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EPIDEMIOLOGIC STUDIES OF THE RISK FACTORS OF ALLERGIC RHINITIS

PH.D. DISSERTATION

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CERTIFICAN

Que **Jurgita Saulyte**, Licenciada en Salud Pública de la Facultad de Medicina de la Universidad de Vilnius (Lituania), ha realizado bajo su dirección los trabajos de investigación de su tesis doctoral sobre **"Epidemiologic studies of the risk factors of allergic rhinitis".**

Revisado el presente trabajo quedan conformes con su presentación, ya que reúne las condiciones para ser defendido como Tesis Doctoral.

Y para que así conste y produzca los efectos oportunos, firman el presente certificado en Santiago de Compostela, a 22 de Septiembre de 2015.

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PRESENTATION

This work consists of two parts, with the aim to identify modifiable, lifestyle-related risk factors, such as smoking and diet habits, of allergic rhinitis.

Part one is a systematic review and meta-analysis on active and passive exposure to tobacco smoking and allergic rhinitis. The objective of this meta-analysis was to examine the evidence for an association between active smoking and passive exposure to secondhand smoke and allergic rhinitis in children and adults. The results of this study were published in the international medical journal *PLOS Medicine* with an impact factor (2014) of 14.429, ranked 7th out of 153 journals of general medicine.

Part two of this work consists of a multicenter case-control study, which was carried out between January 2011 and October 2013. This study had the aim to shed light on modifiable dietary risk factors of allergic rhinitis. The main objectives of this study were to determine the effects of a high dietary intake of proteins, antioxidants and omega-3 and omega-6 polyunsaturated fatty acids on the occurrence of allergic rhinitis.

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ABBREVIATIONS AND ACRONYMS

µg: Microgram

ARIA: Allergic Rhinitis and its Impact on Asthma

BMI: Body mass index

CO: Carbon monoxide

ECRH: The European Community Respiratory Health Survey

FFQ: Food frequency questionnaire

IFN-γ: Interferon gamma

IgA: Immunoglobulin A

IgE: Immunoglobulin-E

IL-10: Interleukin-10

IL-4: Interleukin-4

IL-5: Interleukin-5

ISAAC: The International Study of Asthma and Allergies in Childhood

LT: Leukotriene

n-3: Omega-3

n-6: Omega-6

NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells

NO2: Nitrogen dioxide

NOx: Nitrogen oxide

O3: Ozone

PAR: Perennial allergic rhinitis

PG: Prostaglandin

PM: Particulate matter

SAR: Seasonal allergic rhinitis

SNP: Single nucleotide polymorphisms

SO2: Sulphur dioxide

SPSS: Statistical package for social sciences

SPT: Skin prick tests

STATA: Stata statistical software

T cells: T lymphocytes

Th1: Th1 helper cells

Th2: Th2 helper cells

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1. INTRODUCTION

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The inflammation of the nasal mucous membrane, mediated by immunoglobulin-E (IgE) production, is clinically called allergic rhinitis. Typically it is characterized by one or more of the following symptoms: nasal congestion, rhinorrhea, sneezing and itching of the nose which occurs after certain allergen exposure. Rhinitis is often linked to sinusitis because both block the sinuses causing an obstruction of the nose. As blocked sinuses are also a consequence of a number of other disabilities such as common cold, flu or nasal polyps, differential diagnosis of rhinitis may be difficult. According to specific allergens and seasonality allergic rhinitis may be seasonal or perennial. Classification of allergic rhinitis into intermittent and persistent was also adopted recently to describe duration and severity of symptoms.[1] Recent data suggest that gene-environmental interactions are probably the most important risk factors for atopic diseases such as allergic rhinitis.[2-4]

Allergic rhinitis is one of the most prevalent of all allergic disorders and has high direct and indirect cost as well as substantial impact on the quality of life, since it affects patients well-being and behavior and has serious impact on work and school performance. Over 600 million people suffer from allergic rhinitis worldwide and this number is constantly increasing, especially in developed and industrialized countries.[5,6] Since this condition may be frequently trivialized (by the patient) and unrecognized (by the doctor), resulting in inadequate control of symptoms, this number probably underestimates the true magnitude of the disease which makes of it an important Public Health problem of this century.[7]

Allergy is classically considered to result from an IgE mediated reaction that causes inflammation. In the case of rhinitis, inflammation occurs in the nose lining and may be of variable intensity.[1] In the allergic rhinitis disease, the process of allergen sensitization involves the participation of eosinophils, metachromatic cells, IgE-positive cells, macrophages and monocyte-like cells, which are redistributed towards the nasal epithelial surface due to exposure to allergens.[8] Allergic reactions in allergic rhinitis occur in 2 phases according to

time sequence: one early phase 30 minutes after contact with allergens that causes sneezing and rhinorrhea, and one late phase, 6 hours after contact that produces nasal obstructions.[9]

1.1. CLASSIFICATION

According to the causes that induce rhinitis symptoms, this disease is divided in to three main groups: allergic rhinitis, non-allergic rhinitis and rhinitis of unknown factors. The ARIA Workshop Group in collaboration with WHO proposed a detailed classification, similar to that published by the International Rhinitis Management Working Group in 1994.[1,10] The classification of rhinitis is shown on table1.

Based on the type of allergen that causes the disease, the division of rhinitis into seasonal, perennial and occupational was used for a long time. When allergic rhinitis is caused by outdoor allergens, e.g. trees grass and weed pollens, it is often referred to as seasonal allergic rhinitis (SAR), or "hay fever". Indoor allergens are usually present in perennial allergic rhinitis (PAR).[10] These may include dust mites, molds, animal allergens, cockroaches or certain occupational allergens, as well as pollen in areas where pollen is prevalent perennially.

In 2001 a new classification of allergic rhinitis was proposed by the ARIA Workshop Group and was updated in 2008.[1,11] It recommended to replace the terms "seasonal" and "perennial" allergic rhinitis by "intermittent" and "persistent" according to the duration of the symptoms and included additional description of the severity of the disease. Intermittent allergic rhinitis is diagnosed when symptoms last for less than 4 days a week or less than 4 consecutive weeks, while persistent allergic rhinitis is diagnosed when symptoms persist for more than 4 days/week and more than 4 consecutive weeks. Severity levels of "mild" and "moderate/severe" are used to measure

the effect of symptoms on sleep, work, and other activities. However, this new classification should be evaluated critically, because its validity is still unknown. Several studies confirm that there are no associations between the intermittent/persistent and the seasonal/perennial classifications and therefore these concepts cannot be used as alternative names for the same type of the disease.[12-14] Finally, since this would not lead to a difference in treatment, the ARIA experts propose continuing to classify the severity of rhinitis as "mild" and "moderate/severe".[1]

Table 1. Classification of rhinitis[1,10]

1 • **Allergic**
Intermittent (old term "seasonal")
Persistent (old term "perennial")
2 • **Infectious**
Viral
Bacterial
Other infectious agents
3 • **Other**
Occupational (allergic and non-allergic)
Intermittent
Persistent
Drug-induced
Hormonal
Idiopathic
Other causes
NARES (non-allergic rhinitis with eosinophilia syndrome)
Irritants
Food
Emotional
Atrophic
Gastroesophageal reflux

Occupational allergic rhinitis develops in response to airborne substances in the workplace, such as grain, wood dusts or chemicals.[15] Chronic nasal symptoms without allergic cause are the consequence of non-allergic rhinitis. One of the most common subtypes of non-allergic rhinitis is vasomotor rhinitis which is

defined as nasal symptoms which are not caused by an infection or allergy. The exact cause is unknown and symptoms are triggered by something that irritates the nose, such as temperature or barometric pressure changes, air pollution (including tobacco smoke), perfumes/fragrances, alcohol, medications, spicy foods or even strong emotions.[15]

1.2. DIAGNOSIS

The diagnosis of allergic rhinitis relies mostly on medical examination based on specific questions on existing symptoms, time of onset and duration. As allergic rhinitis is an IgE-mediated immune response against allergens, serum IgE concentration may be measured and skin prick tests (SPT) to common inhaled allergens performed.[1] However the detailed assessment of symptoms, including their severity, is of utmost importance in the diagnosis. One should first determine whether the rhinitis is allergic or nonallergic and differentiate it from other conditions that have similar symptoms.

According to criteria proposed by Allergic Rhinitis and its Impact on Asthma workshop directed by World Health Organization,[1] patients with rhinitis have specific nasal symptoms which are rhinorrhea, nasal obstruction and nasal itching with sneezing. Other relevant symptoms may also be present: itching or watery eyes, postnasal drip, wheezing, chronic cough or headache.

Typically, rhinitis is non-allergic when allergy has not confirmed by proper examination, such as history, SPT and measurement of serum specific IgE antibodies.[1,16] However allergic rhinitis has some typical symptoms that helps differentiate it from the non-allergic form: nasal secretion is more watery and colorless, and symptoms usually are caused by specific allergens like house dust mites, pollen or animal dander. It is more often accompanied by ocular symptoms like itchy or watery eyes.[10] Non-allergic rhinitis causes more

obstructive rhinorrhea and is triggered by factors such as humidity, tobacco smoke and changes in temperature.[1,17]

After the diagnosis of allergic rhinitis has been confirmed, the differentiation of the subtype may be assessed according to the criteria mentioned above. Usually, perennial allergic rhinitis is identified when patients have frequent, non-seasonal, nasal or ocular symptoms. It often overlaps with sinusitis, respiratory infections, and vasomotor rhinitis.[1,18] Seasonal allergic rhinitis is easy to identify because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure. It is common that allergic and nonallergic rhinitis occur in the same patient and produce what is called "mixed rhinitis".[15]

Differential Diagnosis

Allergic rhinitis is frequently associated with other allergic and non-allergic conditions, such as sinusitis, conjunctivitis, otitis media, sleep apnea, and fatigue.[19-21] Sinusitis coexists in between 3.6% and 12.5% of allergic rhinitis patients.[19,20,22] Poorly controlled allergic rhinitis may lead to the development of other nasal or sinus diseases, such as recurrent nasal polyps or acute and chronic sinusitis, ear disorders, such as otitis media, and hearing impairment; conditions caused by mouth breathing resulting from chronic nasal congestion, abnormal craniofacial development in children; sleep apnea and related complications.[21,23-26] Two common medical conditions, otitis media and sinusitis, are often caused by obstruction of the Eustachian tube and sinus ostium due to allergic rhinitis. Patients with allergic rhinitis have significantly more respiratory and non-respiratory co-morbid conditions than patients without rhinitis.[19-21]

Allergic rhinitis is also closely associated with other allergic conditions such as asthma, dermatitis and food allergies. Recent studies have suggested that these diseases are but one unique set of IgE-mediated allergic conditions, linked by the common thread of ''atopic march''.[27] It was stated that this sequence usually

starts with allergic dermatitis during infancy and eventually progresses to food allergy, allergic rhinitis, and finally asthma (inflammation of the airways). These diseases often co-exist in the same patient and can predict the occurrence of each other.[28]

1.3. BURDEN OF THE DISEASE

Although allergic rhinitis is very frequent, the real incidence of this disorder remains unknown, while its prevalence ranges between 10 and 55% in Europe.[29,30] The epidemiologic studies that assess the prevalence of this disorder often lack objective allergen skin testing data, most of them have small sample sizes and are based on questionnaire information only. In addition, self-reported seasonal or perennial rhinitis symptoms significantly overestimate the prevalence of allergic rhinitis defined by a positive history and positive allergy tests. The various nonallergic causes of rhinitis may also lead to inaccurate prevalence estimates.

Incidence

Incidence data worldwide are scarce. Using nation-wide data of primary care institutions, an increase in the recorded incidence of allergic rhinitis was observed between 2001 and 2005 in England: the age-sex standardized incidence of allergic rhinitis was 5.57 per 1000 person-years in 2001 and increased by 33% to 7.41 per 1000 person-years in 2005.[31] These figures are probably underestimated due to the fact that about 19% of patients with allergic rhinitis symptoms do not consult a general practitioner.[32] Furthermore, non-symptomatic cases with positive allergy tests are common.

Prevalence

Allergic rhinitis is an extremely common disease affecting 9.5–40.9% of the European population.[29] Up to 47% of children and up to 55% of adults suffer

from this disorder worldwide.[11,33-35] Most of allergic rhinitis patients suffer from perennial allergic rhinitis, although a large part of them present rhinitis of mixed etiology, involving sensitization to more than one trigger and manifestation of seasonal and perennial symptoms.[7] Within the population with allergic rhinitis, about 40-55% of the cases are found to be perennial and 11-49% seasonal, 4 to 40% of which have mixed etiology.[13,18,19,36]

Authors have used both the seasonal/perennial and the intermittent/persistent classifications. Bauchau et al. used both classifications.[13] Among allergic rhinitis patients 71% were found to be intermittent and 29% persistent. On the other hand, 49% of the cases were seasonal and 52% perennial.[13]

Some studies measure the prevalence of "allergic rhinitis symptoms ever" while other use the prevalence of current allergic rhinitis.[37,38] The difference between the 2 measurements may be large: 9.4% vs. 41.6% for Graif et al. using different definitions of prevalence may lead to conflicting results for the same population.[37] In addition, the fact that patients with perennial allergic rhinitis have more severe symptoms and higher self-awareness may lead to more frequent visits to a doctor.[13,19,22]

The season of the year in which data are collected may influence the results since the incidence of seasonal allergic rhinitis symptoms can be significantly reduced out of the pollen season. The correct case assessment is one of the most complicated goals in studies in which there is no possibility either to carry out an interview of each participant or to obtain laboratory evidence of the immune response. Moreover, it was disclosed, that even when the diagnosis was based on skin prick test results there have been considerable differences in estimations of prevalence and incidence of atopy in populations, depending on the definition of skin prick test criterion used.[1,11]

Differences in the severity

Two-third of allergic rhinitis patients suffer from moderate/severe symptoms of the disease.[19,20,39] Bousquet et al. have examined 3000 allergic rhinitis patients, consulting general practitioners, and found that 93% of the cases we moderate-to-severe rhinitis and only 7% were mild.[40] However, the Iberian Study of Aeroallergens Sensitization in Allergic Rhinitis revealed a higher prevalence of mild forms in intermittent allergic rhinitis in Spain and Portugal (82% and 92% respectively),[14] although persistent types of rhinitis showed exactly the same proportion of severity in both countries, 44% mild and 56% moderate/severe. Usually, subjects with persistent allergic rhinitis have more severe symptoms and higher degree of self-awareness of this disease.[13,19,22,41]

Differences in the prevalence around the world

As mentioned before, the prevalence of symptoms related to allergic rhinitis varies widely all over the world. The lowest prevalence was reported in the less industrialized parts of the world. The European Community Respiratory Health Survey (ECRH) revealed that these symptoms are generally lower in the Mediterranean region (northern, central and southern Europe) and higher in the British Isles, New Zealand, Australia and the United States, with wide variations even within some countries.[34,42] The Prevalence and Rate of Allergic rhinitis in Europe study (PAN-European) confirmed the same in 2001, reporting that allergic rhinitis has a higher prevalence in Western Europe.[7] However the International Study of Asthma and Allergies in Childhood (ISAAC) revealed the lowest prevalence of rhinoconjunctivitis in parts of Eastern Europe, south and central Asia.[43] The most common explanation of the fact that geographical pattern is consistent with the distribution of atopy is that these geographical variations most likely occur due to differences in environmental factors.[42,43]

Changes in the prevalence over the years

One more reason that increases the concern of all researchers over the world is that the prevalence of allergic rhinitis is increasing, especially in developed and industrialized countries.[6,7,31,43-45] According to the largest cross-sectional studies conducted in different years, the prevalence of allergic rhinitis was increasing steadily by 5% in the past and still continues to increase by 5%–20% in the past 15 years.[31,45-48] This increase is confirmed by many descriptive analyses dealing with various medical data bases, collected over the past decades.[6,49,50] This increase concerns severe cases essentially. Mild cases were found to be decreasing.[45,48]

1.4. IMPACT ON QUALITY OF LIFE AND ECONOMIC COST

In addition to the characteristic nasal and ocular symptoms, patients may also experience fatigue, headache, disrupted sleep patterns and reduction in cognitive processing, psychomotor speed, verbal learning and memory.[22] As a result, allergic rhinitis causes significant impairment on quality of life.[22,51-53] Most often health-related quality of life is correlated with disease severity and with the number of days in a defined period of time, in which the symptoms are absent.[19,22] Two-thirds of patients with allergic rhinitis report impact from the symptoms on daily activities and more than half experience sleep disruption.[19,20] Not only quality of life but cognition scores are significantly worse in subjects with allergic rhinitis compared to those without.[52,54] The Burden of Rhinitis in America survey found that only 3.6% of subjects with allergic rhinitis symptoms experienced 100% sleep adequacy compared with 11.7% of subjects with non-allergic rhinitis symptoms and 19.2% of subjects with no symptoms at all.[52] Most often, this sleep inadequacy consists of factors, such as having trouble falling asleep, waking up several times at night and having trouble staying asleep.[22]

Poor night sleep has an impact on daily activities and work/school performance. About two thirds of allergic rhinitis patients report the negative influence of their symptoms on work/school performance and other daily activities.[22,52,54-57] However, some data are contradictory. The Spanish "Alergológica-2005" study revealed that school performance was considered to be good in 79% of children with allergic rhinitis despite the fact that the large majority of them (87%) reported having at least one episode of allergic rhinitis in the previous year which caused absenteeism for several days.[35] But still, health-related quality of life perceived by these patients was lower than that of the general Spanish population.

In the US, it was estimated that in 1994 allergic rhinitis resulted in approximately 811.000 missed workdays, 824.000 missed school days, and 4.230.000 days of reduced activity.[58] These figures increased considerably and now they are as follows: 3.5 million lost workdays and 2 million lost schooldays annually.[51] Worldwide, symptoms related to allergic rhinitis cause a total of 28 million days of reduced function or productivity each year.[56] Comorbid conditions such as asthma and sinusitis can be disabling as well, resulting each year in more than 10 million missed school days and more than 73 million days of restricted activity, respectively.[59] In addition, all these effects lead not only to social harm, but also to substantial economic - direct, indirect, and hidden costs.[51,60-62]

Direct economic cost

The economic impact of allergic rhinitis is high. Direct costs can be medical: such as the cost of medications, medical consultations, emergency room visits, diagnostic testing, home health-care devices, and hospitalizations.[56] It was estimated that direct medical expenditures for the diagnosis and treatment of allergic rhinitis divides into the three main groups: outpatient services, which accounts for the majority of the expenditures (63%), medications (25%) and inpatient services (12%).[63] Overall, about 14.1 million visits to a physician are

attributed to allergic rhinitis in the United States each year.[64] The use of medication, especially of antihistamines, is increasing sharply over the world.[20,31,35] The average annual cost of seasonal allergic rhinitis in Germany is €1089 per child/adolescent and €1543 per adult.[65]

Almost all studies that estimate the economic burden of allergic rhinitis were conducted in the United States. In 1996, the estimated cost when rhinoconjunctivitis was the primary diagnosis was $1.9 billion. As a secondary diagnosis it was $4.0 billion, which gives a total of $5.9 billion for the overall direct medical expenditures.[63] In 2002 the cost of allergic rhinoconjunctivitis as the primary diagnosis was estimated at $2.35 billion and as secondary diagnosis at $4.95 billion.[66] Total expenditures were estimated at $7.3 billion ($4.58 billion for outpatient services, $1.86 billion for medications, and $0.87 billion for inpatient services).

Indirect economic cost

A significant number of lost workdays and lost schooldays annually, as well as side effects of treatment related to allergic rhinitis, lead to high indirect expenditures. Lost productivity can be assessed in terms of absenteeism from work and reduced working capacity, including caregiver absenteeism (absence from work to take care of a sick family member).[67] There are very few studies designed to measure the indirect cost of allergic rhinitis, especially in Europe. In Sweden, the mean annual productivity loss for allergic rhinitis and common cold together was estimated at 5.1 days or €653 per worker, yielding a total productivity loss of €2.7 billion in this country.[67]

Medicines that mitigate the symptoms of allergic rhinitis usually contain sedating antihistamines which are known to have central nervous system side effects such as somnolence and impaired learning, memory, and performance which increases the risk of acute injury.[56,55,61,68] Indirect medical cost associated with traumatic injury in patients with allergic rhinitis was estimated at $143 million in 2001 in the United States.[61]

It was disclosed that people with allergic rhinitis despite their nasal congestion, sneezing, rhinorrhea, and other symptoms, often do not seek medical advice, which leads to more severe health complications and increases the probability of using an inadequate medication. It was estimated that approximately 39 million persons in the United States experienced allergic rhinitis. However, only 12.3% (4.8 million) sought medical treatment for this condition.[58] The fact that allergic rhinitis remains widely untreated or treated inadequately leads to a dramatic increase in the cost of treating comorbid conditions such as asthma, recurrent nasal polyps, sinusitis, and chronic otitis media.[35,58,69,70]

In Europe, allergic rhinitis remains widely untreated and produces high economic cost. It was calculated that the decrease in lost productivity of 1 day per individual and year would potentially save approximately €528 million in each of the European countries.[67]

1.5. RISK FACTORS

According to ARIA Workshop Group, allergic rhinitis is a multi-factorial disease induced by gene-environment interactions.[1] The most plausible cause of the increased prevalence over the last decades may be related to changes in the risk factors related to environment and lifestyle: diet, stress, pollution, immunizations and patterns of infection in childhood.[11,71] The 'hygiene hypothesis' associated with the greatly improved sanitation, typical of a western lifestyle, is gaining credibility.[11,71,72,73] The so called "hygiene hypothesis" states that early life exposures to infectious agents influence the development of the immune system in a manner that reduces a child's likelihood of developing atopic diseases like allergic rhinitis and asthma later in life.[73]

1.5.1. Intrinsic factors

Genetic factors

Familial aggregation of cases of allergic rhinitis suggests that a common predisposing genetic factor might be involved in to the occurrence of this condition. The most important mechanism needed to trigger an episode of allergic rhinitis is the production of IgE. Through this mechanism important mediators such as cytokines and adhesion molecules are produced. Genes that encode total IgE response or functions of IgE receptors, as well as genes that mediate in the inflammation process are involved. They are essentially genes of interleukin (IL) (IL-4, IL-4R, IL-3, IL-28RA) or calcium-binding proteins such as S100A7.

Recently, several single nucleotide polymorphisms (SNP) in different genes, such as S100A7, IL-28RA, and IL-18, were implicated in the occurrence of the disease.[74-76] A locus in 11q13 is found to be important in the regulation of IgE,[77] and 14q11.2 is reported to be a susceptibility locus for allergic rhinitis and asthma.[78] It should be emphasized that the role of the polymorphisms could be twofold. On the one hand, they could be an independent risk factor of allergic rhinitis. On the other hand, they could act as effect modifiers of other non-genetic factors.

Since allergic rhinitis, asthma and atopic dermatitis share common systemic characteristics, it is reasonable to consider that a number of susceptibility genes could contribute to the allergic process regardless of the specific clinical phenotype.

Family history (Heredity)

Probably the best established risk factor for allergic rhinitis is history of allergic rhinitis in family members.[33,44,79,80] Compared with children whose parents are not atopic, children with one atopic parent develop allergies twice more often

and frequently at older age. Children with two atopic parents develop allergies almost four times more often and tend to be symptomatic already in childhood.[81] Moreover, according to recent findings, a family history of rhinitis increases the risk for the comorbidity of rhinitis and asthma from 4 to more than 11 times.[41,82]

Age and Gender

As it was mentioned before, the history of atopic disease usually begins in infancy and early childhood with atopic dermatitis and food allergy and progresses to allergic rhinitis and/or allergic asthma later in life.[10,70,83] A sharp increase in the lifetime prevalence of allergic rhinitis is observed in males and females during the first two decades of life (children and adolescents), with the highest prevalence at the age of 15–19 years.[31,43,47,83] Thereafter, lifetime prevalence is observed to steadily decline in both sexes. In general, allergic rhinitis was found to be more common in the population whose age varies between 10 and 24 years.[31,43] Analyzing the difference between types of rhinitis, some studies reveal that perennial allergic rhinitis is more common in adults than in children, while seasonal allergic rhinitis is more frequent in young population.[80,84]

Differences between sexes are observed as well. Whilst lifetime prevalence of allergic rhinitis is higher in males before the teenage prevalence peak (children and adolescents),[31,45,80,83,85] in the following years (young adults) female prevalence exceeds that of males.[7,31,46,83,86]

Stress

Stress occurs when individual perceive that environmental demands challenge an individual's adaptive capacity, or ability to cope.[87] Typically psychological stress is associated with negative life events such as job loss, death of a loved one, family conflict and similar. It seems that psychological stress operates by altering the magnitude of the airway inflammatory response to environmental

triggers, allergens, and infections and, in doing so, increases the frequency, duration, and severity of patients' symptoms.[88] This mechanism is also thought to be mediated by the effects of stress on neuro-immune regulation, which in turn modulates the hypersensitivity response. An indirect mechanism was also suggested, revealing that the relation between psychosocial factors and atopic disorders might be mediated via behavioral and socioeconomic pathways, such as stress induced changes in diet, smoking or other daily habits.[89]

In general, it was suggested that depression and anxiety have robust effects on the atopic disease, which indicates that psychosocial factors are involved in both the development and prognosis of atopic disorders.[89] Individuals suffering recurrent depression were diagnosed to have allergic rhinitis three times more often than psychiatrically healthy controls.[90]

Personality characteristics seem to play a role as well. Traits such as anxiety and stress vulnerability in situations characterized by failure, job overload or social conflicts were significantly higher in patients suffering from allergic rhinitis.[91] It was found that anxiety enhances the effects of stress even in late phase allergic responses.[4]

However, it is not clear yet whether stress is a cause of allergic rhinitis or a consequence of it. Does stressful lifestyle cause the development of allergy or, on the contrary, do allergy symptoms affect patient's mental stability? Few studies proposed that hay fever by itself increases the risk of panic attack in patients.[89,92] It was found that the effect of atopic disease on future mental health was stronger than that of psychosocial factors on the development and progression of atopic disease.

Some studies found out that stress-relieving activities, such as listening to music, may decrease allergic responses in atopic individuals, whereas stress-inducing activities, such as playing video games, had the opposite effect.[93]

1.5.2. Extrinsic factors

Diet

Lifestyle habits are the one that can be manipulated in order to prevent a disease. One of the most important components of lifestyle that has an influence on human's health is nutrition. A general overview of recent data on the effect of macro and micronutrients on allergic rhinitis is displayed in table 2. We also included asthma in this overview, since these both conditions are closely related to each other and share many risk factors. The outcome "allergic diseases in general" was added to this review as many studies analyzed their data without differentiating the outcome, using atopy as a case definition. Results are not uniform in their conclusions. This may be due to different reasons: different age structure of the population, differences in data collection and study design, and above all, measurement error and misclassification, very frequent in nutritional studies. Moreover, most of the studies analyzing the impact of diet on allergic rhinitis did not correct for energy intake, due to the fact that diet questionnaires are usually incomplete and do not allow to calculate the total daily calorie intake. Also it is important to mention that the large majority of the studies focuses on children and high-risk families in which relatives are atopic of have antecedents of atopy.

Table 2. Systematic review of the impact of food groups and nutrients on the development of allergic rhinitis

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
Mediterranean diet	Saadeh D (2013)[94]	Review	0-18 years				↓
	Chatzi L (2007)[95]	Cross sectional	7-18 years		↓		
	Chatzi L (2008)[96]	Cohort	Infants up to 6.5 years	High Mediterranean Diet Score during pregnancy		↓	↓
	de Batlle J (2008)[97]	Cross sectional	6-7 children		↓	↓	
	Barros R (2008)[98]	Cross sectional	Adults			↓	
	Marcos LG (2007)[99]	Cross sectional	6-7 children		↓ (not sign)	↓ (not sign)	
	Nagel G (2010)[100]	Cross sectional	8-12 children			↓	
Antioxidants	Saadeh D (2013)[94]	Review	0-18 years	Fruits, vegetables			↓
	Murr C (2005)[101]	Review	Not specified	"Healthy food", red vine, green tea		↑	↑
	Kompauer J (2006)[102]	Cross sectional	Adults	Carotenoids in blood serum	↓		
	Devereux (2005)[103]	Review				↓	↓
	Picado (2001)[104]	Case-control	Adults			no	
Fruits	Huang SL (2001)[105]	Cross sectional	13-17 years		no		
	Nagel G (2003)[100]	Cohort	Adults		no		
	Rosenlund H (2011)[106]	Cross sectional	0-8 infants, children		↓		
	Chatzi L (2007)[95]	Cross sectional	7-18 children, teenagers	Grapes, oranges, apples, tomatoes	↓		
	Barros R (2008)[98]	Cross sectional	Adults			↓	
	Farchi S (2003)[107]	Cross sectional	6-7 children		no		
	Marcos LG (2007)[99]	Cross sectional	6-7 children		↓		
	Gutiérrez-Delgado RI (2009)[108]	Cross sectional	6-14 children		↓	↓	

Table 2. *Cont.*

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
	Forastiere F (2000)[109]	Cross sectional	6-7 children	Citrus fruits, kiwi	↓	↓	
	Miyake (2006)[109]	Cross sectional	Adult women		no		
	Rosenkranz RR (2012)[111]	Cross sectional	Adult women		↑	↑	
	Li J (2012)[112]	Cross sectional	Adults				↓
	Nagel G (2010)[113]	Cross sectional	8-12 children			↓	
	Wijga AH (2003)[114]	Cohort	2-3 children			no	
Fiber	Miyake (2006)[110]	Cross sectional	Adult women		no		
Vegetables	Rosenlund H (2011)[106]	Cross sectional	0-8 infants, children		no		
	Farchi S (2003)[107]	Cross sectional	6-7 children		no		
	Gutiérrez-Delgado RS (2009)[108]	Cross sectional	6-14 children		↓	↓	
	Miyake (2006)[110]	Cross sectional	Adult women		no		
	Ellwood P (2001)[115]	Ecological	13-14 children		↓		
	Rosenkranz RR (2012)[111]	Cross sectional	Adult women		↑	↑	
	Li J (2012)[112]	Cross sectional	Adults	Raw vegetables			↓
	Nagel G (2010)[113]	Cross sectional	8-12 children	Cooked green vegetables		↓	
	Wijga AH (2003)[114]	Cohort	2-3 children			no	
	Hijazi N (2000)[116]	Cross sectional	Children, adolescents			↓	
Vit. A	Huang SL (2001)II[117]	Cross sectional	13-17 years			↓	
	Picado (2001)[104]	Case-control	Adults			no	

Table 2. *Cont.*

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
Vit. E	Huang SL (2001)II[117]	Cross sectional	13-17 years			↓	
	Miyake (2006)[110]	Cross sectional	Adult women		no		
	Fogarty A (2000)[118]	Cross sectional	18-70 adults	Vit.E			↓
	Hijazi N (2000)[116]	Cross sectional	Children, adolescents			↓	
	Troisi (1995)[119]	Cohort	Adult women			↓	
Beta carotene	Nagel G (2003)[100]	Cohort	Adults		↑		
	Miyake (2006)[110]	Cross sectional	Adult women		↑		
	Rosenlund H (2011)[106]	Cross sectional	8 years children		↓		
	Devereux (2005)[103]	Review				↓	↓
	Troisi (1995)[119]	Cohort	Adult women			↓ (not sign)	
Vit. C	Nagel G (2003)[100]	Cohort	Adults		no		
	Miyake (2006)[110]	Cross sectional	Adult women		no		
	Kompauer I (2006)[102]	Cross sectional	Adults	Vit.C in serum	no		
	Devereux (2005)[103]	Review				↓	↓
Vit. D	Nagel G (2003)[100]	Cohort	Adults		no		
	Cheng HM (2013)[120]	Cross sectional	Adults	Vit.D in serum	no		
	Arshi S (2012)[121]	Case-control	Adults	Vit.D in serum	↑		
	Bäck O (2009)[122]	Cohort	6 years children	Vit.D supplements in infancy	↑		
	Wjst M (2009)[123]	Review		Vit.D supplements			↑
	Mai XM (2014)[124]	Cohort	Adult men	Serum 25-hydroxyvitamin D	↑		
	Mai XM (2014)[124]	Cohort	Adult women	Serum 25-hydroxyvitamin D	↓		

Table 2. *Cont.*

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
Folate	Okupa AY (2013)[125]	Cohort	8 years children	Folate levels in blood sample		no	↑
Ca	Miyake (2006)[110]	Cross sectional	Adult women		↓		
Mg	Miyake (2006)[110]	Cross sectional	Adult women		↓ (not sign)		
	Rosenlund H (2012)[126]	Cross sectional	8 year children			↓	
	Hijazi N (2000)[116]	Cross sectional	Children, adolescents			↓	
P	Miyake (2006)[110]	Cross sectional	Adult women		↓		
Zn	Miyake (2006)[110]	Cross sectional	Adult women		no		
K	Hijazi N (2000)[116]	Cross sectional	Children, adolescents			↓	
Na	Hijazi N (2000)[116]	Cross sectional	Children, adolescents			↓	
Proteins	Ellwood P (2001)[115]	Ecological (cross sectional)	13-14 years	Proteins from cereal, nuts, starch, vegetables	↓		
Dairy products	Saadeh D (2013)[94]	Review	0-18 years			↓	↓
	Huang SL (2001)[105]	Cross sectional	13-17 years	Milk	↑		
	Miyake Y (2007)[127] *2001-2002 year study*	Cross sectional	Adult women		no		
	Farchi S (2003)[107]	Cross sectional	6-7 children	Milk	↑		
	Farchi S (2003)[107]	Cross sectional	6-7 children	Butter	↓		
	Gutiérrez-Delgado RI (2009)[108]	Cross sectional	6-14 children		no		
	Rosenkranz RR (2012)[111]	Cross sectional	Adult men	Cheese	↑	↑	
			Adult women	Cheese	↓	↓	
	Perkin MR (2006)[128]	Cross sectional	Children	Milk (unpasteurized)			↓
	Tamay Z (2013)[129]	Cross sectional	13-14 children	Butter	↑		
	Wijga AH (2003)[114]	Cohort	2-3 children	Fat milk, butter		↓	
	Dunder T (2001)[130]	Cohort	Children	Butter			↓
	Hijazi N (2000)[116]	Cross sectional	Children, adolescents		↓		

Table 2. *Cont.*

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
	Nwaru BI (2012)[131]	Cohort	Infants up to 5 years	Maternal consumption during pregnancy	↑		
	Kim JL (2005)[132]	Cross sectional	5-14 children	Milk (fresh)		↓	
Fish	Saadeh D (2013)[94]	Review	0-18 years	Fish fat			↓
	Nagel G (2003)[100]	Cohort	Adults		no		
	Miyake Y (2007)[127] *2001-2002 year study*	Cross sectional	Adult women		↓ (not sign)		
	Farchi S (2003)[107]	Cross sectional	6-7 children		no		
	Marcos LG (2007)[99]	Cross sectional	6-7 children	Sea food	↓	↓	
	Gutiérrez-Delgado RI (2009)[108]	Cross sectional	6-14 children		no		
	Kremmyda LS (2011)[133]	Review	Infants and children	Fish, fish oil supplementation			↓
	Virtanen SM (2010)[134]	Cohort	Infants up to 5 years		↓		
	Rosenkranz RR (2012)[111]	Cross sectional	Adults	Seafood	↑	↑	
	Miyake Y (2012)[135] *2007-2008 year study*	Cross sectional	Adult women		no		
	Li J (2012)[112]	Cross sectional	Adults				↓
	Nagel G (2010)[113]	Cross sectional	8-12 children			↓	
	Schnappinger M (2009)[136]	Case-control	Adults				↓
	Tamay Z (2013)[129]	Cross sectional	13-14 children	Fish and seafood	↑		
	Wijga AH (2003)[114]	Cohort	2-3 children			no	
	Molinas JL (2010)[137]	Cross sectional	Adults	Sea fish	↓	↓	
	Nafstand P (2003)[138]	Cohort	4 years children	Fish	↓	↓	
	Andreasyan K (2005)[139]	Cohort	8 years children	Fish	↓	↓	↓

Table 2. *Cont.*

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
	Kull I (2006)[140]	Cohort	4 years children	Fish	↓	↓	
	Takemura Y (2002)[141]	Case-control	6-15 children	Fish		↑	
	Kim JL (2005)[132]	Cross sectional	5-14 children	Fish		↓	
	Magnusson J (2015)[142]	Cohort	8 to 16 years children	Oily fish	↓		
	Dunder T (2001)[130]	Cohort	Children	Fish	no	no	no
Omega-3	Saadeh D (2013)[94]	Review	0-18 years	Fish fat			↓
	Nagel G (2003)[100]	Cohort	Adults	EPA (C20:5)	↓		
	Hoff S (2005)[143]	Cross sectional	Adults		↓		
	Miyake Y (2011)[144]	Cross sectional	6-15 years	Arachidonic (C20:4)	no		
	Wakai K (2001)[145]	Cross sectional	22-57 adult women		no		
	Miyake Y (2007)[127] *2001-2002 year study*	Cross sectional	Adult women	C20:5 & C22:6	no		
	Miyake Y (2012)[135] *2007-2008 year study*	Cross sectional	Adult women		no		
	Schnappinger M (2009)[136]	Case-control	Adults	C22:6 DHA			↓
	Anandan C (2009)[146]	Review and Meta-Analysis	Adults		no	no	
	Yu G (1998)[147]	Case-control	Adolescents	C20:5 in blood serum			↑
	Lowe AJ (2008)[148]	Cohort	Infants	w3 concentration in breast milk	no	no	
	Nwaru BI (2012)[131]	Cohort	Infants up to 5 years	C18:3 and total PUFA maternal consumption during pregnancy	↓		
	Almqvist C (2007)[149]	Cohort	5 year children	w3 plasma levels		no	no
	Kremmyda L-S (2011)[133]	Review	Infants and children	Fish, fish oil supplementation		↓	
	Magnusson J (2015)[142]	Cohort	8 to 16 years children		↓		

Table 2. *Cont.*

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
	Dunder T (2001)[130]	Cohort	Children	Serum EPA (C20:5) & DHA (C22:6)			↓
Omega-6	Saadeh D (2013)[94]	Review	0-18 years				↑
	Nagel G (2003)[100]	Cohort	Adults	Linoleic acid (C18:2)	↓		
	Hoff S (2005)[143]	Cross sectional	Adults		no		
	Chatzi L (2007)[95]	Cross sectional	7-18 years	Margarine (w6)	↑		
	Miyake Y (2011)[144]	Cross sectional	6-15 years	Arachidonic (C20:4)	↓		
	Trak-Fellermeier MA (2004)[150]	Cross sectional	20-64 adult men	Margarine (w6)	↑		
	Bolte G (2005)[151]	Cross sectional	18-29 young adults	Margarine (w6)	no	↑	
	Wakai K (2001)[145]	Cross sectional	22-57 adult women		↑		
	Miyake Y (2007)[127] *2001-2002 year study*	Cross sectional	Adult women		no		
	Bolte G (2001)[152]	Cross sectional	5-14 children	Margarine (w6)	↑		
	Kompauer I (2005)[153]	Cross sectional	20-64 adults	Arachnoidic (C20:4) acid in serum	↑		
	Miyake Y (2012)[135] *2007-2008 year study*	Cross sectional	Adult women		no		
	Anandan C (2009)[146]	Review and Meta-Analysis	Adults		no	no	
	Yu G (1998)[147]	Case control	Adolescents	w6 (C20:2) in serum			↑
	Lowe AJ (2008)[148]	Cohort	Infants	w6 concentration in colostrum	↑	no	
	Almqvist C (2007)[149]	Cohort	5 year children	w6 plasma levels		no	no
Omega-6 / Omega-3 ratio	Saadeh D (2013)[94]	Review	0-18 years	High w6/w3 ratio (more w6)			↓
	Nagel G (2003)[100]	Cohort	Adults	High w6/w3 ratio (more w6)	↓		
	Trak-Fellermeier MA (2004)[150]	Cross sectional	20-64 adult men	High w6/w3 ratio (more w6)	↑		

Table 2. *Cont.*

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
	Miyake Y (2007)[127] *2001-2002 year study*	Cross sectional	Adult women		no		
	Miyake Y (2012)[135] *2007-2008 year study*	Cross sectional	Adult women		no		
	Nwaru BI (2012)[131]	Cohort	Infants up to 5 years	Maternal consumption during pregnancy	↑		
	Oddy WH (2004)[154]	Cohort	6-8 children	Low w6/w3 (more w3)		↓	
Omega-9 (MUFA)	Nagel G (2003)[100]	Cohort	Adults	Oleic acid (C18:1)	↑		
	Hoff S (2005)[143]	Cross sectional	Adults		no		
	Trak-Fellermeier MA (2004)[150]	Cross sectional	20-64 adults	Oleic acid (C18:1)	↑		
	Wakai K (2001)[145]	Cross sectional	22-57 adult women		no		
	Miyake Y (2007)[127] *2001-2002 year study*	Cross sectional	Adult women		no		
	Miyake Y (2012)[135] *2007-2008 year study*	Cross sectional	Adult women		no		
Fish oil	Tamay Z (2013)[129]	Cross sectional	13-14 children		↓		
	Calder PC (2010)[155]	Review	Infants	Fish oil supplementation			↓
	Kremmyda LS (2011)[133]	Review	Infants and children	Fish, fish oil supplementation			↓
	Saadeh D (2013)[94]	Review	0-18 years	Fish fat			↓
Fats (total)	Huang SL (2001)[117] II	Cross sectional	13-17 years		no	↑	
	Chatzi L (2007)[95]	Cross sectional	7-18 years	Margarine	↑		
	de Batlle J (2008)[97]	Cross sectional	6-7 year children				↑

Table 2. *Cont.*

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
	Trak-Fellermeier MA (2004)[150]	Cross sectional	20-64 adult men	Margarine	↑		
	Bolte G (2005)[151]	Cross sectional	18-29 young adults	Margarine	no	↑	
	Bolte G (2001)[152]	Cross sectional	5-14 children	Margarine	↑		
	Miyake Y (2007)[127] *2001-2002 year study*	Cross sectional	Adult women		no		
	Miyake Y (2012)[135] *2007-2008 year study*	Cross sectional	Adult women		no		
	Tamay Z (2013)[129]	Cross sectional	13-14 years	Animal fats	↑		
	Wijga AH (2003)[114]	Cohort	2-3 years	Margarine		no	
	Weiland SK (1999)[156]	Ecological (ISAAC)	13-14 years	Trans fatty acids (dairy products, fat of ruminant animals, and industrially hydrogenated vegetable fats such as margarine)	↑	↑	
	Dunder T (2001)[130]	Cohort	Children	Margarine			↑
	Nwaru BI (2012)[131]	Cohort	Infants up to 5 years	Butter. Maternal consumption during pregnancy	↑		
Fast food	Saadeh D (2013)[94]	Review	0-18 years				↑
	Huang SL (2001)[105]	Cross sectional	13-17 years	Deep fried foods	no	↑	
	de Batlle J (2008)[97]	Cross sectional	6-7 children	Junk food			↑
	Marcos LG (2007)[99]	Cross sectional	6-7 children			↑	
	Gutiérrez-Delgado RS (2009)[108]	Cross sectional	6-14 children		no	↑	
	Peñaranda A (2012)[157]	Cross sectional	13-14 children		↑		
	Nagel G (2010)[113]	Cross sectional	8-12 children	Burger		↑	

Table 2. *Cont.*

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
	Tamay Z (2013)[129]	Cross sectional	13-14 children	Hamburger	↓		
	Hijazi N (2000)[116]	Cross sectional	Children, adolescents			↑	
Liver	Huang SL (2001)[117]	Cross sectional	13-17 years	Butcher's meat	↑	↑	
	Farchi S (2003)[107]	Cross sectional	6-7 children		no		
Meat	Huang SL (2001)[105]	Cross sectional	13-17 years		no	↑	
	Miyake Y (2007)[127] *2001-2002 year study*	Cross sectional	Adult women		no		
	Rosenkranz RR (2012)[111]	Cross sectional	Adults		↑	↑	
	Miyake Y (2012)[135] *2007-2008 year study*	Cross sectional	Adult women		↑		
	Li J (2012)[112]	Cross sectional	Adults				↑
	Peñaranda A (2012)[157]	Cross sectional	13-14 years		↓		
	Nagel G (2010)[113]	Cross sectional	8-12 years	Burger		↑	
Poultry	Rosenkranz RR (2012)111	Cross sectional	Adults		↑	↑	
Kcal	Huang SL (2001)[117] II	Cross sectional	13-17 years		no	↑	
	Ellwood P (2001)[115]	Ecological	13-14 years	Kcal from cereal, rice	↓		
Ethanol (Ethyl alcohol)	Barros R (2008)[98]	Cross sectional	Adults			↑	
	Assing K (2007)[158]	Cross sectional	18-35 adults	Alcohol	↓		
	Bendtsen P (2008)[159]	Cohort	20-29 year women	Alcohol	↑		
	Shaheen SO (2014)[160]	Cohort	Infants up to 7 years	Maternal consumption of alcohol during pregnancy	↓	↓(not sign)	

Table 2. *Cont.*

Factor	Author (year)	Type of the study	Study population (age if specified)	Specific foods (if specified) or specific condition	Allergic rhinitis	Asthma	Allergic diseases in general*
Eggs	Miyake Y (2007)[127] *2001-2002 year study*	Cross sectional	Adult women		no		
Nuts	Farchi S (2003)[107]	Cross sectional	6-7 children		↑		
Cereals	Marcos LG (2007)[99]	Cross sectional	6-7 children			↑	
	Rosenkranz RR (2012)[111]	Cross sectional	Adult women	Brown bread	↓	↓	
	Wijga AH (2003)[114]	Cohort	2-3 children	Brown bread		↓	
Rice, Pasta	Gutiérrez-Delgado RS (2009)[108]	Cross sectional	6-14 children		no		
	Virtanen SM (2010)[134]	Cohort	Infants up to 5 years	Oats	no	↓	
Soy	Nagata C (2008)[161]	Cohort	Adults	Soy isoflavones	no		
	Miyake Y (2005)[162]	Cross sectional	Adult women	Soy isoflavones	↓ (not sign)		

↑ - increases the risk;
↓ - protects; no - no significant association was found;
(not sign) – weak association, but not significant, or have lost their significance after adjustment for confounding factors.
*Allergic diseases in general – atopy, measured as allergic sensitivity (IgE and/or SPT measured).

Fats

The effect of a diet rich in fat is widely analyzed in recent studies. Nevertheless, it is difficult to give a general picture of the effect of fat, because different types of fatty acids may act in opposite directions in the human body systems. Some fatty acids are described as having a protective effect on allergic rhinitis (for example omega-3), while others (such as omega-6 and omega-9) usually have no effect or are related to increased risk of allergy. Moreover, results within the same groups of fatty acids use to vary between studies as well. However, most of these studies are cross-sectional and results should be interpreted with caution, since this study design does not establish a relation between cause and effect properly.

Depending on the length of their chain, fatty acids are divided in three main groups: saturated, monounsaturated and polyunsaturated. There are two essential fatty acids in the human nutrition that are required by the body but which cannot be produced in sufficient quantity from other substrates, and therefore must be obtained from food: *alpha-linolenic acid* (one of the omega-3 fatty acids) and *linoleic acid* (one of the omega-6 fatty acids).

Generally, intakes of saturated, monounsaturated and total fats (especially palmitoleic and oleic acids) are positively associated with increased risk of allergic sensitization and manifestation of atopic diseases like allergic rhinitis.[100,150,152] Usually food of animal origin food such as meat, butter, milk and cheese are the main source of these saturated and monounsaturated fatty acids. The role of polyunsaturated fatty acids is controversial and depends on the length of the chain.

Polyunsaturated fatty acids

There are two main families of polyunsaturated fatty acids: omega-3 and omega-6. According to recent studies, some of the omega-6 polyunsaturated fatty acids (especially arachidonic acid) are related to an increased risk of

allergic rhinitis,[133,153] while omega-3 polyunsaturated fatty acids act to oppose the action of omega-6 and are inversely associated with the risk of allergic sensitization and allergic rhinitis.[100,133,143] Polyunsaturated fatty acids are essential in ensuring the correct environment for the function of membrane protein, by maintaining membrane fluidity and regulating cell signaling, gene expression and cellular function. It was suggested that through these actions polyunsaturated fatty acids can actually influence the functioning of the immune cells and thus could have an impact on the development and manifestation of atopic diseases.[155] One of the key links between these fatty acids and the immunological processes related to atopy may be via eicosanoids, which are signaling molecules and are derived from either omega-3 or omega-6 fatty acids. Eicosanoids act on inflammatory cells, smooth muscles and epithelial cells, and thus are strongly implicated in different immunologic features and clinical manifestations of atopic disease.

