión y aval ético el proyecto: **"PREVALENCIA, SEVERIDAD Y FACTORES DE RIESGO PARA ASMA, RINOCONJUNTIVITIS ALÉRGICA Y ECZEMA ATÓPICO EN NIÑOS DE EDAD ESCOLAR EN CHUQUISACA - BOLIVIA",** por el Programa de Doctorado en Salud Internacional – Centro de Salud Internacional – Ludwig Maximalians – Universitât Mûnchen, Investigadora Principal es la Dra. María Teresa Solís Soto .

Dicho proyecto fue evaluado bajo la normativa internacional, que indica los criterios éticos que se toman en cuenta para todo proyecto de investigación que involucra seres humanos:

1. Validez científica (diseño metodológico bien formulado)
2. Selección equitativa de la muestra (tomando en cuenta principalmente a grupos vulnerables)
3. Validez social (pertinencia, atingencia y relevancia del proyecto)
4. Relación Riesgo/Beneficio (viendo que el riesgo sea mínimo y mayor el beneficio para los sujetos de estudio)
5. El Consentimiento Informado (documento redactado de una manera clara, comprensible y lo suficientemente informativo para el sujeto de investigación)

Una vez verificadas las correcciones hechas por la Investigadora Principal, en base a las observaciones de la CEI, es que se tiene a bien certificar que la mencionada Tesis cumple con todos los requisitos éticos arriba mencionados, por lo que los miembros de la CEI-CNB dan el respectivo AVAL ÉTICO al proyecto **"PREVALENCIA, SEVERIDAD Y FACTTORES DE RIESGO PARA ASMA, RINOCONJUNTIVITIS Y ECZEMA ATÓPICO EN NIÑOS DE EDAD ESCOLAR EN CHUQUISACA - BOLIVIA ",** el mismo que puede proseguir con su ejecución.

Lic. Pablo Almaraz Ossio
COORDINADOR

COMISIÓN DE ÉTICA DE LA INVESTIGACIÓN
COMITE NACIONAL DE BIOETICA

La Paz, 11 de julio de 2011

10.5) EHICS APPROVAL GIVEN BY THE NATIONAL RESEARCH ETHICS COMMITTEE (OFFICIAL TRANSLATION)

NATIONAL BIOETHICS COMMITTEE

ETHICS COMMITTEE OF RESEARCH

CERTIFICATE OF ETHICAL GUARANTEE

To whom it may concern:

The Ethics Committee of Research of the National Bioethics Committee (ECR-NBC), would like to inform that Dr. María Teresa Solis Soto is the Chief Researcher of the project entitled: "**PREVALENCE, SEVERITY AND RISK FACTORS FOR ASTHMA, ALLERGIC RHINOCONJUNCTIVITIS AND ATOPIC ECZEMA IN SCHOOL AGE CHILDREN OF CHUQUISACA - BOLIVIA**" which was submitted to the ECR-NBC by the Doctor's Degree Program in International Health – International Health Center – Ludwig Maximalians and the University of Munich for its review and ethical guarantee.

This project was evaluated under international norms that underlines the ethical aspects taken into account for each project of research, which involves human beings.

1. Scientific Validity (well-formulated methodological design)
2. Equitable selection of the sample (taken into account mainly vulnerable groups)
3. Social validity (pertinence, appropriateness and relevance of the project)
4. Risk / Benefit relation (seeing that risk is minimal and benefit is greater for the study subjects)
5. Informed Consent (a clear, understandable and informative written document for the subject of research)

Once verified the corrections made by the Chief Researcher and based on the observations of ECR, it is certified that the present Thesis accomplishes all the requirements above mentioned to get the corresponding ETHICAL GUARANTEE given by the ECR-NBC's members to the project "**PREVALENCE, SEVERITY AND FACTORS OF RISK FOR ASTHMA, ALLERGIC RHINOCONJUNCTIVITIS AND ATOPIC ECZEMA IN SCHOOL AGE CHILDREN OF CHUQUISACA - BOLIVIA**", which recommend its continuity and implementation.

(SEAL)

ETHICS COMMITTEE OF RESEARCH

NATIONAL BIOETHICS COMMITTEE

(SIGNATURE)

Lic. Pablo Almaraz Ossio
COORDINATOR

La Paz, July 11th, 2011

10.6) CONSENT FORM FOR PARENTS (IN SPANISH)

Sucre, …….. de 2011

Estimado padre de familia:

Ref: Invitación para participar en encuesta sobre problemas de salud en niños

Mi nombre es María Teresa, estudiante de doctorado en la universidad alemana Ludwig Maximilians. Me permito comunicarle estamos llevando adelante un estudio con el objetivo de conocer la situación de algunos problemas en la función respiratoria, en la nariz y en la piel de niños(as) de quinto año de enseñanza básica de Chuquisaca, previa autorización de sus padres. La información obtenida podrá guiar la implementación de programas de salud de manera adecuada a la realidad del departamento.