The main dietary sources of omega-3 are seeds oils, such as flax and hemp, and all type of marine food, including marine algae. This may be one of the reasons why a higher amount of fish in the diet is protective against allergic rhinitis.[133] Early age at introduction of fish in the regular diet was even dose dependently associated with a decreased risk of allergic rhinitis,[134] and reduction of atopy or allergy risk ranged between 22% and 80% with higher consumption of fish.[133]

Most often, omega-6 polyunsaturated fatty acids are linked to an increased risk of allergic rhinitis via increased potential to produce pro-atopic and pro-allergic eicosanoids, derived from arachidonic acid (C20:4).[95,145,148,150,152,153] Omega-6 polyunsaturated fatty acids also participate in the production of E2 prostaglandin, a derived product that shifts the Th1/Th2 balance in the Th2 direction, which favors allergic diseases such as allergic rhinitis.[100] On the other hand, a higher production of prostaglandin E2 and prostaglandin I2 also is associated with inhibition of allergen-induced inflammatory responses, what consequently could play a role in the decrease of allergic conditions like rhinitis.[144] The role of omega-6 is not clear enough, and up to now studies that

analyses impact of consumption of omega-6 fatty acids on allergic rhinitis or atopy in general vary between protective and harmful effects. (Table 2)

In contrast, omega-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (C20:5 n-3), inhibits the conversion of arachidonic acid (20:4 n-6) to prostaglandin E2 and leukotriene B4, oppose the action of omega-6 and, thus, is negatively associated with allergic rhinitis.[100,133] This biological mechanism of opposite actions of omega-6 and omega-3 polyunsaturated fatty acids suggests that the risk of allergic rhinitis increases with an increasing ratio of omega-6/omega-3 intake. However, after summarizing the published data, no substantial association between the ratio of ingested omega-6 and omega-3 polyunsaturated fatty acids and allergic rhinitis or sensitization may be drawn since results are contradictory (table 2). Usually, in a typical western diet, the proportion of omega-6 is much higher than that of omega-3 polyunsaturated fatty acids. Furthermore, it was disclosed that the daily intake of omega-6 polyunsaturated fatty acids increased over the second half of the twentieth century, what relatively overlaps with increasing prevalence of atopy and its clinical manifestations.[133]

Unlike omega-3 and omega-6 fatty acids, omega−9 are not classified as essential fatty acids. They are component of olive, macadamia nuts, rapeseed and some other oils. Most of the published studies found no effect of these fatty acids on the development of allergic rhinitis symptoms. (Table 2). However, oleic acid (18:1 n-9), one of the most important components of the omega-9 group, was related with increased risk of allergic rhinitis in a few studies.[100,150]

Mediterranean diet

The Mediterranean diet is defined as a dietary pattern usually used among the populations around the Mediterranean Sea. It is reported as a model for healthy eating and better quality of life.[163,164] Common components of the Mediterranean diet include high monounsaturated/saturated fat ratio; high consumption of vegetables, fruit, legumes, and grains; rich in fish and seafood;

and moderate consumption of milk and dairy products.[165,166] The Mediterranean diet is then rich in both antioxidants and cis-monounsaturated fatty acids. Most of the studies have found that good adherence to this diet protects from allergic rhinitis. (Table 2) Typically these studies were conducted in children and adolescents, indicating protecting role for atopic diseases in the first years of life or even later in life.[96,164]

Minerals and vitamins

No firm conclusion can be drawn in relation to minerals and vitamins. The beneficial effects of antioxidants on human health are well known, however, different vitamins with antioxidant activity were found to act diversely with regard to allergic rhinitis symptoms. (Table 2) Vitamin E is revealed to have a protective effect on allergic diseases, while high consumption of beta-carotene increases the risk of allergic rhinitis according to most studies. Vitamins A and C do not show any substantial effect on allergic rhinitis, and only asthma and atopy were found to be less prevalent in subjects consuming more of these vitamins. The most probable explanation could be that some of the substances can act as either antioxidants or pro-oxidants, depending on the circumstances. (Herbert, 1996) However, fruits and vegetables protect against allergic rhinitis, according to most studies. Early supplementation with multivitamins during the first years of life was also associated to reduced risk of allergic rhinitis later at school age.[167]

Studies that analyze the effect of specific minerals on the occurrence of atopic diseases are scarce. Apparently, a higher consumption of minerals tends to protect against allergic disease.

Fast food / Food additives

High consumption of fast food was reported to increase the risk of rhinitis and asthma symptoms in children and adolescents. Respiratory allergic diseases in children have been correlated with frequent consumption of hamburgers, salty-

snack eating and frequent takeaway food consumption. These associations were more significant in children with sedentary lifestyle, such as watching television or playing video games. It was suggested that dyes and preservatives, used widely in this kind of food, can act as occupational allergens and contribute to the induction of rhinitis symptoms.[38,168,169]

Non-allergic mechanism of food induced rhinitis

Some food items and alcoholic beverages may induce rhinitis symptoms by unknown, non-allergic mechanisms.[1] For example, some spicy foods such as red pepper can induce rhinorrhoea probably because they contain capsaicin, which stimulates sensory nerve fibres inducing them to release tachykinins and other neuropeptides.[170] Rhinitis caused by this type of triggers is very rare and is called food-induced rhinitis.[1,167,171,172]

Alcohol consumption

Despite the lack of data regarding alcohol consumption and atopic diseases, epidemiologic studies suggest that alcoholic beverages have an influence on allergic sensitization.[1,173,174] It was reported that the risk to have positive skin prick test tended to increase with increasing consumption of alcohol, although these results were not statistically significant.[174] According to one cohort study conducted in women, with a follow up period of 7.8 years, alcohol consumption was positively associated with the risk of developing perennial allergic rhinitis (adjusted odds ratio (OR) 1.78 (95% CI, 1.13-2.80) for women drinking more than 14 drinks/week), while there was no association between alcohol consumption and seasonal allergic rhinitis.[159] In cross sectional study of adult men and women, higher amounts of alcohol consumed were inversely associated with occurrence of allergic rhinitis symptoms.[158] Authors explain that the observed negative association may be a healthy-drinker effect: having respiratory symptoms may cause changes in the behavior towards alcohol consumption and the tendency to avoid it. No evidence was found that prenatal

alcohol exposure increases the risk of allergic rhinitis and asthma in childhood.[160]

Smoking

Smoking is related to numerous diseases. Indeed, the fact that almost 80% of European children and adolescents are exposed to second hand tobacco smoke supposes an important Public Health problem.[175]

A number of studies have examined the association between smoking exposure and allergic disorders, including allergic rhinitis. However the results are conflicting and divide into three parts: revealing that smoking increases the risk, that there is no effect or even those, proclaiming the preventive effect of smoking on allergic rhinitis.[159,176-178] Despite these findings, it seems that age may have an essential role as a modifier of the relation between smoking and allergy. We have carried out a systematic review and meta-analysis of active and passive smoking and the risk of allergic rhinitis, allergic dermatitis and food allergies. The risk of allergic rhinitis was modestly increased only in children for both active and passive smoking, while in the adult population the association was weak.[179] This finding suggests that, in countries where smoking is frequent, 14% of allergic rhinitis among children may be attributable to active smoking. The mechanism involved is that smoking increases nasal responses to allergen in atopic subjects and increases IgE, immunoglobulin G4 (IgG4), and post-allergen histamine levels in nasal lavage fluid.[180,181] The immaturity of the respiratory, nervous and immune systems of children makes them more vulnerable to the harmful health effects of tobacco smoke.[182] Furthermore, smoking facilitates sensitization to perennial indoor allergens, such as animal dander, as well as to some outdoor allergens such as pollen.[183]

Environmental factors

Indoor and outdoor air pollutants are those elements of the environment that influence the presence of specific allergens, which are the targets of the IgE-

mediated immune response.[181] Improvement in the socioeconomic status of individuals is associated with improvement in lifestyle and greatly modernized domestic and professional working conditions, especially of individuals who spend more time indoors. There are evidences that an association exists between the time spent indoors and the changes in patterns of sensitization to allergens.[184] Outdoor pollution has a significant influence, especially since the transport-related carbon emissions from growing motorized land vehicles and aviation are raising constantly.[185] The exploitation of fossil fuels is inherent to modern life and has been a key element of the rapid technological, social and cultural changes of the last 250 years.[186] Although such changes have brought considerable benefits, this exploitation has also contributed to a burden of illness, such as allergic disorders, through pollution of local and regional environments. These findings could confirm the observations made years earlier among migrant populations in the United Kingdom.[187] In the late 1960s Morrison Smith with colleagues reported that the prevalence of asthma in Asian and West Indian children, who were born in the United Kingdom, were very similar to those of English children. However, the prevalence in immigrant children, who were born in their native countries, were generally much lower than those of children born in the United Kingdom. These data suggested that environmental events occurring very early in life, perhaps shortly after the birth have an impact on development of allergic conditions, such as allergic rhinitis and asthma in children, and environmental and lifestyle changes, implying more polluted environment, may be one of the crucial factors.

Studies, that have been analysing the sensitization to the major indoor and outdoor allergens, have indicated that most common ones in patients with allergic rhinitis are: house dust mites, mould, pollen and animal dander.[188-191] Which allergens – from indoor or outdoor environment – are more common in allergic patients, depends also on living area. Urban populations may be less frequently sensitized to pollens, but more frequently sensitized to cockroach and other indoor allergens compared with residents from rural areas.[192,189]

Indoor environment

The most common indoor allergen, associated with allergic rhinitis is house dust mite, the effect of which rises with increasing exposure level.[41,44,193-195] Other factors, such heating type, temperature, or ventilation, have a significant influence on the amount of dust mite indoors. It was observed that a constant warm and humid climate yields to proliferation of dust mites and molds.[191,196] Carpets at home, as well as stuffed toys, were also related with increased risk of allergic rhinitis among children, probably due to their elevated concentration of house dust mites and other allergens.[197,198]

Mold patches were also revealed as an important source of indoor environmental allergens and were associated with a significant increase in the risk of allergic rhinitis in children.[197]

Cockroaches are considered to be important vehicles of inhaled indoor allergens.[188,197,199,200] The highest levels of cockroach allergens at homes were reported in dust samples collected from the wooden houses of urban slums.[199]

Anti-mouse IgE-carrying children were found to be at a higher risk of rhinitis and atopy.[201] However, other studies did not confirm the finding that early life mouse exposure has an impact on developing allergic rhinitis or asthma.[202]

The effect of feather bedding is associated with inconsistent results: some studies found that it significantly increases the risk of allergic rhinitis symptoms,[38] while others link it to fewer allergy symptoms.[85]

It was proved that air conditioning may prevent against contamination with indoor allergens.[203] Patients living in households without air conditioning were at greater risk of mold sensitization.[204] Mechanical ventilation in dwellings was also found to be beneficial for the prevention of allergic rhinitis symptoms, while multiple sealing of buildings showed a direct association with allergy symptoms.[205] It was shown that proper indoor ventilation may reduce the

effects of outdoor air pollution at homes: there were no associations found between traffic densities and allergic rhinitis symptoms in children sleeping in air-conditioned homes, what suggests that appropriate ventilation can mitigate traffic pollution problems.[203]

Despite the existence of studies that showed that wood heating and direct heated electric radiators are associated with increased risk of allergic respiratory symptoms,[205] other studies denied this fact. Heating with wood or coal and biomass were significantly related with fewer symptoms of allergic rhinitis.[85,191,206] The hygiene hypothesis was proposed as a possible explanation: the incomplete combustion of coal and wood during heating releases byproducts with well-known adverse health effects, hence increasing the risk of respiratory infections.[207-209] These infections might thus afford protection against allergic rhinitis and other allergic disorders, such as asthma, since activated Th1-type immune response may shift the balance and reduce Th2-type allergen-induced response.[85] A protective effect of infections may also partly contribute to a lower prevalence of these allergic conditions in some countries, as may explain the differences in prevalence between rural and urban areas.[30,44,191,210,211]

Outdoor environment (pollution)

With modernization of life the problem of outdoor pollution becomes more worrying in all aspects. It is well known that pollutants may play a direct and indirect role in the pathophysiology and the development of allergic diseases.[38,198,212,213,214] It was found that patients with weakly positive skin prick tests for inhaled allergens may be more susceptible to the environmental factors as air pollutants may increase the risk of allergic inflammation in the nasal airway.[216,217]

City life was associated with a higher prevalence of allergic rhinitis compared to country lifestyle.[218] Recent studies revealed that the prevalence of allergic rhinitis is higher for people living near air-polluting factories or mines, as well

as in areas with high exposure to truck traffic. This is probably due to pollutants such as nitrogen oxide (NOx) and carbon monoxide (CO).[38,85,203,216,218,219,220] A high annual average concentration of sulphur dioxide (SO2), carbon monoxide (CO) or nitrogen oxides (NOx) was significantly associated with increased prevalence of allergic rhinitis in children and adults.[221-228] Exposure to increased ozone (O3) levels in summer was also associated with increased risk of hay fever in children and adults and this association with allergic children's symptoms was stronger in urban zones, compared to small metropolitan and rural areas.[221,226,229,230] Nevertheless, not all studies succeeded to find any relationship between air pollutants such as sulphur dioxide (SO2), nitrogen dioxide (NO2) or high ozone (O3) levels with increased risk of allergic rhinitis in children population.[223,224,229]

Studies show that polyaromatic hydrocarbons in diesel exhaust particles can enhance production of IgE, however other studies failed to find evidences that shows that elemental carbon, attributable to traffic, may have an influence on developing allergic rhinitis symptoms.[195]

Particulate matter (PM) of diameter of ≤ 2.5 micron was significantly associated with increased prevalence of allergic rhinitis in children,[229,231,232] while particles of larger diameter, of up to 10 micron, in the surrounding environment were not always significantly related to increased risk of allergy.[223,224,233-235] Besides, most of these associations are statistically significant among children and those who had spent most of their lives in the same community only.

It was found that living within 100 meters from a road with a traffic intensity of more than 10 cars/min (24 hour mean) correlates with the prevalence of allergic rhinitis and current asthma in adults.[236] A distance-dependent relationship was identified, with the highest risk for children living less than 50 meters from busy streets.[231] However, living within 150 meters from a major road was not significantly associated with an increased risk of any of the allergic disorders in any age group.[237]

It was disclosed that air pollution from car exhaust products have stronger impact on developing of allergic rhinitis symptoms than pollution from heating with coal.[238] The prevalence of allergic rhinitis, asthma, and positive skin prick tests to aeroallergens was found to be lower in regions with high degree of air pollution with sulfur dioxide produced by coal (2.7%, 3.9%, and 18.2%) than in those polluted by automobiles (8.6%, 5.9%, and 36.7%).

The environmental pollution with allergens plays an extremely important role in the first few months of life, since it is the most sensitive period, during which inhaled exposure to certain allergens may predispose to the subsequent development of atopic respiratory disease.[239] Subjects born in the pollen season (March to April) have been shown to be at higher risk of being sensitized to birch pollen.[195] Increased risk to develop grass pollen allergy was found in subjects born during grass pollen season (May to June).[239] Increased concentration of ragweed particles in the air was directly related with increased average of daily physician visits for allergic rhinitis but, globally, outdoor air pollution was found to be a poor predictor of physician visits for this condition in adults.[240] The frequency of sensitisation to pollens was reported to be higher in allergic population living in urban areas, while for indoor aeroallergens, such as moulds mixture and cat and dog dander, it was similar in both.[241]

Hygiene hypothesis

The so-called hygiene hypothesis was first suggested by Strachan in 1989, who suggested that atopic diseases, such as asthma and allergic rhinitis, are less prevalent in children from large families, where the probability to transmit infection by unhygienic contact with older siblings is higher.[73] This theory was approved by a large majority of epidemiological studies over the world,[30,195,242-244] although other studies failed to confirm this finding.[38,211] A study conducted in Germany disclosed that children from small families (up to three people) who began to attend day nursery at an older age had higher prevalence of atopy than those who started to attend it at a younger age.[243] However, age of

entry to day nursery had no effect on atopy if children were from families with more than three family members.

One more confirmation of the hygiene hypothesis has been provided later by comparative analysis of various regions in East and West Germany, after the fall of the Berlin Wall.[245] Striking differences were noted between regions, with higher prevalence of atopy (i.e., allergic rhinitis, asthma) and atopic sensitization in West Germany, which was much more economically advanced. According to this, infections with viruses and perhaps other intracellular organisms influence the immune response. The hygiene hypothesis is based on the observations that Th1 responses induced by microbial stimulation can counterbalance allergen-induced Th2 responses.[72]

According to the hygiene hypothesis, increased risk to develop allergic diseases is related with factors such as immunization with a variety of vaccines, wide use of antibiotics and paracetamol in infants and young children.[38,66,246-248] Meanwhile, acute gastroenteritis in infancy was related with decreased risk of allergy later in life: microbial stimulation of the gut may induce a subtle inflammation and secretion of mucosal IgA, which participates in antigen elimination. High intestinal IgA in early life was associated with minimal intestinal inflammation and reduced risk for IgE-associated allergic diseases such as eczema, food allergy, asthma, and rhinitis.[249] However, this theory is applicable only in children, since it was not confirmed in adults.[250]

Despite all these findings, some authors maintain that the hygiene hypothesis has to be specified much more precisely, with respect to some other criteria, such as type of the microorganism (parasites, bacteria, virus, and fungus), type or subtype of disease (IgE-associated or 'intrinsic') and type of contact.[251]

Farming lifestyle

In line with the field of the hygiene hypothesis, farming lifestyle, especially with contact to livestock, was related to a protective factor against development

of allergic disorders such as rhinitis in children and adults.[128,210,211] It was found that children growing up on a farm were less likely to be sensitized to common aeroallergens and to suffer from allergic rhinitis than children living in the same villages but in non-farming families.[252] Living in a farm in childhood is associated with a long term risk reduction: those adults who spent their childhood in a farming surrounding had significantly less atopic diseases later in life compared to those who spent their childhood in the city.[253] However, some parts of the world, like Turkey or New Zeeland, show a greater prevalence of allergic rhinitis in rural areas than in urban.[191,254] These discrepancies could be explained by differences in culture, ethnic origin, style of farming and behaviour. Indeed, it was found that levels of cat and dog allergens in the mattress dust were much higher in those belonging to girls than on those used by boys.[194]

Pets

The association between pet ownership and the risk of allergic rhinitis is contradictory. The hypothesis that having a pet at home increases the risk of allergic rhinitis was approved by number of studies.[86,191,210,255] While, according to some other investigators, an independent inverse association was found for early-life exposures to indoor and outdoor animals and development of allergic disorders, including allergic rhinitis.[256-260] Nevertheless, some studies found a protective relationship only with close contact to cats while for dogs' keepers this association was significant only for asthma.[254,261] Selection bias may have played a role in the existence of discrepancies between studies as it is likely that people with allergic symptoms tend to avoid contact with animals.

Allergen movement from the native source to various surfaces and even unusual places that surround us every day is widely reported and should be taken into account. It was revealed that, although the concentration of cow dander allergen was found to be higher in stables, it was noticeable in dust samples from living-rooms and mattresses as well.[262] Similarly, households

with exclusively outdoor dogs had significantly higher levels of dog allergen at home than homes without any animals at all.[263] Very similar results were reported for cats' allergens.[262] This transporting, perhaps, happens most likely due to adherence on skin and clothing, although wind or air masses also may play a role.

All these allergens that act directly, together with indirect factors that enhance the conditions for outdoor allergens to penetrate the houses and for indoor allergens to remain inside may act as risk factors for allergic rhinitis and should be taken into account when developing preventive measures.

Social class

The most recent studies show that the prevalence of allergic rhinitis increases with the higher social class of the family.[72,211,264,] The Tucson Children's Respiratory Study showed a higher prevalence of allergic rhinitis among children whose mothers had more than a high school education.[33] It was suggested earlier, that the 'psychological environment' created by the western lifestyle with its emphasis on maintaining sanitary conditions, may have interfered in the development of a normal immunity and influenced the development of atopic sensitization and diseases.[245] The prevalence of atopic diseases was found to be significantly higher among children living in a bigger apartment or having more rooms in their homes.[211] Furthermore, mud flooring was associated with reduced risk of allergic rhinitis in children,[257] while living in a house made of concrete was significantly associated with an increased risk of allergic rhinitis symptoms.[38]

Thus, according to the latest studies, city life, within a small family, high social class and exaggerated sanitary standards in infancy may increase the risk of developing atopic conditions such as allergic rhinitis later in life. However, it was suggested that socioeconomic status may merely reflect microbial contamination of water, food, and poorer housing conditions, and current

evidence regarding associations with common specific and non-specific infectious illness neither refutes nor supports the hygiene hypothesis.[72]

1.6. CONTROL

In accordance with the fact that allergic rhinitis is very common and still widely untreated or treated inadequately, education is needed in order to increase early recognition of the symptoms and to apply early treatment.

According to recent studies, many allergic patients lack understanding of the nature of allergic rhinitis and its associated risks of respiratory complications, comorbid diseases, losses in productivity and in health related quality of life.[35,58,69,265] In order to achieve maximum therapeutic responses, the appropriate education of patients and their family members and compliance are essential after diagnosis and initiation of therapy.[1,11] The information of the risk of comorbid conditions and complications such as asthma, recurrent nasal polyps, sinusitis, and chronic otitis media should be explained.

Identification and reduction of exposure to allergens is an essential part of the management of allergic rhinitis. Allergen avoidance was recommended as an integral part of a management strategy for allergic rhinitis and asthma by ARIA Workshop Group and the World Health Organization.[1,11,266] Allergen transport from the outdoor to indoor, especially to bed, must be prevented by optimizing hygiene by measures such as face washing, keeping coat and cap at entry hall, using dust mite impermeable mattress covers, removing carpets from bedrooms.

The most recommended pharmacotherapy for allergic rhinitis is intranasal corticosteroids and antihistamines, which improve both nasal symptoms and pulmonary function.[81] However, the safest recognized treatment is immunotherapy, the use of which in children could significantly reduce allergic

rhinitis-related morbidity and its economic burden.[267,268] Moreover, treatment with allergen immunotherapy lowers the risk to develop new asthma cases in adults with allergic rhinitis.[269] Unfortunately, antihistamines are reported to be most often prescribed for allergic rhinitis patients, despite their side effects on the central nervous system that increase the risk of acute injuries.[55,56,61,68] Pursuant to recent findings, about 82% of allergic rhinitis patients are prescribed antihistamine (in combination or alone), and only for the rest immunotherapy is applied.[35]

In conclusion, appropriate prevention and management of allergic rhinitis may prevent the development of asthma, as well as other serious complications, while on the other hand, management of food allergies and dermatitis in children may reduce the incidence of allergic rhinitis later in life. It was estimated that a three-part approach to management, which includes allergen avoidance, immunotherapy, and pharmacologic treatment, can reduce the progression of the inflammatory process and improve the patient's quality of life. The ARIA Update recommendations reminds that patients with allergic rhinitis, particularly if persistent, should be evaluated for asthma, patients with asthma should be evaluated for rhinitis, and an effective combination strategy should be used to treat diseases of the upper and lower airways.[1]

1.7. FUTURE CHALLENGES FOR INVESTIGATIONS

Further studies on the incidence of allergic diseases are required in order to make conclusions on the real burden of this disease. In a large proportion, today's knowledge on the disease is based solely on prevalence studies of cross-sectional nature, inadequate for proper causal inference related to risk factors.

The search of possible genes as risk factors for developing allergic rhinitis should be one of the main challenges of the future studies.

1.8. REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008; 63:8-160.
2. Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. Curr Opin Allergy Clin Immunol. 2005; 5:23-9.
3. Kilpeläinen M. Koskenvuo M, Helenius H, Terho EO. Stressful life asthma and atopic diseases. Clin Exp Allergy. 2002; 32:256-63.
4. Kiecolt-Glaser JK, Heffner KL, Glaser R, Malarkey WB, Porter K, Atkinson C et al. How stress and anxiety can alter immediate and late phase skin test responses in allergic rhinitis. Psychoneuroendocrinology. 2009; 34:670-80.
5. Asher MI, Montefort S et.al. ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjuctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006; 68:733-43.
6. Simpson CR, Newton J, Hippisley-Cox J, Sheikh A. Incidence and prevalence of multiple allergic disorders recorded in a national primary care database. J R Soc Med. 2008; 101(11):558-63.
7. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J. 2004; 24:758-64.
8. Broide DH. The pathophysiology of allergic rhinoconjunctivitis. Allergy Asthma Proc. 2007; 28(4):398-403.
9. Min YG. The pathophysiology, diagnosis and treatment of allergic rhinitis. Allergy Asthma Immunol Res. 2010; 2(2):65-76.
10. International Consensus Report on Diagnosis and Management of Rhinitis. International Rhinitis Management Working Group. Allergy. 1994; 49:1-34.
11. Bousquet J, Van Cauwenberge P, Khaltaev N. ARIA Workshop Group and World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001; 108:147–336.

12. Demoly P, Allaert FA, Lecasble M, Bousquet J. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy. 2003; 58:672-5.
13. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy. 2005; 60:350-3.
14. Pereira C, Valero A, Loureiro C, Dávila I, Martinez-Cócera C, Murio C et al. Iberian study of aeroallergens sensitisation in allergic rhinitis. Eur Ann Allergy Clin Immunol. 2006; 38(6):186-94.
15. Wallace DV, Dykewicz MS, Bernstein DI et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol. 2008; 122: 1-84.
16. Settipane RA, Lieberman P. Update on nonalergic rhinitis. Ann Allergy Asthma Immunol. 2001; 86:494-507.
17. Lindberg S. Malm L. Comparision of allergic rhinitis and vasomotor rhinitis paients on the basis of a computer questionnaire. Allergy. 1993; 48: 602-607.
18. Skoner DP. Allergic rhinitis: Definition, epidemiology, pathophysiology, detection, and diagnosis. J Allergy Clin Immunol. 2001; 108:2-8.
19. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. Allergy. 2007; 62:17–25.
20. Mullol J. A Survey of the Burden of Allergic Rhinitis in Spain. J Investig Allergol Clin Immunol. 2009; 19(1): 27-34.
21. Schatz M, Zeiger RS, Chen W, Yang SJ, Corrao MA, Quinn VP. The burden of rhinitis in a managed care organization. Ann Allergy Asthma Immunol. 2008; 101(3):240-7.
22. Schatz M. A survey of the burden of allergic rhinitis in the USA. Allergy. 2007; 62:9-16.
23. Settipane RA. Complications of allergic rhinitis. Allergy Asthma Proc. 1999; 20:209-13;
24. Greisner WA, Settipane RJ, Settipane GA. Co-existence of asthma and allergic rhinitis: a 23-year follow-up study of college students. Allergy Asthma Proc. 1998; 19:185-8.

25. Berrettini S, Carabelli A, Sellari-Francheschini S, Bruschini L, Abruzzese A, Quartieri F et al. Perennial allergic rhinitis and chronic sinusitis: correlation with rhinologic risk factors. Allergy. 1999; 54:242-8.
26. Farrell BP. Endoscopic sinus surgery: sinonasal polyposis and allergy. Ear Nose Throat J. 1993; 72:544-59.
27. Spergel JM. From atopic dermatitis to asthma: the atopic march. Ann Allergy Asthma Immunol. 2010; 105: 99–106.
28. Tan RA, Corren J. The relationship of rhinitis and asthma, sinusitis, food allergy, and eczema. Immunol Allergy Clin North Am. 2011; 31: 481–491.
29. Heinrich J, Richter K, Frye C, Meyer I, Wölke G, Wjst M et al. [European Community Respiratory Health Survey in Adults (ECRHS)]. Pneumologie. 2002; 56(5):297-303.
30. Hugg T, Ruotsalainen R, Jaakkola MS, Pushkarev V, Jaakkola JJ. Comparison of allergic diseases, symptoms and respiratory infections between Finnish and Russian school children. Eur J Epidemiol. 2008; 23:123-33.
31. Ghouri N, Hippisley-Cox J, Newton J, Sheikh A. Trends in the epidemiology and prescribing of medication for allergic rhinitis in England. J R Soc Med. 2008; 101:466-72.
32. Didier A, Chanal I, Klossek JM, Mathieu J. La rhinite allergique: le point de vue du patient. Revue Francaise Allergologie. 1999; 39:171–185.
33. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics. 1994; 94:895-901.
34. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. Eur Respir J. 1994; 7:954-60.
35. Navarro A, Colás C, Antón E, Conde J, Dávila I, Dordal MT, et al; Rhinoconjunctivitis Committee of the SEAIC. Epidemiology of allergic rhinitis in allergy consultations in Spain: Alergológica-2005. J Investig Allergol Clin Immunol. 2009; 19:7-13.

36. Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. Thorax. 1991; 46:895-901.
37. Graif Y, Garty BZ, Livne I, Green MS, Shohat T. Prevalence and risk factors for allergic rhinitis and atopic eczema among schoolchildren in Israel: results from a national study. Ann Allergy Asthma Immunol. 2004; 92:245-9.
38. Sultész M, Katona G, Hirschberg A, Gálffy G. Prevalence and risk factors for allergic rhinitis in primary schoolchildren in Budapest. Int J Pediatr Otorhinolaryngol. 2010; 74:503-9.
39. Bousquet J, Annesi-Maesano I, Carat F, Leger D, Rugina M, Pribil C et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. Clin Exp Allergy. 2005; 35:728-32.
40. Bousquet J, Neukirch F, Bousquet PJ, Gehano P, Klossek JM, Le Ga M et al. Severity and impairment of allergic rhinitis in patients consulting in primary care. J Allergy Clin Immunol. 2006; 117:158-62.
41. Navarro A, Valero A, Juliá B, Quirce S. Coexistence of asthma and allergic rhinitis in adult patients attending allergy clinics: ONEAIR study. J Investig Allergol Clin Immunol. 2008; 18(4):233-8.
42. 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.
43. 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.
44. Sly RM. Changing prevalence of allergic rhinitis and asthma. Ann Allergy Asthma Immunol. 1999; 82:233-52.
45. Kusunoki T, Morimoto T, Nishikomori R, Yasumi T, Heike T, Fujii T et al. Changing Prevalence and Severity of Childhood Allergic Diseases in Kyoto, Japan, from 1996 to 2006. Allergol Int. 2009; 58:543-8.

46. Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M. Incidence and prevalence of asthma among adult Finnish men and women of the Finnish Twin Cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. Chest. 1999; 115:928-36.
47. Guerra S, Sherrill DL, Baldacci S, Carrozzi L, Pistelli F, Di Pede F et al. Rhinitis is an independent risk factor for developing cough apart from colds among adults. Allergy. 2005; 60:343-9.
48. Håkansson K, Thomsen SF, Ulrik CS, Porsbjerg C, Backer V. Increase in the prevalence of rhinitis among Danish children from 1986 to 2001. Pediatr Allergy Immunol. 2007; 18(2):154-9.
49. Rinitis/Conjuntivitis. In: Alergológica 1995. Factores epidemiológicos, clínicos y cocioeconómicos de las enfermedades alérgicas en España en 1995. Madrid: Nilo Industria Gráfica Eds, 1995.
50. Rinitis/Conjuntivitis. In: Alergológica 2005. Factores epidemiológicos, clínicos y socioeconómicos de las enfermedades alérgicas en España en 2005. Madrid: Nilo Industria Gráfica Eds, 2005.
51. Nathan RA. The burden of allergic rhinitis. Allergy Asthma Proc. 2007; 28:3-9.
52. Meltzer EO, Nathan R, Derebery J et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: findings from the Burden of Rhinitis in America survey. Allergy Asthma Proc. 2009; 30:244-54.
53. Matterne U, Schmitt J, Diepgen TL, Apfelbacher C. Children and adolescents' health-related quality of life in relation to eczema, asthma and hay fever: results from a population-based cross-sectional study. Qual Life Res. 2011 Feb 24. [Epub ahead of print]
54. Walker S, Khan-Wasti S, Fletcher M et al. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. J Allergy Clin Immunol. 2007; 120:381-7.

55. Fireman P. Treatment of allergic rhinitis: effect on occupation productivity and work force costs. Allergy Asthma Proc. 1997; 18:63-7.
56. Blaiss MS. Cognitive, social, and economic costs of allergic rhinitis. Allergy Asthma Proc. 2000; 21:7-13.
57. Szeinbach SL, Seoane-Vazquez EC, Beyer A, Williams PB. The impact of allergic rhinitis on work productivity. Prim Care Respir J. 2007; 16:98-105.
58. Malone DC, Lawson KA, Smith DH, Arrighi HM, Battista C. A cost of illness study of allergic rhinitis in the United States. J Allergy Clin Immunol. 1997; 99:22-7.
59. Kay GG. The effects of antihistamines on cognition and performance. J Allergy Clin Immunol. 2000; 105:622-7.
60. Crystal-Peters J, Crown WH, Goetzel RZ, Schutt DC. The cost of productivity losses associated with allergic rhinitis. Am J Manage Care. 2000; 6:373-8.
61. Hanrahan LP, Paramore LC. Aeroallergens, allergic rhinitis, and sedating antihistamines: risk factors for traumatic occupational injury and economic impact. Am J Ind Med. 2003; 44:438-46.
62. Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: a critical evaluation of the literature. Pharmacoeconomics. 2004; 22:345-61.
63. Ray NF, Baraniuk JN, Thamer M, Rinehart CS, Gergen PJ, Kaliner M et al. Direct expenditures for the treatment of allergic rhinoconjunctivitis in 1996, including the contributions of related airway illnesses. J Allergy Clin Immunol. 1999; 103:401-7.
64. McCaig LF, Nawar EN. National Hospital Ambulatory Medical Care Survey: 2004 emergency department summary. Advance data from vital and health statistics. Adv Data. 2006; 372:1-29.
65. Schramm B, Ehlken B, Smala A, Quednau K, Berger K, Nowak D. Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. Eur Respir J. 2003; 21(1):116-22.

66. Schoenwetter WF, Dupclay L, Jr, Appajosyula S, Botteman MF, and Pashos ChL. Economic impact and quality-of-life burden of allergic rhinitis. Current Medical Research and Opinion. 2004; 20:305-17.
67. Hellgren J, Cervin A, Nordling S, Bergman A, Cardell LO. Allergic rhinitis and the common cold--high cost to society. Allergy. 2010; 65:776-83.
68. Stokes J, Fenstad E, Casale TB. Managing impairment in patients with allergic rhinitis. Allergy Asthma Proc. 2006; 27:12-6.
69. Maurer M, Zuberbier T. Undertreatment of rhinitis symptoms in Europe: findings from a cross-sectional questionnaire survey Allergy. 2007; 62:1057-63.
70. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J et al. Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Anals of Asthma, Allergy & Immunology. 1998; 81:478-518.
71. Platts-Mills TA, Carter MC, Heymann PW. Specific and nonspecific obstructive lung disease in childhood: causes of changes in the prevalence of asthma. Environ Health Perspect. 2000; 108:725-31.
72. Tanaka K, Miyake Y, Kiyohara Ch. Environmental factors and allergic disorders. Allergology International. 2007; 56:363-396.
73. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989; 299:1259-60.
74. Bryborn M, Halldén C, Säll T, Adner M, Cardell LO. Comprehensive evaluation of genetic variation in S100A7 suggests an association with the occurrence of allergic rhinitis. Respir Res. 2008; 9:29.
75. Chae SC, Park YR, Li CS, Lee JH, Yang YS, Zhang Q et al. Analysis of the variations in IL-28RA gene and their association with allergic rhinitis. Exp Mol Me. 2006; 38:302-9
76. Sebelova S, Izakovicova-Holla L, Stejskalova A, Schüller M, Znojil V, Vasku A. Interleukin-18 and its three gene polymorphisms relating to allergic rhinitis. J Hum Genet. 2007; 52:152-8.

77. Barnes KC. Evidence for common genetic elements in allergic disease. J Allergy Clin Immunol. 2000;106:S192-200.
78. Tang XF, Tang HY, Sun LD, Xiao FL, Zhang Z, Li Y et al. Genetic variant rs4982958 at 14q11.2 is associated with allergic rhinitis in a Chinese Han population running title: 14q11.2 is a susceptibility locus for allergic rhinitis. J Investig Allergol Clin Immunol. 2012; 22(1):55-62.
79. Bahna SL. Factors determining development of allergy in infants. Allergy Proc. 1992; 13:21-5.
80. Kulig M, Klettke U, Wahn V, Forster J, Bauer CP, Wahn U. Development of seasonal allergic rhinitis during the first 7 years of life. J Allergy Clin Immunol. 2000; 106:832-9.
81. Fireman P. Therapeutic approaches to allergic rhinitis: treating the child. J Allergy Clin Immunol. 2000; 105:616-21.
82. Desalu OO, Salami AK, Iseh KR, Oluboyo PO. Prevalence of self reported allergic rhinitis and its relationship with asthma among adult Nigerians. J Investig Allergol Clin Immunol. 2009; 19:474-80.
83. Hwang CY, Chen YJ, Lin MW, Chen TJ, Chu SY, Chen CC et al. Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: a national study 2000 to 2007. Acta Derm Venereol. 2010; 90:589-94.
84. Jessen M, Malm L. Definition, prevalence and development of nasal obstruction. Allergy. 1997; 52:3-6.
85. Duhme H, Weiland SK, Rudolph P, Wienke A, Kramer A, Keil U. Asthma and allergies among children in West and East Germany: a comparison between Münster and Greifswald using the ISAAC phase I protocol. International Study of Asthma and Allergies in Childhood. Eur Respir J. 1998; 11:840-7.
86. Plaschke PP, Janson C, Norrman E, Bjornsson E, Ellbjar S, Jarvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. Am J Respir Crit Care Med. 2000; 162:920–924.

87. Cohen S, Kessler RC, Underwood Gordon L. (Eds.) (1995). Measuring stress: A guide for health and social scientists. New York: Oxford. Chapter 1: Strategies for measuring stress in studies of psychiatric and physical disorders.
88. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. Brain Behav Immun. 2007; 21(8):993-9.
89. Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis. Psychosom Med. 2008; 70:102-16.
90. Farmer A, Korszun A, Owen MJ, Craddock N, Jones L, Jones I et al. Medical disorders in people with recurrent depression. Br J Psychiatry. 2008; 192:351-5.
91. Buske-Kirschbaum A, Ebrecht M, Kern S, Gierens A, Hellhammer DH. Personality characteristics in chronic and non-chronic allergic conditions. Brain Behav Immun. 2008; 22:762–68.
92. Goodwin RD. Self-reported hay fever and panic attacks in the community. Ann Allergy Asthma Immunol. 2002; 88:556-9.
93. Kimata H. Kissing selectively decreases allergen-specific IgE production in atopic patients. J Psychosom Res. 2006; 60:545-7.
94. Saadeh D, Salameh P, Baldi I, Raherison C. Diet and allergic diseases among population aged 0 to 18 years: myth or reality? Nutrients. 2013; 5(9):3399-423.
95. 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.
96. Chatzi L, Torrent M, Romieu I, García-Esteban R, Ferrer C, Vioque J et al. Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. Thorax. 2008; 63:507-13.
97. 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.

98. Barros R, Moreira A, Fonseca J, de Oliveira JF, Delgado L, Castel-Branco MG et al. Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control. Allergy. 2008; 63(7):917-23.

99. García-Marcos L, Canflanca IM, Garrido JB et al. Relationship of asthma and rhinoconjunctivitis with obesity, exercise and Mediterranean diet in Spanish schoolchildren. Thorax. 2007; 62:503-8.

100. Nagel G, Nieters A, Becker N, Linseisen J. The influence of the dietary intake of fatty acids and antioxidants on hay fever in adults. Allergy. 2003; 58:1277-84.

101. Murr C, Schroecksnadel K, Winkler C, Ledochowski M, Fuchs D. Antioxidants may increase the probability of developing allergic diseases and asthma. Med Hypotheses. 2005; 64(5):973-7.

102. Kompauer I, Heinrich J, Wolfram G, Linseisen J. Association of carotenoids, tocopherols and vitamin C in plasma with allergic rhinitis and allergic sensitisation in adults. Public Health Nutr. 2006; 9(4):472-9.

103. Devereux G and Seaton A. Diet as a risk factor for atopy and asthma. J Allergy Clin Immunol. 2005; 115:1109-17.

104. Picado C, Deulofeu R, Lleonart R, Agustí M, Mullol J, Quintó L et al. Dietary micronutrients/antioxidants and their relationship with bronchial asthma severity. Allergy. 2001; 56(1):43-9.

105. Huang SL, Lin KC, Pan WH. Dietary factors associated with physician-diagnosed asthma and allergic rhinitis in teenagers: analyses of the first Nutrition and Health Survey in Taiwan. Clin Exp Allergy. 2001; 31(2):259-64.

106. Rosenlund H, Kull I, Pershagen G, Wolk A, Wickman M, Bergström A. Fruit and vegetable consumption in relation to allergy: disease-related modification of consumption? J Allergy Clin Immunol. 2011; 127(5):1219-25.

107. Farchi S, Forastiere F, Agabiti N, Corbo G, Pistelli R, Fortes C, et al. Dietary factors associated with wheezing and allergic rhinitis in children. Eur Respir J. 2003; 22:772-80.

108. Gutiérrez-Delgado RI, Barraza-Villarreal A, Escamilla-Núñez MC, Solano-González M, Moreno-Macías H, Romieu I. Consumo de alimentos y asma en niños escolares de Cuernavaca. Salud Pública de México. 2009; 51:202-11.

109. Forastiere F, Pistelli R, Sestini P, Fortes C, Renzoni E, Rusconi F et al. Consumption of fresh fruit rich in vitamin C and wheezing symptoms in children. Thorax. 2000; 55:283-8.

110. Miyake Y, Sasaki S, Ohya Y, Miyamoto S, Matsunaga I, Yoshida T, et al.; Osaka Maternal And Child Health Study Group. Dietary intake of seaweed and minerals and prevalence of allergic rhinitis in Japanese pregnant females: baseline data from the Osaka Maternal and Child Health Study. Ann Epidemiol. 2006; 16(8):614-21.

111. Rosenkranz RR, Rosenkranz SK, Neessen KJ. Dietary factors associated with lifetime asthma or hayfever diagnosis in Australian middle-aged and older adults: a cross-sectional study. Nutr J. 2012; 11:84.

112. Li J, Huang Y, Lin X, Zhao D, Tan G, Wu J et al.; China Alliance of Research on Respiratory Allergic Disease (CARRAD). Factors associated with allergen sensitizations in patients with asthma and/or rhinitis in China. Am J Rhinol Allergy. 2012; 26(2):85-91.

113. Nagel G, Weinmayr G, Kleiner A, Garcia-Marcos L, Strachan DP; ISAAC Phase Two Study Group. Effect of diet on asthma and allergic sensitisation in the International Study on Allergies and Asthma in Childhood (ISAAC) Phase Two. Thorax. 2010; 65(6):516-22.

114. Wijga AH, Smit HA, Kerkhof M, de Jongste JC, Gerritsen J, Neijens HJ; PIAMA. Association of consumption of products containing milk fat with reduced asthma risk in pre-school children: the PIAMA birth cohort study. Thorax. 2003; 58(7):567-72.

115. Ellwood P, Asher MI, Björkstén 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(3):436-43.

116. Hijazi N, Abalkhail B, Seaton A. Diet and childhood asthma in a society in transition: a study in urban and rural Saudi Arabia. Thorax. 2000; 55(9):775-9.
117. Huang SL, Pan WH. Dietary fats and asthma in teenagers: analyses of the first Nutrition and Health Survey in Taiwan (NAHSIT). Clin Exp Allergy. 2001; 31(12):1875-80. II
118. Fogarty A, Lewis S, Weiss S, Britton J. Dietary vitamin E, IgE concentrations, and atopy. Lancet. 2000; 356(9241):1573-4.
119. Troisi RJ, Willett WC, Weiss ST, Trichopoulos D, Rosner B, Speizer FE. A prospective study of diet and adult-onset asthma. Am J Respir Crit Care Med. 1995; 151(5):1401-8.
120. Cheng HM, Kim S, Park GH, Chang SE, Bang S, Won CH et al. Low vitamin D levels are associated with atopic dermatitis, but not allergic rhinitis, asthma, or IgE sensitization, in the adult Korean population. J Allergy Clin Immunol. 2014; 133(4):1048-55.
121. Arshi S, Ghalehbaghi B, Kamrava SK, Aminlou M. Vitamin D serum levels in allergic rhinitis: any difference from normal population? Asia Pac Allergy. 2012; 2(1):45-8.
122. Bäck O, Blomquist HK, Hernell O, Stenberg B. Does vitamin D intake during infancy promote the development of atopic allergy? Acta Derm Venereol. 2009; 89:28-32.
123. Wjst M. Introduction of oral vitamin D supplementation and the rise of the allergy pandemic. Allergy Asthma Clin Immunol. 2009; 5:8.
124. Mai XM, Chen Y, Camargo CA Jr, Langhammer A. Serum 25-hydroxyvitamin D levels and self-reported allergic rhinitis in Norwegian adults - The HUNT Study. Allergy. 2014; 69(4):488-93.
125. Okupa AY, Lemanske RF Jr, Jackson DJ, Evans MD, Wood RA, Matsui EC. Early-life folate levels are associated with incident allergic sensitization. J Allergy Clin Immunol. 2013; 131(1):226-8.e1-2.

126. Rosenlund H, Magnusson J, Kull I, Håkansson N, Wolk A, Pershagen G et al. Antioxidant intake and allergic disease in children. Clin Exp Allergy. 2012; 42(10):1491-500.
127. Miyake Y, Sasaki S, Tanaka K, et al. Fish and fat intake and prevalence of allergic rhinitis in Japanese females: the Osaka Maternal and Child Health Study. J Am Coll Nutr 2007; 26:279-87.
128. Perkin MR, Strachan DP. Which aspects of the farming lifestyle explain the inverse association with childhood allergy? J Allergy Clin Immunol. 2006; 117(6):1374-81.
129. Tamay Z, Akcay A, Ergin A, Guler N. Effects of dietary habits and risk factors on allergic rhinitis prevalence among Turkish adolescents. Int J Pediatr Otorhinolaryngol. 2013; 77(9):1416-23.
130. Dunder T, Kuikka L, Turtinen J, Räsänen L, Uhari M. Diet, serum fatty acids, and atopic diseases in childhood. Allergy. 2001; 56(5):425-8.
131. Nwaru BI, Erkkola M, Lumia M, Kronberg-Kippilä C, Ahonen S, Kaila M. Maternal intake of fatty acids during pregnancy and allergies in the offspring. Br J Nutr. 2012; 108(4):720-32.
132. Kim JL, Elfman L, Mi Y, Johansson M, Smedje G, Norbäck D. Current asthma and respiratory symptoms among pupils in relation to dietary factors and allergens in the school environment. Indoor Air. 2005; 15(3):170-82.
133. Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. Clin Rev Allergy Immunol. 2011; 41(1):36-66.
134. Virtanen SM, Kaila M, Pekkanen J, Kenward MG, Uusitalo U, Pietinen P. Early introduction of oats associated with decreased risk of persistent asthma and early introduction of fish with decreased risk of allergic rhinitis. Br J Nutr. 2010; 103:266-73.
135. Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Dietary meat and fat intake and prevalence of rhinoconjunctivitis in pregnant Japanese women:

baseline data from the Kyushu Okinawa Maternal and Child Health Study. Nutr J. 2012; 11:19.

136. Schnappinger M, Sausenthaler S, Linseisen J, Hauner H, Heinrich J. Fish consumption, allergic sensitisation and allergic diseases in adults. Ann Nutr Metab. 2009; 54(1):67-74.
137. Molinas JL, Torrent MC, Zapata ME. Frecuencia de consumo de pescado de mar y síntomas de enfermedades alérgicas en adultos de Rosario. Rev Esp Nutr Comunitaria. 2010; 16(3):120-127
138. Nafstad P, Nystad W, Magnus P, Jaakkola JJ. Asthma and allergic rhinitis at 4 years of age in relation to fish consumption in infancy. J Asthma. 2003; 40(4):343-8.
139. Andreasyan K, Ponsonby AL, Dwyer T, Kemp A, Dear K, Cochrane J et al. A differing pattern of association between dietary fish and allergen-specific subgroups of atopy. Allergy. 2005; 60(5):671-7.
140. Kull I, Bergström A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. Allergy. 2006; 61(8):1009-15.
141. Takemura Y, Sakurai Y, Honjo S, Tokimatsu A, Gibo M, Hara T et al. The relationship between fish intake and the prevalence of asthma: the Tokorozawa childhood asthma and pollinosis study. Prev Med. 2002; 34(2):221-5.
142. Magnusson J, Kull I, Westman M, Håkansson N, Wolk A, Melén E et al. Fish and polyunsaturated fat intake and development of allergic and nonallergic rhinitis. J Allergy Clin Immunol. 2015 Jul 4. [Epub ahead of print]
143. Hoff S, Seiler H, Heinrich J, Kompauer I, Nieters A, Becker N et al. Allergic sensitization and allergic rhinitis are associated with n-3 polyunsaturated fatty acids in the diet and in red blood cell membranes. Eu.r J. Clin. Nutr. 2005; 59:1071-80.
144. Miyake Y, Tanaka K, Sasaki S, Arakawa M. Polyunsaturated fatty acid intake and prevalence of eczema and rhinoconjunctivitis in Japanese

children: the Ryukyus Child Health Study. BMC Public Health. 2011; 11:358.

145. Wakai K, Okamoto K, Tamakoshi A, Lin Y, Nakayama T, Ohno Y. Seasonal allergic rhinoconjunctivitis and fatty acid intake: a cross-sectional study in Japan. Ann Epidemiol. 2001; 11(1):59-64.
146. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. Allergy. 2009; 64(6):840-8.
147. Yu G, Björkstén B. Polyunsaturated fatty acids in school children in relation to allergy and serum IgE levels. Pediatr Allergy Immunol. 1998; 9(3):133-8.
148. Lowe AJ, Thien FC, Stoney RM, Bennett CM, Hosking CS, Hill DJ et al. Associations between fatty acids in colostrum and breast milk and risk of allergic disease. Clin Exp Allergy. 2008; 38(11):1745-51.
149. Almqvist C, Garden F, Xuan W, Mihrshahi S, Leeder SR, Oddy W, et al.; CAPS team. Omega-3 and omega-6 fatty acid exposure from early life does not affect atopy and asthma at age 5 years. J Allergy Clin Immunol. 2007; 119(6):1438-44.
150. Trak-Fellermeier MA, Brasche S, Winkler G, Koletzko B, Heinrich J. Food and fatty acid intake and atopic disease in adults. Eur Respir J. 2004; 23:575-82.
151. Bolte G, Winkler G, Hölscher B, Thefeld W, Weiland SK, Heinrich J. Margarine consumption, asthma, and allergy in young adults: results of the German National Health Survey 1998. Ann Epidemiol. 2005; 15(3):207-13.
152. Bolte G, Frye C, Hoelsher B, Meyer I, Wjst M, Heinrich J. Margarine consumption and allergy in children. Am J Respir Crit Care Med. 2001; 163:277-9.
153. Kompauer I, Demmelmair H, Koletzko B, Bolte G, Linseisen J, Heinrich J. Association of fatty acids in serum phospholipids with hay fever, specific and total immunoglobulin E. Br J Nutr. 2005; 93:529-35.

154. Oddy WH, de Klerk NH, Kendall GE, Mihrshahi S, Peat JK. Ratio of omega-6 to omega-3 fatty acids and childhood asthma. J Asthma. 2004; 41(3):319-26.

155. Calder PC, Kremmyda LS, Vlachava M, Noakes PS, Miles EA. Is there a role for fatty acids in early life programming of the immune system? Proc Nutr Soc 2010; 69(3):373-80.

156. Weiland SK, von Mutius E, Hüsing A, Asher MI. Intake of trans fatty acids and prevalence of childhood asthma and allergies in Europe. ISAAC Steering Committee. Lancet. 1999; 353(9169):2040-1.

157. Peñaranda A, Aristizabal G, García E, Vásquez C, Rodríguez-Martinez CE. Rhinoconjunctivitis prevalence and associated factors in school children aged 6-7 and 13-14 years old in Bogota, Colombia. Int J Pediatr Otorhinolaryngol. 2012; 76(4):530-5.

158. Assing K, Bodtger U, Linneberg A, Malling HJ, Poulsen LK. Association between alcohol consumption and skin prick test reactivity to aeroallergens. Ann Allergy Asthma Immunol. 2007; 98:70-4.

159. Bendtsen P, Grønbaek M, Kjaer SK, Munk C, Linneberg A, Tolstrup JS. Alcohol consumption and the risk of self-reported perennial and seasonal allergic rhinitis in young adult women in a population-based cohort study. Clin Exp Allergy. 2008; 38(7):1179-85.

160. Shaheen SO, Rutterford C, Zuccolo L, Ring SM, Davey Smith G, Holloway JW et al. Prenatal alcohol exposure and childhood atopic disease: a Mendelian randomization approach. J Allergy Clin Immunol. 2014; 133(1):225-32.e1-5.

161. Nagata C, Nakamura K, Fujii K, Kawachi T, Takatsuka N, Oba S et al. Soy isoflavone intake is not associated with the development of cedar pollinosis in adults. J Nutr. 2008; 138(7):1372-6.

162. Miyake Y, Sasaki S, Ohya Y, Miyamoto S, Matsunaga I, Yoshida T et al. Soy, isoflavones, and prevalence of allergic rhinitis in Japanese women: the Osaka Maternal and Child Health Study. J. Allergy Clin. Immunol 2005; 115:1176-83.

163. Yang J, Farioli A, Korre M, Kales SN. Modified Mediterranean diet score and cardiovascular risk in a North American working population. PLoS One. 2014; 9(2):e87539.

164. Castro-Rodriguez JA, García-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.

165. Willett WC. The Mediterranean diet: science and practice. Public Health Nutr. 2006; 9(1A):105-10.

166. Trichopoulou A, Lagiou P. Healthy traditional Mediterranean diet: an expression of culture, history, and lifestyle. Nutr Rev. 1997; 55(11 Pt 1):383-9.

167. Marmsjö K, Rosenlund H, Kull I, Håkansson N, Wickman M, Pershagen G et al. Use of multivitamin supplements in relation to allergic disease in 8-y-old children. Am J Clin Nutr. 2009; 90(6):1693-8.

168. Quirce S, Cuevas M, Olaguibel JM, Tabar AI. Occupational asthma and immunologic responses induced by inhaled carmine among employees at a factory making natural dyes. J Allergy Clin Immunol. 1994; 93:44-52.

169. Bousquet J, Metcalfe D, Warner J. Food allergy. Report of the Codex Alimentarius. ACI International. 1997; 9:10-21.

170. Lacroix JS, Buvelot JM, Polla BS, Lundberg JM. Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. Clin Exp Allergy. 1991; 21:595-600.

171. Malik V, Ghosh S, Woolford TJ. Rhinitis due to food allergies: fact or fiction? J Laryngol Otol. 2007; 121(6):526-9.

172. Cingi C, Demirbas D, Songu M. Allergic rhinitis caused by food allergies. Eur Arch Otorhinolaryngol. 2010; 267:1327-35.

173. González-Quintela A, Vidal C, Lojo S, Pérez LF, Otero-Antón E, Gude F et al. Serum cytikines and increased total serum IgE in alcoholics. Ann Allergy Asthma Immunol. 1999; 83:61-7.

174. Linneberg A, Petersen J, Nielsen NH, Madsen F, Frølund L, Dirksen A et al. The relationship of alcohol consumption to total immunoglobulin E and

the development of immunoglobulin E sensitization: the Copenhagen Allergy Study. Clin Exp Allergy. 2003; 33(2):192-8.

175. Warren CW, Jones NR, Peruga A, Chauvin J, Baptiste JP, Costa de Silva V et al. Global youth tobacco surveillance, 2000–2007. MMWR Surveill Summ. 2008; 57:1–28.
176. Cakir E, Ersu R, Uyan ZS, Oktem S, Varol N, et al. The prevalence and risk factors of asthma and allergic diseases among working adolescents. Asian Pac J Allergy Immunol. 2010; 28:122–9.
177. McKeever TM, Lewis SA, Smith C, Collins J, Heatlie H, et al. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. Thorax. 2001; 56:758–62.
178. Magnusson LL, Olesen AB, Wennborg H, Olsen J. Wheezing, asthma, hay fever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life. Clin Exp Allergy. 2005; 35:1550–6.
179. Saulyte J, Regueira C, Montes-Martı´nez A, Khudyakov P, Takkouche B. Active or Passive Exposure to Tobacco Smoking and Allergic Rhinitis, Allergic Dermatitis, and Food Allergy in Adults and Children: A Systematic Review and Meta-Analysis. PLoS Med. 2014; 11(3): e1001611.
180. Diaz-Sanchez D, Rumold R, Gong H Jr. Challenge with environmental tobacco smoke exacerbates allergic airway disease in human beings. J Allergy Clin Immunol. 2006; 118:441–6.
181. Peden D, Reed CE. Environmental and occupational allergies. J Allergy Clin Immunol. 2010; 125:150-60.
182. US Department of Health and Human Services. Children and secondhand smoke exposure. Excerpts from The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2007.

183. Lannero E, Wickman M, van Hage M, Bergstrom A, Pershagen G, et al. Exposure to environmental tobacco smoke and sensitisation in children. Thorax. 2008; 63:172–6.

184. Mosges R, Klimek L. Today's allergic rhinitis patients are different: new factors that may play a role. Allergy. 2007; 62:969-75.

185. Woodcock J, Banister D, Edwards P, Prentice AM, Roberts I. Energy and Health 3. Energy and transport. Lancet. 2007; 370:1078–88.

186. Wilkinson P, Smith KR, Joffe M, Haines A. Energy and Health 1. A global perspective on energy: health effects and injustices. Lancet. 2007; 370: 965–78.

187. Van Niekerk CH, Weinberg EG, Shore SC, Heese HV, Van Schalkwyk DJ. Prevalence of asthma: a comparative study of urban and rural Xhosa children. Clin Allergy. 1979; 9:319-24.

188. Sattar HA, Mobayed H, al-Mohammed AA, Ibrahim AS, Jufairi AA, Balamurugan P et al. The pattern of indoor and outdoor respiratory allergens in asthmatic adult patients in a humid and desert newly developed country. Eur Ann Allergy Clin Immunol. 2003; 35:300-5.

189. Bibi H, Shoseyov D, Feigenbaum D, Nir P, Shiachi R, Scharff S et al. Comparison of positive allergy skin tests among asthmatic children from rural and urban areas living within small geographic area. Ann Allergy Asthma Immunol. 2002; 88:416-20.

190. Boulet LP, Turcotte H, Laprise C, Lavertu C, Bédard PM, Lavoie A, et al. Comparative degree and type of sensitization to common indoor and outdoor allergens in subjects with allergic rhinitis and/or asthma. Clin Exp Allergy. 1997; 27:52-9.

191. Kurt E, Metintas S, Basyigit I, Bulut I, Coskun E, Dabak S et al. PARFAIT Study of the Turkish Thoracic Society Asthma and Allergy Working Group. Prevalence and Risk Factors of Allergies in Turkey (PARFAIT): results of a multicentre cross-sectional study in adults. Eur Respir J. 2009; 33:724-33.

192. American Lung Associacion. Urban air pollution and health inequalities: a workshop report. Environ Health Perspect. 2001; 109:357-74.
193. Wuthrich B, Schindler C, Leuenberger P, Ackermann-Liebrich U. Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). Swiss Study on Air Pollution and Lung Diseases in Adults. Int Arch Allergy Immunol. 1995; 106:149-56.
194. Bertelsen RJ, Instanes C, Granum B, Lødrup Carlsen KC, Hetland G, Carlsen KH, Mowinckel P et al. Gender differences in indoor allergen exposure and association with current rhinitis. Clin Exp Allergy. 2010; 40:1388-97.
195. Codispoti CD, Levin L, LeMasters GK, Ryan P, Reponen T, Villareal M et al. Breast-feeding, aeroallergen sensitization, and environmental exposures during infancy are determinants of childhood allergic rhinitis. J Allergy Clin Immunol. 2010; 125:1054-60.
196. Wang DY, Goh DY, Ho AK, Chew FT, Yeoh KH, Lee BW. The upper and lower airway responses to nasal challenge with house dust mite Blomia tropicalis. Allergy. 2003; 58(1):78-82.
197. Chen WY, Tseng HI, Wu MT, Hung HC, Wu HT, Chen HL, et al. Synergistic effect of multiple indoor allergen sources on atopic symptoms in primary school children. Environ Res. 2003; 93:1-8.
198. Hsu SP, Lin KN, Tan CT, Lee FP, Huang HM. Prenatal risk factors and occurrence of allergic rhinitis among elementary school children in an urban city. Int J Pediatr Otorhinolaryngol. 2009; 73:807-10.
199. Sookrung N, Chaicumpa W. A revisit to cockroach allergens. Asian Pac J Allergy Immunol. 2010; 28(2-3):95-106.
200. Soares FA, Segundo GR, Alves R, Ynoue LH, Resende RO, Sopelete MC et al. [Indoor allergen sensitization profile in allergic patients of the allergy clinic in the University Hospital in Uberlândia, Brazil]. Rev Assoc Med Bras. 2007; 53(1):25-8.
201. Donohue KM, Al-alem U, Perzanowski MS, Chew GL, Johnson A, Divjan A et al. Anti-cockroach and anti-mouse IgE are associated with early

wheeze and atopy in an inner-city birth cohort. J Allergy Clin Immunol. 2008; 122:914-20.

202. Phipatanakul W, Celedón JC, Hoffman EB, Abdulkerim H, Ryan LM, Gold DR. Mouse allergen exposure, wheeze and atopy in the first seven years of life. Allergy. 2008; 63(11):1512-8.
203. Zuraimi MS, Tham KW, Chew FT, Ooi PL, Koh D. Home air-conditioning, traffic exposure, and asthma and allergic symptoms among preschool children. Pediatr Allergy Immunol. 2011; 22(1 Pt 2): e112-8.
204. Kidon MI, See Y, Goh A, Chay OM, Balakrishnan A. Aeroallergen sensitization in pediatric allergic rhinitis in Singapore: is air-conditioning a factor in the tropics? Pediatr Allergy Immunol. 2004; 15:340-3.
205. Engvall K, Norrby C, Norbäck D. Ocular, nasal, dermal and respiratory symptoms in relation to heating, ventilation, energy conservation, and reconstruction of older multi-family houses. Indoor Air. 2003; 13:206-11.
206. Kilpeläinen M, Koskenvuo M, Helenius H, Terho E. Wood stove heating, asthma and allergies. Respir Med. 2001; 95:911-6.
207. Bruce N, Perez-Padilla R, Albalak R. Indoor air pollution in developing countries: a major environmental and public health challenge. Bull World Health Organ. 2000; 78:1078-92.
208. Smith KR, Samet JM, Romieu I, Bruce N. Indoor air pollution in developing countries and acute lower respiratory infections in children. Thorax. 2000; 55:518–532.
209. Kaplan C. Indoor air pollution from unprocessed solid fuels in developing countries. Rev Environ Health. 2010; 25:221-42.
210. Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. Clin Exp Allergy. 2000; 30:194-200.
211. Zeyrek CD, Zeyrek F, Sevinc E, Demir E. Prevalence of Asthma and Allergic Diseases in Sanliurfa, Turkey, and the Relation to Environmental and Socioeconomic Factors: Is the Hygiene Hypothesis Enough? J Investig Allergol Clin Immunol. 2006; 16(5):290-295.

212. Shima M, Nitta Y, Adachi M. Traffic-related air pollution and respiratory symptoms in children living along trunk roads in Chiba Prefecture, Japan. J Epidemiol. 2003; 13:108–119.

213. Brauer M, Hoek G, Van Vliet P, Meliefste K, Fischer PH , Wijga A et al. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children, Am J Respir Crit Care Med. 2002; 166:1092-8.

214. Zmirou D, Gauvin S, Pin I, Momas I, Sahraoui F, Just J et al. Traffic related air pollution and incidence of childhood asthma: results of the Vesta case-control study. J Epidemiol Community Health. 2004; 58:18–23.

215. Janssen NAH, Brunekreef B, Van Vliet P, Aarts F, Meliesfste K, Harssema H. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. Environ Health Perspect. 2003; 111:1512–8.

216. Czarnobilska E, Klimaszewska-Rembiasz M, Gaweł B, Obtułowicz A. [Prevalence of allergic diseases in primary school children in Cracow and surroundings--risk factors]. Przegl Lek. 2002; 59:422-6.

217. Peden DB. Effect of pollutants in rhinitis. Curr Allergy Asthma Rep. 2001; 1(3):242-6.

218. Montnémery P, Popovic M, Andersson M, Greiff L, Nyberg P, Löfdahl CG et al. Influence of heavy traffic, city dwelling and socio-economic status on nasal symptoms assessed in a postal population survey. Respir Med 2003; 97:970-7.

219. Weiland SK, Mundt KA, Ruckmann A, Keil U. Self-reported wheezing and allergic rhinitis in children and traffic density on street of residence. Ann Epidemiol. 1994; 4:243–247.

220. Duhme H, Weiland SK, Keil U, Kraemer B, Schmid M, Stender M et al. The association between self reported symptoms of asthma and allergic rhinitis and self-reported traffic density on street of residence in adolescents. Epidemiol. 1996; 7:578-82.

221. Lee YL, Shaw CK, Su HJ, Lai JS, Ko YC, Huang SL et al. Climate, traffic-related air pollutants and allergic rhinitis prevalence in middle-school children in Taiwan. Eur Respir J. 2003; 21:964-70.

222. Arnedo-Pena A, García-Marcos L, Carvajal Urueña I, Busquets Monge R, Morales Suárez-Varela M, Miner Canflanca I, et al. Air pollution and recent symptoms of asthma, allergic rhinitis, and atopic eczema in schoolchildren aged between 6 and 7 years. Arch Bronconeumol. 2009; 45:224-9.

223. Hwang BF, Jaakkola JJ, Lee YL, Lin YC, Guo YL. Relation between air pollution and allergic rhinitis in Taiwanese schoolchildren. Respir Res. 2006; 7:23.

224. Pénard-Morand C, Charpin D, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F et al. Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. Clin Exp Allergy. 2005; 35(10):1279-87.

225. Yu JH, Lue KH, Lu KH, Sun HL, Lin YH, Chou MC. The relationship of air pollution to the prevalence of allergic diseases in Taichung and Chu-Shan in 2002. J Microbiol Immunol Infect. 2005; 38(2):123-6.

226. Hajat S, Haines A, Atkinson RW, Bremner SA, Anderson HR, Emberlin J. Association between air pollution and daily consultations with general practitioners for allergic rhinitis in London, United Kingdom. Am J Epidemiol. 2001; 153:704-14.

227. Bhattacharyya N. Air quality influences the prevalence of hay fever and sinusitis. Laryngoscope. 2009; 119:429-33.

228. de Marco R, Poli A, Ferrari M, Accordini S, Giammanco G, Bugiani M et al. ISAYA study group. Italian Study on Asthma in Young Adults. The impact of climate and traffic-related NO2 on the prevalence of asthma and allergic rhinitis in Italy. Clin Exp Allergy. 2002; 32:1405-12.

229. Parker JD, Akinbami LJ, Woodruff TJ. Air pollution and childhood respiratory allergies in the United States. Environ Health Perspect. 2009; 117(1):140-7.

230. Hoffman CD, Henneberger PK, Olin AC, Mehta A, Torén K. Exposure to ozone gases in pulp mills and the onset of rhinitis. Scand J Work Environ Health. 2004; 30:445-9.

231. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Krämer U et al; GINI Study Group; LISA Study Group. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. Am J Respir Crit Care Med. 2008; 177(12):1331-7.

232. 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(1):8-16.

233. Bayer-Oglesby L, Grize L, Gassner M, Takken-Sahli K, Sennhauser FH, Neu U, et al. Decline of ambient air pollution levels and improved respiratory health in Swiss children. Environ Health Perspect. 2005; 113:1632-7.

234. Pénard-Morand C, Raherison C, Charpin D, Kopferschmitt C, Lavaud F, Caillaud D, Annesi-Maesano I. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. Eur Respir J. 2010; 36(1):33-40.

235. Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M et al. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. Am J Respir Crit Care Med. 2010; 181:596-603.

236. Lindgren A, Stroh E, Nihlén U, Montnémery P, Axmon A, Jakobsson K. Traffic exposure associated with allergic asthma and allergic rhinitis in adults. A cross-sectional study in southern Sweden. Int J Health Geogr. 2009; 8:25.

237. Pujades-Rodríguez M, Lewis S, McKeever T, Britton J, Venn A. Effect of living close to a main road on asthma, allergy, lung function and chronic obstructive pulmonary disease. Occup Environ Med. 2009; 66(10):679-84.

238. von Mutius E, Fritzsch C, Weiland SK, Roll G, Magnussen H. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. BMJ. 1992; 305:1395-1399

239. Graf N, Johansen P, Schindler C, Wuthrich B, Ackermann-Liebrich U, Gassner M et al. Analysis of the relationship between pollinosis and date of birth in Switzerland. Int Arch Allergy Immunol. 2007; 143:269-75.

240. Villeneuve PJ, Doiron MS, Stieb D, Dales R, Burnett RT, Dugandzic R. Is outdoor air pollution associated with physician visits for allergic rhinitis among the elderly in Toronto, Canada? Allergy. 2006; 61(6):750-8.

241. Loureiro G, Rabaça MA, Blanco B, Andrade S, Chieira C, Pereira C. Urban versus rural environment--any differences in aeroallergens sensitization in an allergic population of Cova da Beira, Portugal? Eur Ann Allergy Clin Immunol. 2005; 37:187-93.

242. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Reitmeir P, Thiemann HH. Skin test reactivity and number of siblings. BMJ. 1994; 308(6930):692-5.

243. Krämer U, Heinrich J, Wjst M, Wichmann HE. Age of entry to day nursery and allergy in later childhood. Lancet. 1999; 353:450–4.

244. Resch A, Schlipköter U, Crispin A, Behrendt H, Heinrich J, Wichmann HE, Ring J, Schäfer T; KORA study group. Atopic disease and its determinants -- a focus on the potential role of childhood infection. Clin Exp Allergy. 2004; 34:1184-91.

245. Ring J, Krämer U, Schafer T, Abeck D, Vieluf D, Behrendt H. Environmental risk factors for respiratory and skin atopy: results from epidemiological studies in former East and West Germany. Int Arch Allergy Immunol. 1999; 118:403-7.

246. Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. Lancet. 1999; 353:1485–8.

247. Ahn KM, Lee MS, Hong SJ, Lim DH, Ahn YM, Lee HR et al. Fever, Use of Antibiotics, and Acute Gastroenteritis During Infancy as Risk Factors for the Development of Asthma in Korean School-Age Children. J Asthma. 2005; 42:745–50.

248. Bach J-F. The Effect of Infections on Susceptibility to Autoimmune and Allergic Diseases. N Engl J Med. 2002; 347:911-20.

249. Kukkonen K, Kuitunen M, Haahtela T, Korpela R, Poussa T, Savilahti E. High intestinal IgA associates with reduced risk of IgE-associated allergic diseases. Pediatr Allergy Immunol. 2010; 21:67-73.

250. Di Lorenzo G, Pacor ML, Mansueto P, Esposito-Pellitteri M, Scichilone N, Ditta V et al. Relationship between specific serum IgE to Ascaris lumbricoides and onset of respiratory symptoms in Bangladesh immigrants. Int J Immunopathol Pharmacol. 2006; 19(3):629-38.

251. Ring J, Krämer U, Behrendt H. A critical approach to the hygiene hypothesis Clin Exp All Rev. 2004; 4:40-44

252. Braun-Fahrlander C, Gassner M, Grize L, Neu U, Sennhauser FH, Varonier HS et al. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution. Clin Exp Allergy. 1999; 29:28-34.

253. Leynaert B, Neukirch C, Jarvis D, Chinn S, Burney P, Neukirch F; European Community Respiratory Health Survey. Does living on a farm during childhood protect against asthma, allergic rhinitis, and atopy in adulthood? Am J Respir Crit Care Med. 2001; 164:1829-34.

254. Wickens K, Lane JM, Fitzharris P, Siebers R, Riley G, Douwes J et al. Farm residence and exposures and the risk of allergic diseases in New Zealand children. Allergy 2002; 57:1171–1179.

255. Mungan D, Celik G, Bavbek S, Misirligil Z. Pet allergy: how important for Turkey where there is a low pet ownership rate. Allergy Asthma Proc. 2003; 24(2):137-42.

256. Takkouche B, González-Barcala FJ, Etminan M, Fitzgerald M. Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. Allergy. 2008; 63(7):857-64.

257. Vedanthan PK, Mahesh PA, Vedanthan R, Holla AD, Liu AH. Effect of animal contact and microbial exposures on the prevalence of atopy and

asthma in urban vs rural children in India. Ann Allergy Asthma Immunol. 2006; 96:571-8.

258. de Meer G, Toelle BG, Ng K, Tovey E, Marks GB. Presence and timing of cat ownership by age 18 and the effect on atopy and asthma at age 28. J Allergy Clin Immunol. 2004; 113:433-8.

259. Bornehag CG, Sundell J, Hagerhed L, Janson S. DBH Study Group. Pet-keeping in early childhood and airway, nose and skin symptoms later in life. Allergy. 2003; 58:939-44.

260. Hesselmar B, Aberg N, Aberg B, Eriksson B, Björkstén B. Does early exposure to cat or dog protect against later allergy development? Clin Exp Allergy 1999; 29:611–17.

261. Kurosaka F, Nakatani Y, Terada T, Tanaka A, Ikeuchi H, Hayakawa A et al. Current cat ownership may be associated with the lower prevalence of atopic dermatitis, allergic rhinitis, and Japanese cedar pollinosis in schoolchildren in Himeji, Japan. Pediatr Allergy Immunol. 2006; 17:22-8.

262. Berger I, Schierl R, Ochmann U, Egger U, Scharrer E, Nowak D. Concentrations of dust, allergens and endotoxin in stables, living rooms and mattresses from cattle farmers in southern Bavaria. Ann Agric Environ Med. 2005; 12:101-7.

263. Nicholas C, Wegienka G, Havstad S, Zoratti E, Ownby D, Johnson CC. Dog characteristics and allergen levels in the home. Ann Allergy Asthma Immunol. 2010; 105(3):228-33.

264. Mercer MJ, Joubert G, Ehrlich RI, Nelson H, Poyser MA, Puterman A et al. Socioeconomic status and prevalence of allergic rhinitis and atopic eczema symptoms in young adolescents. Pediatr Allergy Immunol. 2004; 15(3):234-41.

265. Fireman P. Rhinitis and asthma connection: management of coexisting upper airway allergic diseases and asthma. Allergy Asthma Proc. 2000; 21:45-54.

266. Custovic A, Wijk RG. The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA(2)LEN). Allergy. 2005; 60:1112-5.

267. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. Allergy 2005; 60:4-12.

268. Hankin CS, Cox L, Lang D, Bronstone A, Fass P, Leatherman B, Wang Z. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. Ann Allergy Asthma Immunol. 2010; 104:79-85.

269. Polosa R, Al-Delaimy WK, Russo C, Piccillo G, Sarvà M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. Respir Res. 2005; 28(6):153.

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2. OBJECTIVES

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2. OBJECTIVES

The identification of modifiable risk factors of allergic rhinitis has important implications for the quality of life of patients as well as for the mitigation of the very costs of this disease. Changes in lifestyle such as those related to smoking and diet is crucial. Therefore we decided to conduct a comprehensive study in 2 parts: a meta-analysis and a case-control study with the following objectives.

1. Using a meta-analysis of published studies, to determine the effect of active and passive smoking on the development of allergic rhinitis.

2. To determine the effect of a high dietary intake of proteins on the occurrence of allergic rhinitis.

3. To determine the effect of a high intake of antioxidants: β-carotene, vitamin A, vitamin E, vitamin C, selenium and zinc on the occurrence of allergic rhinitis.

4. To determine the effect of consumption of dietary omega-3 and omega-6 polyunsaturated fatty acids on the occurrence of allergic rhinitis.

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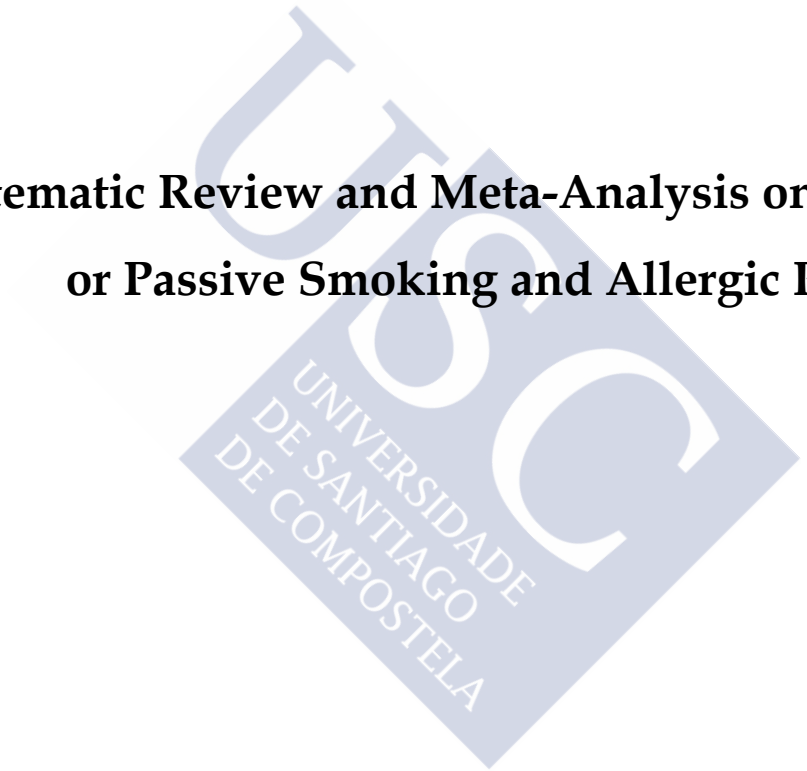
3.1.

A Systematic Review and Meta-Analysis on Active or Passive Smoking and Allergic Rhinitis



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3.1.1. INTRODUCTION

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Allergic rhinitis, together with other closely related conditions like allergic dermatitis, food allergies and asthma, are extremely common diseases worldwide. Indeed, allergic rhinitis affects 10% to 20% of the general population in Europe and the US and up to 40% of children.[1-3] The prevalence of allergy to any food varies between 3% and 35%,[4] while that of allergic dermatitis reaches 20% in many countries.[5] These diseases have profound consequences on the patient's quality of life and imply a high cost both to the patient and insurance providers.[6,7] Among infants, these costs reach more than US$4,000 per year per case of food allergy.[8] Recent studies have suggested that these diseases are but one unique set of immunoglobulin-E (IgE)-mediated allergic conditions, linked by the common thread of ''atopic march''.[9] This concept postulates that those conditions are a continuous state that starts with dermatitis and food allergy and eventually progresses to asthma and allergic rhinitis. Indeed, these diseases often co-exist in the same patient and can predict the occurrence of each other.[10]

Worldwide, the prevalence of allergic diseases has increased substantially in the last few decades,[11,12] which may have two explanations. On the one hand, increased clinician awareness, as well as patient and parental awareness, may have led to improved identification and increased case presentation to physicians.[12] On the other hand, it is possible that this increase is due to changing exposure to known and unknown risk factors,[13] and among these factors, smoking may play a role. An increased risk of allergic diseases among individuals exposed to tobacco smoke is biologically plausible as smoking is known to facilitate sensitization to perennial indoor allergens, such as those caused by furry animals, as well as to some outdoor allergens such as pollen.[14] Furthermore, smoking augments nasal responses to allergen in atopic subjects and increases IgE, immunoglobulin G4 (IgG4), and postallergen histamine levels in nasal lavage fluid.[15,16]

Allergic conditions are, in general, more prevalent in children. A potential effect of smoking would have a considerable impact on public health due to the

frequency of exposure worldwide. Indeed, children and adolescents are exposed to secondhand smoke in a proportion that varies between 27.6% in Africa and 77.8% in Europe and approximately 14% of all children were exposed to maternal smoking during pregnancy.[17,18]

Several studies have assessed the association between smoking exposure and allergic diseases. In each of the allergic conditions, results were conflicting and alternated between the harmful effects of smoking and protection,[14,19-23] while some studies could not find evidence of any effect.[24-26]

Except for a systematic review and meta-analysis examining the relationship between smoking and asthma in children,[27] to our knowledge, there is no comprehensive meta-analysis that examines the evidence for a relationship between smoking and allergic conditions like allergic rhinitis. We, therefore, summarized the scientific evidence and carried out a meta-analysis on exposure to active and passive smoking and the risk of allergic rhinitis among adults and children/adolescents

3.1.2. METHODS

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Data sources and searches

We searched databases from 1966 to end of February, 2013, to identify all potentially eligible studies. For Medline, we applied the following algorithm both in Medical Subject Heading and in free-text words: ("SEASONAL ALLERGIC RHINITIS" OR "ALLERGIC RHINITIDES, SEASONAL" OR "ALLERGIC RHINITIS, SEASONAL" OR "RHINITIDES, SEASONAL ALLERGIC" OR "RHINITIS, SEASONAL ALLERGIC" OR "SEASONAL ALLERGIC RHINITIDES" OR "POLLEN ALLERGY" OR "ALLERGIES, POLLEN" OR "ALLERGY, POLLEN" OR "POLLEN ALLERGIES" OR "POLLINOSIS" OR "POLLINOSES" OR "HAY FEVER" OR "FEVER, HAY" OR "HAYFEVER" OR "RHINITIS, ALLERGIC, NONSEASONAL" OR "RHINITIS, ALLERGIC, PERENNIAL") AND (SMOKING OR TOBACCO OR CIGARETT*). We used similar strategies to search Embase and LILACS (Latin American and Carribean database). We searched meeting abstracts using the ISI Proceedings database from its inception in 1990 to 2013. We also examined the references of every article retrieved and those of recent reviews of allergic rhinitis and smoking.[16,28-33] We considered including any relevant article, independently of the language of the publication. Unpublished and ecologic studies were not considered.

Study selection

Studies were included if: 1) they presented original data from cohort, case-control or cross-sectional studies (ecologic studies were not considered), 2) the outcome of interest was clearly defined as allergic rhinitis 3) one of the exposure factors was smoking, either by the subjects themselves or their relatives, 4) they provided estimates of odds ratio (OR), relative risk (RR), or prevalence odds ratio and their confidence intervals, or enough data to calculate them. If data on the same population were duplicated in more than one study, the most recent study was included in the analysis. When data for different types or levels of exposure were available in the same study, such as

passive smoking, active smoking, maternal smoking during pregnancy, we considered each type of exposure separately. We developed a standard data-recording form in which we recorded authors, year of publication, study location, study design including whether ISAAC methodology was followed, sample size, outcome, outcome measurement details, effect estimator (OR, RR, other), effect estimate, 95% Confidence Intervals, and adjustment factors used. When further clarification was necessary, we attempted to contact the authors. We considered odds ratios as estimates of the Relative Risk.

Quality assessment

Study quality was assessed using a five-point binary scale specifically developed for this study. The scale is based on the Newcastle-Ottawa scale with modifications in view of standard guidelines and our own judgment.[34] We used the following criteria labelled as "yes" or "no": 1) whether assessment of the smoking habit included duration and/or quantity (yes) or else (no), 2) whether rhinitis diagnosis included clinical features and IgE or SPT measurements (yes) or was based on clinical examination only (no) 3) whether results were adjusted for age, sex and other potential confounders (yes), or else (no), 4) whether participations exceeded 80% of the people initially approached (yes) or else (no), and, finally 5) whether the target population was clearly defined (yes) or on the contrary, based on convenience sampling of subjects such as patients of a single consultation (no). Throughout this assessment, when the information on a specific item was not provided by the authors, we graded this item as "no". We carried out a pooled analysis on those studies that fulfilled at least 3 criteria and compared with those that scored less than 3.

Data extraction and quality scoring were performed independently by two reviewers (BT and JS) and results were merged by consensus. The results for quality scoring are presented in the annex I.

Data synthesis and analysis

We weighted the study-specific adjusted log odds ratios for case control and cross-sectional studies, and log relative risks for cohort studies by the inverse of their variance to compute a pooled relative risk and its 95% confidence interval. For each study, we used the estimate of the effect measure that was adjusted for the largest number of confounders.

We present both fixed-effects and random-effects pooled estimates but use and report the latter when heterogeneity was present, as in our main analysis and most subgroup analyses the random-effects model is generally thought to give more reliable results than the fixed-effects model, including a more conservative (wider) CI, when the studies being considered show a considerable degree of heterogeneity. Odds ratios from case-control studies were assumed to be unbiased estimates of the relative risk.[35]

We used a version adapted to small samples of the DerSimonian and Laird Q test to check for heterogeneity.[36] The null hypothesis of this test is the absence of heterogeneity. To quantify this heterogeneity we calculated the proportion of the total variance due to between-study variance (Ri statistic).[36] Furthermore, we explored the origin of heterogeneity by restricting the analysis to subgroups of studies defined by study characteristics such as study design, type of exposure (active or passive smoking) and age of the participants (children/adolescents or adults).

We assessed publication bias first, visually, using funnel plots and then, more formally, using the test proposed by Egger and colleagues.[37] All analyses were performed with the software HEpiMA® version 2.1.3 and STATA version 12.[38]

The secondary analyses (children and adolescent's population/adults, ISAAC/other, cohort and case-control studies combined/cross-sectional studies, high quality/low quality) were planned a priori.

3.1.3. RESULTS

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In total we identified 196 studies, published in 139 different articles and carried out in 51 countries, on active or passive smoking and allergic diseases at large that met our inclusion criteria. (Figure 1) The data from one study were obtained from the authors.[39] We found 97 studies on allergic rhinitis.[19,21,24,39-118] A large majority of the articles retrieved initially were excluded either because they did not provide any effect measure or the outcome was allergy at large. Globally, heterogeneity was substantial overall and similarly high after stratification by design, quality features (including adjustment for confounders) and study population. Given the substantial heterogeneity, we focused on the random effects results, however the fixed effects analyses are presented for comparison and only discussed where they differ from the random effects results.

Thirty-four studies on active smoking and 63 studies on second-hand smoking were available. (Tables 1 and 2, and Figures 2 and 3) The overwhelming majority of the studies assessed diagnosis through questionnaire and only 7 studies used skin prick test or IgE measurements for the case definition.[39,42,46,52,57,101,113] The study by Wright et al. measured skin prick test (SPT) reactivity but used a definition of physician diagnosed allergic rhinitis that included both SPT-positive and SPT-negative children.[42] More than half of the studies used ISAAC criteria for the definition of allergic rhinitis. Finally, 11 studies assessed maternal smoking during pregnancy.[44,45,47-49,60,70,81,93,99,114] Table 3 shows the results for associations between smoking and allergic rhinitis.

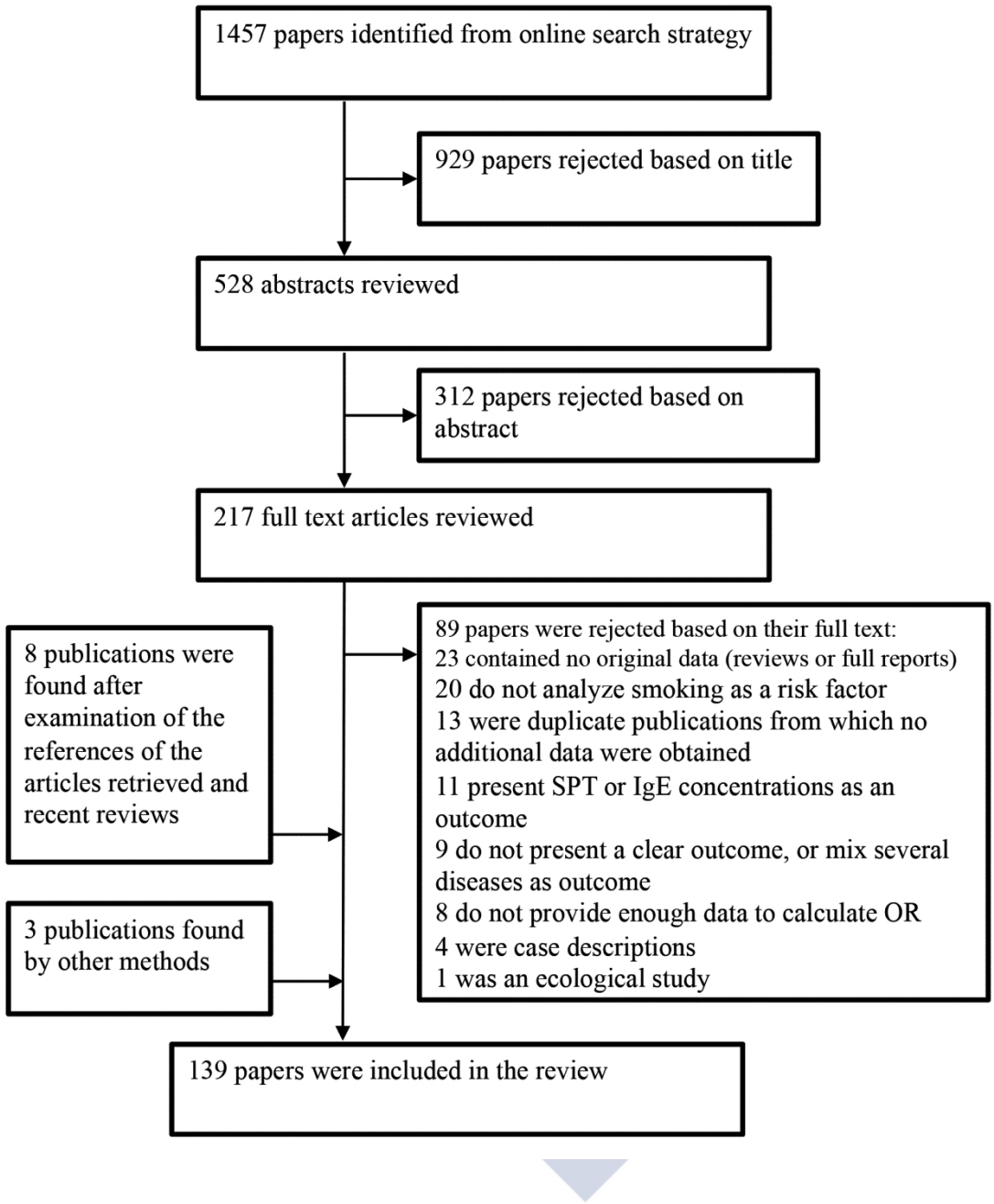

Figure 1. Flow diagram for study selection.

Table 1. Relative risks and 95% confidence intervals of allergic rhinitis by smoking exposure in case-control and cohort studies

Author	Country of the study	Population	Active smoking	Passive smoking	Cases/Controls or Cohort size	Variables of adjustment, matching, restriction
Case-control studies						
Ozasa 1995[39]	Japan	Adults	0.38 (0.19-0.76)	0.45 (0.31-0.65)	89/89	Age
Cakir 2010[19]	Turkey	adolescents	1.57 (1.16-2.11)	1.61 (1.17-2.21)	436/366	Age, sex, family atopy, pets, income, occupation
Lin 2011[40]	USA	Adults	--	2.05 (1.34-3.15)	83/117	Age, sex, education
Miyake 2011[41]	Japan	adult women	1.13 (0.86-1.48)	--	393/767	Sex
Cohort studies						
Wright 1994[42]	USA	children	--	1.93 (1.63-2.30)	311/747	Not specified
Annesi-Maesano 1997[43]	France	adult men	1.75 (1.15-2.68)	--	126/191	Sex
Lewis 1998[44]	UK	children	--	0.89 (0.82-0.97)	1.646/6.281	Age, sex, social class, low birth weight, gestational age, breast feeding, maternal age, parity
Shaheen 1999[45]	UK	young adults	0.91 (0.83-1.00)	--	?/6.420	Age, sex, birth weight, social class, siblings, education, height, BMI
Bergmann 2000[46]	Germany	children	--	1.05 (0.72-1.55)	178/825	Age, sex, parental atopy, socioeconomic status, breast feeding, aeroallergen sensit., food sensit, study center
Tariq 2000[47]	UK	children	--	0.88 (0.47-1.65)	65/1.218	Age
McKeever 2001[24]	UK	children	--	1.02 (0.94-1.11)	1.113/29.238	Age, sex, family atopy, siblings
Magnusson 2005[48]	Denmark	children	--	1.1 (1.0-1.4)	1.083/7.844	Sex, social class, occupation, maternal age in pregnancy, coffee, parity, breastfeeding
Johansson 2008[49]	Sweden	children	--	1.20 (1.10-1.31)	?/8.850	Age, mothers' education, family type
Nagata 2008[50]	Japan	Adults	0.76 (0.66-0.89)	--	1.000/12.221	Age, sex, marital status, education, BMI, farming, alcohol
Bendtsen 2008[21]	Denmark	adult women	0.84 (0.76-0.94)	--	1.354/5.870	Age, sex, education, alcohol follow-up time, passive smoking status, parental asthma
Keil 2009[51]	Germany	children	--	1.03 (0.74-1.44)	198/784	Age, sex, birth weight, breast feeding, siblings, pets, parental education, IgE, location
Codispoti 2010[52]	USA	high risk children	--	1.29 (0.74-2.25)	116/361	Age, parental allergies

Table 2. Relative risks and 95% confidence intervals of allergic rhinitis by smoking exposure in cross-sectional studies

Author	Country of the study	Population	Active smoking	Passive smoking	Total sample size	Variables of adjustment, matching, restriction
Bakke 1990[53]	Norway	adolescents and adults	0.68 (0.58-0.80)	--	4.270	Age, sex, occupational exposure, residence
Leuenberger 1994[54]	Switzerland	Adults	--	1.02 (0.82-1.28)	3.494	Not specified
Ng 1994[55]	Singapore	Adults	1.16 (0.82-1.65)	--	2.868	Age, race, flat, housing, past smoker, cockroach, occupation, fumes
Moyes 1995[56]	New Zealand	schoolchildren	--	0.80 (0.55-1.15)	5.360	Age
Wutrich 1996[57]	Switzerland	Adults	0.62 (0.53-0.71)	--	8.344	Age, sex, location
Min 1997[58]	Korea	children and adults	0.81 (0.38-1.34)	--	8.853	Age
Siracusa 1997[59]	Italy	children and adults	0.9 (0.5-1.9)	--	824	Age, sex, allergens
Austin 1997[60]	UK	children	--	0.63 (0.51-0.77)	1.537	Age
Farooqi 1998[61]	UK	children	--	1.04 (0.82-1.32)	1.934	Not specified
Lam 1998[62]	Hong Kong	schoolchildren	0.97 (0.86-1.09)	0.98 (0.86-1.12)	6.304	Age, sex, residence, housing
Ponsonby 1998[63]	Australia	children	--	0.95 (0.86-1.05)	6.378	Age
Montefort 1998[64]	Maltese islands	schoolchildren	1.67 (1.43-1.95)	1.13 (1.0-1.28)	4.184	Age, sex, road, pets, parental atopy, blankets
Duhme 1998[65]	Germany	schoolchildren	1.37 (1.17-1.59)	1.01 (0.90-1.13)	13.123	Age, sex
Burr 1999[66]	UK	schoolchildren	1.30 (1.23-1.36)	1.04 (1.00-1.09)	25.393	Age, sex, location, residence, pets, cooking fuel, heating fuel, housing
Dotterud 1999[67]	Russia	adults	0.69 (0.40-1.17)	--	3.368	Not specified
Keles 1999[68]	Turkey	adolescents	0.6 (0.2-1.6)	0.8 (0.4-1.3)	386	Age, sex, heating, households, location
Plaschke 2000[69]	Sweden	Adults	0.82 (0.49-1.37)	--	1.370	Age, sex, location, pets, allergens
Zacharasiewicz 2000[70]	Austria	children	--	1.04 (0.93-1.17)	18.606	Age, sex, family history of hay fever, education
Upton 2000[71]	UK	adults	0.70 (0.54-0.91)	--	2.832	Age
Ozdemir 2000[72]	Turkey	university freshmen	1.28 (0.82-1.98)	--	1.515	Age
Hjern 2001[73]	Sweden	children	--	0.96 (0.83-1.12)	4.472	Age, sex, siblings, parental education, residence, single parent household, country of birth of parent, location
Hjern 2001[73]	Sweden	Adults	0.78 (0.72-0.84)	--	6.909	Age, sex, education, residence, country of birth, location
Janson 2001[74]	Europe	Adults	--	1.02 (0.81-1.20)	7.882	Age, sex, other allergens, IgE, location
Simpson 2001[75]	UK	Adults	0.78 (0.65-0.93)	--	5.687	Sex, other allergens, pets

Table 2 Cont.