Durante una visita programada al establecimiento educativo se pedirá a los niños(as) que llenen un cuestionario sobre salud y algunos factores de riesgo, posteriormente se les mostrará a los niños(as) un video de 5 minutos sobre ejercicio y respiración y se les pedirá que llene otro cuestionario corto, finalmente se medirá peso y talla a todos los niños(as) participantes. Todas estas actividades tomarán alrededor de 2 horas del horario de clases y no representan ningún riesgo para la salud.

Junto con extenderle la invitación para que su hijo(a) participe, le aseguramos que la información obtenida será tratada de forma estrictamente confidencial, sólo se trabajará con un código en la computadora y en ningún caso los nombres de los niños(as) serán usados para el análisis individual.
Este estudio ha sido evaluado y aprobado por la *Comisión Nacional de Éti ca en la investigación* y es de conocimiento del Servicio Departamental de Educación de Chuquisaca, y las autoridades del Colegio de su hijo(a). Todo esto se ha realizado en procura de brindarle la mayor seguridad y confianza para que su hijo(a) participe en este estudio.

Considerando la información anterior,

Yo.....……, padre del menor: ……

NO deseo que mi hijo participe ☐ **SI** deseo que mi hijo participe ☐

Si desea escribir el motivo para no participar puede mencionarlo aquí (opcional): ……

Cualquier decisión **NO** tendrá ninguna consecuencia desfavorable en la relación de usted o de su hijo con la escuela.

Nombre de su hijo/hija:……

Nombre del padre/madre/tutor……

Firma del padre/madre/tutor ……

Fecha _____

Día/Mes/Año

Se ha programado la visita al establecimiento de su hijo(a) en fecha……de……del presente año, por lo que solicitamos devolver esta hoja firmada antes del día de la visita.

Si usted necesita mayor información, por favor no dude en comunicarse.

Dra. María Teresa Solís Soto
Investigador responsable

Fono: 64- 35869 - Celular: 734 63935
e-mail: maritesolissoto@yahoo.es
c. Manuel Durán #17
Sucre-Bolivia

10.7) CONSENT FORM FOR PARENTS (IN ENGLISH)

Sucre, …….. 2011

I am María Teresa Solís Soto, a PhD Student at Ludwig Maximilians University in Germany. I am doing some research in order to know the prevalence and risk factors of some respiratory, nose and skin problems in children in the fifth elementary grade of Chuquisaca. The information obtained will guide the implementation of health programs according the needs of the region.

In our research we will talk to many children, both girls and boys, and ask them a number of questions. Whenever researchers study children, we talk to the parents and ask them for their permission. If you agree, then the next thing I will do is ask your daughter/son for their agreement as well. Both of you have to agree independently before I can begin.

During a visit scheduled to the school, your daughter/son will fill out a health questionnaire, then your children will see a video questionnaire of seven minutes about exercise and breathing and asked to complete another short questionnaire, finally we will measure the weight and height for all children participants. All these activities will take about 2 hours of class.

The information recorded is confidential, and no one else except the principal investigator will have access to their questionnaire, and in any case the names of the children will be used for individual analysis. At the end of the study, a written report will be given to the school which they can share with their families.

You may choose not to have your child participate in this study and your child does not have to take part in this research if she/he does not wish to do so. Choosing to participate or not will not affect either your own or your child's future treatment at the school in any way.

This proposal has been reviewed and approved by National Commission on Ethics in Research (CEI – San Andrés University), which is a committee whose task it is to make sure that research participants are protected from harm.

I have read the foregoing information, and:

I CONSENT the participation of my child ☐ I REJECT the participation of my child ☐

Name of your daughter/son:……

Name of Parent/Mather/Tutor……

Signature of Parent/Mather/Tutor……

Date _____

Day/month/year

We have scheduled the visit to the educational establishment of your child on **(day/month/year)**, so we ask you to return this signed form before the day of the visit.

If you need more information, please feel free to contact.

Maria Teresa Solis Soto, MD, MPH, MEP
Principal Investigator
Phone: 64-35869 - Cell: 734 63 935
E-mail: maritesolissoto@yahoo.es
17 Manuel Duran Street. Sucre, Bolivia

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