Author	Country of the study	Population	Active smoking	Passive smoking	Total sample size	Variables of adjustment, matching, restriction
Dotterud 2001[76]	Russia	schoolchildren	---	0.90 (0.69-1.17)	1.684	Age, sex, carpets, dampness, pets, heating type
Kalyoncu 2001[77]	Turkey	university students	1.24 (1.01-1.53)	1.20 (1.06-1.35)	4.639	Age, sex, region, family atopy, pets, elder siblings
Lee 2001[78]	Korea	schoolchildren	--	1.19 (1.11-1.28)	38.955	Age, sex, region, BMI, electricity bill, carpets, pets, location
Stazi 2002[79]	Italy	children	--	2.2 (1.2-4.1)	201	Age, sex
Peroni 2003[80]	Italy	Preschool children	--	1.19 (0.89-1.59)	1.402	Age
Barraza 2003[81]	Mexico	schoolchildren	--	1.37 (1.23-1.52)	6.174	Age, school, cockroaches, respiratory problems, carpeting, humidity, family history of asthma
Monteil 2004[82]	Trinidad & Tobago	schoolchildren	--	1.41 (1.26-1.59)	3.170	Age
Lee 2004[83]	Hong Kong	school children	--	0.81 (0.72-0.91)	4.448	Age, sex, birth weight, siblings, respiratory tract infections, parental atopy, pets, study period
Kramer 2004[84]	Germany	school beginners	--	0.86 (0.38-1.96)	1.220	Age, sex, atopy, nationality
Demir 2004[85]	Turkey	schoolchildren	--	2.43 (1.32-4.52)	1.064	Age
Miyake 2004[86]	Japan	schoolchildren	--	1.11 (0.98-1.27)	5.539	Age, sex, grade, older siblings, maternal age at child birth, pets, history of other allergic diseases
Annesi-Maesano 2004[87]	France	adolescents	1.65 (1.48-1.84)	1.15 (1.09-1.22)	14.578	Age, sex
De 2005[88]	Ireland	children	--	1.16 (0.43-3.12)	81	Not specified
Topp 2005[89]	Germany	Adults	--	1.10 (0.93-1.30)	4.093	Age, sex, social class, location
Maziak 2005[90]	Syria	Adults	--	1.12 (0.85-1.48)	1.118	Age, sex, familial atopy, socioeconomic status, occupational exposure
Miyake 2005[91]	Japan	pregnant women	1.10 (0.85-1.42)	1.33 (1.09-1.62)	1.002	Age, sex, familial atopy, pets, gestation, parity, family income, education, mite antigen level
Bugiani 2005[92]	Italy	young adults	0.76 (0.69-0.84)	--	17.666	Not specified
Obihara 2005[93 A]	South Africa	children	--	--	861	Age, sex, maternal atopy, breast feeding, siblings, household income, tuberculin test
Strumylaite 2005[94]	Lithuania	children	--	0.85 (0.20-3.45)	594	Age

Table 2. Cont.

Author	Country of the study	Population	Active smoking	Passive smoking	Total sample size	Variables of adjustment, matching, restriction
Lund 2006[95 B]	France	mature women	1.10 (0.92-1.30)	1.31 (1.0-1.6)	2.197	Age, sex
Kurosaka 2006[96]	Japan	schoolchildren	--	0.82 (0.78-0.87)	35.213	Age, sex, pets
Sakar 2006[97]	Turkey	adults	1.30 (0.99-1.71)	1.33 (0.96-1.83)	1.336	Age, sex, family atopy
Ho 2007[98]	Hong Kong	adults	--	1.34 (0.93-1.94)	200	Age, sex, education, occupational exposures
Horak 2007[99]	Austria	preschool children	--	1.31 (0.90-1.90)	1.737	Age, sex, familial atopy, education, family size, pets, breastfeeding, healthy nutrition
Ebbert 2007[100]	USA	adults	--	1.16 (0.85-1.59)	1.007	Not specified
Tanaka 2007[101]	Japan	children	--	1.07 (0.98-1.16)	23.044	Age, sex, location, familial atopy, siblings, education level
Zuraimi 2008[102]	Singapore	preschool children	--	1.22 (1.11-1.35)	4.759	Age, sex, familial atopy, race, socioeconomic status, housing type, breastfeeding, food allergy, respiratory infections, dampness, air condition, wall paper, carpet, traffic density
Foliaki 2008[103]	Pacific countries	children	--	1.05 (0.99-1.12)	17.683	Age, sex, country
Gomez 2008[104]	Argentina	adolescents	1.72 (1.48-1.99)	--	3.000	Age
Kabir 2009[105]	Ireland	children		1.30 (1.01-1.67)	2.809	Age, sex
Brescianini 2009[106]	Italy	schoolchildren	--	1.17 (0.79-1.76)	481	Age, sex, family atopy, BMI, pets, physical activity, diet, location
Musharrafieh 2009[107]	Lebanon	adolescents	--	1.0 (0.8-1.2)	3.115	Age, sex, nationality, regions, school type, traffic, asthma, rhinitis
Gonzalez-Diaz 2010[108]	Mexico	children and adolescents	--	1.37 (1.23-1.53)	23.191	Age
Bedolla-Barajas 2010[109]	Mexico	schoolchildren	--	1.01 (0.48-2.13)	740	Age
Wang 2010[110]	Canada	schoolchildren	--	1.00 (0.81-1.24)	8.334	Age, sex, BMI, location, birthplace, ethnicity, maternal education, siblings, nº of smokers, fuel use, truck exp., pets, acetaminophen, physical activity, time watching TV
Vlaski 2011[111]	Macedonia	adolescents	--	0.99 (0.88-1.11)	3.026	Age, sex, diet, type of cooking and heating, pets, maternal education, siblings

Table 2. Cont.

Author	Country of the study	Population	Active smoking	Passive smoking	Total sample size	Variables of adjustment, matching, restriction
Virkkula 2011[112]	Finland	children	--	2.29 (1.07-4.87)	38	Age
Hakansson 2011[113]	Denmark	adults	0.79 (0.68-0.92)	---	3.471	Age, sex
Chen 2012[114]	Taiwan	children	--	--	4.221	Age, sex, parental atopy, parental education
Peñaranda 2012[115]	Colombia	children	--	1.19 (0.99-1.42)	3.256	Age, asthma, dermatitis, use of acetaminophen, use of antibiotics, maternal education, caesarean delivery
Peñaranda 2012[115]	Colombia	adolescents	1.4 (1.2-1.7)	--	3.829	Age, asthma, dermatitis, use of acetaminophen, consumption of fast-food, cats
Tanaka 2012[116]	Japan	pregnant women	1.01 (0.84-1.23)	1.50 (1.14-1.96)	1.743	Age, sex, region of residence, parental atopy, household income, education
Montefort 2012[117]	Maltese Islands	children	1.40 (1.11-1.76)	1.11 (1.02-1.20)	7.955	Age
Mitchell 2012[118]	Worldwide	children	--	1.10 (1.08-1.12)	573.061	Age, sex, language, region, gross national income

A - Only data on maternal smoking during pregnancy are available.
B - This study used cases of rhinitis at large, not only allergic rhinitis.

Active smoking

Using random effects analysis, there was no significant association between active smoking and the risk of allergic rhinitis when all studies are considered (RR=1.02; 95% CI: 0.92-1.15). Using fixed effect analysis for all studies, there was a significant association between active smoking and risk of rhinitis (RR=1.06; 95% CI: 1.03-1.08), however this may be explained by the considerable amount of heterogeneity due to differences in designs, case and exposure definitions and adjustment for confounders. It is remarkable that, under the fixed effects model, the result of the cross-sectional subgroup (RR=1.09; 95% CI: 1.06-1.12) is statistically significant and opposed to the result of the cohort studies subgroup (RR=0.87; 95% CI: 0.82-0.93). When restricting the analysis to the 10 studies carried out on children and adolescents populations, active smoking was associated with an increased pooled relative risk of 1.40 (95% CI: 1.24-1.59). In further sub-group analyses, the association was significant in the studies that used the standardized ISAAC protocol (RR=1.50; 95% CI: 1.35-1.66), but not those that used their own protocol (RR=0.96; 95% CI: 0.88-1.08). A reverse association between active smoking and allergic rhinitis was observed in adults only (RR=0.90; 95% CI: 0.82-0.99)

Passive smoking

Using random effects analysis, there was a significant association passive smoking and allergic rhinitis (RR=1.10; 95% CI: 1.06-1.15). Similar findings were observed in subgroup analyses by adjustment for confounding variables (RR=1.07; 95% CI: 1.03-1.12 for full adjustment, RR=1.15; 95% CI: 1.04-1.27 for incomplete adjustment), quality scores (RR=1.10; 95% CI: 1.04-1.15 for high quality, RR=1.10; 95% CI: 1.02-1.19 for low quality), and for cross-sectional studies (RR=1.09; 95% CI: 1.05-1.14); however, there was no significant association between passive smoking and allergic rhinitis when restricting the analysis to cohort studies (RR=1.14; 95% CI: 0.96-1.34) or case-control studies (RR=1.14; 95% CI: 0.46-2.82).

Figure 2. Study-specific and random effects pooled risks of smoking and allergic rhinitis

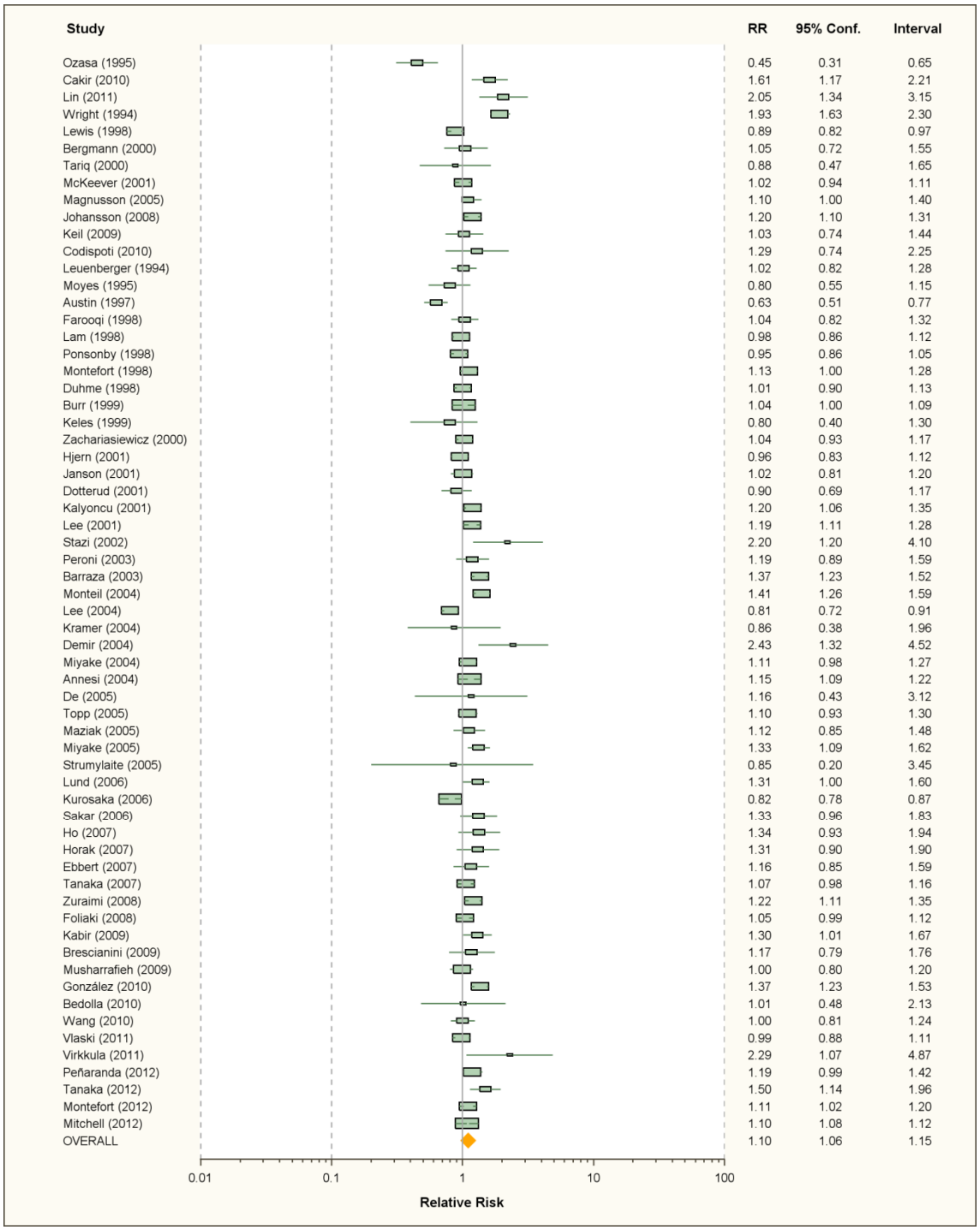

Figure 3. Study-specific and random effects pooled relative risks of passive smoking and allergic rhinitis.

In subgroup analyses based on age group, a significant association between passive smoking and allergic rhinitis was observed in adults only (RR=1.17; 95% CI: 1.03-1.32) and in children and adolescents (RR=1.09; 95% CI: 1.04-1.14). For maternal pregnancy smoking, there was no evidence for a significant increase in the risk of allergic rhinitis in the offspring (RR=1.07; 95% CI: 0.92-1.28).

Publication Bias

The funnel plot of active smoking seems to be slightly skewed to the left, which indicates a potential lack of studies that favor a positive association of the disease with smoking. (Figure 4) However, the Egger's test of asymmetry yielded a non-significant p-value of 0.27 and no hypothetical study was suggested as missing in the trim-and-fill procedure. The funnel plot for passive smoking (figure 5) and the corresponding results of the Egger's test did not show any evidence of publication bias (p=0.53), but two new studies were imputed in the trim-and-fill procedure yielding a modified pooled relative risk of 1.10 (95% CI: 1.05-1.14).

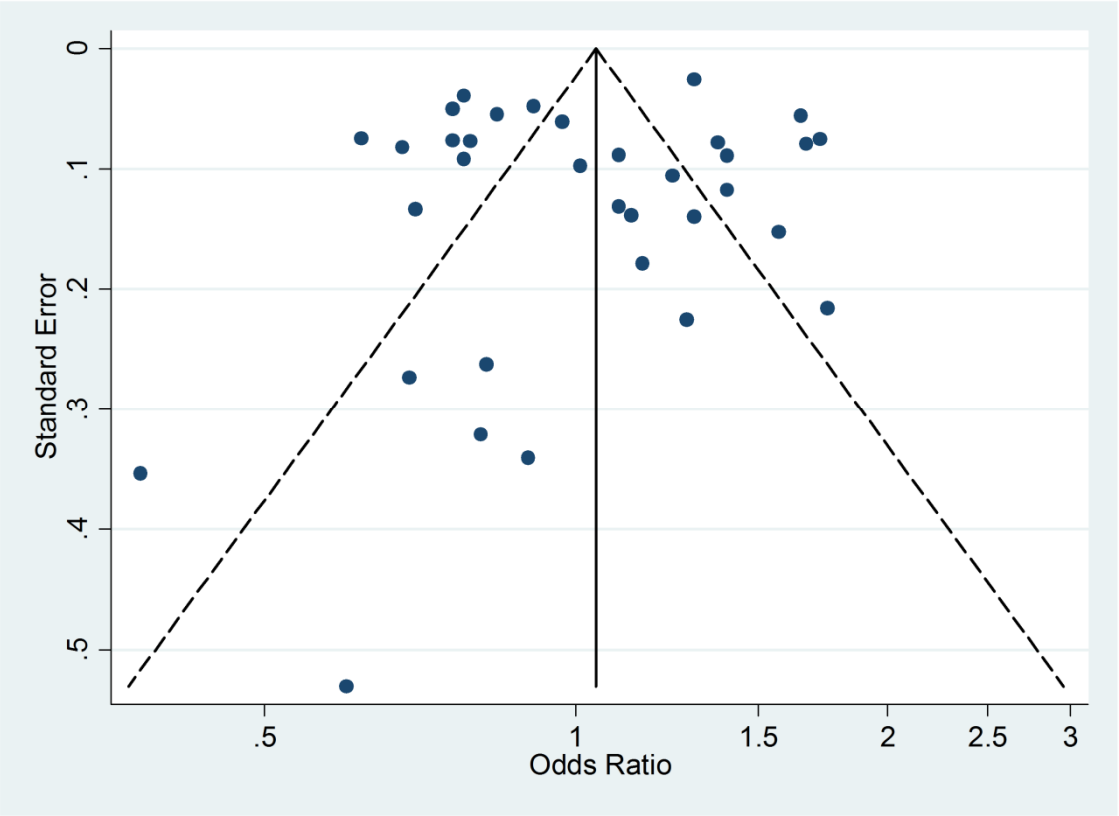

Figure 4. Funnel plot of relative risk versus standard error of relative risk: allergic rhinitis, active smoking.

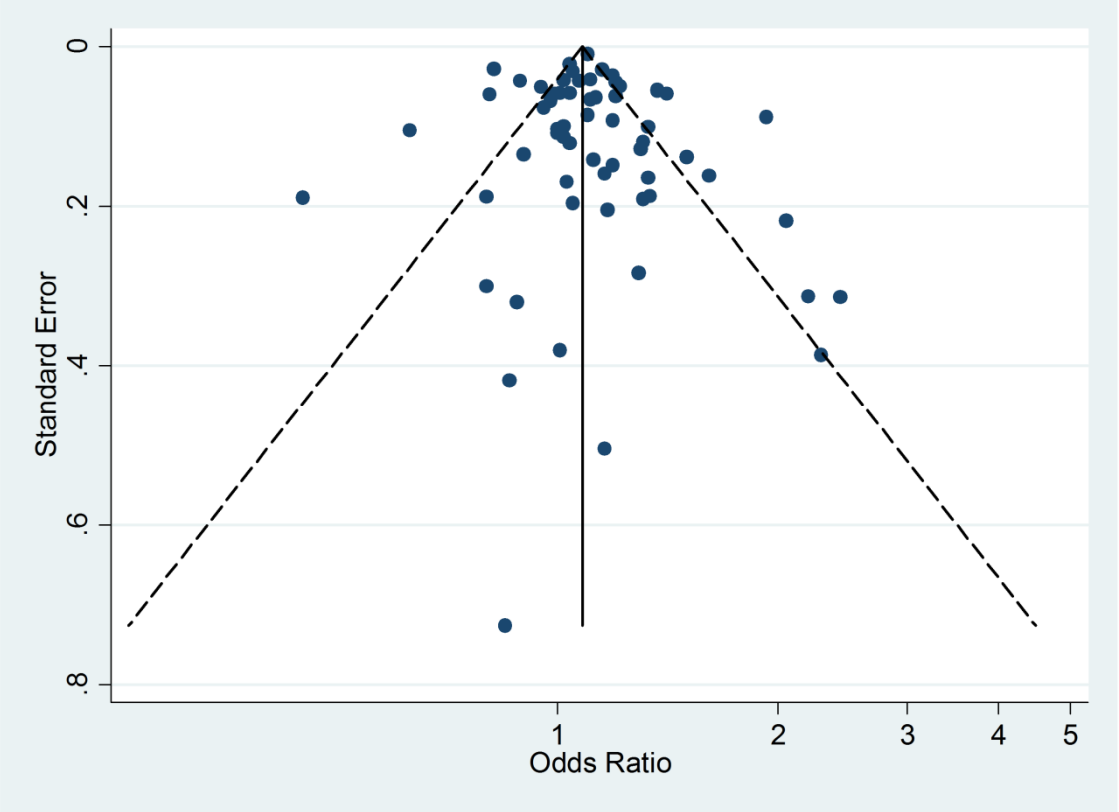

Figure 5. Funnel plot of relative risk versus standard error of relative risk: allergic rhinitis, passive smoking.

Meta-regression

The meta-regression with the pooled log relative risk as a dependent variable and the population variable as a moderator, introduced in the model as a dichotomous variable (adults/pediatric population), yielded the following results for the children and adolescents when compared to the adults for allergic rhinitis and active smoking: RR=1.55; 95% CI: 1.30-1.84; allergic rhinitis and passive smoking: RR=0.93; 95% CI: 0.81-1.06. These results suggest that the associations between allergic rhinitis with active smoking are significantly greater among children and adolescents than among adults. Although these meta-regression RRs were not statistically significant at a 95% level for passive smoking, in table 3 we present the results of children and adolescent populations as a subgroup both for active and passive smoking.

Table 3. Pooled relative risks (RR) and 95% confidence intervals (CI) of allergic rhinitis and smoking

Study type	Number of studies	RR (95% CI) Fixed effects	RR (95% CI) Random effects	Ri * (95% CI)	Q test (p value)
Active smoking					
All studies	34	1.06 (1.03-1.08)	1.02 (0.92-1.15)	0.95 (0.90-0.99)	0.00001
Cohort studies	4	0.87 (0.82-0.93)	0.91 (0.77-1.07)	0.82 (0.47-1.00)	0.0024
Case-control studies	3	1.19 (0.99-1.45)	0.97 (0.55-1.70)	0.88 (0.59-1.00)	0.0009
Cross-sectional studies	27	1.09 (1.06-1.12)	1.03 (0.91-1.18)	0.95 (0.91-1.00)	0.00001
Incidence studies †	7	0.90 (0.85-0.96)	0.98 (0.81-1.18)	0.87 (0.66-1.00)	0.00001
Full adjustment	18	1.07 (1.04-1.10)	1.02 (0.88-1.20)	0.96 (0.92-1.00)	0.00001
Incomplete adjustment	16	1.03 (0.98-1.08)	1.02 (0.86-1.22)	0.91 (0.83-0.99)	0.00001
Adults only	21	0.84 (0.81-0.87)	0.90 (0.82-0.99)	0.82 (0.66-0.97)	0.00001
Children/adolescents only	10	1.35 (1.30-1.39)	1.40 (1.24-1.59)	0.90 (0.77-1.00)	0.00001
Children ISAAC method	8	1.39 (1.34-1.44)	1.50 (1.35-1.66)	0.85 (0.63-1.00)	0.00001
Children non-ISAAC method	2	0.96 (0.86-1.08)	0.96 (0.86-1.08)	0.00 (0.00-1.00)	0.34
Quality score ≥ 3	15	0.89 (0.86-0.93)	0.95 (0.85-1.06)	0.86 (0.73-0.99)	0.00001
Quality score < 3	19	1.19 (1.16-1.23)	1.09 (0.92-1.29)	0.96 (0.91-1.00)	0.00001
Passive smoke					
All studies	63	1.08 (1.07-1.10)	1.10 (1.06-1.15)	0.87 (0.75-0.99)	0.00001
Cohort studies	9	1.08 (1.03-1.13)	1.14 (0.96-1.34)	0.90 (0.76-1.00)	0.00001
Case-control studies	3	1.13 (0.91-1.39)	1.14 (0.46-2.82)	0.95 (0.84-1.00)	0.00001
Cross-sectional studies	51	1.08 (1.07-1.10)	1.09 (1.05-1.14)	0.86 (0.72-0.99)	0.00001
Incidence studies †	12	1.08 (1.03-1.13)	1.13 (0.96-1.34)	0.91 (0.79-1.00)	0.00001
Full adjustment	37	1.07 (1.06-1.09)	1.07 (1.03-1.12)	0.86 (0.72-1.00)	0.00001
Incomplete adjustment	26	1.17 (1.13-1.20)	1.15 (1.04-1.27)	0.86 (0.74-0.97)	0.00001
Adults only	13	1.17 (1.10-1.24)	1.17 (1.03-1.32)	0.74 (0.50-0.98)	0.00001
Children/adolescents only	50	1.08 (1.07-1.09)	1.09 (1.04-1.14)	0.89 (0.77-0.99)	0.00001
Maternal pregnancy smoking	11	1.01 (0.96-1.06)	1.07 (0.92-1.28)	0.83 (0.60-1.00)	0.00001
Children ISAAC method	28	1.10 (1.09-1.12)	1.11 (1.07-1.16)	0.84 (0.66-1.00)	0.00001
Children non-ISAAC method	21	0.98 (0.95-1.01)	1.06 (0.95-1.19)	0.89 (0.78-1.00)	0.00001
Quality score ≥ 3	30	1.09 (1.08-1.11)	1.10 (1.04-1.15)	0.86 (0.71-1.00)	0.00001
Quality score < 3	33	1.07 (1.04-1.09)	1.10 (1.02-1.19)	0.88 (0.78-0.98)	0.00001

* Proportion of total variance due to between-study variance † Incidence studies: Cohort studies + case-control studies (cross-sectional studies excluded)

Sub-group Analyses in Children and Adolescents

We calculated the random effects pooled relative risks for children cohort studies, then for children cohort studies and case-control studies combined. For cohort studies, passive smoking was not significantly associated with allergic rhinitis (RR=1.14; 95% CI: 0.96-1.34, nine studies), but the association of increased risk was significant for cohort and case-control studies combined: RR=1.17; 95% CI: 1.00-1.38, ten studies.

Sensitivity Analysis

To further evaluate the possibility that the results obtained for children/adolescents were due to publication bias, we assumed that cross-sectional studies are the kind of studies that are most probably rejected by journals in case of null results and recalculated our pooled estimates under the following extreme assumptions: (1) published cross-sectional studies are only half of the studies of smoking and allergic rhinitis ever conducted among children, (2) all unpublished studies found an RR of 1, (3) the unpublished studies found the same prevalence of allergic rhinitis as the average of the published studies. Under these extreme assumptions, the random effects pooled estimates for active smoking still show a significant increase in risk: RR=1.16; 95% CI: 1.08-1.25.

Summary of the results of smoking effect on allergic dermatitis and food allergies

We also retrieved 91 studies on allergic dermatitis and eight on food allergy. Very modest associations were observed between smoking and allergic dermatitis and food allergies among adults. When all studies were analysed together, allergic dermatitis was associated with both active (random effects pooled RR=1.21; 95% CI: 1.14-1.29) and passive smoking (random effects pooled RR=1.07; 95% CI: 1.03-1.12). Among children and adolescents, both active and passive exposure to tobacco smoke was associated with a modest increased risk

for allergic dermatitis (random effects pooled RR=1.36; 95% CI: 1.17-1.46 and 1.06; 95% CI: 1.01-1.11 respectively). Food allergy was associated with passive smoking (random effects pooled RR=1.43; 95% CI: 1.12-1.83) when cohort studies only were examined, but not when all studies were combined.

3.1.4. DISCUSSION

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In the overall population, active smoking was associated with a modest increase in the risk for allergic dermatitis but not allergic rhinitis, while passive smoking was associated with modest increases in the risks for both allergic dermatitis and allergic rhinitis. Among children and adolescents, we observed significant associations between both active and passive smoking and allergic rhinitis and allergic dermatitis, and passive smoking was associated with an increased risk for food allergy. In children and adolescents, while the observed increase in risk for allergic diseases associated with smoking was small, the findings are important given that to the prevalence of active and passive smoking in this population can be high. Worldwide, 14% of adolescents aged 13 to 15 are active smokers with some countries reaching a prevalence of 40%, and nearly 25% of the children who smoke have smoked their first cigarette before the age of 10 years.[119] Furthermore, in the US, more than one-third of children live with at least one adult smoker.[120] In other parts of the world, passive exposure to tobacco among children is even higher as nearly half of children were exposed to tobacco smoke at home.[121] On the basis of the figures above, in countries with high smoking prevalence we estimate that 14% of allergic rhinitis and 13% of allergic dermatitis are attributable to active smoking.[122] Eliminating active smoking in children and adolescents would then prevent one in every seven cases of allergic rhinitis and one in every eight cases of allergic dermatitis.

That age is an important effect modifier for the relation between tobacco exposure and risk of allergic diseases is biologically plausible. The US Surgeon General has suggested that the immaturity of the respiratory, nervous, and immune systems in children may make them vulnerable to health effects of smoking.[123] Furthermore, unlike adults, children have limited options for avoiding exposure to second-hand smoke and are unable to reduce the quantity of products inhaled.[123]

Our finding that maternal exposure is not associated with the risk of allergic diseases in the offspring confirms the results from a previous meta-analysis that focused on the risk of allergic sensitization measured through skin prick

positivity or IgE concentrations.[30] It is possible that the lack of observed association is due to the existence of bias given that parents of children at high risk of allergy may selectively avoid smoking during pregnancy.

The findings from our meta-analysis are subject to several limitations. The majority of studies were cross-sectional, a design that does not allow for causal inference and can overestimate relative risks given its reliance on prevalence ratios. When restricted to cohort studies our analyses showed that many of the results were no longer significant, especially for the subgroup analysis in children and adolescents. There is then some evidence that the findings may be impacted by study design.

Residual confounding (confounding remaining after adjustment) may explain some of our findings. For some of our analyses, we were unable to detect meaningful differences in the results between studies that had incomplete adjustment for confounders and those with more complete adjustment for confounders and our findings were broadly similar when restricting the analyses to studies with higher quality scores. However, there are likely to be other factors, such as genetic factors that were not controlled for and may play a role in the relationship between smoking and allergic diseases. Although publication bias cannot be ruled out, its magnitude is likely to be low as shown by the robustness of our sensitivity analysis.

Several studies assessed allergic diseases through self-report only, which can lead to misclassification of allergic and nonallergic conditions. Similarly, the findings are limited by measurement error in the smoking exposure given that a majority of studies assessed exposure to smoking in a qualitative fashion and often on a yes/no basis instead of using a quantitative assessment. Misclassification and measurement error in SHS assessment may result from a respondent's lack of knowledge about current or past exposure, biased recall, whether intentional or unintentional, and the difficulty in characterizing an exposure in complex indoor environments.[124] A standard set of items to identify

passive smoking in distinct settings is needed.[125] If misclassification exists, it is probable that the outcome misclassification is not differential in regard to smoking and, similarly, measurement error in smoking assessment is not differential in regard to diagnosis. In this case, the results would be biased towards the null value, which means that the association with smoking observed in our meta-analysis is underestimated.

In our subgroup analyses, we were unable to identify any factors that accounted for study heterogeneity. Given the high heterogeneity estimates, we focused our interpretation on the random effects estimates. The random effects model gives increased weights to the effect of small studies, which may introduce bias in the estimation. It is worth noting that for some of the analyses, the fixed effects and random effects estimates differ substantially; this may be due to differences in case or exposure definition and in adjustment for potential confounders.

Our subgroup analyses found stronger evidence for associations between smoking and allergic diseases in children and adolescents than adults. Furthermore, our meta-regression suggested that the association between active smoking and allergic disorders is larger in children and adolescents than in adults, which advocates for a transient effect through life. This finding is in accordance with the "atopic march" concept that suggests that the sequence of sensitization which starts in childhood may show a tendency to spontaneous remission later in life.[126] It is then plausible that sensitization to tobacco is mitigated by increasing age. Further research is needed to verify whether the association between smoking and risk of allergy in adults is similar for those who started smoking as an adult and those who started smoking during childhood or adolescents.

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3.1.5. REFERENCES

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1. Ozdoganoglu T, Songu M. The burden of allergic rhinitis and asthma. Ther Adv Respir Dis 2012; 6:11–23.
2. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004; 24:758–64.
3. Berger WE. Allergic rhinitis in children: diagnosis and management strategies. Paediatr Drugs 2004; 6:233–50.
4. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, et al. The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol 2007; 120:638– 46.
5. DaVeiga SP. Epidemiology of atopic dermatitis: a review. Allergy Asthma Proc 2012; 33:227–34.
6. Meltzer EO, Blaiss MS, Derebery MJ, Mahr TA, Gordon BR, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. J Allergy Clin Immunol 2009; 124:S43–S70.
7. Nathan RA. The burden of allergic rhinitis. Allergy Asthma Proc 2007; 28:3–9.
8. Alanne S, Maskunitty A, Nermes M, Laitinen K, Pekurinen M. Costs of allergic diseases from birth to two years in Finland. Public Health 2012; 126:866–72.
9. Spergel JM. From atopic dermatitis to asthma: the atopic march. Ann Allergy Asthma Immunol 2010; 105:99–106.
10. Tan RA, Corren J. The relationship of rhinitis and asthma, sinusitis, food allergy, and eczema. Immunol Allergy Clin North Am 2011; 31:481–91.
11. Asher MI, Montefort S, Bjorkstén B, Lai CK, Strachan DP, 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.
12. Ghouri N, Hippisley-Cox J, Newton J, Sheikh A. Trends in the epidemiology and prescribing of medication for allergic rhinitis in England. J R Soc Med 2008; 101:466–72.

13. Mosges R, Klimek L. Today's allergic rhinitis patients are different: new factors that may play a role. Allergy 2007; 62:969–75.
14. Lannero E, Wickman M, van Hage M, Bergstrom A, Pershagen G, et al. Exposure to environmental tobacco smoke and sensitisation in children. Thorax 2008; 63:172–6.
15. Diaz-Sanchez D, Rumold R, Gong H Jr. Challenge with environmental tobacco smoke exacerbates allergic airway disease in human beings. J Allergy Clin Immunol 2006; 118:441–6.
16. Peden D, Reed CE. Environmental and occupational allergies. J Allergy Clin Immunol 2010; 125(2 Suppl 2):S150–S160.
17. Warren CW, Jones NR, Peruga A, Chauvin J, Baptiste JP, et al. Global youth tobacco surveillance, 2000–2007. MMWR Surveill Summ 2008; 57:1–28.
18. Murin S, Rafii R, Bilello K. Smoking and smoking cessation in pregnancy. Clin Chest Med 2011; 32:75–91.
19. Cakir E, Ersu R, Uyan ZS, Oktem S, Varol N, et al. The prevalence and risk factors of asthma and allergic diseases among working adolescents. Asian Pac J Allergy Immunol 2010; 28:122–9.
20. Lee CH, Chuang HY, Hong CH, Huang SK, Chang YC, et al. Lifetime exposure to cigarette smoking and the development of adult-onset atopic dermatitis. Br J Dermatol 2011; 164:483–89.
21. Bendtsen P, Grønbaek M, Kjaer SK, Munk C, Linneberg A, et al. Alcohol consumption and the risk of self-reported perennial and seasonal allergic rhinitis in young adult women in a population-based cohort study. Clin Exp Allergy 2008; 38:1179–85.
22. Ludvigsson JF, Mostrom M, Ludvigsson J, Duchen K. Exclusive breastfeeding and risk of atopic dermatitis in some 8300 infants. Pediatr Allergy Immunol 2005; 16:201–8.
23. Metsala J, Lundqvist A, Kaila M, Gissler M, Klaukka T, et al. Maternal and perinatal characteristics and the risk of cow's milk allergy in infants

up to 2 years of age: a case-control study nested in the Finnish population. Am J Epidemiol 2010; 171:1310-6.

24. McKeever TM, Lewis SA, Smith C, Collins J, Heatlie H, et al. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. Thorax 2001; 56:758–62.
25. Wang IJ, Guo YL, Lin TJ, Chen PC, Wu YN. GSTM1, GSTP1, prenatal smoke exposure, and atopic dermatitis. Ann Allergy Asthma Immunol 2010; 105:124–9.
26. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, et al. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. J Allergy Clin Immunol 1998; 101:587–93.
27. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics 2012; 129:735–44.
28. Baena-Cagnani CE, Gómez RM, Baena-Cagnani R, Canonica GW. Impact of environmental tobacco smoke and active tobacco smoking on the development and outcomes of asthma and rhinitis. Curr Opin Allergy Clin Immunol 2009; 9:136–40.
29. Pattenden S, Antova T, Neuberger M, Nikiforov B, De Sario M, et al. Parental smoking and children's respiratory health: independent effects of prenatal and postnatal exposure. Tob Control 2006 15:294–301.
30. Strachan DP, Cook DG (1998) Health effects of passive smoking. 5. Parental smoking and allergic sensitisation in children. Thorax 53:117–23.
31. Freiman A, Bird G, Metelitsa AI, Barankin B, Lauzon GJ. Cutaneous effects of smoking. J Cutan Med Surg 2004; 8:415–23.
32. Just-Sarobé M. Smoking and the skin. Actas Dermosifiliogr 2008; 99:173–84.

33. National Institute for Public Health and the Environment. Risk factors for food allergy. Bilthoven (The Netherlands): RIVM Report 2010; 340007001.
34. Wells G, Shea B, O'Connell D, Peterson J, Welch V, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2012. Ottawa Health Research Institute website. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 16 August 2012
35. Rothman KJ, Greenland S, Lash TL. Measure of effect and measures of association. Modern epidemiology. 3rd edition. Philadelphia: Lippincott, Williams and Wilkins. 2008; P61.
36. Takkouche B, Cadarso-Suarez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. Am J Epidemiol 1999; 150:206–15.
37. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997; 315:629–34.
38. Costa-Bouzas J, Takkouche B, Cadarso-Suarez C, Spiegelman D. HEpiMA: software for the identification of heterogeneity in meta-analysis. Comput Methods Programs Biomed 2001; 64:101–7.
39. Ozasa K, Takenaka H, Takagi N, Aoike A, Kawai K. A case-control study of risk factors for Japanese cedar pollinosis. Jpn J Hyg 1995; 50:622–30.
40. Lin SY, Reh DD, Clipp S, Irani L, Navas-Acien A. Allergic rhinitis and secondhand tobacco smoke: a population-based study. Am J Rhinol Allergy 2011; 25:e66–e71.
41. Miyake Y, Tanaka K, Arakawa M. Case-control study of IL13 polymorphisms, smoking, and rhinoconjunctivitis in Japanese women: the Kyushu Okinawa Maternal and Child Health Study. BMC Med Genet 2011; 12:143.

42. Wright AL, Holberg CJ, Halonen M, Martinez FD, Morgan W, et al. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics 1994; 94:895–901.
43. Annesi-Maesano I, Oryszczyn M-P, Neukirch F, Kauffmann F. Relationship of upper airway disease to tobacco smoking and allergic markers: a cohort study of men followed up for 5 years. Int Arch Allergy Immunol 1997; 114:193–201.
44. Lewis SA, Britton JR. Consistent effects of high socioeconomic status and low birth order, and the modifying effect of maternal smoking on the risk of allergic disease during childhood. Respir Med 1998; 92:1237–44.
45. Shaheen SO, Sterne JAC, Montgomery SM, Azima H. Birth weight, body mass index and asthma in young adults. Thorax 1999; 54:396–402.
46. Bergmann RL, Edenharter G, Bergmann KE, Lau S, Wahn U. Socioeconomic status is a risk factor for allergy in parents but not in their children. Clin Exp Allergy 2000; 30:1740–5.
47. Tariq SM, Hakim EA, Matthews SM, Arshad SH. Influence of smoking on asthmatic symptoms and allergen sensitisation in early childhood. Postgrad Med J 2000; 76:694–9.
48. Magnusson LL, Olesen AB, Wennborg H, Olsen J. Wheezing, asthma, hay fever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life. Clin Exp Allergy 2005; 35:1550–6.
49. Johansson A, Ludvigsson J, Hermansson G. Adverse health effects related to tobacco smoke exposure in a cohort of three-year olds. Acta Pædiatr 2008; 97: 354–7.
50. Nagata C, Nakamura K, Fujii K, Kawachi T, Takatsuka N, et al. Smoking and risk of cedar pollinosis in Japanese men and women. Int Arch Allergy Immunol 2008; 147:117–24.
51. Keil T, Lau S, Roll S, Gruber C, Nickel R, et al. Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. Allergy 2009; 64:445–51.

52. Codispoti CD, Levin L, LeMasters GK, Ryan P, Reponen T, et al. Breast-feeding, aeroallergen sensitization, and environmental exposures during infancy are determinants of childhood allergic rinitis. J Allergy Clin Immunol 2010; 125:1054–60.
53. Bakke P, Gulsvik A, Eide GE. Hay fever, eczema and urticaria in southwest Norway. Lifetime prevalences and association with sex, age, smoking habits, occupational airborne exposures and respiratory symptoms. Allergy 1990; 45:515–22.
54. Leuenberger P, Schwartz J, Ackermann-Liebrich U, Blaser K, Bolognini G, et al. Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study) Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. Am J Respir Crit Care Med 1994; 150:1222–8.
55. Ng TP, Tan WC. Epidemiology of allergic rhinitis and its associated risk factors in Singapore. Int J Epidemiol 1994; 23:553–8.
56. Moyes CD, Waldon J, Ramadas D, Crane J, Pearce N. Respiratory symptoms and environmental factors in schoolchildren in the Bay of Plenty. N Z Med J 1995; 108:358–61.
57. Wuthrich B, Schindler C, Medici TC, Zellweger JP, Leuenberger P. IgE levels, atopy markers and hay fever in relation to age, sex and smoking status in a normal adult Swiss population. SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) Team. Int Arch Allergy Immunol 1996; 111:396–402.
58. Min Y-G, Jung H-W, Kim HS, Park SK, Yoo KY. Prevalence and risk factors for perennial allergic rhinitis in Korea: results of a nationwide survey. Clin Otolaryngol 1997; 22:139–44.
59. Siracusa A, Marabini A, Sensi L, Bacoccoli R, Ripandelli A, et al. Prevalence of asthma and rhinitis in Perugia, Italy. Monaldi Arch Chest Dis 1997; 52: 434–439.
60. Austin JB, Russell G. Wheeze, cough, atopy, and indoor environment in the Scottish Highlands. Arch Dis Child 1997; 76:22–6.

61. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. Thorax 1998; 53:927–32.
62. Lam TH, Chung SF, Betson CL, Wong CM, Hedley AJ. Respiratory symptoms due to active and passive smoking in junior secondary school students in Hong Kong. Int J Epidemiol 1998; 27:41–8.
63. Ponsonby AL, Couper D, Dwyer T, Carmichael A. Cross sectional study of the relation between sibling number and asthma, hay fever, and eczema. Arch Dis Child 1998; 79:328–33.
64. Montefort S, Lenicker HM, Caruna S, Agius Muscat H. Asthma, rhinitis and eczema in Maltese 13–15 year-old schoolchildren – prevalence, severity and associated factors [ISAAC]. International Study of Asthma and Allergies in Childhood. Clin Exp Allergy 1998; 28:1089–99.
65. Duhme H, Weiland SK, Rudolph P, Wienke A, Kramer A, et al. Asthma and allergies among children in West and East Germany: a comparison between Munster and Greifswald using the ISAAC phase I protocol. International Study of Asthma and Allergies in Childhood. Eur Respir J 1998; 11:840–7.
66. Burr ML, Anderson HR, Austin JB, Harkins LS, Kaur B, et al. Respiratory symptoms and home environment in children: a national survey. Thorax 1999; 54:27–32.
67. Dotterud LK, Falk ES. Atopic disease among adults in northern Russia, an area with heavy air pollution. Acta Derm Venereol 1999; 79:448–50.
68. Keles¸ N, Ilicali C, Deger K. The effects of different levels of air pollution on atopy and symptoms of allergic rhinitis. Am J Rhinol 1999; 13:185–90.
69. Plaschke PP, Janson C, Norrman E, Bjornsson E, Ellbjar S, et al. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. Am J Respir Crit Care Med 2000; 162:920–4.
70. Zacharasiewicz A, Zidek T, Haidinger G, Waldhor T, Vutuc C. Symptoms suggestive of atopic rhinitis in children aged 6–9 years and the indoor environment. Allergy 2000; 55: 945–50.

71. Upton MN, McConnachie A, McSharry C, Hart CL, Smith GD, et al. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. BMJ 2000; 321:88–92.
72. Ozdemir N, Uc¸gun I, Metintas S, Kolsuz M, Metintas M. The prevalence of asthma and allergy among university freshmen in Eskisehir, Turkey. Respir Med 2000; 94:536–41.
73. Hjern A, Hedberg A, Haglund B, Rosén M. Does tobacco smoke prevent atopic disorders? A study of two generations of Swedish residents. Clin Exp Allergy 2001; 31: 908–14.
74. Janson C, Chinn S, Jarvis D, Zock JP, Torén K, et al. Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. Lancet 2001; 358:2103–9.
75. Simpson BM, Custovic A, Simpson A, Hallam CL, Walsh D, et al. NAC Manchester asthma and allergy study (NACMAAS): risk factors for asthma and allergic disorders in adults. Clin Exp Allergy 2001; 31:391–9.
76. Dotterud LK, Odland JO, Falk ES. Atopic diseases among schoolchildren in Nikel, Russia, an Arctic area with heavy air pollution. Acta Derm Venereol 2001; 81:198–201.
77. Kalyoncu AF, Demir AU, Ozcakar B, Bozkurt B, Artvinli M. Asthma and allergy in Turkish university students: Two cross-sectional surveys 5 years apart. Allergol Immunopathol (Madr) 2001; 29:264–71.
78. Lee SI, Shin MH, Lee HB, Lee JS, Son BK, et al. Prevalences of symptoms of asthma and other allergic diseases in Korean children: a nationwide questionnaire survey. J Korean Med Sci 2001; 16:155–64.
79. Stazi MA, Sampogna F, Montagano G, Grandolfo ME, Couilliot MF, et al. Early life factors related to clinical manifestations of atopic disease but not to skin-prick test positivity in young children. Pediatr Allergy Immunol 2002; 13:105–12.

80. Peroni DG, Piacentini GL, Alfonsi L, Zerman L, Di Blasiw P, et al. Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. Clin Exp Allergy 2003; 33:1349–54.
81. Villarreal A, Sanín Aguirre LH, Téllez Rojo MM, Lacasaña Navarro M, Romieu I. Risk factors for asthma in school children from Ciudad Juárez, Chihuahua. J Asthma 2003; 40:413–23.
82. Monteil MA, Joseph G, Chang Kit C, Wheeler G, Antoine RM. Smoking at home is strongly associated with symptoms of asthma and rhinitis in children of primary school age in Trinidad and Tobago. Rev Panam Salud Publica 2004; 16:193–8.
83. Lee SL, Wong W, Lau YL. Increasing prevalence of allergic rhinitis but not asthma among children in Hong Kong from 1995 to 2001 (Phase 3 International Study of Asthma and Allergies in Childhood). Pediatr Allergy Immunol 2004; 15:72–8.
84. Kramer U, Lemmen CH, Behrendt H, Link E, Schafer T, et al. The effect of environmental tobacco smoke on eczema and allergic sensitization in children. Br J Dermatol 2004; 150:111–8.
85. Demir AU, Karakaya G, Bozkurt B, Sekerel BE, Kalyoncu AF. Asthma and allergic diseases in schoolchildren: third cross-sectional survey in the same primary school in Ankara, Turkey. Pediatr Allergy Immunol 2004; 15:531–8.
86. Miyake Y, Yura A, Iki M. Cross-sectional study of allergic disorders in relation to familial factors in Japanese adolescents. Acta Paediatr 2004; 93:380–5.
87. Annesi-Maesano I, Oryszczyn MP, Raherison C, Kopferschmitt C, Pauli G, et al. Increased prevalence of asthma and allied diseases among active adolescent tobacco smokers after controlling for passive smoking exposure. A cause for concern? Clin Exp Allergy 2004; 34:1017–23.
88. De S, Fenton JE, Jones AS, Clarke RW. Passive smoking, allergic rhinitis and nasal obstruction in children. J Laryngol Otol 2005; 119:955–7.

89. Topp R, Thefeld W, Wichmann HE, Heinrich J. The effect of environmental tobacco smoke exposure on allergic sensitization and allergic rhinitis in adults. Indoor Air 2005; 15:222–7.
90. Maziak W, Kenneth D, Ward KD, Rastam S, Mzayek F, et al. Extent of exposure to environmental tobacco smoke (ETS) and its dose-response relation to respiratory health among adults. Respir Res 2005; 6:13.
91. Miyake Y, Miyamoto S, Ohya Y, Sasaki S, Matsunaga I, et al. Association of active and passive smoking with allergic disorders in pregnant Japanese women: baseline data from the Osaka Maternal and Child Health Study. Ann Allergy Asthma Immunol 2005; 94:644–51.
92. Bugiani M, Carosso A, Migliore E, Piccioni P, Corsico A, et al. ISAYA (ECRHS Italy) Study Group. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. Allergy 2005; 60:165–70.
93. Obihara CC, Marais BJ, Gie RP, Potter P, Bateman ED, et al. The association of prolonged breastfeeding and allergic disease in poor urban children. Eur Respir J 2005; 25:970–7.
94. Strumylaite L, Kregzdyte R, Vaitkaitiene E. Pasyvus rukymas ir vaiku kvepavimo sutrikimai [Passive smoking and respiratory health of children]. Medicina (Kaunas) 2005; 41:348–54.
95. Lund VJ, Preziosi P, Hercberg S, Hamoir M, Dubreuil C, et al. Yearly incidence of rhinitis, nasal bleeding, and other nasal symptoms in mature women. Rhinology 2006; 44:26–31.
96. Kurosaka F, Nakatani Y, Terada T, Tanaka A, Ikeuchi H, et al. Current cat ownership may be associated with the lower prevalence of atopic dermatitis, allergic rhinitis, and Japanese cedar pollinosis in schoolchildren in Himeji, Japan. Pediatr Allergy Immunol 2006; 17:22–8.
97. Sakar A, Yorgancioglu A, Dinc G, Yuksel H, Celik P, et al. The prevalence of asthma and allergic symptoms in Manisa, Turkey (A western city from a country bridging Asia and Europe). Asian Pac J Allergy Immunol 2006; 24:17–25.

98. Ho SY, Lam TH, Chung SF, Lam TP. Cross-sectional and prospective associations between passive smoking and respiratory symptoms at the workplace. Ann Epidemiol 2007; 17:126–31.
99. Horak E, Morassa B, Ulmerb H. Association between environmental tobacco smoke exposure and wheezing disorders in Austrian preschool children. Swiss Med Wkly 2007; 137:608–13.
100. Ebbert JO, Croghan IT, Schroeder DR, Murawski J, Hurt RD. Association between respiratory tract diseases and secondhand smoke exposure among never smoking flight attendants: a cross-sectional survey. Environ Health 2007; 6:28.
101. Tanaka K, Miyake Y, Arakawa M, Sasaki S, Ohya Y. Prevalence of asthma and wheeze in relation to passive smoking in Japanese children. Ann Epidemiol 2007; 17:1004–10.
102. Zuraimi MS, Tham KW, Chew FT, Ooi PL, David K. Home exposures to environmental tobacco smoke and allergic symptoms among young children in Singapore. Int Arch Allergy Immunol 2008; 146:57–65.
103. Foliaki S, Annesi-Maesano I, Tuuau-Potoi N, Waqatakirewa L, Cheng S, et al. Risk factors for symptoms of childhood asthma, allergic rhinoconjunctivitis and eczema in the Pacific: an ISAAC Phase III study. Int J Tuberc Lung Dis 2008; 12:799–80.
104. Gómez R, Teijeiro A, Zernotti M, Canonica G, Mimessi G, et al. Smoking is a risk factor for having rhinitis in adolescents. Allergy 2008; 63:419.
105. Kabir Z, Manning PJ, Holohan J, Keogan S, Goodman PG, et al. Second-hand smoke exposure in cars and respiratory health effects in children. Eur Respir J 2009; 34:629–33.
106. Brescianini S, Brunetto B, Iacovacci P, D'Ippolito C, Alberti G, et al. Prevalence of self-perceived allergic diseases and risk factors in Italian adolescents. Pediatr Allergy Immunol 2009; 20:578–84.
107. Musharrafieh U, Al-Sahab B, Zaitoun F, El-Hajj MA, Ramadan F, et al. Prevalence of asthma, allergic rhinitis and eczema among Lebanese adolescents. J Asthma 2009; 46:382–7.

108. González-Díaz SN, Del Río-Navarro BE, Pietropaolo-Cienfuegos DR, Escalante-Domínguez AJ, García-Almaraz RG, et al. Factors associated with allergic rhinitis in children and adolescents from northern Mexico: International Study of Asthma and Allergies in Childhood Phase IIIB. Allergy Asthma Proc 2010; 31:53–62.
109. Bedolla-Barajas M, Cuevas-Ríos G, García-Barboza E, Barrera-Zepeda AT, Morales-Romero J. Prevalencia y factores asociados a la rinitis alérgica en escolares de Ciudad Guzmán, Mexico. [Prevalence and factors associated to allergic rhinitis among schoolchildren of Ciudad Guzmán, Mexico] Rev Invest Clin 2010; 62:244–51.
110. Wang HY, Pizzichini MM, Becker AB, Duncan JM, Ferguson AC, et al. Disparate geographic prevalences of asthma, allergic rhinoconjunctivitis and atopic eczema among adolescents in five Canadian cities. Pediatr Allergy Immunol 2010; 21:867–77.
111. Vlaski E, Stavric K, Seckova L, Kimovska M, Isjanovska R. Do household tobacco smoking habits influence asthma, rhinitis and eczema among 13–14 year-old adolescents? Allergol Immunopathol 2011; 39:39–44.
112. Virkkula P, Liukkonen K, Suomalainen AK, Aronen ET, Kirjavainen T, et al. Parental smoking, nasal resistance and rhinitis in children. Acta Paediatr 2011; 100:1234–8.
113. Hakansson K, von Buchwald C, Thomsen SF, Thyssen JP, Backer V, et al. Nonallergic rhinitis and its association with smoking and lower airway disease: a general population study. Am J Rhinol Allergy 2011; 25:25–9.
114. Chen BY, Chan CC, Han YY, Wu HP, Guo YL. The risk factors and quality of life in children with allergic rhinitis in relation to seasonal attack patterns. Paediatr Perinat Epidemiol 2012; 26:146–55.
115. Peñaranda A, Aristizabal G, Garcia E, Vasquez C, Rodriguez-Martinez CE, et al. Allergic rhinitis and associated factors in schoolchildren from Bogota, Colombia. Rhinology 2012; 50:122–8.

116. Tanaka K, Miyake Y, Arakawa M. Smoking and prevalence of allergic disorders in Japanese pregnant women: baseline data from the Kyushu Okinawa Maternal and Child Health Study. Environ Health 2012; 11:15.
117. Montefort S, Ellul P, Montefort M, Caruana S, Grech V, et al. The effect of cigarette smoking on allergic conditions in Maltese children (ISAAC). Pediatr Allergy Immunol 2012; 23: 472–8.
118. Mitchell EA, Beasley R, Keil U, Montefort S, Odhiambo J, et al. 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.
119. The Global Youth Tobacco Survey Collaborative Group. Tobacco use among youth: a cross country comparison. Tob Control 2002; 11:252–70.
120. King K, Martynenko M, Bergman MH, Liu YH, Winickoff JP, et al. Family composition and children's exposure to adult smokers in their homes. Pediatrics 2009; 123:e559–64.
121. Centers for Disease Control and Prevention. Exposure to secondhand smoke among students aged 13–15 years-worldwide, 2000–2007. MMWR 2007; 56:497–500.
122. Rothman KJ. Modern epidemiology. Boston: Little, Brown and Co. 1986; p.39.
123. US Department of Health and Human Services. Children and secondhand smoke exposure. Excerpts from The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2007.
124. US Department of Health and Human Services. The Health Consequences of Involuntary Smoking. A Report of the Surgeon General. Rockville (Maryland): US Department of Health and Human

Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health, 1986.

125. Pérez-Ríos M, Schiaffino A, López MJ, Nebot M, Galán I, et al. Questionnaire-based second-hand smoke assessment in adults. Eur J Public Health 2013; 23: 763–767.
126. Wahn U. What drives the allergic march? Allergy 2000; 55:591–9.

3.1.6. ANNEXES

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Annex I. Quality scoring of the allergic rhinitis studies

Criteria:

1. Smoking definition:
   Duration – duration of smoking considered
   "or"
   Number of cigarettes smoked (usually per day/per year)

2. Determination of allergic rhinitis well defined, with one of these:
   -SKP "or"
   - IgE "or"
   - Medical diagnosis

3. Adjusted for:
   - Sex
   - Age and
   - Any other

4. Participation rate ≥ 80%

5. Target population clearly defined

Abbreviations:
AS – active smoking
SHS – second hand smoking
SHS in Utero – mothers smoking during pregnancy
SHS + in Utero – second hand smoking + mothers smoking during pregnancy

Annex I. Quality scoring of allergic rhinitis studies

Nº	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE (max 5)
I. Case-control studies								
1	Ozasa K (1995)	AS SHS	-Duration=0 -Nº=1 1	-SPT =0 - IgE=1 - Being positive of eosinophils in nasal discharge or positive to nasal provocation test..=1 1	- sex=0 - age=1 -any other=0 0	Unknown 0	Simply a convenience sample as for instance patients of a consultation 0	2
2	Cakir E (2010)	AS SHS	-Duration=0 -Nº=1 1	-SPT =0 - IgE=0 (ISAAC) 0	- sex=1 - age=1 -any other=1 1	Not specified 0	Working adolescents 0	2
3	Lin SY (2011)	SHS	-Duration=1 -Nº=0 1	-SPT=0 - IgE=0 0	- sex=1 - age=1 -any other=1 1	35% 0	Cohort of nonsmokers in Washington country 1	3
4	Miyake Y (2011)	AS Women only	-Duration=0 -Nº=0 0	-SPT=0 - IgE=0 0	- sex=1 - age=0 -any other=0 0	84,9% 1	All pregnant women in the hospitals 1	2

Annex I. Cont.

Nº	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
	II. Cohort studies							
1	Wright AL (1994)	SHS	-Duration=0 -Nº=1 **1**	-SPT =1 - IgE=1 **1**	- sex=0 - age=0 -any other=0 **0**	77% **0**	From Tucson Children Resp. survey **1**	**3**
2	Annesi-Maesano (1997)	AS (men only)	-Duration=0 -Nº=1 **1**	-SPT =0 - IgE=0 **0**	- sex=0 - age=1 -any other=0 **0**	65% **0**	All police officers **0**	**1**
3	Lewis SA (1998)	SHS SHS in Utero	-Duration=0 -Nº=1 **1**	-SPT =0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	69% (5-10years) 54% (16years) **0**	British Birth Cohort: all children **1**	**3**
4	Shaheen SO (1999)	AS SHS in Utero	-Duration=0 -Nº=1 **1**	-SPT =0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	66% **0**	British Birth Cohort: all children **1**	**3**
5	Bergmann (2000)	SHS	-Duration=0 -Nº=0 **0**	-SPT =0 - IgE=1 **1**	- sex=1 - age=1 -any other=1 **1**	17.3% (67.0%after follow-up) **0**	Germany Birth Cohort **1**	**3**
6	Tariq (2000)	SHS SHS in utero	-Duration=0 -Nº=0 **0**	-SPT =0 - IgE=0 **0**	- sex=0 - age=1 -any other=0 **0**	79.3% **0**	All newborns in certain period **1**	**1**

Annex I. Cont.

Nº	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
7	McKeever TM (2001)	SHS	-Duration=0 -Nº=1 **1**	-SPT =0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	Not specified **0**	Historical Birth Cohort of West Midland **1**	**3**
8	Magnusson LL (2005)	SHS SHS in Utero SHS + in Utero	-Duration=0 -Nº=1 **1**	-SPT =0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	74% **0**	All pregnant women during period **1**	**2**
9	Johansson AK (2008)	SHS SHS in Utero	-Duration=0 -Nº=0 **0**	-SPT =0 - IgE=0 **0**	- sex=0 - age=1 -any other=1 **0**	51,9 % **0**	- All babies in South west Sweden **1**	**1**
10	Nagata C (2008)	AS	-Duration=1 -Nº=1 **1**	-SPT =0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	82% **1**	From population based cohort study **1**	**4**
11	Bendtsen P (2008)	AS (female only)	-Duration=0 -Nº=1 **1**	-SPT =0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	87% **1**	randomly sampled general female population **1**	**4**
12	Keil T (2009)	SHS + in Utero	-Duration=0 -Nº=0 - Cotinine level in blood serum **1**	-SPT =0 - IgE=0 (ISAAC) **0**	- sex=1 - age=1 -any other=1 **1**	73% **0**	Germany Birth Cohort **1**	**3**

Annex I. Cont.

Nº	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
13	Codispoti CD (2010)	SHS	-Duration=0 -Nº=1 **1**	-SPT =1 - IgE=0 -(Examination) **1**	- sex=0 - age=1 -any other=1 **0**	Not specified **0**	CCAAPS cohort **1**	**3**
	III. Cross-Sectional Studies							
1	Bakke P (1990)	AS	-Duration=0 -Nº=0 **0**	I phase: -SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	I-90% II-86% **1**	Population comprised **1**	**3**
2	Leuenberger P (1994)	SHS	-Duration=0 -Nº=1 **1**	-SPT=0 - IgE=1 **1**	- sex=0 - age=0 -any other=0 **0**	80% **1**	(SPALDIA) A random selection of adults from 8 representative cities of Switzerland **1**	**4**
3	Ng TP (1994)	AS	-Duration=0 -Nº=1 **1**	-SPT=1 - IgE=0 **1**	- sex=0 - age=1 -any other=1 **0**	72.8% **0**	A stratified two-stage cluster disproportionate sampling **1**	**3**
4	Moyes CD (1995)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	85% **1**	All schools **1**	**2**
5	Wutrich B (1996)	AS	-Duration=0 -Nº=0 **0**	-SPT=1 - IgE=1 **1**	- sex=1 - age=1 -any other=1 **1**	Not specified **0**	(SPALDIA) Subjects from the 8 study areas **0**	**2**

Annex I. Cont.

Nº	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
6	Min Y –G (1997)	AS	-Duration=0 -Nº=0 **0**	-SPT=1 - IgE=0 **1**	- sex=0 - age=1 -any other=0 **0**	90,2% **1**	Multi-stage cluster-stratified randomly selected subjects from 60 districts throughout the country **1**	**3**
7	Siracusa A (1997)	AS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	61% **0**	A randomized sample from the National Health Service list of all Perugia area **1**	**2**
8	Austin JB (1997)	SHS SHS in Utero	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=1 -any other=0 **0**	85% **1**	Children attending secondary schools (Ref 3) **1**	**2**
9	Farooqi IS (1998)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	36,7% **0**	Oxford shire general practice cohort **0**	**0**
10	Lam TH (1998)	AS SHS	-Duration=0 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	96% **1**	Randomly selected classes from randomly selected schools **1**	**4**
11	Ponsonby A-L (1998)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	89% **1**	All schools, home learning & distance education organizations **0**	**1**
12	Montefort S (1998)	AS SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	88,7% **1**	randomly selected schools of Malta and Gozo **0**	**2**

Annex I. Cont.

Nº	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
13	Duhme H (1998)	AS SHS	-Duration=1 -Nº=0 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=0 **0**	81,2% & 85,9% **1**	All schools in each region, with all children target **1**	**3**
14	Burr ML (1999)	AS SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	79,3% **0**	ISAAC. Randomly selected schools of each region **1**	**2**
15	Dotterud 1999	AS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	Nickel(Russia)-93,6% **1**	**0**	**1**
16	Keles N (1999)	AS SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	Not specified **0**	2 schools from different polluted areas **1**	**2**
17	Plaschke PP (2000)	AS	-Duration=0 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	86% **1**	ECRH: random sample of the general population from 3 areas of Sweden **1**	**4**
18	Zacharasiewicz A (2000)	SHS SHS in Utero	-Duration=0 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	63,7% **0**	**1**	**3**
19	Upton MN (2000)	AS	-Duration=0 -Nº=0 **0**	-SPT=1 - IgE=0 **1**	- sex=0 - age=1 -any other=0 **0**	78% **0**	All residents of 2 cities of west Scotland **1**	**2**

Annex I. Cont.

Nº	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
20	Ozdemir N (2000)	AS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=1 -any other=0 **0**	94,5% **1**	Newly enrolled university freshman **0**	**1**
21 a	Hjern A (2001a)	SHS	-Duration=0 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	80% **1**	Simple random sample **1**	**4**
21 b	Hjern A (2001b)	AS	-Duration=0 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	80% **1**	Simple random sample **1**	**4**
22	Janson C (2001)	SHS	-Duration=1 -Nº=0 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	Not specified **0**	Randomly selected persons of the same sex and age in the different centers (36 centers in 16 countries) **1**	**3**
23	Simpson BM (2001)	AS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=1 **1**	- sex=1 - age=0 -any other=1 **0**	Not specified **0**	All pregnant women attending two hospitals **1**	**2**
24	Dotterud LK (2001)	AS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	Nickel(Russia)-93,6% **1**	**0**	**2**
25	Kalyoncu (2001)	AS, SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	85.8% **1**	**1**	**3**

Annex I. Cont.

Nº	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
26	Lee SII (2001)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	90.8% **1**	Random sample of elementary and middle school **1**	**3**
27	Stazi M-A (2002)	SHS	-Duration=0 -Nº=0 -(Carbon Monohydrate assessment=1) **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=0 **0**	95% **1**	Sample from the vaccination center of a rural zone **0**	**2**
28	Peroni DG (2003)	SHS	-Duration=0 -Nº=0 **0**	-SPT=1 - IgE=0 **1**	- sex=1 - age=1 -any other=1 **1**	92% **1**	Randomly selected 18 nursery schools in Verone (Italy) **1**	**4**
29	Barraza Villarreal A (2003)	SHS SHS in Utero	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	92% **1**	The city divided into 3 areas according to pollution – schools **1**	**2**
30	Monteil MA (2004)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	50,2% & 47,5% **0**	Randomly selected 20% cities **1**	**1**
31	Lee S-L (2004)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	95% **1**	Random selected schools in Hong Kong **1**	**3**
32	Kramer U(2004)	SHS	-Duration=0 -Nº=0 -Cotinine spot in the urine sample=1 **1**	-SPT=1 - IgE=0 **1**	- sex=1 - age=1 -any other=1 **1**	68% **0**	Children registered for admission to school in one year **1**	**4**

Annex I. Cont.

№	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
33	Demir AU (2004)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	85% **1**	1 school **0**	**1**
34	Miyake Y (2004)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	61% **0**	All schools in the region **1**	**2**
35	A-Maesano I (2004)	AS SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=0 -any other=1 **0**	82% **1**	School children from five different centers **1**	**2**
36	De S (2005)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 - Med.diagn.=1 **0**	- sex=0 - age=0 -any other=0 **0**	Not specified **0**	Children from outpatient department **0**	**0**
37	Topp R (2005)	SHS	-Duration=0 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	84,7% **1**	The data from German National Health Interview and Examination Survey **1**	**4**
38	Maziak W (2005)	SHS	-Duration=1 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	86% **1**	Stratified cluster sampling, with randomly selection **1**	**4**
39	Miyake Y (2005)	AS SHS (women)	-Duration=1 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age= 1 -any other=1 **1**	17,2% **0**	Women, who become pregnant in one city during 3 years **1**	**3**

Annex I. Cont.

№	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
40	Bugiani M (2005)	AS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	75% **0**	Random sample of adult general population of 5 cities in Italy **1**	**1**
41	Obihara CC (2005)	SHS in Utero	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	88% **1**	15% of randomly selected houses in the area **1**	**3**
42	Strumylaite 2005	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=1 -any other=0 **0**	58.6%-69.2% **0**	20 kindergarten of Kaunas city **0**	**0**
43	Lund VJ (2006)	AS SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=0 **0**	Not specified **0**	**1**	**1**
44	Kurosaka F (2006)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=0 -any other=1 **0**	99% & 99,3% **1**	58 primary schools of Himeji (Japan) **1**	**2**
45	Sakar 2006	AS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	88.8% **1**	Household records of the 9 health centers of Manisa city **1**	2
46	Sai Yin Ho (2007)	SHS	-Duration=1 -Nº=0 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	64,7% & 61,2% (stage II-64,9%) **0**	Randomly selected telephone Nº **1**	**3**

Annex I. Cont.

№	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
47	Horak E (2007)	SHS SHS in Utero	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	42% **0**	Randomly selected 100 kinder gardens (out of 435 in Tyrol(Austria) **1**	**2**
48	Ebbert JO (2007)	SHS	-Duration=1 -Nº=0 **1**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	6,7% **0**	Subjects from member database of Flight Attendants **1**	**2**
49	Tanaka K (2007)	SHS	-Duration=0 -Nº=1 **1**	-SPT=1 - IgE=1 **1**	- sex=1 - age=1 -any other=1 **1**	60,3% **0**	All schools **1**	**4**
50	Zuraimi MS (2007)	SHS	-Duration=0 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	70% **0**	Randomly selected child care centers(18%) in Singapore **1**	**3**
51	Foliaki S (2008)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	(Results of 8 distinct countries) **0**	8 Pacific countries **0**	**1**
52	Gomez R (2008)	AS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	Not specified **0**	**1**	**1**
53	Kabir Z (2009)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=0 -any other=1 **0**	90% **1**	Stratified random sampling of schools **1**	**2**

Annex I. Cont.

Nº	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
54	Brescianini S (2009)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	Not specified **0**	Children from 3 schools **0**	**1**
55	Musharrafieh U (2009)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	Not specified **0**	Random sample of 55 schools and only 13 agreed to participate **0**	**1**
56	Gonzalez-Diaz SN (2010)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	92% **1**	All schools in three cities of Mexico **1**	**2**
57	Bedolla-Barajas M (2010)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	6,5% **0**	Muestreo probabilístico estratificado y por conglomerados **1**	**1**
58	Wang H-Y (2010)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	97,6% **1**	Randomly selected schools from each region **1**	**3**
59	Vlaski E (2010)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	90.9% **1**	17 randomly selected schools in the region **1**	**3**
60	Virkkula P (2011)	SHS	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=1 **1**	- sex=0 - age=1 -any other=0 **0**	71,8% **0**	A random sample from the children register, which were divided into snorers and non-snorers as a controls **1**	**2**

Annex I. Cont.

№	Author (Year)	OR calculated	1. Smoking well defined	2. AR diagnosis well defined	3. Full adjustment	4. Participation rate ≥80%	5. Clearly defined target population	TOTAL SCORE
61	Hakansson K (2011)	AS	-Duration=0 -Nº=1 **1**	-SPT=0 - IgE=1 **1**	- sex=1 - age=1 -any other=0 **0**	80% **1**	Random sample of subjects invited to health examination **1**	**4**
62	Chen (2012)	SHS in Utero	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=0 -any other=0 **0**	74.5% (48.5%) **0**	3 elementary and 2 middle schools **1**	**1**
63	Peñaranda (2012)	SHS (6-7years) AS (13-14years)	-Duration=0 -Nº=0 **0**	-SPT=0 - IgE=0 **0**	- sex=0 - age=1 -any other=1 **0**	89.5% & 98.7% **1**	Randomly selected 74 (for 6-7years) and 48 (for 13-14 years) schools **1**	**2**
64	Tanaka K (2012) ISAAC q	AS Women only	-Duration=1 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	99.2% **1**	423 obstetric hospitals **1**	**4**
65	Montefort (2012) ISAAC III	AS SHS	-Duration=1 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=0 - age=1 -any other=0 **0**	80% (5-8year) 90% (13-15year) **1**	All state primary schools in Malta and Gozo were randomly Chosen(44+18 schools) **1**	**3**
66	Mitchell (2012) ISAACIII	SHS	-Duration=0 -Nº=1 **1**	-SPT=0 - IgE=0 **0**	- sex=1 - age=1 -any other=1 **1**	Not specified **0**	Random sample of schools **1**	**3**

Annex II.

Copy of the article **"Active or passive exposure to tobacco smoking and allergic rhinitis, allergic dermatitis, and food allergy in adults and children: a systematic review and meta-analysis"**, published in the journal *PLOS Medicine.*

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Active or Passive Exposure to Tobacco Smoking and Allergic Rhinitis, Allergic Dermatitis, and Food Allergy in Adults and Children: A Systematic Review and Meta-Analysis

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Abstract

Background: Allergic rhinitis, allergic dermatitis, and food allergy are extremely common diseases, especially among children, and are frequently associated to each other and to asthma. Smoking is a potential risk factor for these conditions, but so far, results from individual studies have been conflicting. The objective of this study was to examine the evidence for an association between active smoking (AS) or passive exposure to secondhand smoke and allergic conditions.

Methods and Findings: We retrieved studies published in any language up to June 30th, 2013 by systematically searching Medline, Embase, the five regional bibliographic databases of the World Health Organization, and ISI-Proceedings databases, by manually examining the references of the original articles and reviews retrieved, and by establishing personal contact with clinical researchers. We included cohort, case-control, and cross-sectional studies reporting odds ratio (OR) or relative risk (RR) estimates and confidence intervals of smoking and allergic conditions, first among the general population and then among children. We retrieved 97 studies on allergic rhinitis, 91 on allergic dermatitis, and eight on food allergy published in 139 different articles. When all studies were analyzed together (showing random effects model results and pooled ORs expressed as RR), allergic rhinitis was not associated with active smoking (pooled RR, 1.02 [95% CI 0.92–1.15]), but was associated with passive smoking (pooled RR 1.10 [95% CI 1.06–1.15]). Allergic dermatitis was associated with both active (pooled RR, 1.21 [95% CI 1.14–1.29]) and passive smoking (pooled RR, 1.07 [95% CI 1.03–1.12]). In children and adolescent, allergic rhinitis was associated with active (pooled RR, 1.40 (95% CI 1.24–1.59) and passive smoking (pooled RR, 1.09 [95% CI 1.04–1.14]). Allergic dermatitis was associated with active (pooled RR, 1.36 [95% CI 1.17–1.46]) and passive smoking (pooled RR, 1.06 [95% CI 1.01–1.11]). Food allergy was associated with SHS (1.43 [1.12–1.83]) when cohort studies only were examined, but not when all studies were combined. The findings are limited by the potential for confounding and bias given that most of the individual studies used a cross-sectional design. Furthermore, the studies showed a high degree of heterogeneity and the exposure and outcome measures were assessed by self-report, which may increase the potential for misclassification.

Conclusions: We observed very modest associations between smoking and some allergic diseases among adults. Among children and adolescents, both active and passive exposure to SHS were associated with a modest increased risk for allergic diseases, and passive smoking was associated with an increased risk for food allergy. Additional studies with detailed measurement of exposure and better case definition are needed to further explore the role of smoking in allergic diseases.

Please see later in the article for the Editors' Summary.

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Abbreviations: AS, active smoking; IgE, immunoglobulin-E; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; RR, relative risk; SHS, secondhand smoke; SPT, skin prick test.

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Introduction

Allergic rhinitis, allergic dermatitis, and food allergy, in addition to asthma, are extremely common diseases worldwide. Indeed, allergic rhinitis affects 10% to 20% of the general population in Europe and the US [1,2] and up to 40% of children [3]. The prevalence of allergy to any food varies between 3% and 35% [4], while that of allergic dermatitis reaches 20% in many countries [5]. These diseases have profound consequences on the patient's quality of life and imply a high cost both to the patient and insurance providers [6,7]. Among infants, these costs reach more than US$4,000 per year per case of food allergy [8].

Recent studies have suggested that these diseases are but one unique set of immunoglobulin-E (IgE)-mediated allergic conditions, linked by the common thread of "atopic march" [9]. This concept postulates that those conditions are a continuous state that starts with dermatitis and food allergy and eventually progresses to asthma and allergic rhinitis. Indeed, these diseases often co-exist in the same patient and can predict the occurrence of each other [10].

Worldwide, the prevalence of allergic diseases has increased substantially in the last few decades [11,12], which may have two explanations. On the one hand, increased clinician awareness, as well as patient and parental awareness, may have led to improved identification and increased case presentation to physicians [12]. On the other hand, it is possible that this increase is due to changing exposure to known and unknown risk factors [13], and among these factors, smoking may play a role. An increased risk of allergic diseases among individuals exposed to tobacco smoke is biologically plausible as smoking is known to facilitate sensitization to perennial indoor allergens, such as those caused by furry animals, as well as to some outdoor allergens such as pollen [14].

Increased risk of food allergy among infants exposed to tobacco smoke is also plausible. Food allergens are likely to be found in house dust. Swallowed foods are also inhaled or aspirated by infants, and thus, may cause sensitization that could be facilitated by exposure to tobacco smoke. The early and simultaneous exposure to tobacco smoke and food allergens may interfere with

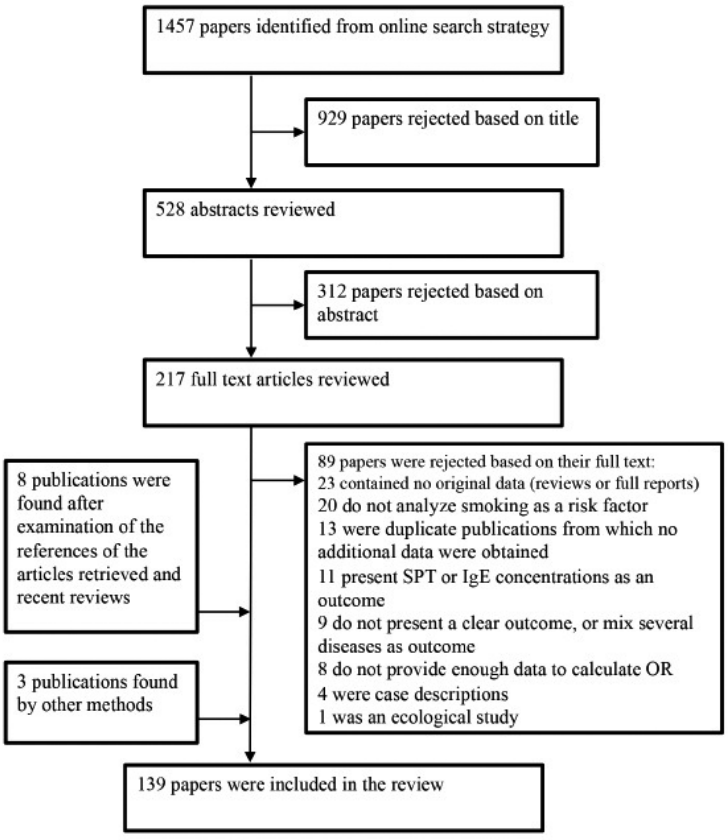

Figure 1. Flow diagram for study selection.
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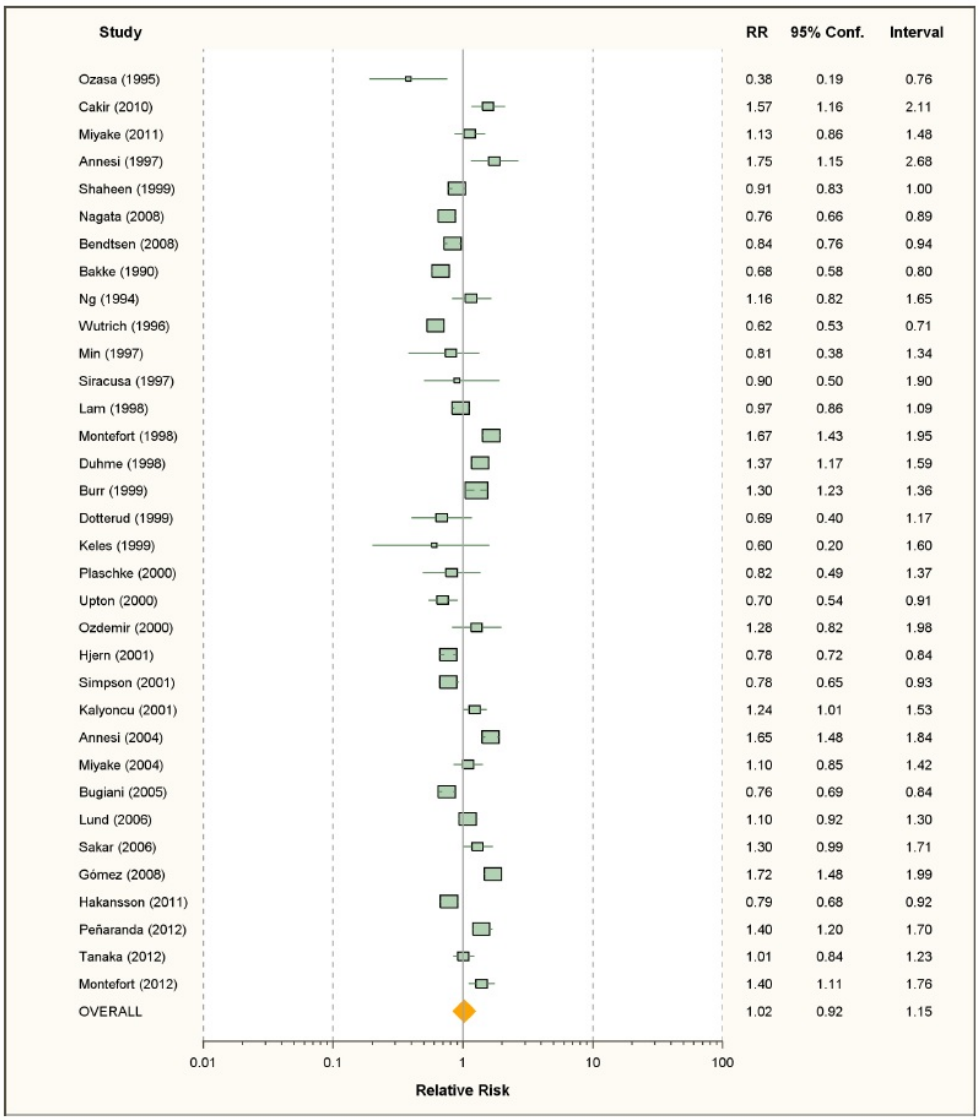

Figure 2. Study-specific and random effects pooled relative risks of active smoking and allergic rhinitis.
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the normal development of immunologic tolerance and thus, facilitate sensitization to food [14].

Furthermore, smoking augments nasal responses to allergen in atopic subjects and increases IgE, immunoglobulin G4 (IgG4), and postallergen histamine levels in nasal lavage fluid [15,16].

Allergic conditions are, in general, more prevalent in children. A potential effect of smoking would have a considerable impact on public health due to the frequency of exposure worldwide. Indeed, children and adolescents are exposed to secondhand smoke in a proportion that varies between 27.6% in Africa and 77.8% in

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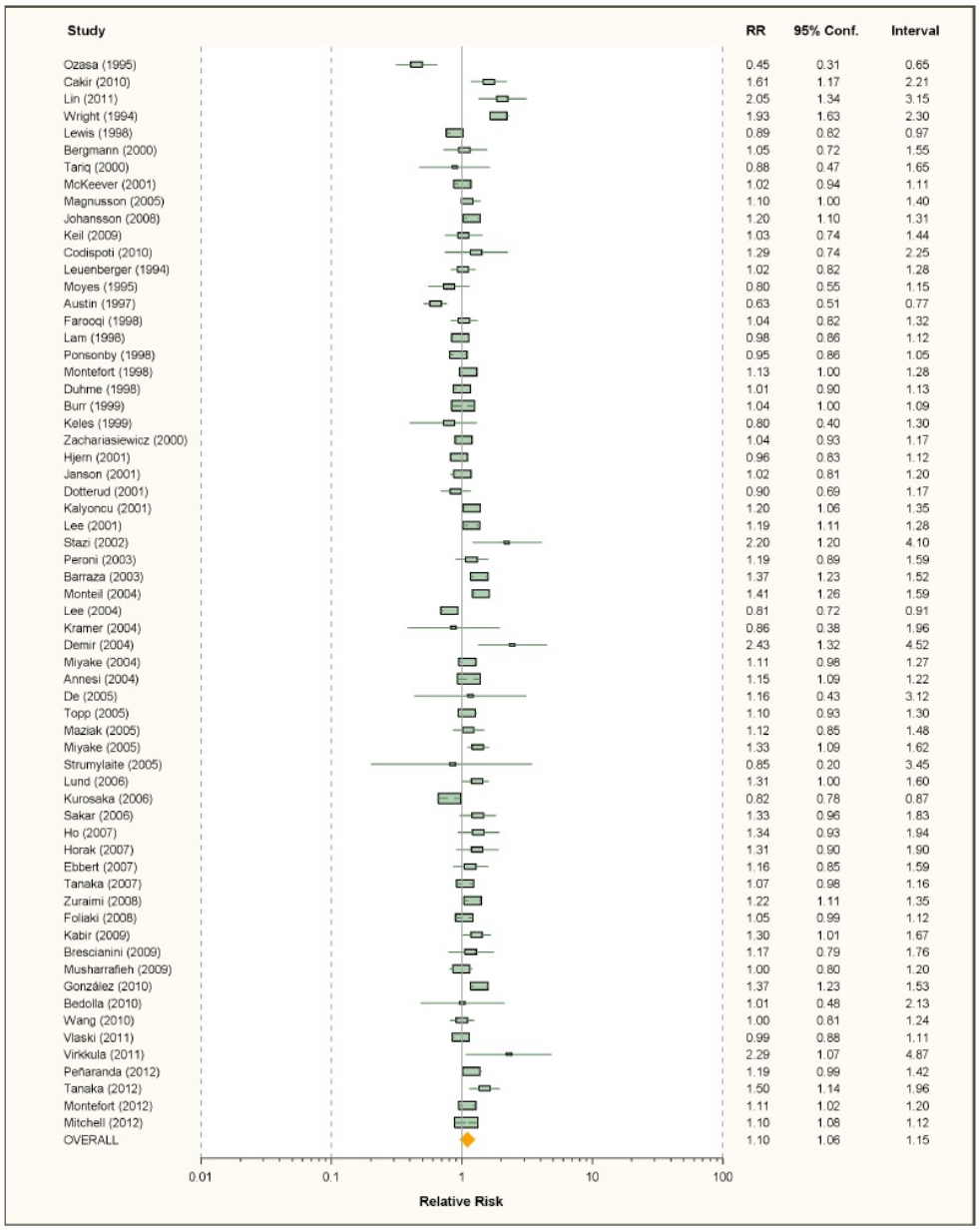

Figure 3. Study-specific and random effects pooled relative risks of passive smoking and allergic rhinitis.
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Table 1. Relative risks and 95% confidence intervals of allergic rhinitis by smoking exposure in case-control and cohort studies.

Source	Country	Population	Follow-up (y)	Complete Follow-up (%)	Active Smoking	Passive Smoking	Cases/Controls or Cohort Size	Variables of Adjustment, Matching, or Restriction
Case-control studies								
Ozasa 1995 [39]	Japan	Adults	—	—	0.38 (0.19–0.76)	0.45 (0.31–0.65)	89/89	Age
Cakir 2010 [19]	Turkey	Adolescents	—	—	1.57 (1.16–2.11)	1.61 (1.17–2.21)	436/366	Age, sex, family atopy, pets, income, occupation
Lin 2011 [40]	USA	Adults	—	—	—	2.05 (1.34–3.15)	83/117	Age, sex, education
Miyake 2011 [41]	Japan	Adult women	—	—	1.13 (0.86–1.48)	—	393/767	Sex
Cohort studies								
Wright 1994 [42]	USA	Children	6	76.8	—	1.93 (1.63–2.30)	311/747	Not specified
Annesi-Maesano 1997 [43]	France	Adult men	5	49	1.75 (1.15–2.68)	—	126/191	Sex
Lewis 1998 [44]	UK	Children	16	55	—	0.89 (0.82–0.97)	1,646/6,281	Age, sex, social class, low birth weight, gestational age, breast feeding, maternal age, parity
Shaheen 1999 [45]	UK	Young adults	26	51.1	0.91 (0.83–1.00)	—	?/6,420	Age, sex, birth weight, social class, siblings, education, height, body mass index
Bergmann 2000 [46]	Germany	Children	6	75	—	1.05 (0.72–1.55)	178/825	Age, sex, parental atopy, socioeconomic status, breast feeding, aeroallergen and food sensitivity, study center
Tariq 2000 [47]	UK	Children	4	79.3	—	0.88 (0.47–1.65)	65/1218	Age
McKeever 2001 [24]	UK	Children	11	95	—	1.02 (0.94–1.11)	1,113/29,238	Age, sex, family atopy, siblings
Magnusson 2005 [48]	Denmark	Children	18	74	—	1.1 (1.0–1.4)	1,083/7,844	Sex, social class, occupation, maternal age in pregnancy, coffee consumption, parity, breastfeeding
Johansson 2008 [49]	Sweden	Children	3	51.9	—	1.20 (1.10–1.31)	?/8,850	Age, mothers' education, family type
Nagata 2008 [50]	Japan	Adults	10	81.6	0.76 (0.66–0.89)	—	1,000/12,221	Age, sex, marital status, education, body mass index, farming, alcohol
Bendtsen 2008 [21]	Denmark	Adult women	9	87	0.84 (0.76–0.94)	—	1,354/5,870	Age, sex, education, alcohol, parental asthma
Keil 2009 [51]	Germany	Children	10	73	—	1.03 (0.74–1.44)	198/784	Age, sex, birth weight, breast feeding, siblings, pets, parental education, IgE, location
Codispoti 2010 [52]	USA	High risk children	2	?	—	1.29 (0.74–2.25)	116/361	Age, parental allergies

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Table 2. Relative risks and 95% confidence intervals of allergic rhinitis by smoking exposure in cross-sectional studies.

Source	Country	Population	Active Smoking	Passive Smoking	Study Size	Variables of Adjustment, Matching, or Restriction
Bakke 1990 [53]	Norway	Adolescents and adults	0.68 (0.58–0.80)	—	4,270	Age, sex, occupational exposure, residence
Leuenberger 1994 [54]	Switzerland	Adults	—	1.02 (0.82–1.28)	3,494	Not specified
Ng 1994 [55]	Singapore	Adults	1.16 (0.82–1.65)	—	2,868	Age, race, housing, cockroaches, occupation, fumes
Moyes 1995 [56]	New Zealand	Schoolchildren	—	0.80 (0.55–1.15)	5,360	Age
Wutrich 1996 [57]	Switzerland	Adults	0.62 (0.53–0.71)	—	8,344	Age, sex, location
Min 1997 [58]	Korea	Children and adults	0.81 (0.38–1.34)	—	8,853	Age
Siracusa 1997 [59]	Italy	Children and adults	0.9 (0.5–1.9)	—	824	Age, sex, allergens
Austin 1997 [60]	UK	Children	—	0.63 (0.51–0.77)	1,537	Age
Farooqi 1998 [61]	UK	Children	—	1.04 (0.82–1.32)	1,934	Not specified
Lam 1998 [62]	Hong Kong	Schoolchildren	0.97 (0.86–1.09)	0.98 (0.86–1.12)	6,304	Age, sex, residence, housing
Ponsonby 1998 [63]	Australia	Children	—	0.95 (0.86–1.05)	6,378	Age
Montefort 1998 [64]	Malta	Schoolchildren	1.67 (1.43–1.95)	1.13 (1.0–1.28)	4,184	Age, sex, road, pets, parental atopy, blankets
Duhme 1998 [65]	Germany	Schoolchildren	1.37 (1.17–1.59)	1.01 (0.90–1.13)	13,123	Age, sex
Burr 1999 [66]	UK	Schoolchildren	1.30 (1.23–1.36)	1.04 (1.00–1.09)	25,393	Age, sex, location, residence, pets, cooking and heating fuel, housing
Dotterud 1999 [67]	Russia	Adults	0.69 (0.40–1.17)	—	3,368	Not specified
Keles 1999 [68]	Turkey	Adolescents	0.6 (0.2–1.6)	0.8 (0.4–1.3)	386	Age, sex, heating, location
Plaschke 2000 [69]	Sweden	Adults	0.82 (0.49–1.37)	—	1,370	Age, sex, location, pets, allergens
Zacharasiewicz 2000 [70]	Austria	Children	—	1.04 (0.93–1.17)	18,606	Age, sex, family history of hay fever, education
Upton 2000 [71]	UK	Adults	0.70 (0.54–0.91)	—	2,832	Age
Ozdemir 2000 [72]	Turkey	University freshmen	1.28 (0.82–1.98)	—	1,515	Age
Hjern 2001 [73]	Sweden	Children	—	0.96 (0.83–1.12)	4,472	Age, sex, siblings, parental education, residence, single parent household, country of birth of parents, location
Hjern 2001 [73]	Sweden	Adults	0.78 (0.72–0.84)	—	6,909	Age, sex, education, residence, country of birth, location
Janson 2001 [74]	World	Adults	—	1.02 (0.81–1.20)	7,882	Age, sex, allergens, IgE, location
Simpson 2001 [75]	UK	Adults	0.78 (0.65–0.93)	—	5,687	Sex, allergens, pets
Dotterud 2001 [76]	Russia	Schoolchildren	—–	0.90 (0.69–1.17)	1,684	Age, sex, carpets, dampness, pets, heating type
Kalyoncu 2001 [77]	Turkey	University students	1.24 (1.01–1.53)	1.20 (1.06–1.35)	4,639	Age, sex, region, family atopy, pets, elder siblings
Lee 2001 [78]	Korea	Schoolchildren	—	1.19 (1.11–1.28)	38,955	Age, sex, region, body mass index, carpets, pets, location
Stazi 2002 [79]	Italy	Children	—	2.2 (1.2–4.1)	201	Age, sex
Peroni 2003 [80]	Italy	Preschool children	—	1.19 (0.89–1.59)	1,402	Age
Barraza 2003 [81]	Mexico	Schoolchildren	—	1.37 (1.23–1.52)	6,174	Age, school, cockroaches, respiratory problems, use of carpets, humidity, family history of asthma
Monteil 2004 [82]	Trinidad & Tobago	Schoolchildren	—	1.41 (1.26–1.59)	3,170	Age
Lee 2004 [83]	Hong Kong	School children	—	0.81 (0.72–0.91)	4,448	Age, sex, birth weight, siblings, respiratory tract infections, parental atopy, pets, study period

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Table 2. Cont.

Source	Country	Population	Active Smoking	Passive Smoking	Study Size	Variables of Adjustment, Matching, or Restriction
Kramer 2004 [84]	Germany	School beginners	—	0.86 (0.38–1.96)	1,220	Age, sex, atopy, nationality
Demir 2004 [85]	Turkey	Schoolchildren	—	2.43 (1.32–4.52)	1,064	Age
Miyake 2004 [86]	Japan	Schoolchildren	—	1.11 (0.98–1.27)	5,539	Age, sex, grade, older siblings, maternal age at child birth, pets, history of other allergic diseases
Annesi-Maesano 2004 [87]	France	Adolescents	1.65 (1.48–1.84)	1.15 (1.09–1.22)	14,578	Age, sex
De 2005 [88]	Ireland	Children	—	1.16 (0.43–3.12)	81	Not specified
Topp 2005 [89]	Germany	Adults	—	1.10 (0.93–1.30)	4,093	Age, sex, social class, location
Maziak 2005 [90]	Syria	Adults	—	1.12 (0.85–1.48)	1,118	Age, sex, familial atopy, socioeconomic status, occupational
Miyake 2005 [91]	Japan	Pregnant women	1.10 (0.85–1.42)	1.33 (1.09–1.62)	1,002	Age, sex, familial atopy, pets, gestation, parity, family income, education, mite antigen level
Bugiani 2005 [92]	Italy	Young adults	0.76 (0.69–0.84)	—	17,666	Not specified
Obihara 2005 [93][a]	South Africa	Children	—	—	861	Age, sex, maternal atopy, breast feeding, siblings, household income, tuberculin test
Strumylaite 2005 [94]	Lithuania	Children	—	0.85 (0.20–3.45)	594	Age
Lund 2006 [95][b]	France	Mature women	1.10 (0.92–1.30)	1.31 (1.0–1.6)	2,197	Age, sex
Kurosaka 2006 [96]	Japan	Schoolchildren	—	0.82 (0.78–0.87)	35,213	Age, sex, pets
Sakar 2006 [97]	Turkey	Adults	1.30 (0.99–1.71)	1.33 (0.96–1.83)	1,336	Age, sex, family atopy
Ho 2007 [98]	Hong Kong	Adults	—	1.34 (0.93–1.94)	200	Age, sex, education, occupational exposures
Horak 2007 [99]	Austria	Preschool children	—	1.31 (0.90–1.90)	1,737	Age, sex, familial atopy, education, family size, pets, breastfeeding, healthy nutrition
Ebbert 2007 [100]	USA	Adults	—	1.16 (0.85–1.59)	1,007	Not specified
Tanaka 2007 [101]	Japan	Children	—	1.07 (0.98–1.16)	23,044	Age, sex, location, familial atopy, siblings, education level
Zuraimi 2008 [102]	Singapore	Preschool children	—	1.22 (1.11–1.35)	4,759	Age, sex, familial atopy, race, socioeconomic status, housing type, breastfeeding, food allergy, respiratory infections, housing conditions, traffic density
Foliaki 2008 [103]	Pacific countries	Children	—	1.05 (0.99–1.12)	17,683	Age, sex, country
Gomez 2008 [104]	Argentina	Adolescents	1.72 (1.48–1.99)	—	3,000	Age
Kabir 2009 [105]	Ireland	Children		1.30 (1.01–1.67)	2,809	Age, sex
Brescianini 2009 [106]	Italy	Schoolchildren	—	1.17 (0.79–1.76)	481	Age, sex, family atopy, body mass index, pets, physical activity, diet, location
Musharrafieh 2009 [107]	Lebanon	Adolescents	—	1.0 (0.8–1.2)	3,115	Age, sex, nationality, regions, school type, traffic
Gonzalez-Diaz 2010 [108]	Mexico	Children and Adolescents	—	1.37 (1.23–1.53)	23,191	Age
Bedolla-Barajas 2010 [109]	Mexico	Schoolchildren	—	1.01 (0.48–2.13)	740	Age
Wang 2010 [110]	Canada	Schoolchildren	—	1.00 (0.81–1.24)	8,334	Age, sex, body mass index, location, birthplace, ethnicity, maternal education, siblings, fuel use, pets, acetaminophen, physical activity

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Table 2. Cont.

Source	Country	Population	Active Smoking	Passive Smoking	Study Size	Variables of Adjustment, Matching, or Restriction
Vlaski 2011 [111]	Macedonia	Adolescents	—	0.99 (0.88–1.11)	3,026	Age, sex, diet, type of cooking and heating, pets, maternal education, siblings
Virkkula 2011 [112]	Finland	Children	—	2.29 (1.07–4.87)	38	Age
Hakansson 2011 [113]	Denmark	Adults	0.79 (0.68–0.92)	—	3,471	Age, sex
Chen 2012 [114]	Taiwan	Children	—	—	4,221	Age, sex, parental atopy, parental education
Peñaranda 2012 [115]	Colombia	Children	—	1.19 (0.99–1.42)	3,256	Age, asthma, dermatitis, use of acetaminophen and antibiotics, maternal education, caesarean delivery
Peñaranda 2012 [115]	Colombia	Adolescents	1.4 (1.2–1.7)	—	3,829	Age, asthma, dermatitis, use of acetaminophen, consumption of fast-food, cats
Tanaka 2012 [116]	Japan	Pregnant women	1.01 (0.84–1.23)	1.50 (1.14–1.96)	1,743	Age, sex, region of residence, parental atopy, household income, education
Montefort 2012 [117]	Malta	Children	1.40 (1.11–1.76)	1.11 (1.02–1.20)	7,955	Age
Mitchell 2012 [118]	Multiple countries	Children	—	1.10 (1.08–1.12)	573,061	Age, sex, language, region, gross national income

[a]Only data on maternal smoking during pregnancy are available.
[b]This study used cases of rhinitis at large, not only allergic rhinitis.
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Europe [17] and approximately 14% of all children were exposed to maternal smoking during pregnancy [18].

Several studies have assessed the association between smoking exposure and allergic diseases. In each of the allergic conditions, results were conflicting and alternated between the harmful effects of smoking [14,19,20] and protection [21–23], while some studies could not find evidence of any effect [24–26].

Except for a systematic review and meta-analysis examining the relationship between smoking and asthma in children [27], to our knowledge, there is no comprehensive meta-analysis that examines the evidence for a relationship between smoking and allergic conditions. We, therefore, summarized the scientific evidence and carried out a meta-analysis on exposure to active and passive smoking and the risk of allergic rhinitis, allergic dermatitis, and food allergy among adults and children/adolescents.

Methods

Data Sources and Searches

We searched databases from 1966 to June 30th, 2013, to identify all potentially eligible studies. For Medline, we applied the following algorithm both in medical subject heading and in free text words: ("SEASONAL ALLERGIC RHINITIS" OR "POLLEN ALLERG*" OR "POLLINOSIS" OR "POLLINOSES" OR "HAY FEVER" OR "RHINITIS, ALLERGIC, NONSEASONAL" OR "RHINITIS, ALLERGIC, PERENNIAL" OR "DERMATITIS, ATOPIC" OR ECZEMA OR "FOOD ALLERGIES" OR "HYPERSENSITIVITY, FOOD") AND (SMOKING OR TOBACCO OR CIGARETT*). We used similar strategies to search Embase and the five regional bibliographic databases of the World Health Organization (AIM, LILACS, IMEMR, IMSEAR, WPRIM). We searched meeting abstracts using the ISI Proceedings database from its inception in 1990 to 2013. We also examined the references of every article retrieved and those of recent reviews of allergic rhinitis and smoking [16,28–33] and established personal contact with clinical researchers to trace further publications or reports. We considered including any relevant article, independently of the language of publication.

Study Selection

Studies were included if: (1) they presented original data from cohort, case-control, or cross-sectional studies (ecologic studies were not included); (2) the outcome of interest was clearly defined as allergic rhinitis, allergic dermatitis, or food allergy; (3) one of the exposure factors was smoking, either by the subjects themselves or their relatives; (4) they provided estimates of odds ratio (OR), relative risk (RR), or prevalence odds ratio and their confidence intervals, or enough data to calculate them. If data on the same population were duplicated in more than one study, the most recent study was included in the analysis. When data for different types or levels of exposure were available in the same study, such as passive smoking, active smoking, or maternal smoking during pregnancy, we considered each type of exposure separately. We developed a standard data-recording form in which we recorded authors, year of publication, study location, sample size, outcome, outcome measurement details, effect estimator (OR, RR, other), effect estimate, 95% CIs, adjustment factors used, and study design including if the International Study of Asthma and Allergies in Childhood (ISAAC) methodology was followed. ISAAC is a large international epidemiologic study on risk factors of allergic diseases, the methods of which are widely used. When further clarification was necessary, we attempted to contact the authors. Abstracts were reviewed independently by two authors (BT and JS).

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Table 3. Pooled relative risks and 95% confidence intervals of allergic rhinitis and smoking.

Study Type	Number of Studies	RR (95% CI) Fixed Effects	RR (95% CI) Random Effects	Ri[a] (95% CI)	Q test (*p*-Value)
Active smoking					
All studies	34	1.06 (1.03–1.08)	1.02 (0.92–1.15)	0.95 (0.90–0.99)	0.00001
Cohort studies	4	0.87 (0.82–0.93)	0.91 (0.77–1.07)	0.82 (0.47–1.00)	0.0024
Case-control studies	3	1.19 (0.99–1.45)	0.97 (0.55–1.70)	0.88 (0.59–1.00)	0.0009
Cross-sectional studies	27	1.09 (1.06–1.12)	1.03 (0.91–1.18)	0.95 (0.91–1.00)	0.00001
Cohort+case-control studies	7	0.90 (0.85–0.96)	0.98 (0.81–1.18)	0.87 (0.66–1.00)	0.00001
Full adjustment	18	1.07 (1.04–1.10)	1.02 (0.88–1.20)	0.96 (0.92–1.00)	0.00001
Incomplete adjustment	16	1.03 (0.98–1.08)	1.02 (0.86–1.22)	0.91 (0.83–0.99)	0.00001
Adults only	21	0.84 (0. 81–0.87)	0.90 (0.82–0.99)	0.82 (0.66–0.97)	0.00001
Children/adolescents only	10	1.35 (1.30–1.39)	1.40 (1.24–1.59)	0.90 (0.77–1.00)	0.00001
Children ISAAC method	8	1.39 (1.34–1.44)	1.50 (1.35–1.66)	0.85 (0.63–1.00)	0.00001
Children non-ISAAC method	2	0.96 (0.86–1.08)	0.96 (0.86–1.08)	0.00 (0.00–1.00)	0.34
Quality score ≥3	15	0.89 (0.86–0.93)	0.95 (0.85–1.06)	0.86 (0.73–0.99)	0.00001
Quality score <3	19	1.19 (1.16–1.23)	1.09 (0.92–1.29)	0.96 (0.91–1.00)	0.00001
Passive Smoking					
All studies	63	1.08 (1.07–1.10)	1.10 (1.06–1.15)	0.87 (0.75–0.99)	0.00001
Cohort studies	9	1.08 (1.03–1.13)	1.14 (0.96–1.34)	0.90 (0.76–1.00)	0.00001
Case-control studies	3	1.13 (0.91–1.39)	1.14 (0.46–2.82)	0.95 (0.84–1.00)	0.00001
Cross-sectional studies	51	1.08 (1.07–1.10)	1.09 (1.05–1.14)	0.86 (0.72–0.99)	0.00001
Cohort+case-control studies	12	1.08 (1.03–1.13)	1.13 (0.96–1.34)	0.91 (0.79–1.00)	0.00001
Full adjustment	37	1.07 (1.06–1.09)	1.07 (1.03–1.12)	0.86 (0.72–1.00)	0.00001
Incomplete adjustment	26	1.17 (1.13–1.20)	1.15 (1.04–1.27)	0.86 (0.74–0.97)	0.00001
Adults only	13	1.17 (1.10–1.24)	1.17 (1.03–1.32)	0.74 (0.50–0.98)	0.00001
Children/adolescents only	50	1.08 (1.07–1.09)	1.09 (1.04–1.14)	0.89 (0.77–0.99)	0.00001
Children ISAAC method	28	1.10 (1.09–1.12)	1.11 (1.07–1.16)	0.84 (0.66–1.00)	0.00001
Children non-ISAAC method	21	0.98 (0.95–1.01)	1.06 (0.95–1.19)	0.89 (0.78–1.00)	0.00001
Maternal pregnancy smoking	11	1.01 (0.96–1.06)	1.07 (0.92–1.28)	0.83 (0.60–1.00)	0.00001
Quality score ≥3	30	1.09 (1.08–1.11)	1.10 (1.04–1.15)	0.86 (0.71–1.00)	0.00001
Quality score <3	33	1.07 (1.04–1.09)	1.10 (1.02–1.19)	0.88 (0.78–0.98)	0.00001

[a]Proportion of total variance due to between-study variance.
doi:10.1371/journal.pmed.1001611.t003

Quality Assessment

Study quality was assessed using a five-point binary scale specifically developed for this study. The scale is based on the Newcastle-Ottawa scale [34] with modifications in view of standard guidelines and our own judgment. The Newcastle-Ottawa scale is a scoring system that assesses every aspect of an observational epidemiologic study from a methodological point of view. For this meta-analysis, we tried to use those elements that were common to all epidemiologic designs and thus shortened the scale considerably. We used the following criteria labelled as "yes" or "no": (1) whether assessment of the smoking habit included duration and/or quantity (yes) or not (no); (2) whether rhinitis diagnosis included clinical features and IgE or skin prick test (SPT) measurements (yes) or was based on clinical examination or questionnaire only (no), whether dermatitis diagnosis included clinically assessed diagnosis (yes) or was based on questionnaire information only (no), whether the diagnosis of food allergy was based on clinical diagnosis with SPT, IgE, or open-challenge test (yes) or was based on questionnaire information only (no); (3) whether results were adjusted for age, sex, and at least one other potential confounder (yes) or not (no); (4) whether participation exceeded 80% of the people initially approached (yes) or not (no); and, finally (5) whether the target population was clearly defined (yes) or, on the contrary, based on convenience sampling of subjects such as patients of a single consultation (no). Throughout this assessment, when the information on a specific item was not provided by the authors, we graded this item as "no." We carried out a pooled analysis on those studies that fulfilled at least three criteria and compared with those that scored fewer than three. As a secondary analysis, we stratified our results on criterion 1 and present the pooled relative risks in Table S2.

Data extraction and quality scoring were performed independently by two reviewers (BT and JS) and the results were merged by consensus. The complete protocol and results for quality scoring are available in Table S1.

Data Synthesis and Analysis

We weighted the study-specific log odds ratios for case control and cross-sectional studies, and log relative risks for cohort studies by the inverse of their variance to compute a pooled relative risk

Annex II. Cont.

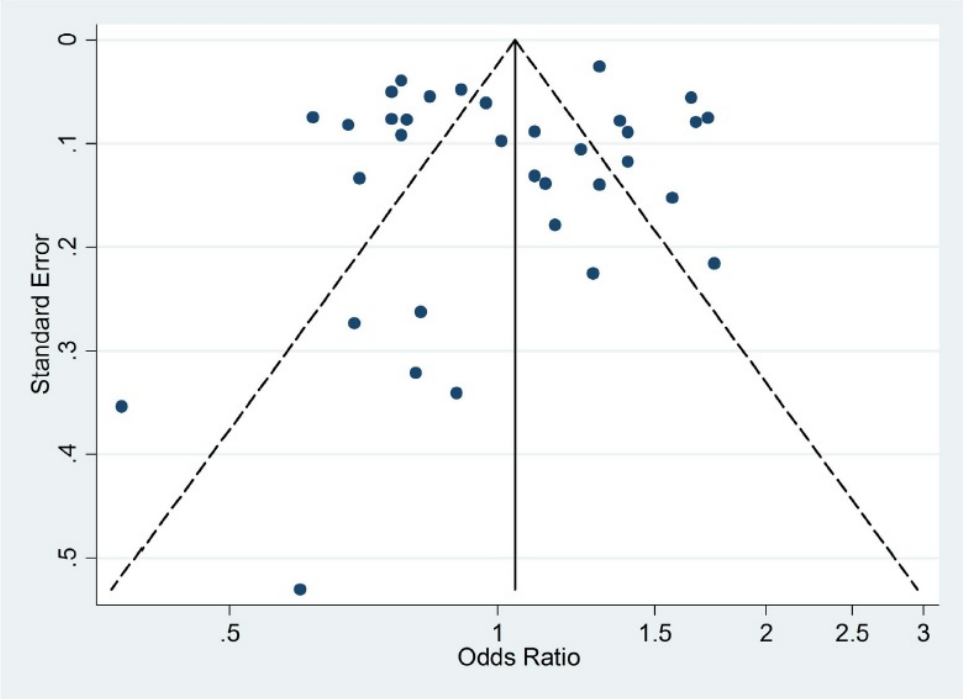

Figure 4. Funnel plot of relative risk versus standard error of relative risk: allergic rhinitis, active smoking.
doi:10.1371/journal.pmed.1001611.g004

and its 95% confidence interval. For each study, we used the estimate of the effect measure that was adjusted for the largest number of confounders. We present both fixed-effects and random effects pooled estimates but use the latter when heterogeneity was present. Odds ratios from case-control studies were assumed to be unbiased estimates of the relative risk [35].

We used a version adapted to small samples of the DerSimonian and Laird Q test to check for heterogeneity [36]. The null hypothesis of this test is the absence of heterogeneity. To quantify this heterogeneity we calculated the proportion of the total variance due to between-study variance (Ri statistic) [36]. Furthermore, we explored the origin of heterogeneity by restricting the analysis to subgroups of studies defined by study characteristics such as study design, type of exposure (active or passive smoking), and age of the participants (children/adolescents or adults).

To check whether the pooled estimates were significantly different between subgroups we carried out a meta-regression with the global effect as dependent variable and the subgroup variable as moderator.

We assessed publication bias, first visually, using funnel plots and then, more formally, using the test proposed by Egger and colleagues [37]. We also used the trim-and-fill method to correct for potential publication bias. All analyses were performed with the software HEpiMA version 2.1.3 [38] and STATA version 12 with its macros metabias, metareg, and metatrim.

The secondary analyses (children and adolescents/adults, ISAAC/other, cohort and case-control studies combined/cross-sectional studies, high quality/low quality) were planned a priori.

Results

We identified 196 studies, published in 139 different articles and carried out in 51 countries, on active or passive smoking and allergic diseases that met our inclusion criteria (Figure 1). The data from one study were obtained from the authors [39]. We found 97 studies on allergic rhinitis [19,21,24,39–118], 91 on allergic dermatitis [19,20,22,24–26,44–46,48,53,60–65,67,73,75,76,78,83–87,91,93,96,97,99,101–103,105–107,110,111,116–165], and eight on food allergies [14,23,26,73,126,136,166–168].

A large majority of the articles retrieved initially were excluded either because they did not provide any effect measure or the outcome was allergy at large. More specifically, of the studies that could have been relevant to our meta-analysis but were finally excluded, eight were discarded because they were an early version of cohort studies updated in subsequent publications [169–176]. Other studies published their results several times [175–181] in which case we chose to include the most complete report. Some studies were excluded because the outcome was not allergic rhinitis, dermatitis, or food allergy but rather SPT or IgE concentrations

Annex II. Cont.

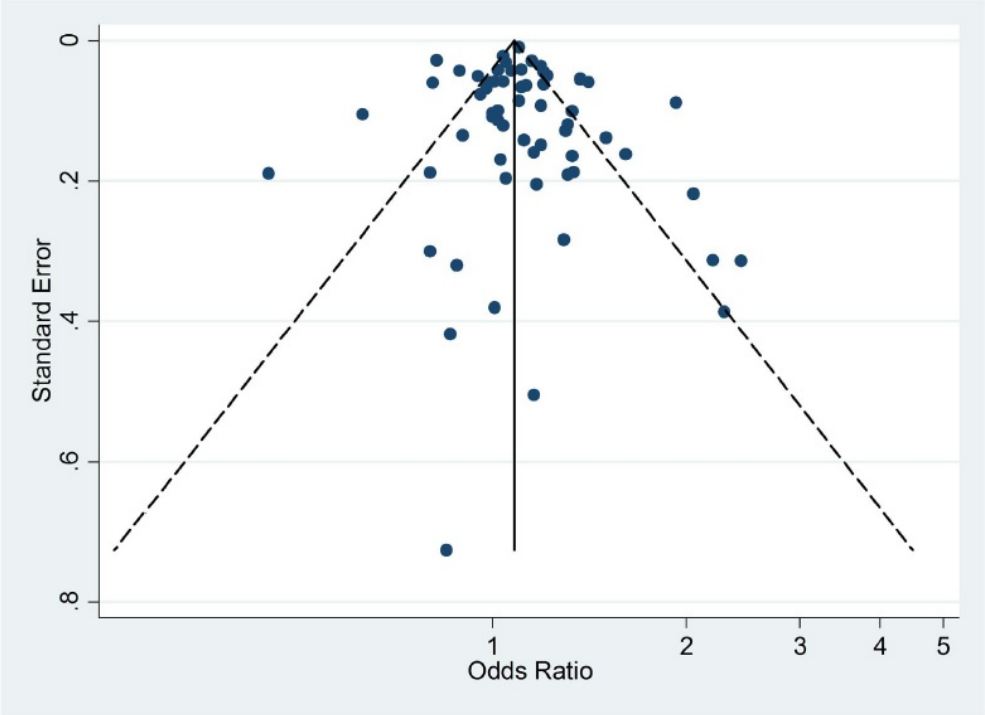

Figure 5. Funnel plots of relative risk versus standard error of relative risk: allergic rhinitis, passive smoking.
doi:10.1371/journal.pmed.1001611.g005

[182–192]. We also excluded nine studies that used either unspecific outcomes such as nasal symptoms [193,194], or a mixture of allergic diseases as a single outcome [195–201]. Eight studies [138,202–208] were excluded as they did not present any effect measure. Finally, one ecologic study was not considered further [209].

Globally, heterogeneity was substantial overall and similarly high after stratification by design, quality features (including adjustment for confounders), and study population. Given the substantial heterogeneity, we focused on the random effects analyses; however, the fixed effects analyses are presented for comparison and only discussed where they differ.

Allergic Rhinitis

Thirty-four studies on active smoking and 63 studies on passive smoking were available (Figures 2 and 3; Tables 1 and 2). The overwhelming majority of the studies assessed diagnosis through questionnaire and only seven studies used SPT or IgE measurements for the case definition [39,42,46,52,57,101,113]. The study by Wright and colleagues [42] measured SPT reactivity but used a definition of physician diagnosed allergic rhinitis that included both SPT-positive and SPT-negative children. More than half of the studies used ISAAC criteria for the definition of allergic rhinitis. Finally, 11 studies assessed maternal smoking during pregnancy [44,45,47–49,60,70,81,93,99,114].

Table 3 shows the results for associations between smoking and allergic rhinitis.

Active Smoking

Using random effects analysis, there was no significant association between active smoking and the risk of allergic rhinitis when all studies are considered (RR = 1.02; 95% CI 0.92–1.15). Using fixed effect analysis for all studies, there was a significant association between active smoking and risk of rhinitis (RR = 1.06, 95% CI 1.03–1.08); however, this may be explained by the considerable amount of heterogeneity due to differences in designs, case, and exposure definitions and adjustment for confounders. It is remarkable that, under the fixed effects model, the result of the cross-sectional subgroup (RR = 1.09; 95% CI 1.06–1.12) is statistically significant and opposed to the result of the cohort studies subgroup (RR = 0.87; 95% CI 0.82–0.93).

When restricting the analysis to the ten studies carried out on children and adolescents, active smoking was associated with an increased pooled relative risk of 1.40 (95% CI 1.24–1.59). In further sub-group analyses, the association was significant in the studies that used the standardized ISAAC protocol (RR = 1.50, 95% CI 1.35–1.66), but not those that used their own protocol (RR = 0.96, 95% CI 0.88–1.08). A reverse association between active smoking and allergic rhinitis was observed in adults only (RR = 0.90, 95% CI 0.82–0.99)

Annex II. Cont.

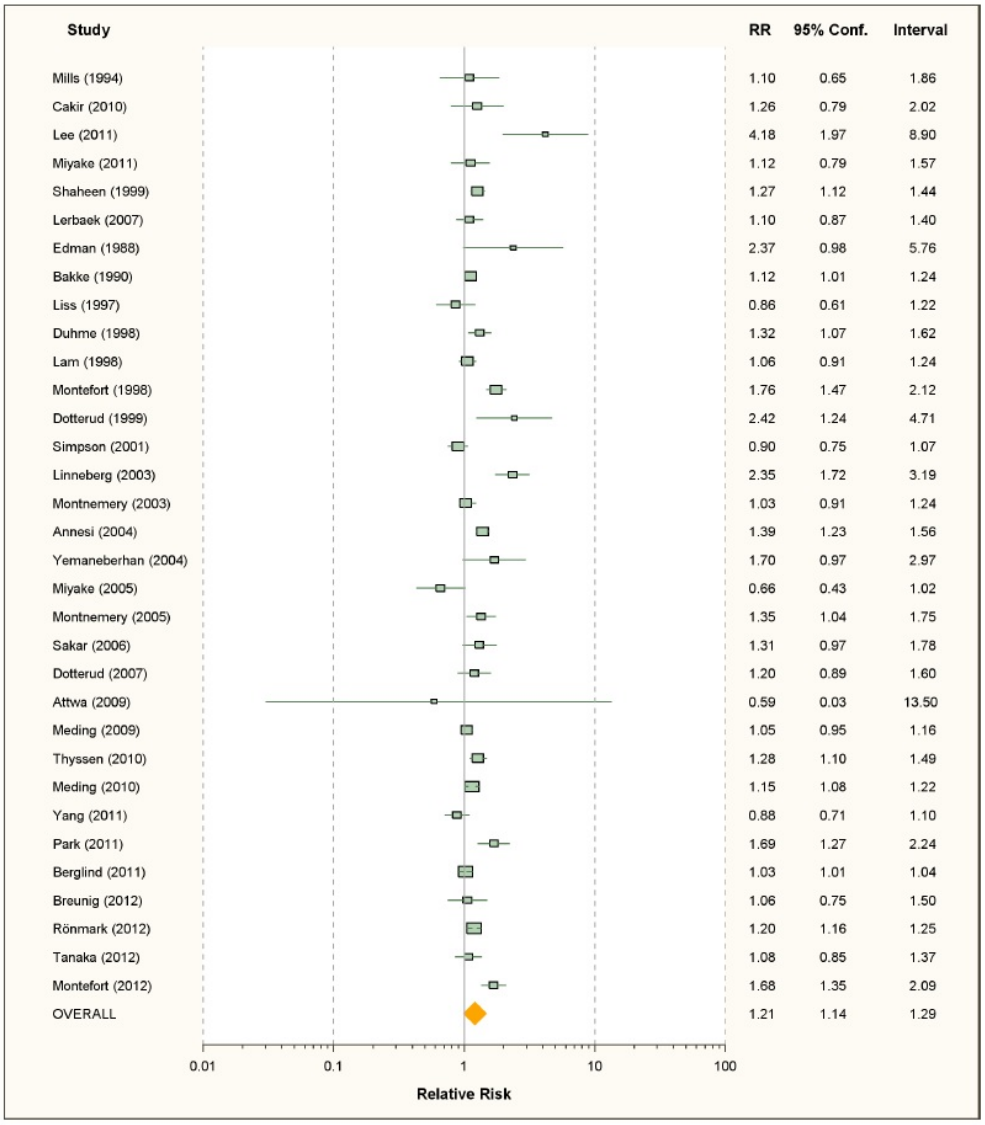

Figure 6. Study-specific and random effects pooled relative risks of active smoking and allergic dermatitis.
doi:10.1371/journal.pmed.1001611.g006

Passive Smoking

Using random effects analysis, there was a significant association passive smoking and allergic rhinitis (RR = 1.10, 95% CI 1.06–1.15). Similar findings were observed in subgroup analyses by adjustment for confounding variables (RR = 1.07; 95% CI 1.03–1.12 for full adjustment, RR = 1.15; 95% CI 1.04–1.27 for incomplete adjustment), quality scores (RR = 1.10; 95% CI 1.04–1.15 for high quality, RR = 1.10; 95% CI 1.02–1.19 for low quality), and for cross-sectional studies (RR = 1.09; 95% CI 1.05–1.14); however, there was no significant association between passive smoking and allergic rhinitis when restricting the analysis to cohort studies (RR = 1.14; 95% CI 0.96–1.34) or case-control studies (RR = 1.14; 95% CI 0.46–2.82).

Annex II. Cont.

Figure 7. Study-specific and random effects pooled relative risks of passive smoking and allergic dermatitis.
doi:10.1371/journal.pmed.1001611.g007

In subgroup analyses based on age group, a significant association between passive smoking and allergic rhinitis was observed in adults only (RR = 1.17; 95% CI 1.03–1.32) and in children and adolescents (RR = 1.09; 95% CI 1.04–1.14). For maternal pregnancy smoking, there was no evidence for a a significant increase in the risk of allergic rhinitis in the offspring (RR = 1.07; 95% CI 0.92–1.28).

Publication Bias

The funnel plot of active smoking seems to be slightly skewed to the left, which indicates a potential lack of studies that favor a positive association of the disease with smoking (Figure 4). However, the Egger's test of asymmetry yielded a nonsignificant *p*-value of 0.27 and no hypothetical study was suggested as missing in the trim-and-fill procedure. The funnel plot for passive

Annex II. Cont.

Table 4. Relative risks and 95% confidence intervals of dermatitis by smoking exposure in case-control and cohort studies.

Source	Country	Population	Follow-up (y)	Complete Follow-up (%)	Active Smoking	Passive Smoking	Cases/Controls or Cohort Size	Variables of Adjustment, Matching, Restriction
Case-control studies								
Mills 1994 [119]	UK	Adults	—	—	1.1 (0.65–1.86)	—	127/127	Not specified
Yang 2000 [120]	Taiwan	School children	—	—	—	0.75 (0.46–1.25)	144/144	Age, sex, parental education, breast feeding, parental eczema
Purvis 2005 [121]	New Zealand	Children	—	—	—	—	87/463	Age
Haileamlak 2005 [122]	Ethiopia	Children	—	—	—	1.07 (0.75–1.54)	306/426	Age
Sebok 2006 [123]	Hungary	Children	—	—	—	1.15 (0.93–1.42)	461/343	Age, sex, residence
Wang 2010 [25]	Taiwan	Children	—	—	—	1.02 (0.43–2.43)	34/106	Age
Cakir 2010 [19]	Turkey	Adolescents	—	—	1.26 (0.79–2.02)	—	436/366	Age, sex, family atopy, pets, income, occupation
Lee 2011 [20]	Taiwan	Adults	—	—	4.18 (1.97–8.90)	2.22 (1.01–4.84)	83/142	Age, sex
Miyake 2011 [124]	Japan	Adult women	—	—	1.12 (0.79–1.57)	—	188/1,082	Age, sex, residence, siblings, education
Cohort studies								
Burr 1989 [125]	UK	Infants	1	93.1	—	2.03 (1.28–3.22)	184/468	Age
Zeiger 1995 [126]	USA	High risk children	7	57	—	7.9 (1.0–61.0)	9/165	Age, sex, maternal ethnicity, parental asthma, food allergy
Olesen 1997 [127]	Denmark	Children	9.5	93	—	—	184/985	Age, sex, mother's age at birth, parity, birth weight, family atopy
Lewis 1998 [30]	UK	Children	16	55	—	1.05 (0.94–1.18)	1,213/6,352	Age, sex, social class, birth weight, gestational age, breast feeding, maternal age, parity
Tariq 1998 [26]	UK	Children	4	83.6	—	0.58 (0.36–0.94)	145/1,218	Age
Shaheen 1999 [45]	UK	Adults	26	51.1	1.27(1.12–1.44)	—	?/6,420	Age, sex, birth weight, social class, siblings, qualification, height, body mass index
Bergmann 2000 [46]	Germany	Infants	6	75	—	1.21 (0.83–1.76)	206/825	Age, sex, parental atopy, socioeconomic status, breast feeding, aeroallergen and food sensitization, study centre
McKeever 2001 [24]	UK	Children	11	95	—	0.89 (0.87–0.92)	8,839/29,238	Age, sex, family atopy, siblings
Bergmann 2002 [128]	Germany	Infants	7	71.5	—	—	?/937	Age, sex, breastfeeding duration, familial atopy, social status, allergic rhinoconjunctivitis, asthma, upper respiratory tract infections, mother's age, parity, IgE.
Kerkhof 2003 [129]	Netherlands	Infants	1	?	—	1.17 (0.72–1.89)	76/304	Sex, age, birth weight, gestation age, mother's age, breastfeeding, siblings, day-care attendance, pets, region, parental education

Annex II. Cont.

Table 4. Cont.

Source	Country	Population	Follow-up (y)	Complete Follow-up (%)	Active Smoking	Passive Smoking	Cases/Controls or Cohort Size	Variables of Adjustment, Matching, Restriction
Ludvigsson 2005 [21]	Sweden	Infants	1	66.5	—	0.83 (0.71–0.96)	2,038/8,784	Age, sex, pets, preterm birth, maternal education, parity, parental atopy
Magnusson 2005 [48]	Denmark	Children	18	74	—	1.0 (0.8–1.1)	1,248/7,844	Sex, social class, occupation, maternal age at pregnancy, coffee, parity, breastfeeding
Linneberg 2006 [130]	Denmark	Infants	1.5	67	—	—	3,327/34,793	Age, sex, breast feeding, parental atopy, season of birth, gestation age, head circumference, birth weight, residence, maternal occupation, household income, siblings, day care attendance, pets
Lerbaek 2007 [131]	Denmark	Twin adults	9	82	1.10 (0.87–1.40)	—	244/3,393	Not specified
Noakes 2007 [132]	Australia	Infants	1	67	—	0.80 (0.28–2.24)[a]	41/82	Age
Sariachvili 2007 [133]	Belgium	Infants	1	87	—	1.8 (1.0–3.1)	227/975	Age, sex, parental atopy, pregnancy duration, maternal educational and age, pets, antibiotics use, parity, day care attendance.
Tanaka 2008 [134]	Japan	Children	2	76	—	1.10 (0.86–1.41)	142/763	Age, sex, birth weight, family income, parental atopy, pets, older siblings, maternal age
Böhme 2010 [135]	Sweden	Children	4	61.2	—	1.68 (1.22–2.30)	529/2,505	Age, sex, parental atopy, breastfeeding, pets, parental education.
Jedrychowski 2011 [136]	Poland	Infants	1	100	—	1.46 (0.84–2.55)	183/469	Age

[a]Relative risk for pre- and post- natal smoking of mother.
doi:10.1371/journal.pmed.1001611.t004

Annex II. Cont.

Table 5. Relative risks and 95% confidence intervals of allergic dermatitis by smoking exposure in cross-sectional studies.

Source	Country	Population	Active Smoking	Passive Smoking	Study Size	Variables of Adjustment, Matching, or Restriction
Edman 1988 [137]	Sweden	Adults	2.37 (0.98–5.76)	—	425	Not specified
Bakke 1990 [53]	Norway	Adolescents and adults	1.12 (1.01–1.24)	—	4,270	Age, sex, occupational exposure, residence
Volkmer 1995 [138]	Australia	Preschool children	—	0.80 (0.71–0.91)	14,124	Natural gas for cooking, heating and cooling sources
Austin 1997 [60]	UK	Children	—	0.88 (0.74–1.05)	1,537	Age
Liss 1997 [139]	Canada	Adults	0.86 (0.61–1.22)	—	1,326	Not specified
Schäfer 1997 [140]	Germany	Preschool children	—	—	678	Age
Duhme 1998 [65]	Germany	Schoolchildren	1.32 (1.07–1.62)	0.97 (0.85–1.10)	13,123	Age, sex
Lam 1998 [62]	Hong Kong	Schoolchildren	1.06 (0.91–1.24)	0.91 (0.80–1.03)	6,304	Age, sex, residence, housing
Montefort 1998 [64]	Malta	Schoolchildren	1.76 (1.47–2.12)	—	4,184	Age, sex, road, pets, parental atopy, blankets
Farooqi 1998 [61]	UK	Children	—	0.97 (0.75–1.26)*	1,934	Not specified
Dotterud 1999 [67]	Russia	Adults	2.42 (1.24–4.71)	—	3,368	Not specified
Dotterud 2001 [76]	Russia	Schoolchildren	—	0.93 (0.78–1.11)	1,684	Age, sex, carpets, dampness, pets, heating type
Hjern 2001 [73]	Sweden	Children	—	0.88 (0.75–1.03)	4,472	Age, sex, siblings, parental education, residence, single parent household, country of birth of parent, location
Lee 2001 [78]	Korea	Schoolchildren	—	1.09 (0.99–1.20)	38,955	Age, sex, region, BMI, carpets, pets, location
Simpson 2001 [75]	UK	Adults	0.9 (0.75–1.07)	—	5,687	Not specified
Linneberg 2003 [141]	Denmark	Adolescents and adults	2.35 (1.72–3.19)	—	1,112	Age, sex, ear piercing
Montnemery 2003 [142]	Sweden	Adults	1.03 (0.91–1.24)	—	8,469	Not specified
Kramer 2004 [84]	Germany	School beginners	—	1.97 (1.23–3.16)	1,220	Age, sex, atopy, nationality
Demir 2004 [85]	Turkey	Schoolchildren	—	1.30 (0.46–3.83)	621	Age
Annesi-Maesano 2004 [87]	France	Adolescents	1.39 (1.23–1.56)	0.9 (0.9–1.3)	14,578	Age, sex
Miyake 2004 [86]	Japan	Schoolchildren	—	1.04 (0.89–1.22)	5,539	Age, sex, grade, older siblings, maternal age at child birth, pets, parental allergic diseases.
Yemaneberhan 2004 [143]	Ethiopia	Children and adults	1.70 (0.97–2.97)	2.13 (1.31–3.46)	12,876	Age, sex, socioeconomic status, residence, kerosene use
Lee 2004 [83]	Hong Kong	Schoolchildren	—	—	4,448	Age, sex, birth weight, siblings, respiratory tract infections, parental atopy, pets, study period
Heudorf 2005 [144]	Germany	Children	—	2.34 (1.04–5.28)	287	Age
Miyake 2005 [91]	Japan	Pregnant women	0.66 (0.43–1.02)	1.08 (0.81–1.44)	1,002	Age, sex, familial atopy, pets, gestation, parity, family income, education, mite antigen level
Montnemery 2005 [145]	Sweden	Adults	1.35 (1.04–1.75)	—	6,109	Not specified
Obihara 2005 [93]	South Africa	Children	—	—	861	Age, sex, maternal atopy, breast feeding, siblings, household income, tuberculin test
Kurosaka 2006 [96]	Japan	Schoolchildren	—	0.99 (0.93–1.05)	35,242	Age
Sakar 2006 [97]	Turkey	Adults	1.31 (0.97–1.78)	—	1,336	Not specified
Dotterud 2007 [146]	Norway	Adults	1.20 (0.89–1.60)	—	1,236	Age, sex, atopic dermatitis, rhinitis and asthma
Horak 2007 [99]	Austria	Preschool children	—	1.06 (0.76–1.48)	1,737	Age, sex, familial atopy, education, family size, pets, breastfeeding, nutrition

Annex II. Cont.

Table 5. Cont.

Source	Country	Population	Active Smoking	Passive Smoking	Study Size	Variables of Adjustment, Matching, or Restriction
Tanaka 2007 [101]	Japan	Children	—	1.08 (1.02–1.14)	23,044	Age, sex, location, familial atopy, siblings, education level
Zuraimi 2008 [102]	Singapore	Preschool children	—	1.02 (0.95–1.09)	4,759	Age, familial atopy, race, socioeconomic status, housing type, breastfeeding, food allergy, respiratory infections, dampness
Al-Sahab 2008 [147]	Lebanon	Adolescents	—	1.46 (1.11–1.94)	2,893	Age, sex, exercise, traffic, asthma, rhinitis
Ergin 2008 [148]	Turkey	Schoolchildren	—	1.30 (0.89–1.91)	1,644	Age
Foliaki 2008 [103]	Pacific countries	Children	—	1.20 (1.11–1.30)	20,876	Age, sex and country
Suárez-Varela 2008 [149]	Spain	Schoolchildren	—	1.03 (0.99–1.06)	59,040	Age, sex, asthma, rhinitis, siblings, mother's education
Attwa 2009 [150]	Egypt	Adult men	3.59 (1.0–13.5)	—	163	Sex
Meding 2009 [151]	Sweden	Adults	1.05 (0.95–1.16)	—	13,452	Age, sex, history of atopy
Brescianini 2009 [106]	Italy	Schoolchildren	—	1.22 (0.77–1.95)	481	Age, sex, family atopy, BMI, pets, physical activity, diet, location
Musharrafieh 2009 [107]	Lebanon	Adolescents	—	1.1 (0.9–1.4)	3,115	Age, sex, nationality, regions, school type, traffic, asthma, rhinitis
Kabir 2009 [105]	Ireland	Children	—	1.24 (0.90–1.70)	2,809	Age, sex
Lipinska 2009 [152]	Poland	Children	—	3.40 (1.19–11.86)	283	Not specified
Xepapadaki 2009 [153]	Greece	Preschool children	—	0.98 (0.79–1.22)	2,374	Age, sex
Wang 2010 [110]	Canada	Schoolchildren	—	1.05 (0.79–1.41)	8,334	Age, sex, BMI, location, birthplace, ethnicity, maternal education, siblings, pets, acetaminophen, physical activity
Röhrl 2010 [154]	Sweden	Adolescents	—	0.85 (0.59–1.23)	6,095	Age, sex, flexural eczema and nickel allergy
Thyssen 2010 [155]	Denmark	Adults	1.28 (1.10–1.49)	—	3,471	Age, sex, alcohol consumption, educational level
Meding 2010 [156]	Sweden	Adults	1.15 (1.08–1.22)	—	25,428	Age, sex, history of atopy
Yang 2011 [157]	USA	Adults	0.88 (0.71–1.10)	1.21 (0.85–1.74)	2,974	Not specified
Vlaski 2011 [111]	Macedonia	Adolescents	—	0.93 (0.80–1.09)	3,026	Age, sex, diet, source of heating, pets, maternal education, siblings
Civelek 2011 [158]	Turkey	Schoolchildren	—	1.35 (1.17–1.56)	6,755	Age
Dei-Cas 2011 [159]	Argentina	Children	—	1.45 (1.02–2.08)	722	Age
Apfelbacher 2011 [160]	Germany	Children and adolescents	—	0.90 (0.77–1.04)	17,270	Age, sex, socioeconomic status, migrant status, siblings, breastfeeding, mother's alcohol consumption, pets, infection, parental atopy.
Park 2011 [161]	Korea	Adults	1.69 (1.27–2.24)	—	1,990	Age, sex, BMI, education, income, alcohol, fish consumption.
Berglind 2011 [162]	Sweden	Adults	1.03 (1.01–1.04)	—	27,793	Neck and shoulder pain, depression, well-being, job strain, low back pain, physical activity at work
Breunig 2012 [163]	Brazil	Male adolescents	1.06 (0.75–1.50)	—	2,201	Age, sex, white race, socioeconomic level, triceps skin fold, acne

Annex II. Cont.

Table 5. Cont.

Source	Country	Population	Active Smoking	Passive Smoking	Study Size	Variables of Adjustment, Matching, or Restriction
Yi 2012 [164]	Korea	Children	—	1.30 (1.23–1.38)	6,372	Age, sex, residence, income, parental education, atopy, IgE level, rhinitis
Rönmark 2012 [165]	Sweden	Adults	1.20 (1.16–1.25)	—	18,087	Age, sex, family history of atopy, exposure to gas, dust or fumes at work
Tanaka 2012 [116]	Japan	Pregnant women	1.08 (0.85–1.37)	1.42 (0.99–2.05)	1,743	Age, sex, region of residence; parental atopy, income, education
Montefort 2012 [117]	Malta	Children	1.68 (1.35–2.09)	1.24 (1.13–1.37)	7,955	Age
Mitchell 2012 [118]	Worldwide	Children	—	1.11 (1.09–1.14)	573,061	Age, sex, language, region, gross national income

doi:10.1371/journal.pmed.1001611.t005

smoking (Figure 5) and the corresponding results of the Egger's test did not show any evidence of publication bias ($p = 0.53$), but two new studies were imputed in the trim-and-fill procedure yielding a modified pooled relative risk of 1.10 (95% CI 1.05–1.14).

Allergic Dermatitis

We retrieved 33 studies on active smoking and 58 studies on passive smoking (Figures 6 and 7; Tables 4 and 5). About one-third of the studies used ISAAC criteria for case definition. Nineteen

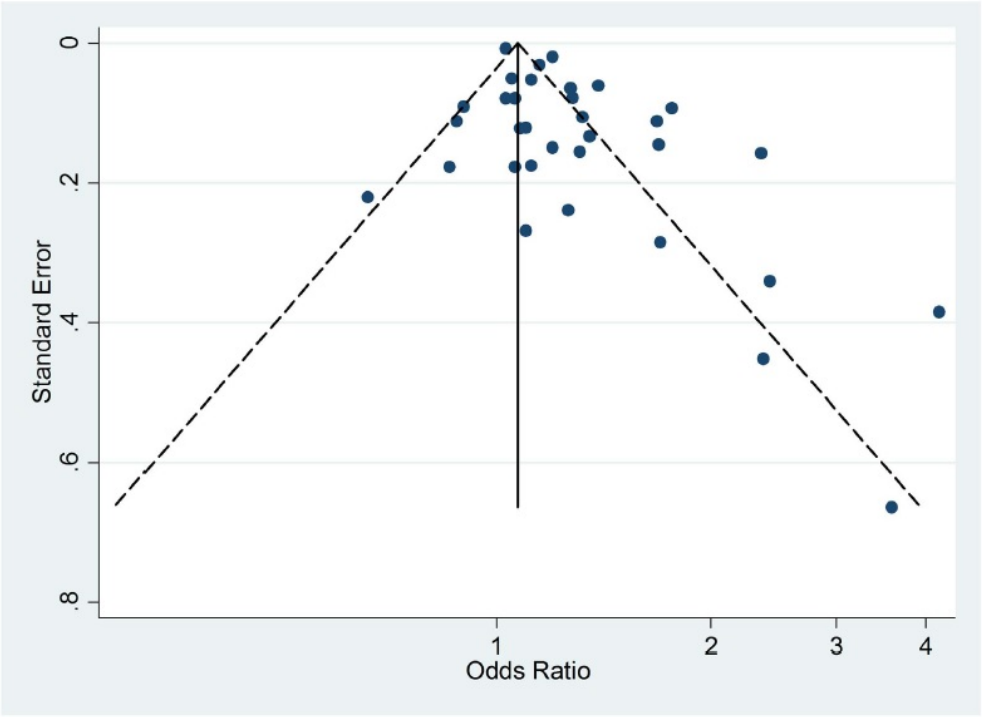

Figure 8. Funnel plots of relative risk versus standard error of relative risk: allergic dermatitis, active smoking.
doi:10.1371/journal.pmed.1001611.g008

Annex II. Cont.

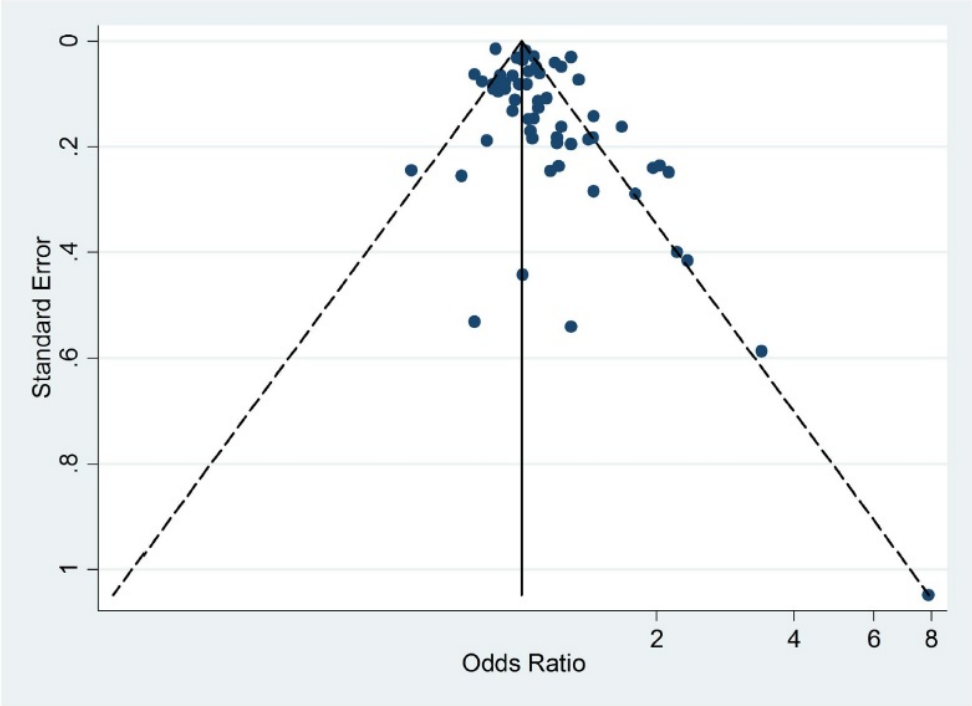

Figure 9. Funnel plot of relative risk versus standard error of relative risk: allergic dermatitis, passive smoking.
doi:10.1371/journal.pmed.1001611.g009

studies assessed maternal smoking during pregnancy [44,45,48, 83,93,99,121,127,128,130,133–136,140,153,158,160,164].

Active Smoking

Using random effects analysis, active smoking was significantly associated with an increased risk of allergic dermatitis overall (RR = 1.21; 95% CI 1.14–1.29) and in both adults (RR = 1.14; 95% CI 1.07–1.22) and in children and adolescents (RR = 1.36; 95% CI 1.17–1.46)

In sub-group analyses, the association between active smoking and allergic dermatitis was similar based on age, adjustment for confounding, quality scores, and for cohort studies and cross-sectional studies, although there was no significant association between active smoking and allergic dermatitis observed in the four case-control studies (RR = 1.47; 95% CI 0.92–2.32).

Passive Smoking

Using random effects analysis, passive smoking was associated with an increased risk of allergic dermatitis in the general population (RR = 1.07; 95% CI 1.03–1.12).

In sub-group analyses, the association between passive smoking and allergic dermatitis was significant when restricted to cross-sectional studies (RR = 1.07; 95% CI 1.02–1.12), but not for cohort (RR = 1.09; 95% CI 0.96–1.23) or case-control studies (RR = 1.10; 95% CI 0.88–1.38). A significant association between passive smoking and allergic dermatitis was observed for those studies with adjustment for confounding variables (RR = 1.08; 95% CI 1.03–1.13) and higher quality scores (RR = 1.11; 95% CI 1.05–1.18), but not those without adjustment (RR = 1.06; 95% CI 0.98–1.14) or low quality scores (RR = 1.03; 95% CI 0.96–1.11).

A significant association was observed in those studies including adults only (RR = 1.26; 95% CI 1.02–1.55) and in those including children and adolescents only (RR = 1.06; 95% CI 1.01–1.11). No significant association was observed between maternal smoking and allergic dermatitis (RR = 1.07; 95% CI 0.96–1.19).

Publication Bias

The Egger's test for asymmetry of the funnel plot of active smoking (Figure 8) yielded a p-value of 0.28 and no study was added in the trim-and-fill procedure. No asymmetry was detected for passive smoking (Figure 9) through the Egger's test ($p = 0.33$) but the trim-and-fill procedure suggested that ten potential studies were missing. The modified random effects pooled relative risk was 1.04 (95% CI 1.00–1.08).

Food Allergies

We retrieved only one study for active smoking and six studies for passive smoking, while three studies assessed maternal smoking

Annex II. Cont.

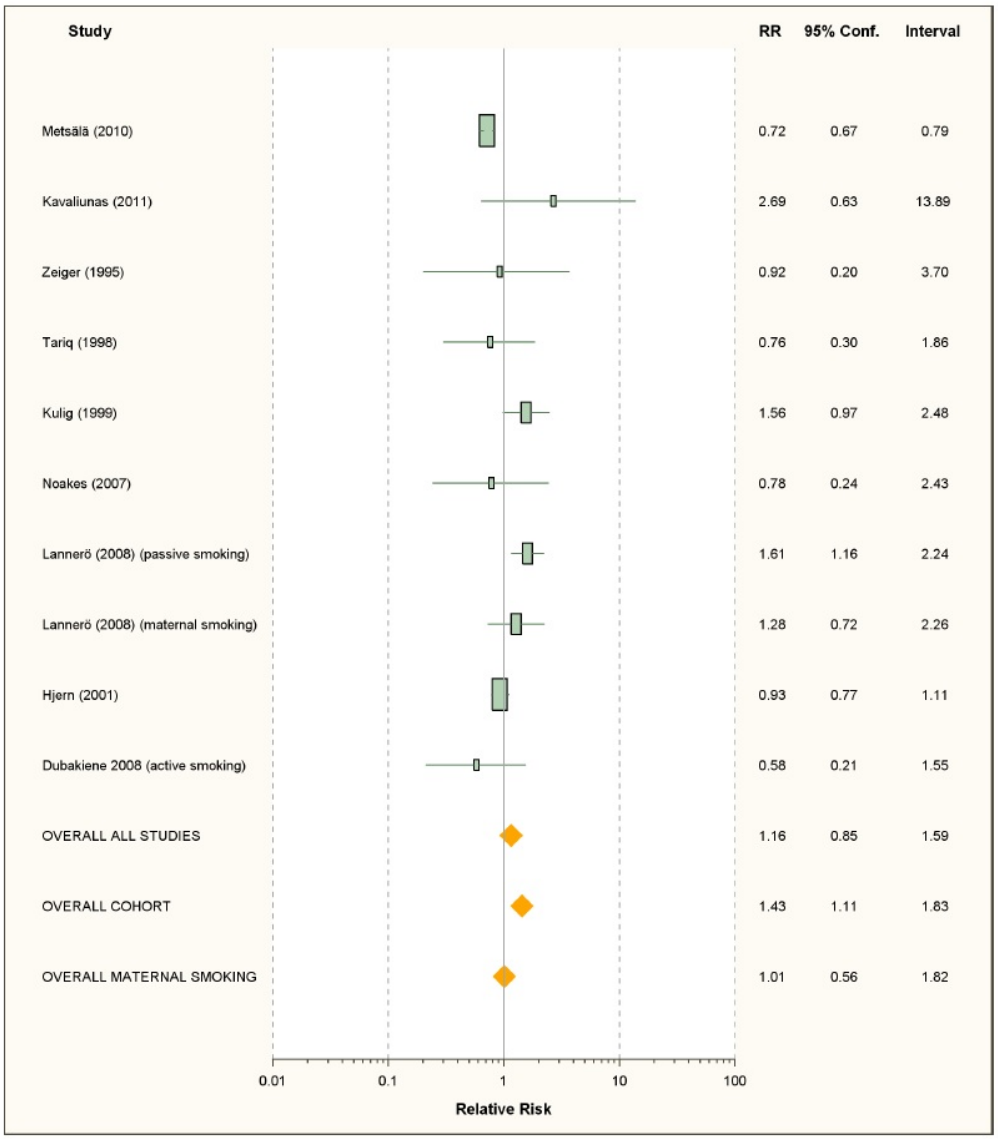

Figure 10. Study-specific and random effects pooled relative risks of passive smoking and food allergies.
doi:10.1371/journal.pmed.1001611.g010

during pregnancy (Figure 10; Table 7). All were carried out in children or infants populations.

Active Smoking

The only available study on active smoking and food allergies did not show any significant association (RR = 0.58; 95% CI 0.21–1.55).

Passive Smoking

Using random effect analysis, including the six studies investigating exposure to secondhand smoke, showed that passive smoking was associated with a nonsignificant increase of the risk of food allergy (RR = 1.16; 95% CI 0.85–1.59). When the only cross-sectional study was excluded and the analysis was based on five

Annex II. Cont.

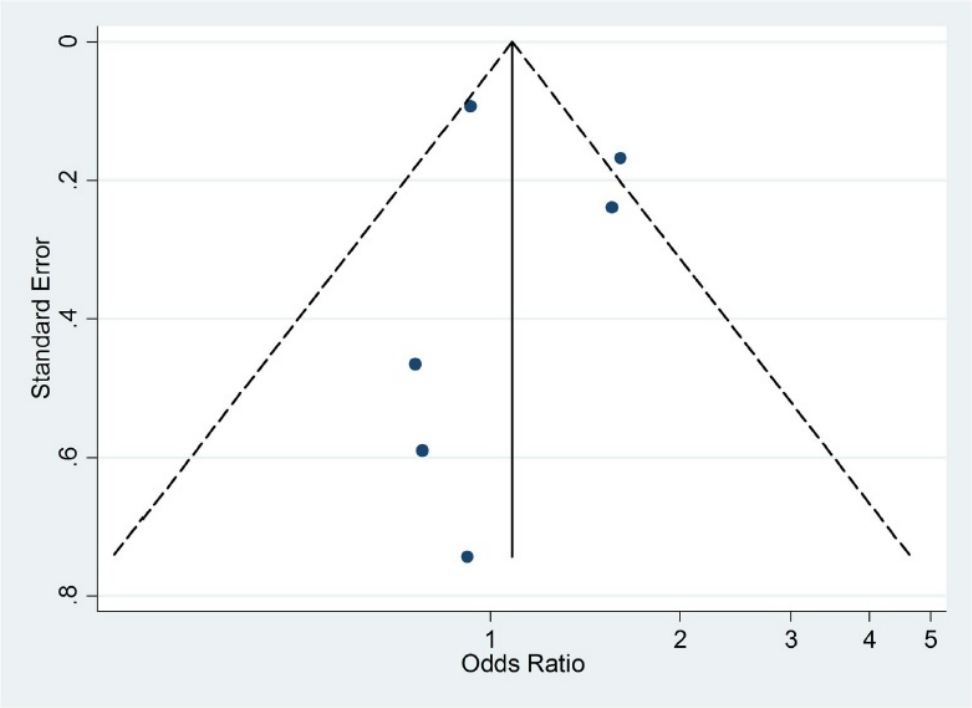

Figure 11. Funnel plot of relative risk versus standard error of relative risk: food allergy, passive smoking.
doi:10.1371/journal.pmed.1001611.g011

cohort studies, passive smoking was significantly associated with an increased risk of food allergy (RR = 1.43; 95% CI 1.12–1.83) (Table 8). As with allergic rhinitis and allergic dermatitis, we could not detect any association with maternal smoking during pregnancy with food allergies (RR = 1.01; 95% CI 0.56–1.82) (Table 8).

Publication Bias

The funnel plot (Figure 11), although not a valuable way to assess publication bias in this case due to the small sample size, did not provide evidence of asymmetry ($p = 0.09$).

Meta-regression

The meta-regression with the pooled log relative risk as a dependent variable and the population variable as a moderator, introduced in the model as a dichotomous variable (adults/pediatric population), yielded the following results for the children and adolescents when compared to the adults: allergic rhinitis and active smoking: RR = 1.55, 95% CI 1.30–1.84; allergic rhinitis and passive smoking: RR = 0.93, 95% CI 0.81–1.06; allergic dermatitis and active smoking: RR = 1.18, 95% CI 1.01–1.39; and allergic dermatitis and passive smoking: RR = 0.83, 95% CI 0.65–1.06. These results suggest that the associations between allergic rhinitis and allergic dermatitis with active smoking are significantly greater among children and adolescents than among adults. Although these meta-regression RRs were not statistically significant at a 95% level for passive smoking, in Tables 3 and 6 we present the results of children and adolescent populations as a subgroup both for active and passive smoking.

Sub-group Analyses in Children and Adolescents

We calculated the random effects pooled relative risks for children cohort studies, then for children cohort studies and case-control studies combined. For cohort studies, passive smoking was not significantly associated with allergic rhinitis (RR = 1.14; 95% CI 0.96–1.34, nine studies), or allergic dermatitis (RR = 1.09; 95% CI 0.96–1.23, 14 studies), but was significantly associated with an increased risk of food allergy (RR = 1.43; 95% CI 1.11–0.83, five studies). For cohort and case-control studies combined, passive smoking was significantly associated with an increased risk for allergic rhinitis: RR = 1.17 (95% CI 1.00–1.38, ten studies), but not for allergic dermatitis: RR = 1.07 (95% CI 0.96–1.19, 18 studies).

Sensitivity Analysis

To further evaluate the possibility that the results obtained for children/adolescents were due to publication bias, we assumed that cross-sectional studies are the kind of studies that are most probably rejected by journals in case of null results and recalculated our pooled estimates under the following extreme assumptions: (1) published cross-sectional studies are only half of

Annex II. Cont.

Table 6. Pooled relative risks and 95% confidence intervals of allergic dermatitis and smoking.

Study Type	Number of Studies	RR (95% CI) Fixed Effects	RR (95% CI) Random Effects	Ri[a] (95% CI)	Q test (*p*-Value)
Active smoking					
All studies	33	1.05 (1.04–1.06)	1.21 (1.14–1.29)	0.96 (0.91–1.00)	0.00001
Cohort studies	2	1.23 (1.10–1.38)	1.23 (1.09–1.38)	0.10 (0.00–1.00)	0.3003
Case-control studies	4	1.30 (1.03–1.64)	1.47 (0.92–2.32)	0.73 (0.27–1.00)	0.0160
Cross-sectional studies	27	1.05 (1.04–1.06)	1.21 (1.13–1.30)	0.97 (0.92–1.00)	0.00001
Cohort+case-control studies	6	1.24 (1.13–1.38)	1.27 (1.04–1.56)	0.67 (0.11–1.00)	0.0412
Full adjustment	17	1.05 (1.04–1.06)	1.21 (1.12–1.31)	0.98 (0.93–1.00)	0.00001
Incomplete adjustment	16	1.21 (1.14–1.29)	1.25 (1.09–1.45)	0.77 (0.56–0.98)	0.00001
Adults only	23	1.04 (1.03–1.05)	1.14 (1.07–1.22)	0.96 (0.89–1.00)	0.00001
Children/adolescents only	7	1.36 (1.27–1.46)	1.36 (1.17–1.46)	0.76 (0.44–1.00)	0.0008
Quality score ≥3	17	1.18 (1.13–1.23)	1.22 (1.11–1.34)	0.78 (0.55–1.00)	0.00001
Quality score <3	16	1.04 (1.03–1.05)	1.22 (1.11–1.34)	0.98 (0.94–1.00)	0.00001
Passive Smoking					
All studies	58	1.04 (1.03–1.06)	1.07 (1.03–1.12)	0.84 (0.71–0.98)	0.00001
Cohort studies	14	0.92 (0.90–0.95)	1.09 (0.96–1.23)	0.89 (0.72–1.00)	0.00001
Case-control studies	5	1.11 (0.94–1.31)	1.10 (0.88–1.38)	0.34 (0.00–1.00)	0.2411
Cross-sectional studies	39	1.08 (1.06–1.09)	1.07 (1.02–1.12)	0.81 (0.63–0.99)	0.00001
Cohort+case-control studies	19	0.93 (0.90–0.95)	1.09 (0.98–1.21)	0.86 (0.66–1.00)	0.00001
Full adjustment	32	1.08 (1.07–1.10)	1.08 (1.03–1.13)	0.81 (0.60–1.00)	0.00001
Incomplete adjustment	26	0.96 (0.94–0.98)	1.06 (0.98–1.14)	0.84 (0.65–1.00)	0.00001
Adults only	4	1.24 (1.03–1.50)	1.26 (1.02–1.55)	0.17 (0.00–1.00)	0.31
Children/adolescents only	53	1.04 (1.03–1.05)	1.06 (1.01–1.11)	0.85 (0.72–0.98)	0.00001
Children ISAAC method	22	1.07 (1.06–1.09)	1.09 (1.04–1.14)	0.73 (0.41–1.00)	0.00001
Children non-ISAAC method	29	0.99 (0.97–1.01)	1.05 (0.97–1.15)	0.89 (0.77–1.00)	0.00001
Maternal pregnancy smoking	19	0.99 (0.95–1.03)	1.07 (0.96–1.19)	0.80 (0.62–0.98)	0.00001
Quality score ≥3	28	1.04 (1.02–1.05)	1.11 (1.05–1.18)	0.88 (0.74–1.00)	0.00001
Quality score <3	30	1.06 (1.03–1.09)	1.03 (0.96–1.11)	0.80 (0.63–0.98)	0.00001

[a]Proportion of total variance due to between-study variance.

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the studies of smoking and allergic rhinitis ever conducted among children, (2) all unpublished studies found an RR of 1, (3) the unpublished studies found the same prevalence of allergic diseases as the average of the published studies. Under these extreme assumptions, the random effects pooled estimates for active smoking still show a significant increase in risk: RR = 1.16 (95% CI 1.08–1.25) for allergic rhinitis and RR = 1.13 (95% CI 1.05–1.21) for allergic dermatitis.

Discussion

The results of our systematic review and meta-analysis suggest that active and passive smoking are associated with a modest increase in risk for some allergic diseases. In the overall population, active smoking was associated with a modest increase in the risk for allergic dermatitis but not allergic rhinitis, while passive smoking was associated with modest increases in the risks for both allergic dermatitis and allergic rhinitis. Among children and adolescents, we observed significant associations between both active and passive smoking and allergic rhinitis and allergic dermatitis, and passive smoking was associated with an increased risk for food allergy

In children and adolescents, while the observed increase in risk for allergic diseases associated with smoking was small, the findings are important given that to the prevalence of active and passive smoking in this population can be high. Worldwide, 14% of adolescents aged 13 to 15 are active smokers with some countries reaching a prevalence of 40%, and nearly 25% of the children who smoke have smoked their first cigarette before the age of 10 years [210]. Furthermore, in the US, more than one-third of children live with at least one adult smoker [211]. In other parts of the world, passive exposure to tobacco among children is even higher as nearly half of children were exposed to tobacco smoke at home [212]. On the basis of the figures above, in countries with high smoking prevalence we estimate that 14% of allergic rhinitis and 13% of allergic dermatitis are attributable to active smoking [213]. Eliminating active smoking in children and adolescents would then prevent one in every seven cases of allergic rhinitis and one in every eight cases of allergic dermatitis.

That age is an important effect modifier for the relation between tobacco exposure and risk of allergic diseases is biologically plausible. The US Surgeon General has suggested that the immaturity of the respiratory, nervous, and immune systems in children may make them vulnerable to health effects of smoking [214]. Furthermore, unlike adults, children have limited options for avoiding exposure to secondhand smoke and are unable to reduce the quantity of products inhaled [214].

Annex II. Cont.

Table 7. Study-specific and 95% confidence intervals of food allergies and smoking.

Author	Country	Population	Follow-up (y)	Complete Follow-up (%)	Active Smoking	Passive Smoking	Maternal Pregnancy Smoking	Cases/Controls or Cohort Size or Total Sample Size	Variables of Adjustment, Matching, or Restriction
Case-control studies									
Metsälä 2010 [23]	Finland	Infants	—	—	—	—	0.72 (0.67–0.79)	16,237/16,237	Age, multiple pregnancy, gestational age, ponderal index, socioeconomic status, previous deliveries
Kavaliunas 2011 [166]	Lithuania	Children	—	—	—	—	2.69 (0.63–13.89)	42/144	Age
Cohort studies									
Zeiger 1995 [126]	USA	Children	7	57	—	0.92 (0.20–3.70)	—	22/165	Age
Tariq 1998 [26]	UK	Children	4	83.6	—	0.76 (0.30–1.86)	—	34/1,280	Age
Kulig 1999 [167]	Germany	Children	3	?	—	1.56 (0.97–2.48)	—	?/328	Age, parental education, study center
Noakes 2007 [136]	Australia	Infants	1	67.2	—	0.78 (0.24–2.43)	—	25/82	Age
Lannerö 2008 [14]	Sweden	Children	4	62	—	1.61 (1.16–2.24)	1.28 (0.72–2.26)	331/2,529	Age, parental atopy, socioeconomic status
Cross-sectional studies									
Hjern 2001 [73]	Sweden	Children	—	—	—	0.93 (0.77–1.11)	—	4,472	Age, sex, siblings, parental education, residence, single parent household, country of birth of parents, location
Dubakiene 2008 [168]	Lithuania	Children	—	—	0.58 (0.21–1.55)	—	—	540	Not specified

doi:10.1371/journal.pmed.1001611.t007

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Table 8. Pooled relative risks and 95% confidence intervals of food allergies and smoking.

Pooled Results	Passive Smoking All Studies	Passive Smoking Cohort Studies	Maternal Pregnancy Smoking
n studies	6	5	3
RR (95% CI), fixed effects	1.08 (0.93–1.24)	1.43 (1.12–1.83)	0.73 (0.67–0.80)
RR (95% CI), random effects	1.16 (0.85–1.59)	1.43 (1.11–1.83)	1.01 (0.56–1.82)
Ri[a] (95% CI)	0.68 (0.13–1.00)	0.01 (0.00–1.00)	0.96 (0.84–1.00)
Q Test (*p*-value)	0.0386	0.4026	0.0440

[a]Proportion of total variance due to between-study variance.

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Our finding that maternal exposure is not associated with the risk of allergic diseases in the offspring confirms the results from a previous meta-analysis that focused on the risk of allergic sensitization measured through skin prick positivity or IgE concentrations [30]. It is possible that the lack of observed association is due to the existence of bias given that parents of children at high risk of allergy may selectively avoid smoking during pregnancy.

The findings from our meta-analysis are subject to several limitations. The majority of studies were cross-sectional, a design that does not allow for causal inference and can overestimate relative risks given its reliance on prevalence ratios. When restricted to cohort studies our analyses showed that many of the results were no longer significant, especially for the subgroup analysis in children and adolescents. There is then some evidence that the findings may be impacted by study design.

Residual confounding (confounding remaining after adjustment) may explain some of our findings. For some of our analyses, we were unable to detect meaningful differences in the results between studies that had incomplete adjustment for confounders and those with more complete adjustment for confounders and our findings were broadly similar when restricting the analyses to studies with higher quality scores. However, there are likely to be other factors, such as genetic factors that were not controlled for and may play a role in the relationship between smoking and allergic diseases. Although publication bias cannot be ruled out, its magnitude is likely to be low as shown by the robustness of our sensitivity analysis.

Several studies assessed allergic diseases through self-report only, which can lead to misclassification of allergic and non-allergic conditions. Similarly, the findings are limited by measurement error in the smoking exposure given that a majority of studies assessed exposure to smoking in a qualitative fashion and often on a yes/no basis instead of using a quantitative assessment. Misclassification and measurement error in SHS assessment may result from a respondent's lack of knowledge about current or past exposure, biased recall, whether intentional or unintentional, and the difficulty in characterizing an exposure in complex indoor environments [215]. A standard set of items to identify passive smoking in distinct settings is needed [216]. If misclassification exists, it is probable that the outcome misclassification is not differential in regard to smoking and, similarly, measurement error in smoking assessment is not differential in regard to diagnosis. In this case, the results would be biased towards the null value, which means that the association with smoking observed in our meta-analysis is underestimated.

In our subgroup analyses, we were unable to identify any factors that accounted for study heterogeneity. Given the high heterogeneity estimates, we focused our interpretation on the random effects estimates. The random effects model gives increased weights to the effect of small studies, which may introduce bias in the estimation. It is worth noting that for some of the analyses, the fixed effects and random effects estimates differ substantially; this may be due to differences in case or exposure definition and in adjustment for potential confounders. AU: ok to delete>it appears that you have said this in the previous sentence.

Our subgroup analyses found stronger evidence for associations between smoking and allergic diseases in children and adolescents than adults. Furthermore, our meta-regression suggested that the association between active smoking and allergic disorders is larger in children and adolescents than in adults, which advocates for a transient effect through life. This finding is in accordance with the "atopic march" concept that suggests that the sequence of sensitization that starts in childhood may show a tendency to spontaneous remission later in life [217]. It is then plausible that sensitization to tobacco is mitigated by increasing age. Further research is needed to verify whether the association between smoking and risk of allergy in adults is similar for those who started smoking as an adult and those who started smoking during childhood or adolescents.

Future studies should minimize measurement error in the exposure and misclassification bias in the outcome. These studies should avoid cross-sectional designs, use extensive validated questionnaires in order to assess smoking in a quantitative fashion, and should be based on an optimal diagnosis of allergic diseases.

Supporting Information

Table S1 Quality scoring of allergic rhinitis, dermatitis, and food allergies studies.
(DOC)

Table S2 Pooled relative risks and 95% confidence intervals of criterion 1 of the quality scale, region of the world, and allergic rhinitis and dermatitis.
(DOC)

Table S3 Results of heterogeneity statistics Ri and I2 for subgroups of active and passive smoking.
(DOC)

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Author Contributions

Conceived and designed the experiments: JS CR AMM BT PK. Performed the experiments: JS CR AMM BT PK. Analyzed the data: JS BT.

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Contributed reagents/materials/analysis tools: JS BT PK. Wrote the first draft of the manuscript: JS BT. Contributed to the writing of the manuscript: JS CR AMM BT. ICMJE criteria for authorship read and met: JS CR AMM PK BT. Agree with manuscript results and conclusions: JS CR AMM PK BT.

References

1. Ozdoganoglu T, Songu M (2012) The burden of allergic rhinitis and asthma. Ther Adv Respir Dis 6: 11–23.
2. Bauchau V, Durham SR (2004) Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 24: 758–764.
3. Berger WE (2004) Allergic rhinitis in children: diagnosis and management strategies. Paediatr Drugs 6: 233–250.
4. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, et al. (2007) The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol 120: 638–646.
5. DaVeiga SP (2012) Epidemiology of atopic dermatitis: a review. Allergy Asthma Proc 33: 227–234
6. Meltzer EO, Blaiss MS, Derebery MJ, Mahr TA, Gordon BR, et al. (2009) Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. J Allergy Clin Immunol 124: S43–S70
7. Nathan RA (2007) The burden of allergic rhinitis. Allergy Asthma Proc 28: 3–9.
8. Alanne S, Maskunitty A, Nermes M, Laitinen K, Pekurinen M (2012). Costs of allergic diseases from birth to two years in Finland. Public Health 126: 866–872
9. Spergel JM (2010) From atopic dermatitis to asthma: the atopic march. Ann Allergy Asthma Immunol 105: 99–106
10. Tan RA, Corren J (2011) The relationship of rhinitis and asthma, sinusitis, food allergy, and eczema. Immunol Allergy Clin North Am 31: 481–491.
11. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, et al. (2006) 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 368: 733–743.
12. Ghouri N, Hippisley-Cox J, Newton J, Sheikh A (2008) Trends in the epidemiology and prescribing of medication for allergic rhinitis in England. J R Soc Med 101: 466–72.
13. Mosges R, Klimek L (2007) Today's allergic rhinitis patients are different: new factors that may play a role. Allergy 62: 969–975.
14. Lannerö E, Wickman M, van Hage M, Bergström A, Pershagen G, et al. (2008) Exposure to environmental tobacco smoke and sensitisation in children. Thorax 63: 172–176.
15. Diaz-Sanchez D, Rumold R, Gong H Jr (2006) Challenge with environmental tobacco smoke exacerbates allergic airway disease in human beings. J Allergy Clin Immunol 118: 441–446.
16. Peden D, Reed CE (2010) Environmental and occupational allergies. J Allergy Clin Immunol 125(2 Suppl 2): S150–S160.
17. Warren CW, Jones NR, Peruga A, Chauvin J, Baptiste JP, et al. (2008) Global youth tobacco surveillance, 2000–2007. MMWR Surveill Summ 57: 1–28.
18. Murin S, Rafii R, Bilello K (2011) Smoking and smoking cessation in pregnancy. Clin Chest Med 32: 75–91.
19. Cakir E, Ersu R, Uyan ZS, Oktem S, Varol N, et al. (2010) The prevalence and risk factors of asthma and allergic diseases among working adolescents. Asian Pac J Allergy Immunol 28: 122–129.
20. Lee CH, Chuang HY, Hong CH, Huang SK, Chang YC, et al. (2011) Lifetime exposure to cigarette smoking and the development of adult-onset atopic dermatitis. Br J Dermatol 164: 483–489.
21. Bendtsen P, Grønbaek M, Kjaer SK, Munk C, Linneberg A, et al. (2008) Alcohol consumption and the risk of self-reported perennial and seasonal allergic rhinitis in young adult women in a population-based cohort study. Clin Exp Allergy 38: 1179–1185.
22. Ludvigsson JF, Mostrom M, Ludvigsson J, Duchen K (2005) Exclusive breastfeeding and risk of atopic dermatitis in some 8300 infants. Pediatr Allergy Immunol 16: 201–208.
23. Metsälä J, Lundqvist A, Kaila M, Gissler M, Klaukka T, et al. (2010) Maternal and perinatal characteristics and the risk of cow's milk allergy in infants up to 2 years of age: a case-control study nested in the Finnish population. Am J Epidemiol 171: 1310–1316.
24. McKeever TM, Lewis SA, Smith C, Collins J, Heatlie H, et al. (2001). Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. Thorax 56: 758–762.
25. Wang IJ, Guo YL, Lin TJ, Chen PC, Wu YN (2010) GSTM1, GSTP1, prenatal smoke exposure, and atopic dermatitis. Ann Allergy Asthma Immunol 105: 124–129.
26. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, et al. (1998) The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. J Allergy Clin Immunol 101: 587–593.
27. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, et al. (2012) Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics 129: 735–744.
28. Baena-Cagnani CE, Gómez RM, Baena-Cagnani R, Canonica GW (2009) Impact of environmental tobacco smoke and active tobacco smoking on the development and outcomes of asthma and rhinitis. Curr Opin Allergy Clin Immunol 9: 136–140.
29. Pattenden S, Antova T, Neuberger M, Nikiforov B, De Sario M, et al. (2006) Parental smoking and children's respiratory health: independent effects of prenatal and postnatal exposure. Tob Control 15: 294–301.
30. Strachan DP, Cook DG (1998) Health effects of passive smoking. 5. Parental smoking and allergic sensitisation in children. Thorax 53: 117–123.
31. Freiman A, Bird G, Metelitsa AI, Barankin B, Lauzon GJ (2004) Cutaneous effects of smoking. J Cutan Med Surg 8: 415–423.
32. Just-Sarobé M (2008) Smoking and the skin. Actas Dermosifiliogr 99: 173–184.
33. National Institute for Public Health and the Environment (2010) Risk factors for food allergy. Bilthoven (The Netherlands): RIVM Report 340007001.
34. Wells G, Shea B, O'Connell D, Peterson J, Welch V, et al. (2012) The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Health Research Institute website. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 16 August 2012.
35. Rothman KJ, Greenland S, Lash TL (2008) Measure of effect and measures of association. Modern epidemiology. 3rd edition. Philadelphia: Lippincott, Williams and Wilkins. P61.
36. Takkouche B, Cadarso-Suarez C, Spiegelman D (1999) Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. Am J Epidemiol 150: 206–215.
37. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. Br Med J 315: 629–634.
38. Costa-Bouzas J, Takkouche B, Cadarso-Suarez C, Spiegelman D (2001) HEpiMA: software for the identification of heterogeneity in meta-analysis. Comput Methods Programs Biomed 64: 101–107.
39. Ozasa K, Takenaka H, Takagi N, Aoike A, Kawai K (1995) A case-control study of risk factors for Japanese cedar pollinosis. Jpn J Hyg 50: 622–630.
40. Lin SY, Reh DD, Clipp S, Irani L, Navas-Acien A (2011) Allergic rhinitis and secondhand tobacco smoke: a population-based study. Am J Rhinol Allergy 25: e66–e71.
41. Miyake Y, Tanaka K, Arakawa M (2011) Case-control study of IL13 polymorphisms, smoking, and rhinoconjunctivitis in Japanese women: the Kyushu Okinawa Maternal and Child Health Study. BMC Med Genet 12: 143.
42. Wright AL, Holberg CJ, Halonen M, Martinez FD, Morgan W, et al. (1994) Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics 94: 895–901.
43. Annesi-Maesano I, Oryszczyn M-P, Neukirch F, Kauffmann F (1997) Relationship of upper airway disease to tobacco smoking and allergic markers: a cohort study of men followed up for 5 years. Int Arch Allergy Immunol 114: 193–201.
44. Lewis SA, Britton JR (1998) Consistent effects of high socioeconomic status and low birth order, and the modifying effect of maternal smoking on the risk of allergic disease during childhood. Respir Med 92: 1237–1244.
45. Shaheen SO, Sterne JAC, Montgomery SM, Azima H (1999) Birth weight, body mass index and asthma in young adults. Thorax 54: 396–402.
46. Bergmann RL, Edenharter G, Bergmann KE, Lau S, Wahn U (2000) Socioeconomic status is a risk factor for allergy in parents but not in their children. Clin Exp Allergy 30: 1740–1745.
47. Tariq SM, Hakim EA, Matthews SM, Arshad SH (2000) Influence of smoking on asthmatic symptoms and allergen sensitisation in early childhood. Postgrad Med J 76: 694–699.
48. Magnusson LL, Olesen AB, Wennborg H, Olsen J (2005) Wheezing, asthma, hayfever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life. Clin Exp Allergy 35: 1550–1556.
49. Johansson A, Ludvigsson J, Hermansson G (2008) Adverse health effects related to tobacco smoke exposure in a cohort of three-year olds. Acta Pædiatr 97: 354–357.
50. Nagata C, Nakamura K, Fujii K, Kawachi T, Takatsuka N, et al. (2008) Smoking and risk of cedar pollinosis in Japanese men and women. Int Arch Allergy Immunol 147: 117–124.
51. Keil T, Lau S, Roll S, Gruber C, Nickel R, et al. (2009) Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. Allergy 64: 445–451.
52. Codispoti CD, Levin L, LeMasters GK, Ryan P, Reponen T, et al. (2010) Breast-feeding, aeroallergen sensitization, and environmental exposures during infancy are determinants of childhood allergic rinitis. J Allergy Clin Immunol 125: 1054–1060.
53. Bakke P, Gulsvik A, Eide GE (1990) Hay fever, eczema and urticaria in southwest Norway. Lifetime prevalences and association with sex, age, smoking habits, occupational airborne exposures and respiratory symptoms. Allergy 45: 515–522.
54. Leuenberger P, Schwartz J, Ackermann-Liebrich U, Blaser K, Bolognini G, et al. (1994) Passive smoking exposure in adults and chronic respiratory

Annex II. Cont.

symptoms (SAPALDIA Study) Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. Am J Respir Crit Care Med 150: 1222–1228.
55. Ng TP, Tan WC (1994) Epidemiology of allergic rhinitis and its associated risk factors in Singapore. Int J Epidemiol 23: 553–558.
56. Moyes CD, Waldon J, Ramadas D, Crane J, Pearce N (1995) Respiratory symptoms and environmental factors in schoolchildren in the Bay of Plenty. N Z Med J 108: 358–361.
57. Wüthrich B, Schindler C, Medici TC, Zellweger JP, Leuenberger P (1996) IgE levels, atopy markers and hay fever in relation to age, sex and smoking status in a normal adult Swiss population. SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) Team. Int Arch Allergy Immunol 111: 396–402.
58. Min Y-G, Jung H-W, Kim HS, Park SK, Yoo KY (1997) Prevalence and risk factors for perennial allergic rhinitis in Korea: results of a nationwide survey. Clin Otolaryngol 22: 139–144.
59. Siracusa A, Marabini A, Sensi L, Bacoccoli R, Ripandelli A, et al. (1997) Prevalence of asthma and rhinitis in Perugia, Italy. Monaldi Arch Chest Dis 52: 434–439.
60. Austin JB, Russell G (1997) Wheeze, cough, atopy, and indoor environment in the Scottish Highlands. Arch Dis Child 76: 22–26.
61. Farooqi IS, Hopkin JM (1998) Early childhood infection and atopic disorder. Thorax 53: 927–32.
62. Lam TH, Chung SF, Betson CL, Wong CM, Hedley AJ (1998) Respiratory symptoms due to active and passive smoking in junior secondary school students in Hong Kong. Int J Epidemiol 27: 41–48.
63. Ponsonby AL, Couper D, Dwyer T, Carmichael A (1998) Cross sectional study of the relation between sibling number and asthma, hay fever, and eczema. Arch Dis Child 79: 328–333.
64. Montefort S, Lenicker HM, Caruna S, Agius Muscat H (1998) Asthma, rhinitis and eczema in Maltese 13–15 year-old schoolchildren – prevalence, severity and associated factors [ISAAC]. International Study of Asthma and Allergies in Childhood. Clin Exp Allergy 28: 1089–1099.
65. Duhme H, Weiland SK, Rudolph P, Wienke A, Kramer A, et al. (1998) Asthma and allergies among children in West and East Germany: a comparison between Münster and Greifswald using the ISAAC phase I protocol. International Study of Asthma and Allergies in Childhood. Eur Respir J 11: 840–847.
66. Burr ML, Anderson HR, Austin JB, Harkins LS, Kaur B, et al. (1999) Respiratory symptoms and home environment in children: a national survey. Thorax 54: 27–32.
67. Dotterud LK, Falk ES (1999) Atopic disease among adults in northern Russia, an area with heavy air pollution. Acta Derm Venereol 79: 448–450.
68. Keleş N, Ilicali C, Değer K (1999) The effects of different levels of air pollution on atopy and symptoms of allergic rhinitis. Am J Rhinol 13: 185–190.
69. Plaschke PP, Janson C, Norrman E, Björnsson E, Ellbjär S, et al. (2000) Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. Am J Respir Crit Care Med 162: 920–924.
70. Zacharasiewicz A, Zidek T, Haidinger G, Waldhor T, Vutuc C (2000) Symptoms suggestive of atopic rhinitis in children aged 6–9 years and the indoor environment. Allergy 55: 945–950.
71. Upton MN, McConnachie A, McSharry C, Hart CL, Smith GD, et al. (2000) Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. BMJ 321: 88–92.
72. Ozdemir N, Uçgun I, Metintas S, Kolsuz M, Metintas M (2000) The prevalence of asthma and allergy among university freshmen in Eskisehir, Turkey. Respir Med 94: 536–541.
73. Hjern A, Hedberg A, Haglund B, Rosén M (2001) Does tobacco smoke prevent atopic disorders? A study of two generations of Swedish residents. Clin Exp Allergy 31: 908–914.
74. Janson C, Chinn S, Jarvis D, Zock JP, Torén K, et al. (2001) Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. Lancet 358: 2103–2109.
75. Simpson BM, Custovic A, Simpson A, Hallam CL, Walsh D, et al. (2001) NAC Manchester asthma and allergy study (NACMAAS): risk factors for asthma and allergic disorders in adults. Clin Exp Allergy 31: 391–399.
76. Dotterud LK, Odland JO, Falk ES (2001) Atopic diseases among schoolchildren in Nikel, Russia, an Arctic area with heavy air pollution. Acta Derm Venereol 81: 198–201.
77. Kalyoncu AF, Demir AU, Ozcakar B, Bozkurt B, Artvinli M (2001) Asthma and allergy in Turkish university students: Two cross-sectional surveys 5 years apart. Allergol Immunopathol (Madr) 29: 264–271.
78. Lee SI, Shin MH, Lee HB, Lee JS, Son BK, et al. (2001) Prevalences of symptoms of asthma and other allergic diseases in Korean children: a nationwide questionnaire survey. J Korean Med Sci 16: 155–164.
79. Stazi MA, Sampogna F, Montagano G, Grandolfo ME, Couilliot MF, et al. (2002) Early life factors related to clinical manifestations of atopic disease but not to skin-prick test positivity in young children. Pediatr Allergy Immunol 13: 105–112.
80. Peroni DG, Piacentini GL, Alfonsi L, Zerman L, Di Blasiw P, et al. (2003) Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. Clin Exp Allergy 33: 1349–1354.
81. Barraza Villarreal A, Sanin Aguirre LH, Téllez Rojo MM, Lacasaña Navarro M, Romieu I (2003) Risk factors for asthma in school children from Ciudad Juárez, Chihuahua. J Asthma 40: 413–423.
82. Monteil MA, Joseph G, Chang Kit C, Wheeler G, Antoine RM (2004) Smoking at home is strongly associated with symptoms of asthma and rhinitis in children of primary school age in Trinidad and Tobago. Rev Panam Salud Publica 16: 193–198.
83. Lee SL, Wong W, Lau YL (2004) Increasing prevalence of allergic rhinitis but not asthma among children in Hong Kong from 1995 to 2001 (Phase 3 International Study of Asthma and Allergies in Childhood). Pediatr Allergy Immunol 15: 72–78.
84. Krämer U, Lemmen CH, Behrendt H, Link E, Schäfer T, et al. (2004) The effect of environmental tobacco smoke on eczema and allergic sensitization in children. Br J Dermatol 150: 111–118.
85. Demir AU, Karakaya G, Bozkurt B, Sekerel BE, Kalyoncu AF (2004) Asthma and allergic diseases in schoolchildren: third cross-sectional survey in the same primary school in Ankara, Turkey. Pediatr Allergy Immunol 15: 531–538.
86. Miyake Y, Yura A, Iki M (2004) Cross-sectional study of allergic disorders in relation to familial factors in Japanese adolescents. Acta Paediatr 93: 380–385.
87. Annesi-Maesano I, Oryszczyn MP, Raherison C, Kopferschmitt C, Pauli G, et al. (2004) Increased prevalence of asthma and allied diseases among active adolescent tobacco smokers after controlling for passive smoking exposure. A cause for concern? Clin Exp Allergy 34: 1017–1023.
88. De S, Fenton JE, Jones AS, Clarke RW (2005) Passive smoking, allergic rhinitis and nasal obstruction in children. J Laryngol Otol 119: 955–957.
89. Topp R, Thefeld W, Wichmann HE, Heinrich J (2005) The effect of environmental tobacco smoke exposure on allergic sensitization and allergic rhinitis in adults. Indoor Air 15: 222–227.
90. Maziak W, Kenneth D, Ward KD, Rastam S, Mzayek F, et al. (2005) Extent of exposure to environmental tobacco smoke (ETS) and its dose-response relation to respiratory health among adults. Respir Res 6: 13.
91. Miyake Y, Miyamoto S, Ohya Y, Sasaki S, Matsunaga I, et al. (2005) Association of active and passive smoking with allergic disorders in pregnant Japanese women: baseline data from the Osaka Maternal and Child Health Study. Ann Allergy Asthma Immunol 94: 644–651.
92. Bugiani M, Carosso A, Migliore E, Piccioni P, Corsico A, et al. (2005) ISAYA (ECRHS Italy) Study Group. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. Allergy 60: 165–70.
93. Obihara CC, Marais BJ, Gie RP, Potter P, Bateman ED, et al. (2005) The association of prolonged breastfeeding and allergic disease in poor urban children. Eur Respir J 25: 970–977.
94. Strumylaite L, Kregzdyte R, Vaitkaitiene E (2005) Pasyvus rukymas ir vaiku kvepavimo sutrikimai [Passive smoking and respiratory health of children]. Medicina (Kaunas) 41: 348–354.
95. Lund VJ, Preziosi P, Hercberg S, Hamoir M, Dubreuil C, et al. (2006) Yearly incidence of rhinitis, nasal bleeding, and other nasal symptoms in mature women. Rhinology 44: 26–31.
96. Kurosaka F, Nakatani Y, Terada T, Tanaka A, Ikeuchi H, et al. (2006) Current cat ownership may be associated with the lower prevalence of atopic dermatitis, allergic rhinitis, and Japanese cedar pollinosis in schoolchildren in Himeji, Japan. Pediatr Allergy Immunol 17: 22–28.
97. Sakar A, Yorgancioglu A, Dinc G, Yuksel H, Celik P, et al. (2006) The prevalence of asthma and allergic symptoms in Manisa, Turkey (A western city from a country bridging Asia and Europe). Asian Pac J Allergy Immunol 24: 17–25.
98. Ho SY, Lam TH, Chung SF, Lam TP (2007) Cross-sectional and prospective associations between passive smoking and respiratory symptoms at the workplace. Ann Epidemiol 17: 126–131.
99. Horak E, Morassa B, Ulmerb H (2007) Association between environmental tobacco smoke exposure and wheezing disorders in Austrian preschool children. Swiss Med Wkly 137: 608–613.
100. Ebbert JO, Croghan IT, Schroeder DR, Murawski J, Hurt RD (2007) Association between respiratory tract diseases and secondhand smoke exposure among never smoking flight attendants: a cross-sectional survey. Environ Health 6: 28.
101. Tanaka K, Miyake Y, Arakawa M, Sasaki S, Ohya Y (2007) Prevalence of asthma and wheeze in relation to passive smoking in Japanese children. Ann Epidemiol 17: 1004–1010.
102. Zuraimi MS, Tham KW, Chew FT, Ooi PL, David K (2008) Home exposures to environmental tobacco smoke and allergic symptoms among young children in Singapore. Int Arch Allergy Immunol 146: 57–65.
103. Foliaki S, Annesi-Maesano I, Tuuau-Potoi N, Waqatakirewa L, Cheng S, et al. (2008) Risk factors for symptoms of childhood asthma, allergic rhinoconjunctivitis and eczema in the Pacific: an ISAAC Phase III study. Int J Tuberc Lung Dis 12: 799–780.
104. Gómez R, Teijeiro A, Zernotti M, Canonica G, Mimessi G, et al. (2008) Smoking is a risk factor for having rhinitis in adolescents. Allergy 63: 419.
105. Kabir Z, Manning PJ, Holohan J, Keogan S, Goodman PG, et al. (2009) Second-hand smoke exposure in cars and respiratory health effects in children. Eur Respir J 34: 629–633.
106. Brescianini S, Brunetto B, Iacovacci P, D'Ippolito C, Alberti G, et al. (2009) Prevalence of self-perceived allergic diseases and risk factors in Italian adolescents. Pediatr Allergy Immunol 20: 578–84.

Annex II. Cont.

107. Musharrafieh U, Al-Sahab B, Zaitoun F, El-Hajj MA, Ramadan F, et al. (2009) Prevalence of asthma, allergic rhinitis and eczema among Lebanese adolescents. J Asthma 46: 382–87.
108. González-Diaz SN, Del Río-Navarro BE, Pietropaolo-Cienfuegos DR, Escalante-Domínguez AJ, García-Almaraz RG, et al. (2010) Factors associated with allergic rhinitis in children and adolescents from northern Mexico: International Study of Asthma and Allergies in Childhood Phase IIIB. Allergy Asthma Proc 31: 53–62.
109. Bedolla-Barajas M, Cuevas-Ríos G, García-Barboza E, Barrera-Zepeda AT, Morales-Romero J (2010) Prevalencia y factores asociados a la rinitis alérgica en escolares de Ciudad Guzmán, Mexico. [Prevalence and factors associated to allergic rhinitis among schoolchildren of Ciudad Guzmán, Mexico] Rev Invest Clin 62: 244–251.
110. Wang HY, Pizzichini MM, Becker AB, Duncan JM, Ferguson AC, et al. (2010) Disparate geographic prevalences of asthma, allergic rhinoconjunctivitis and atopic eczema among adolescents in five Canadian cities. Pediatr Allergy Immunol 21: 867–877.
111. Vlaski E, Stavric K, Seckova L, Kimovska M, Isjanovska R (2011) Do household tobacco smoking habits influence asthma, rhinitis and eczema among 13–14 year-old adolescents? Allergol Immunopathol 39: 39–44.
112. Virkkula P, Liukkonen K, Suomalainen AK, Aronen ET, Kirjavainen T, et al. (2011) Parental smoking, nasal resistance and rhinitis in children. Acta Paediatr 100: 1234–1238.
113. Håkansson K, von Buchwald C, Thomsen SF, Thyssen JP, Backer V, et al. (2011) Nonallergic rhinitis and its association with smoking and lower airway disease: a general population study. Am J Rhinol Allergy 25: 25–29.
114. Chen BY, Chan CC, Han YY, Wu HP, Guo YL (2012) The risk factors and quality of life in children with allergic rhinitis in relation to seasonal attack patterns. Paediatr Perinat Epidemiol 26: 146–155.
115. Peñaranda A, Aristizabal G, Garcia E, Vasquez C, Rodriguez-Martinez CE, et al. (2012) Allergic rhinitis and associated factors in schoolchildren from Bogota, Colombia. Rhinology 50: 122–128.
116. Tanaka K, Miyake Y, Arakawa M (2012) Smoking and prevalence of allergic disorders in Japanese pregnant women: baseline data from the Kyushu Okinawa Maternal and Child Health Study. Environ Health 11: 15.
117. Montefort S, Ellul P, Montefort M, Caruana S, Grech V, et al. (2012) The effect of cigarette smoking on allergic conditions in Maltese children (ISAAC). Pediatr Allergy Immunol 23: 472–478.
118. Mitchell EA, Beasley R, Keil U, Montefort S, Odhiambo J, et al. (2012) 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 67: 941–949.
119. Mills CM, Srivastava ED, Harvey IM, Swift GL, Newcombe RG, et al. (1994) Cigarette smoking is not a risk factor in atopic dermatitis. Int J Dermatol 33: 33–34.
120. Yang CY, Cheng MF, Hsieh YL (2000) Effects of indoor environmental factors on risk for atopic eczema in a subtropical area. J Toxicol Environ Health A 61: 245–253.
121. Purvis DJ, Thompson JM, Clark PM, Robinson E, Black PN, et al. (2005) Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. Br J Dermatol 152: 742–749.
122. Haileamlak A, Dagoye D, Williams H, Venn AJ, Hubbard R, et al. (2005) Early life risk factors for atopic dermatitis in Ethiopian children. J Allergy Clin Immunol 115: 370–376.
123. Sebök B, Schneider I, Harangi F (2006) Primary Care Paediatricians in Baranya County. Familiar and environmental factors influencing atopic dermatitis in the childhood. J Eur Acad Dermatol Venereol 20: 418–422.
124. Miyake Y, Tanaka K, Arakawa M (2011) IL13 genetic polymorphisms, smoking, and eczema in women: a case-control study in Japan. BMC Med Genet 12: 142.
125. Burr ML, Miskelly FG, Butland BK, Merrett TG, Vaughan-Williams E (1989) Environmental factors and symptoms in infants at high risk of allergy. J Epidemiol Community Health 43: 125–132.
126. Zeiger RS, Heller S (1995) The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. J Allergy Clin Immunol 95: 1179–1190.
127. Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K (1997) Atopic dermatitis and birth factors: historical follow up by record linkage. BMJ 314: 1003–1008.
128. Bergmann RL, Diepgen TL, Kuss O, Bergmann KE, Kujat J, et al. (2002) Breastfeeding duration is a risk factor for atopic eczema. Clin Exp Allergy 32: 205–209.
129. Kerkhof M, Koopman LP, van Strien RT, Wijga A, Smit HA, et al. (2003) Risk factors for atopic dermatitis in infants at high risk of allergy: the PIAMA study. Clin Exp Allergy 33: 1336–1341.
130. Linneberg A, Simonsen JB, Petersen J, Stensballe LG, Benn CS (2006) Differential effects of risk factors on infant wheeze and atopic dermatitis emphasize a different etiology. J Allergy Clin Immunol 117: 184–189.
131. Lerbaek A, Kyvik KO, Ravn H, Menné T, Agner T (2007) Incidence of hand eczema in a population-based twin cohort: genetic and environmental risk factors. Br J Dermatol 157: 552–557.
132. Noakes P, Taylor A, Hale J, Breckler L, Richmond P, et al. (2007) The effects of maternal smoking on early mucosal immunity and sensitization at 12 months of age. Pediatr Allergy Immunol 18: 118–127.
133. Sariachvili M, Droste J, Dom S, Wieringa M, Vellinga A, et al. (2007) Is breast feeding a risk factor for eczema during the first year of life? Pediatr Allergy Immunol 18: 410–417.
134. Tanaka K, Miyake Y, Sasaki S, Ohya Y, Hirota Y, et al. (2008) Maternal smoking and environmental tobacco smoke exposure and the risk of allergic diseases in Japanese infants: the Osaka Maternal and Child Health Study. J Asthma 45: 833–838.
135. Böhme M, Kull I, Bergström A, Wickman M, Nordvall L, et al. (2010) Parental smoking increases the risk for eczema with sensitization in 4-year-old children. J Allergy Clin Immunol 125: 941–943.
136. Jedrychowski W, Perera F, Maugeri U, Mrozek-Budzyn D, Miller RL, et al. (2011) Effects of prenatal and perinatal exposure to fine air pollutants and maternal fish consumption on the occurrence of infantile eczema. Int Arch Allergy Immunol 155: 275–281.
137. Edman B (1988) Palmar eczema: a pathogenetic role for acetylsalicylic acid, contraceptives and smoking? Acta Derm Venereol 68: 402–407.
138. Volkmer RE, Ruffin RE, Wigg NR, Davies N (1995) The prevalence of respiratory symptoms in South Australian preschool children. II. Factors associated with indoor air quality. J Paediatr Child Health 31: 116–120.
139. Liss GM, Sussman GL, Deal K, Brown S, Cividino M, et al. (1997) Latex allergy: epidemiological study of 1351 hospital workers. Occup Environ Med 54: 335–342.
140. Schäfer T, Dirschedl P, Kunz B, Ring J, Uberla K (1997) Maternal smoking during pregnancy and lactation increases the risk for atopic eczema in the offspring. J Am Acad Dermatol 36: 550–556.
141. Linneberg A, Nielsen NH, Menné T, Madsen F, Jørgensen T (2003) Smoking might be a risk factor for contact allergy. J Allergy Clin Immunol 111: 980–984.
142. Montnemery P, Nihlén U, Göran Löfdahl C, Nyberg P, Svensson A (2003) Prevalence of self-reported eczema in relation to living environment, socio-economic status and respiratory symptoms assessed in a questionnaire study. BMC Dermatol 3: 4.
143. Yemaneberhan H, Flohr C, Lewis SA, Bekele Z, Parry E, et al. (2004) Prevalence and associated factors of atopic dermatitis symptoms in rural and urban Ethiopia. Clin Exp Allergy 34: 779–785.
144. Heudorf U, Schümann M, Angerer J, Exner M (2005) Dermal and bronchial symptoms in children: are they caused by PAH containing parquet glue or by passive smoking? Int Arch Occup Environ Health 78: 655–662.
145. Montnemery P, Nihlén U, Löfdahl CG, Nyberg P, Svensson A (2005) Prevalence of hand eczema in an adult Swedish population and the relationship to risk occupation and smoking. Acta Derm Venereol 85: 429–432.
146. Dotterud LK, Smith-Sivertsen T (2007) Allergic contact sensitization in the general adult population: a population-based study from Northern Norway. Contact Dermatitis 56: 10–15.
147. Al-Sahab B, Atoui M, Musharrafieh U, Zaitoun F, Ramadan F, et al. (2008) Epidemiology of eczema among Lebanese adolescents. Int J Public Health 53: 260–267.
148. Ergin S, Ozşahin A, Erdoğan BS, Aktan S, Zencir M (2008) Epidemiology of atopic dermatitis in primary schoolchildren in Turkey. Pediatr Dermatol 25: 399–401.
149. Suárez-Varela M, García-Marcos L, Kogan MD, Llopis González A, Martínez Gimeno A, et al. (2008) 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) 36: 336–442.
150. Attwa E, el-Laithy N (2009) Contact dermatitis in car repair workers. J Eur Acad Dermatol Venereol 23: 138–145.
151. Meding B, Alderling M, Albin M, Brisman J, Wrangsjö K (2009) Does tobacco smoking influence the occurrence of hand eczema? Br J Dermatol 160: 514–518.
152. Lipińska KI, Elgalal A, Kuna P (2009) Epidemiologia atopowego zapalenia skory w populacji ogolnej mieszkancow wojewodztwa lodzkiego [Epidemiology of atopic dermatitis in general population of Lodz province's citizens]. Pneumonol Alergol Pol 77: 145–151.
153. Xepapadaki P, Manios Y, Liarigkovinos T, Grammatikaki E, Douladiris N, et al. (2009) Association of passive exposure of pregnant women to environmental tobacco smoke with asthma symptoms in children. Pediatr Allergy Immunol 20: 423–429.
154. Röhrl K, Stenberg B (2010) Lifestyle factors and hand eczema in a Swedish adolescent population. Contact Dermatitis 62: 170–176.
155. Thyssen JP, Linneberg A, Menné T, Nielsen NH, Johansen JD (2010) The effect of tobacco smoking and alcohol consumption on the prevalence of self-reported hand eczema: a cross-sectional population-based study. Br J Dermatol 162: 619–626.
156. Meding B, Alderling M, Wrangsjö K (2010) Tobacco smoking and hand eczema: a population-based study. Br J Dermatol 163: 752–756.
157. Yang YW, Chen YH, Huang YH (2011) Cigarette smoking may modify the risk of depression in eczema among adults: a preliminary study using NHANES 2005–2006. J Eur Acad Dermatol Venereol 25: 1048–1053.
158. Civelek E, Sahiner UM, Yüksel H, Boz AB, Orhan F, et al. (2011) Prevalence, burden, and risk factors of atopic eczema in schoolchildren aged 10–11 years: a national multicenter study. J Investig Allergol Clin Immunol 21: 270–277.

Annex II. Cont.

159. Dei-Cas P, Acuña MK, Dei-Cas I (2011) Atopic dermatitis in children: a comparative survey among 2 age groups. Rev Chil Pediatr 82: 410–418.
160. Apfelbacher CJ, Diepgen TL, Schmitt J (2011) Determinants of eczema: population-based cross-sectional study in Germany. Allergy 66: 206–213.
161. Park H, Kim K (2011) Association of blood mercury concentrations with atopic dermatitis in adults: a population-based study in Korea. Environ Res 111: 573–578.
162. Berglind IA, Alderling M, Meding B (2011) Life-style factors and hand eczema. Br J Dermatol 165: 568–575.
163. Breunig JA, de Almeida HL Jr, Duquia RP, Souza PR, Staub HL (2012) Scalp seborrheic dermatitis: prevalence and associated factors in male adolescents. Int J Dermatol 51: 46–49.
164. Yi O, Kwon HJ, Kim H, Ha M, Hong SJ, et al. (2012) Effect of environmental tobacco smoke on atopic dermatitis among children in Korea. Environ Res 113: 40–45.
165. Rönmark EP, Ekerljung L, Lötvall J, Wennergren G, Rönmark E, et al. (2012) Eczema among adults: prevalence, risk factors and relation to airway diseases. Results from a large-scale population survey in Sweden. Br J Dermatol 166: 1301–1308.
166. Kavaliūnas A (2011) Padidėjusio jautrumo maisto produktams ir alergijos maistui paplitimas tarp Vilniaus miesto gyventojų [The prevalence of adverse reactions to food and food allergy among Vilnius city (Lithuania) inhabitants] [dissertation]. Vilnius: Institute of Public Health, Vilnius University.
167. Kulig M, Luck W, Lau S, Niggemann B, Bergmann R, et al. (1999) Effect of pre- and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first 3 years of life. Multicenter Allergy Study Group, Germany. Allergy 54: 220–228.
168. Dubakienė R, Šurkienė G, Stukas R, Pirmaitytė-Vilesko J, Kavaliūnas A (2008) Food allergies among 5th–9th grade schoolchildren in Vilnius (Lithuania). Ekologija 54: 1–4.
169. Taylor B, Wadsworth J, Golding J, Butler N (1983) Breast feeding, eczema, asthma, and hayfever. J Epidemiol Community Health 37: 95–99.
170. Butland BK, Strachan DP, Lewis S, Bynner J, Butler N, et al. (1997) Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts. BMJ 315: 717–721.
171. Arshad SH, Stevens M, Hide DW (1993) The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. Clin Exp Allergy 23: 504–511.
172. Biagini JM, LeMasters GK, Ryan PH, Levin L, Reponen T, et al. (2006) Environmental risk factors of rhinitis in early infancy. Pediatr Allergy Immunol 17: 278–284.
173. Reh DD, Lin SY, Clipp SL, Irani L, Alberg AJ, et al. (2009) Secondhand tobacco smoke exposure and chronic rhinosinusitis: a population-based case-control study. Am J Rhinol Allergy 23: 562–567.
174. Merrett TG, Burr ML, Butland BK, Merrett J, Miskelly FG, et al. (1988) Infant feeding and allergy: 12-month prospective study of 500 babies born into allergic families. Ann Allergy 61: 13–20.
175. Dei-Cas I, Dei-Cas P, Acuña K (2009) Atopic dermatitis and risk factors in poor children from Great Buenos Aires, Argentina. Clin Exp Dermatol 34: 299–303.
176. Wang IJ, Hsieh WS, Wu KY, Guo YL, Hwang YH, et al. (2008) Effect of gestational smoke exposure on atopic dermatitis in the offspring. Pediatr Allergy Immunol 19: 580–586.
177. Dotterud LK, Odland JØ, Falk ES (2004) Atopic dermatitis and respiratory symptoms in Russian and northern Norwegian school children: a comparison study in two arctic areas and the impact of environmental factors. J Eur Acad Dermatol Venereol 18: 131–136.
178. Dotterud LK, Odland JO, Falk ES (2000) Atopic diseases among adults in the two geographically related arctic areas Nikel, Russia and Sør-Varanger, Norway: possible effects of indoor and outdoor air pollution. J Eur Acad Dermatol Venereol 14: 107–111.
179. Kulig M, Luck W, Wahn U (1999) The association between pre- and postnatal tobacco smoke exposure and allergic sensitization during early childhood. Multicentre Allergy Study Group, Germany. Hum Exp Toxicol 18: 241–244.
180. Miyake Y, Ohya Y, Tanaka K, Yokoyama T, Sasaki S, et al. (2007) Home environment and suspected atopic eczema in Japanese infants: the Osaka Maternal and Child Health Study. Pediatr Allergy Immunol 18: 425–432.
181. Thyssen JP, Johansen JD, Menné T, Nielsen NH, Linneberg A (2010) Effect of tobacco smoking and alcohol consumption on the prevalence of nickel sensitization and contact sensitization. Acta Derm Venereol 90: 27–33.
182. Barbee RA, Halonen M, Kaltenborn WT, Burrows B (1991) A longitudinal study of respiratory symptoms in a community population sample. Correlations with smoking, allergen skin-test reactivity, and serum IgE. Chest 99: 20–26.
183. Thomsen SF, Ulrik CS, Porsbjerg C, Backer V (2006) Early life exposures and risk of atopy among Danish children. Allergy Asthma Proc 27: 110–114.
184. Larsson ML, Magnuson A, Montgomery SM (2005) Parental smoking and allergic sensitization in offspring defined by skin prick testing. Pediatr Allergy Immunol 16: 449–452.
185. Liptay S, Bauer CP, Grübl A, Franz R, Emmrich P (1991) Atopieentwicklung in der fruhen Kindheit–Pradisponierende Faktoren [Development of atopic disease in early childhood–predisposing factors]. Monatsschr Kinderheilkd 139: 130–135.
186. Wittig HJ, McLaughlin ET, Leifer KL, Belloit JD (1978) Risk factors for the development of allergic disease: analysis of 2,190 patient records. Ann Allergy 41: 84–88.
187. Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, et al. (2001) Smoking and the development of allergic sensitization to aeroallergens in adults: a prospective population-based study. The Copenhagen Allergy Study. Allergy 56: 328–332.
188. Zetterström O, Osterman K, Machado L, Johansson SG (1981) Another smoking hazard: raised serum IgE concentration and increased risk of occupational allergy. BMJ 283: 1215–1217.
189. Bråbäck L, Kjellman NI, Sandin A, Björkstén B (2001) Atopy among schoolchildren in northern and southern Sweden in relation to pet ownership and early life events. Pediatr Allergy Immunol 12: 4–10.
190. Raherison C, Pénard-Morand C, Moreau D, Caillaud D, Charpin D, et al. (2008) Smoking exposure and allergic sensitization in children according to maternal allergies. Ann Allergy Asthma Immunol 100: 351–357.
191. Bakos N, Schöll I, Szalai K, Kundi M, Untersmayr E, et al. (2006) Risk assessment in elderly for sensitization to food and respiratory allergens. Immunol Lett 107: 15–21.
192. Harris-Roberts J, Robinson E, Waterhouse JC, Billings CG, Proctor AR, et al. (2009) Sensitization to wheat flour and enzymes and associated respiratory symptoms in British bakers. Am J Ind Med 52: 133–140.
193. Tsunoda K, Ohta Y, Shinogami M, Soda Y (1995) Does passive smoking affect the incidence of nasal allergies? Am J Public Health 85: 1019–1020.
194. Jeebhay MF, Robins TG, Miller ME, Bateman E, Smuts M, et al. (2008) Occupational allergy and asthma among salt water fish processing workers. Am J Ind Med 51: 899–910.
195. Angioni AM, Fanciulli G, Corchiat C (1989) Frequency of and risk factors for allergy in primary school children: results of a population Survey. Paediatr Perinat Epidemiol 3: 248–255.
196. Frank P, Morris J, Hazell M, Linehan M, Frank T (2006) Smoking, respiratory symptoms and likely asthma in young people: evidence from postal questionnaire surveys in the Wythenshawe Community Asthma Project (WYCAP). BMC Pulm Med 6: 10.
197. Guedes HTV, Souza LSF (2009) Exposure to maternal smoking in the first year of life interferes in breast-feeding protective effect against the onset of respiratory allergy from birth to 5 yr. Pediatr Allergy Immunol 20: 30–34.
198. Staikūniene J, Sakalauskas R (2003) Ziedadulkiu sukelto alerginio rinito ir bronchu astmos imunologines savybes bei rizikos veiksniai [The immunological parameters and risk factors for pollen-induced allergic rhinitis and asthma]. Medicina (Kaunas) 39: 244–253.
199. Dubakienė R, Vaicekauskaitė D, Židanavičiūtė J, Jonelūnienė I, Drąsutienė G, et al. (2006) Human ecology studies: the role of environmental factors in pregnancy. Ekologija 4: 18–21.
200. Woods RK, Abramson M, Raven JM, Bailey M, Weiner JM, et al. (1998) Reported food intolerance and respiratory symptoms in young adults. Eur Respir J 11: 151–155.
201. Huang SW (2007) Follow-up of children with rhinitis and cough associated with milk allergy. Pediatr Allergy Immunol 18: 81–85.
202. Pegas PN, Alves CA, Scotto MG, Evtyugina MG, Pio CA, et al. (2011) Factores de risco e prevalencia de asma e rinite em criancas em idade escolar em Lisboa [Risk factors and prevalence of asthma and rhinitis among schoolchildren in Lisbon]. Rev Port Pneumol 17: 109–116.
203. Gustafsson D, Andersson K, Fagerlund I, Kjellman NI (1996) Significance of indoor environment for the development of allergic symptoms in children followed up to 18 months of age. Allergy 51: 789–795.
204. Hagendorens MM, Bridts CH, Lauwers K, van Nuijs S, Ebo DG, et al. (2005) Perinatal risk factors for sensitization, atopic dermatitis and wheezing during the first year of life (PIPO study). Clin Exp Allergy 35: 733–740.
205. Lucas A, Brooke OG, Cole TJ, Morley R, Bamford MF (1990) Food and drug reactions, wheezing, and eczema in preterm infants. Arch Dis Child 65: 411–415.
206. Vessey MP, Painter R, Powell J (2000) Skin disorders in relation to oral contraception and other factors, including age, social class, smoking and body mass index. Findings in a large cohort study. Br J Dermatol 143: 815–820.
207. Girolomoni G, Abeni D, Masini C, Sera F, Ayala F, et al. (2003) The epidemiology of atopic dermatitis in Italian schoolchildren. Allergy 58: 420–425.
208. Dubakiene R, Rudzeviciene O, Butiene I, Sezaite I, Petronyte M, et al. (2012) Studies on early allergic sensitization in the Lithuanian birth cohort. Sci World J 2012: 909524.
209. Mitchell EA, Stewart AW, ISAAC Phase One Study Group (2001) International Study of Asthma and Allergy in Childhood. The ecological relationship of tobacco smoking to the prevalence of symptoms of asthma and other atopic diseases in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Eur J Epidemiol 17: 667–673.
210. The Global Youth Tobacco Survey Collaborative Group (2002) Tobacco use among youth: a cross country comparison. Tob Control 11: 252–270.
211. King K, Martynenko M, Bergman MH, Liu YH, Winickoff JP, et al. (2009) Family composition and children's exposure to adult smokers in their homes. Pediatrics 123: e559–64.
212. Centers for Disease Control and Prevention (2007) Exposure to secondhand smoke among students aged 13–15 years-worldwide, 2000–2007. MMWR 56: 497–500.

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213. Rothman KJ (1986) Modern epidemiology. Boston: Little, Brown and Co. p.39.
214. US Department of Health and Human Services (2007) Children and secondhand smoke exposure. Excerpts from The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
215. US Department of Health and Human Services (1986) The Health Consequences of Involuntary Smoking. A Report of the Surgeon General. Rockville (Maryland): US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health.
216. Pérez-Ríos M, Schiaffino A, López MJ, Nebot M, Galán I, et al. (2013) Questionnaire-based second-hand smoke assessment in adults. Eur J Public Health 23: 763–767
217. Wahn U (2000) What drives the allergic march? Allergy 55: 591–599.

Annex II. Cont.

Editors' Summary

Background. The immune system protects the human body from viruses, bacteria, and other pathogens. Whenever a pathogen enters the body, immune system cells called T lymphocytes recognize specific molecules on its surface and release chemical messengers that recruit and activate other types of immune cells, which then attack the pathogen. Sometimes, however, the immune system responds to harmless materials (for example, pollen; scientists call these materials allergens) and triggers an allergic disease such as allergic rhinitis (inflammation of the inside of the nose; hay fever is a type of allergic rhinitis), allergic dermatitis (also known as eczema, a disease characterized by dry, itchy patches on the skin), and food allergy. Recent studies suggest that all these allergic (atopic) diseases are part of a continuous state called the "atopic march" in which individuals develop allergic diseases in a specific sequence that starts with allergic dermatitis during infancy, and progresses to food allergy, allergic rhinitis, and finally asthma (inflammation of the airways).

Why Was This Study Done? Allergic diseases are extremely common, particularly in children. Allergic rhinitis alone affects 10%–30% of the world's population and up to 40% of children in some countries. Moreover, allergic diseases are becoming increasingly common. Allergic diseases affect the quality of life of patients and are financially costly to both patients and health systems. It is important, therefore, to identify the factors that cause or potentiate their development. One potential risk factor for allergic diseases is active or passive exposure to tobacco smoke. In some countries up to 80% of children are exposed to second-hand smoke so, from a public health point of view, it would be useful to know whether exposure to tobacco smoke is associated with the development of allergic diseases. Here, the researchers undertake a systematic review (a study that uses predefined criteria to identify all the research on a given topic) and a meta-analysis (a statistical approach for combining the results of several studies) to investigate this issue.

What Did the Researchers Do and Find? The researchers identified 196 observational studies (investigations that observe outcomes in populations without trying to affect these outcomes in any way) that examined the association between smoke exposure and allergic rhinitis, allergic dermatitis, or food allergy. When all studies were analyzed together, allergic rhinitis was not associated with active smoking but was slightly associated with exposure to second-hand smoke. Specifically, compared to people not exposed to second-hand smoke, the pooled relative risk (RR) of allergic rhinitis among people exposed to second-hand smoke was 1.10 (an RR of greater than 1 indicates an increased risk of disease development in an exposed population compared to an unexposed population). Allergic dermatitis was associated with both active smoking (RR = 1.21) and exposure to second-hand smoke (RR = 1.07). In the populations of children and adolescents included in the studies, allergic rhinitis was associated with both active smoking and exposure to second-hand smoke (RRs of 1.40 and 1.09, respectively), as was allergic dermatitis (RRs of 1.36 and 1.06, respectively). Finally food allergy was associated with exposure to second-hand smoke (RR = 1.43) when cohort studies (a specific type of observational study) only were examined but not when all the studies were combined.

What Do These Findings Mean? These findings provide limited evidence for a weak association between smoke exposure and allergic disease in adults but suggest that both active and passive smoking are associated with a modestly increased risk of allergic diseases in children and adolescents. The accuracy of these findings may be affected by the use of questionnaires to assess smoke exposure and allergic disease development in most of the studies in the meta-analysis and by the possibility that individuals exposed to smoke may have shared other characteristics that were actually responsible for their increased risk of allergic diseases. To shed more light on the role of smoking in allergic diseases, additional studies are needed that accurately measure exposure and outcomes. However, the present findings suggest that, in countries where many people smoke, 14% and 13% of allergic rhinitis and allergic dermatitis, respectively, among children may be attributable to active smoking. Thus, the elimination of active smoking among children and adolescents could prevent one in seven cases of allergic rhinitis and one in eight cases of allergic dermatitis in such countries.

Additional Information. Please access these websites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001611.

- The UK National Health Service Choices website provides information about allergic rhinitis, hay fever (including personal stories), allergic dermatitis (including personal stories), and food allergy (including personal stories)
- The US National Institute of Allergy and Infectious Disease provides information about allergic diseases
- The UK not-for-profit organization Allergy UK provides information about all aspects of allergic diseases and a description of the atopic march
- MedlinePlus encyclopedia has pages on allergic rhinitis and allergic dermatitis (in English and Spanish)
- MedlinePlus provides links to further resources about allergies, eczema, and food allergy (in English and Spanish)

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3.2.

Dietary Intake of Proteins, Antioxidants and Polyunsaturated Fatty Acids and Risk of Allergic Rhinitis: a Case-Control Study

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3.2.1. INTRODUCTION

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Allergic rhinitis, in spite of its benign evolution, represents a global health problem. The identification of modifiable risk factors of allergic rhinitis is crucial in order to reduce its high economic cost and substantial impact on the quality of life of the patients and their relatives, as well as to apply effective preventive measures.

Although allergic rhinitis is known to have genetic determinants,[1] the prevalence increase, observed in the last decade, has occurred far too rapidly for genetic changes to explain it.[2] Gene-environmental interactions were proposed recently as the most important risk factor for atopic diseases including allergic rhinitis.[3,4] Changing industrialization, urbanization, economic development and market globalization have a significant impact on the health and nutritional status of populations, particularly in developing countries.[5] These changes in diet and lifestyle are considered as the main determinant of the increase in prevalence of atopic conditions over the world. Nutrition is coming to the fore as a major modifiable determinant of disease including allergies, with scientific evidence supporting the view that alterations in diet may have strong effects, both positive and negative, on health throughout life.[5]

Existing studies regarding the relation between diet and allergic rhinitis yielded contradictory results. Further research is still required to establish the feasibility and efficacy of dietary manipulation as a public health measure to reduce the risk of allergic diseases.

We, therefore, decided to conduct a multicenter case-control study in order to determine possible modifiable dietary risk factors of allergic rhinitis.

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3.2.2. METHODS

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3.2.2.1. Study Design

A multicenter case-control study was carried out between January 2011 and October 2013.

3.2.2.2. Study Population

387 cases and 387 controls were recruited from 6 large pharmacies in 2 cities in Northwest Spain and from the pulmonology and allergology units of 2 main hospitals of the same cities: Santiago de Compostela and Pontevedra. The emergency care unit of the Hospital of Santiago de Compostela was also included for the collection of control subjects.

3.2.2.3. Data Collection

All participants were asked to answer a 4-page questionnaire (Annex I). Cases were selected from patients attending the hospital units for allergy symptoms. Also, pharmacy customers who were buying over-the-counter medicines for rhinitis symptoms such as antihistaminics and corticosteroids (complete list of medicines available at annex II) were invited to participate in the study as potential cases. Customers attending the pharmacy for any other reason than allergy or respiratory symptoms and who fulfilled our matching criteria were invited to take part in the study as potential controls. Hospital controls were subjects attending for reasons other than allergic or respiratory symptoms. We included subjects attending for injuries, cardiovascular and gastrointestinal diseases as well as for gynecological motives. Case or control status was confirmed by means of an algorithm as explained in the chapter "Disease assessment". In each location (pharmacy or hospital unit), controls were age- and sex-matched to the cases on a one-to-one basis.

The questionnaire consisted of a series of rhinitis symptoms, a medical history, a Food Frequency Questionnaire (FFQ) and questions on other lifestyle variables that could be potential confounders of the relation between diet and

allergic rhinitis. The questionnaire needed approximately 30 minutes to be completed. In the nutritional part we incorporated 7 food groups, asking to record the average frequency of consumption of each of 86 foods and beverages during last year. The questionnaire was anonymous in order to increase the response rate. Signed informed consent was obtained from all participants (Annex III).

Additionally, we asked all participants to provide a sample of saliva for genetic determinations. However, as the study of genetic factors is beyond the scope of this dissertation that concentrates on modifiable environmental factors, results on genetic polymorphisms will not be presented here but in future publications.

3.2.2.4. Disease Assessment

To determine cases of allergic rhinitis, we used The Allergic Rhinitis and its Impact on Asthma (ARIA) questionnaire, together with criteria of the Joint Task Force on Practice Parameters.[6,7,8] The participants were asked to record the presence of six main symptoms of rhinitis on the peak day of the current episode and to rate their frequency from 0 (no attack per day) to 4 (more than 20 attacks per day). These symptoms were: nasal congestion, sneezing, runny nose, postnasal drip, itching of the nose and itchy or watery eyes. We also asked the participants to rate the thickness of their nasal secretion from 0 (very watery) to 4 (very thick), and its color from 0 (colorless) to 4 (green). A list of potential triggers of these symptoms was also suggested.

After the validation of the outcome (see chapter "Validation of the outcome"), we required four criteria to define allergic rhinitis: (1) minimum symptom score of 4 out of 12 for three main symptoms of allergic rhinitis (nasal congestion, sneezing and runny nose) (2) consistency of nasal secretion from very watery to medium, (3) color of nasal secretion to be white or colorless, and (4) at least one of the irritants causing rhinitis symptoms should have been pollen, house dust mites or animal dander. We selected the cutoff point of 4 for the first criterion as this figure maximized the sensitivity and specificity of the allergic rhinitis

diagnosis in the concurrent validation substudy explained below. However, our main study results did not change substantially when we used other cutoff points.

As allergic and non-allergic conditions often overlap in the same patient and the symptoms may be similar in both conditions,[9,10] one of our aims was to disentangle allergic and non-allergic rhinitis cases and exclude the latter from our analysis. Subjects were considered as having non-allergic rhinitis if they reported: (1) a minimum score of rhinitis symptoms of 4 out of 12 (nasal congestion, sneezing and runny nose), (2) postnasal drip at least 6 times a day or a thickness score of nasal secretion from medium to very thick, and (3) rhinitis symptoms were triggered by either tobacco smoke, changes in temperature, high humidity or exposure to aerosol sprays. The criteria for the diagnosis of nonallergic rhinitis were based on clinical updates of the disease.[10,11]

For the analysis of the risk factors of allergic rhinitis, we selected only those cases that did not have any coexisting non-allergic form of rhinitis. We did not differentiate between seasonal and perennial types of allergic rhinitis.

Controls were selected from customers attending the pharmacy for reasons other than allergic and respiratory diseases. The control group included customers who sought medicine related to minor traumatic injuries, digestive disorders, high blood pressure, diabetes, antidepressants. We also included customers who were buying medications for their relatives.

Occasional sneezing and rhinorrhea in the morning after exposure to cold and polluted air is considered to be a normal nasal response.[7] We therefore assumed that some occasional nasal symptoms may be present in the healthy population and thus accepted controls with minor symptoms. Customers were selected as potential controls if (1) their score of rhinitis symptoms (nasal congestion, sneezing and runny nose) was 3 or less out of 12, (2) they did not have any subjective feeling or any confirmed diagnosis of rhinitis, (3) they did not use

any medication that could hide possible rhinitis symptoms such as medicines for asthma, and any type of mucolytic, decongestant and expectorant drug used for common cold, flu, bronchitis and sinusitis. We used the same criterion to select hospital-based controls.

3.2.2.5. Exposure Assessment

To assess the regular diet and obtain daily intakes of macro and micronutrients, together with daily energy intake, we used an 86-item semi-quantitative food frequency questionnaire which was developed based on the validated food frequency questionnaire in Spain.[12] Participants were asked about their average frequency of consumption of standard portions of selected dietary items, representative of the local diet, during the last year. Each food frequency was reported with an eight-grade scale ranging from "never" to "more than three times a day." To calculate the content of macro and micronutrients for each food item we used Spanish food composition databases that we completed with European and American sources when the data was not available in the Spanish sources.[13-18]

The variable of daily protein intake for each participant was created from all food items, calculating their content of protein. The same methodology was applied for calculation of other macro and micronutrient's intake per day. Consumption of meat contains daily amount of all types of meat and meat products including offal. Daily consumption of dairy includes milk, all types of cheese, butter and yoghurts. Proteins of animal origin include only those that are from meat products, and proteins of vegetable origin consist only of those proteins that are provided by fruits and vegetables, including all types of cereal products, potatoes, beans and rice.

We calculated the daily intake of the following antioxidants: β-carotene, vitamin A, vitamin E, vitamin C, selenium and zinc. Daily consumption of all fruits included: orange, grapefruit, tangerine, apples, pears, peach, apricot, cherries, banana, strawberries, kiwi, melon, watermelon, pineapple. Avocado

and olives also were considered as fruits. The variables of vegetable consumption consisted of the mean intake of carrots, beets, onions, eggplant, zucchini, pumpkin, asparagus, spinach, chard, leeks, tomatoes, lettuce, endive, peppers, cabbage, turnips, beans, peas and potatoes.

Daily intake of omega 3 and omega 6 was obtained from the intake of fish and seafood, including, among others, mussels, crustaceans and octopus. Oil intake was calculated from the average consumption of olive oil or any other type of vegetable oil which was used for cooking or for dressing.

An estimate of the total daily average alcohol intake was derived according to the Spanish Health Survey (ENSE 2011/12) using average ethanol content in 100g of each type of beverage (10g for wine (red and white), 10g for beer and 20g for spirits).[19]

Cigarette consumption was assessed using the standard World Health Organization questionnaire.[20] Smoking status categories were: never-smoker, ex-smoker, occasional smoker, and current smoker of 1–19, 20–40, or more than 40 cigarettes a day.

3.2.2.6. Data Analysis

Those variables that did not follow a normal distribution were log-transformed. We then categorized them into tertiles or quartiles according to the width of the interval. Those variables the distribution of which remained highly asymmetric after logarithmic conversion were divided into categories with similar sample size. Crude and adjusted odds ratios and corresponding 95% confidence intervals of possible risk factors for allergic rhinitis were estimated by conditional logistic regression.

Possible risk factors for allergic rhinitis that were considered in the analyses as candidates for potential confounders included level of education, history of asthma, history of dermatitis, familial history of allergy, body mass index,

energy expenditure in Kcal/hour, smoking habits, rural residency, alcohol consumption, contact with animals, and humidity in the house. We also considered additional adjustments for variables such as macro- and micro-nutrients other than those considered as potential risk or protection factors for allergic rhinitis.

Potential confounding variables were identified from those that showed a relation with allergic rhinitis in the univariate analysis. In the final model, we included those variables that changed the estimate of the odds ratio of the main exposure and allergic rhinitis in more than 10%.[21]

Finally, based on the criteria mentioned above, 5 variables were kept in the final model: level of education, personal history of asthma, personal history of allergic dermatitis, family history of allergy and total fat intake.

All analyses were performed using SPSS (*Statistical Package for Social Sciences*) version 18.0 and STATA, version 12, software.[22,23]

3.2.2.7. Validation of the Outcome

The main challenge of our diagnosis was to separate cases of allergic rhinitis from cases of non-allergic rhinitis as typical symptoms are often similar in both diseases. Furthermore, other diseases or syndromes such as common cold or sinusitis may also lead to erroneous diagnosis of allergic rhinitis as they cause nasal obstruction and block the sinuses.[24,25]

Therefore, concurrently with the main study, we carried out a validation study aimed at documenting the validity of our diagnosis of allergic rhinitis. For this purpose, we used as a *gold standard* a sample of 255 persons randomly selected from our hospital subjects for whom the diagnosis of either allergic rhinitis, non-allergic rhinitis or no rhinitis was firmly established. Specifically, we selected 70 subjects whose diagnosis of allergic rhinitis was firmly established using a) clinical examination, b) positive skin prick tests (SPT) to common

inhaled allergens and/or presence of serum-specific IgE against these allergens and c) absence of previous medication against rhinitis. We further selected 25 subjects with confirmed diagnosis of non-allergic rhinitis established after clinical examination, negative SPT and normal serum IgE level, and no use of any medication against rhinitis. Finally, we included 160 subjects who were confirmed as free of allergic and non-allergic rhinitis as well as of common cold and sinusitis. They had to fulfil the following criteria: 1) score of rhinitis symptoms ≤ 3 out of 12, (2) absence of any subjective feeling and diagnosis of rhinitis, (3) no use of any medication that could hide possible rhinitis symptoms. We asked those subjects to complete our disease questionnaire and we calculated the sensitivity and specificity of our diagnosis using different cutoff points for the symptom scores. The final figures were as follows for the diagnosis of allergic rhinitis: sensitivity 0.74 and specificity 0.92. These figures were reached using the cut-off point of allergic rhinitis symptoms score of 4 or more out of 12.

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3.2.3. RESULTS

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3.2.3.1. Sample Description

The final sample of this study consisted of 774 subjects: 387 cases and 387 age and sex-matched controls. The global response rate was 72.5%. Table 1 displays the distribution of the most important variables for cases and controls. Mean age of participants was 34.5 years and range from 18 to 77, with 129 (33%) men and 258 (67%) women in each group. The most important determinants associated with allergic rhinitis, in terms of odds ratio magnitude, which were introduced as variables of adjustment in the final model were level of education, comorbid asthma, comorbid dermatitis, allergy history in family members and total kilocalorie intake. Control subjects had higher education level (48%) compared with cases (33%). Comorbid asthma and comorbid dermatitis were much more frequent in cases (63% and 23% respectively) than in controls (4% and 4% respectively) and were significantly associated with the risk of allergic rhinitis risk (odds ratio (OR) = 41.6, 95% confidence interval (CI): 17.13-101.00 for asthma and OR = 7.88, CI: 3.94-15.78 for dermatitis). Cases reported having family members with a history of allergic diseases such as rhinitis, asthma or dermatitis more frequently than the control group (60% of cases and 12% of controls). Moreover, allergic persons more often declared their residence of living in rural areas, while controls showed a higher proportion of smokers and alcohol drinkers. Overweight was more frequent among cases than among controls while levels of physical activity and energy expenditure were similar in both groups.

Table 1. Distribution of covariables for allergic rhinitis cases and controls

Variable		Cases (387)		Controls (387)	
		No.	%	No.	%
Sex	Male	129	33.3	129	33.3
Age	18-30	164	42.4	164	42.4
	31-40	120	31.0	117	30.2
	41-50	66	17.1	67	17.3
	51-60	23	5.9	25	6.5
	61-80	14	3.6	14	3.6
Education					
	No or Primary	111	29.4	70	19.0
	Secondary	143	37.9	121	32.8
	Higher	123	32.6	178	48.2
History of Asthma					
	No	144	37.2	328	95.6
	Yes	243	62.8	15	4.4
History of Dermatitis					
	No	299	77.3	329	95.9
	Yes	88	22.7	14	4.1
Allergy history in family members					
	No	154	39.8	298	87.6
	Yes	233	60.2	42	12.4
BMI					
	<19	14	3.7	23	6.1
	19-25	206	53.8	226	59.5
	>25	163	42.6	131	34.5
Energy expenditure in Kcal/h					
	<9.75	71	22.2	71	20.8
	9.75-19.5	165	51.6	188	55.1
	>19.5	84	26.2	82	24.0
Physical activity					
	Low	54	17.4	82	23.6
	Light	170	54.7	166	47.8
	Moderate to Intense	87	28.0	99	28.5
Smoking habits					
	No smoking	276	71.9	248	64.8
	Former smoker	53	13.8	51	13.3
	Active/Occasional smoker	55	14.3	84	21.9
Heating at home					
	Do not have	51	13.8	29	9.2
	Butane	50	13.6	52	16.6
	Electrical	81	22.0	56	17.8
	Central	187	50.7	177	56.4
Residency of living					
	City	203	52.9	233	70.4
	Rural	181	47.1	98	29.6
Alcohol consumption					
	0 g/day	197	51.2	168	43.6
	1-4 g/day	62	16.1	51	13.2
	4-11 g/day	77	20.0	83	21.6
	>11 g/day	49	12.7	83	21.6
Contact with animals					
	No	174	45.1	178	51.9
	Little	66	17.1	28	8.2
	Frequent	33	8.5	82	23.9
	Daily	113	29.3	55	16.0
Humidity at home					
	No	278	72.6	243	75.7
	Yes	105	27.4	78	24.3

3.2.3.2. Dietary Patterns

Protein consumption

Association of allergic rhinitis and protein consumption, as well as other potential confounding and effect modifying variables is shown in table 2. A direct relation was observed between high protein consumption and allergic rhinitis (OR=3.79; 95% CI: 2.40-5.97 for the highest quartile of intake). The association was stronger after adjusting for confounders (OR=9.07; 95% CI: 1.92-42.83 for the 4th quartile).

Table 2. Odds ratios of allergic rhinitis by protein, energy and total fat intake

Variable	Cases		Controls		OR*	95% CI	OR†	95% CI
	No.	%	No.	%				
Protein intake (median g/day)								
1st quartile (72.25)	55	14.5	134	35.5	1.00	Reference	1.00	Reference
2nd quartile (93.89)	92	24.2	97	25.7	2.39	1.52-3.75	2.29	0.81-6.50
3rd quartile (118.31)	119	31.3	71	18.8	4.14	2.60-6.60	7.53	1.82-31.22
4th quartile (151.54)	114	30.0	75	19.9	3.79	2.40-5.97	9.07	1.92-42.83
Kcal intake (median Kcal/day)								
1st quartile (1557.64)	63	16.6	126	33.4	1.00	Reference	1.00	Reference
2nd quartile (1975.59)	103	27.1	86	22.8	2.35	1.53-3.60	1.72	0.64-4.66
3rd quartile (2400.46)	104	27.4	86	22.8	2.30	1.49-3.54	2.00	0.53-7.51
4th quartile (3071.00)	110	28.9	79	21.0	2.91	1.85-4.58	2.97	0.54-16.23
Total fat intake¥ (median g/day)								
1st quartile (55.72)	74	19.5	115	30.5	1.00	Reference	1.00	Reference
2nd quartile (74.26)	95	25.0	94	24.9	1.53	0.99-2.37	1.15	0.40-3.29
3rd quartile (89.65)	104	27.4	86	22.8	1.82	1.19-2.79	0.45	0.11-1.81
4th quartile (123.92)	107	28.2	82	21.8	1.94	1.27-2.97	0.29	0.06-1.44

** ORs were estimated from conditional logistic regression models, conditioned on age and sex*
† OR's of Protein and Kcal intake adjusted for education, history of asthma, history of dermatitis, allergy history in family members, and total fat intake (except for the variable of Total fat intake¥);
¥OR's of Total fat intake adjusted for education, history of asthma, history of dermatitis, allergy history in family members, and Protein intake.

Our results show that thirty percent of our allergic rhinitis patients consume more than 134 grams of protein per day, while in the control group this figure was one-third lower (20%). After adjustment of potential confounders, subjects with high intakes of protein (third and fourth quartile) have a considerable

increase in the risk of allergic rhinitis. (Table 2) Assuming linearity of the effect we performed a logistic regression where intake of protein was introduced as a continuous variable. We found that every 10 g of protein augments the risk of allergic rhinitis by 10 percent (data not shown).

Although the association is not statistically significant, energy intake is probably related to the risk of allergic rhinitis (OR for the 4th quartile = 2.97; 95% CI: 0.54-16.23). Energy intake of a healthy and well-nourished population should maintain an adequate body mass index (BMI) at the population's usual level of energy expenditure.[26] According to WHO recommendations, energy requirements are specific to each person and vary with age, gender, body weight, physical activity level and basal metabolic rate, ranging from 1550 up to 4500 Kcal/day.[26] Mean daily Kcal intake of our control subgroup was 2181 Kcal/day while that of cases was 2351 Kcal/day.

The association of a high intake of proteins with increased risk of allergic rhinitis, persisted after adjustment for lifestyle variables such as physical activity, smoking habits or alcohol consumption, as well as after control of education level, history of asthma, history of dermatitis and allergy history in family members. Energy intake and total fat intake were clearly associated with protein consumption. However, adjustment for these variables did not mitigate the effect of protein consumption on the risk of allergic rhinitis, but, on the contrary, increased it. (Table 3) Our results showed a considerable increase in the risk of allergic rhinitis among subjects with high intakes of fish, meat, and dairy products. (Table 3) Proteins of animal origin seemed to exert higher effect than proteins of vegetable origin, although both showed increase in the effect for the highest quartile after total adjustment. (Table 3)

Table 3. Odds ratios of allergic rhinitis by selected food groups used in multivariate model introducing each food group one by one

Variable	Median (g/day)	Cases		Controls		OR*	95% CI	OR†	95% CI
		No.	%	No.	%				
Fish and sea products									
1st quartile	51.51	81	21.3	108	28.6	1.00	Reference	1.00	Reference
2nd quartile	82.41	74	19.5	116	30.7	0.94	0.62-1.41	1.16	0.45-2.99
3rd quartile	121.90	115	30.3	75	19.8	2.12	1.38-3.26	2.20	0.75-6.45
4th quartile	190.97	110	28.9	79	20.9	1.80	1.19-2.72	2.13	0.72-6.24
Meat									
1st quartile	59.53	63	16.6	126	33.3	1.00	Reference	1.00	Reference
2nd quartile	105.80	100	26.3	90	23.8	2.21	1.42-3.43	1.90	0.70-5.17
3rd quartile	156.56	118	31.1	72	19.0	3.05	1.97-4.71	1.98	0.60-6.15
4th quartile	215.85	99	26.1	90	23.8	2.08	1.35-3.20	0.94	0.29-3.08
Dairy									
1st quartile	123.14	89	23.4	100	26.5	1.00	Reference	1.00	Reference
2nd quartile	256.78	82	21.6	107	28.4	0.90	0.61-1.35	0.47	0.18-1.24
3rd quartile	350.57	99	26.1	91	24.1	1.31	0.87-1.96	0.91	0.35-2.40
4th quartile	623.76	110	28.9	79	21.0	1.70	1.12-2.59	0.82	0.26-2.57
Eggs									
1st quartile	17.80	107	28.2	97	25.7	1.00	Reference	1.00	Reference
2nd quartile	25.83	86	22.6	87	23.1	0.90	0.59-1.38	0.48	0.16-1.44
3rd quartile	56.03	125	32.9	121	32.1	0.96	0.65-1.42	0.53	0.20-1.38
4th quartile	77.48	62	16.3	72	19.1	0.77	0.49-1.21	0.79	0.23-2.73
Proteins of Animal origin									
1st quartile	43.50	62	16.3	127	33.7	1.00	Reference	1.00	Reference
2nd quartile	59.92	94	24.7	95	25.2	2.24	1.41-3.58	3.50	1.09-11.22
3rd quartile	78.31	113	29.7	77	20.4	3.05	1.93-4.81	3.62	0.88-14.89
4th quartile	105.90	111	29.2	78	20.7	2.93	1.87-4.59	7.66	1.35-43.38
Proteins of Vegetable origin									
1st quartile	18.67	66	17.4	123	32.6	1.00	Reference	1.00	Reference
2nd quartile	26.08	84	22.1	105	27.9	1.63	1.03-2.57	0.92	0.33-2.55
3rd quartile	34.54	115	30.3	75	19.9	2.94	1.87-4.63	2.19	0.66-7.33
4th quartile	47.48	115	30.3	74	19.6	3.36	2.09-5.38	4.60	1.02-20.83

** ORs were estimated from conditional logistic regression models, conditioned on age and sex*
†Adjusted for Kcal, education, history of asthma, history of dermatitis, allergy history in family members, and total fat intake.

In general, high intakes of individual amino acids were related with increased risk of allergic rhinitis. (Table 4) Especifically, high intakes of leucine, tyrosine, valine and serine are associated with an increase in the risk of allergic rhinitis in a dose-response fashion.

Table 4. Odds ratios of allergic rhinitis and amino acids

Amino acid	Median (g/day)	Cases		Controls		OR*	95% CI	OR†	95% CI
		No.	%	No.	%				
Overall		387		387					
ESSENCIAL AMINO ACIDS									
Histidine									
1st quartile	1.87	56	14.7	132	35.0	1.00	Reference	1.00	Reference
2nd quartile	2.47	92	24.2	98	26.0	2.32	1.48-3.62	2.65	0.90-7.79
3rd quartile	3.16	117	30.8	73	19.4	4.01	2.50-6.43	5.50	1.26-23.95
4th quartile	4.16	115	30.3	74	19.6	3.84	2.43-6.08	11.53	2.27-58.60
Isoleucine									
1st quartile	3.33	64	16.8	125	33.2	1.00	Reference	1.00	Reference
2nd quartile	4.34	92	24.2	97	25.7	1.91	1.25-2.92	1.67	0.60-4.68
3rd quartile	5.45	109	28.7	81	21.5	2.63	1.70-4.07	4.05	1.02-16.09
4th quartile	7.15	115	30.3	74	19.6	3.11	2.01-4.81	8.86	1.86-42.32
Leucine									
1st quartile	5.53	60	15.8	129	34.2	1.00	Reference	1.00	Reference
2nd quartile	7.26	85	22.4	104	27.6	1.86	1.20-2.86	2.04	0.73-5.73
3rd quartile	9.14	123	32.4	67	17.8	4.00	2.54-6.32	8.18	1.20-34.20
4th quartile	12.09	112	29.5	77	20.4	3.36	2.14-5.27	16.95	3.13-91.82
Lysine									
1st quartile	4.70	56	14.7	133	35.3	1.00	Reference	1.00	Reference
2nd quartile	6.15	89	23.4	100	26.5	2.21	1.41-3.46	3.63	1.19-11.02
3rd quartile	7.92	121	31.8	69	18.3	4.31	2.69-6.91	6.95	1.72-28.02
4th quartile	10.63	114	30.0	75	19.9	3.89	2.44-6.20	11.69	2.36-57.90
Methionine									
1st quartile	1.53	63	16.6	126	33.4	1.00	Reference	1.00	Reference
2nd quartile	2.03	86	22.6	103	27.3	1.69	1.09-2.61	1.80	0.65-4.98
3rd quartile	2.57	119	31.3	71	18.8	3.31	2.12-5.17	2.22	0.61-8.02
4th quartile	3.43	112	29.5	77	20.4	2.82	1.83-4.33	3.65	0.88-15.22
Phenylalanine									
1st quartile	3.22	58	15.3	131	34.7	1.00	Reference	1.00	Reference
2nd quartile	4.14	87	22.9	102	27.1	2.11	1.34-3.34	1.76	0.61-5.08
3rd quartile	5.20	125	32.9	65	17.2	4.50	2.81-7.21	9.42	2.10-42.28
4th quartile	6.81	110	28.9	79	21.0	3.64	2.27-5.84	15.40	2.60-91.25
Threonine									
1st quartile	2.71	57	15.0	132	35.0	1.00	Reference	1.00	Reference
2nd quartile	3.55	90	23.7	99	26.3	2.13	1.38-3.29	2.58	0.92-7.27
3rd quartile	4.49	121	31.8	69	18.3	4.01	2.53-6.36	7.03	1.74-28.37
4th quartile	5.97	112	29.5	77	20.4	3.44	2.18-5.41	7.07	1.58-31.55
Tryptophan									
1st quartile	0.49	52	13.7	136	36.1	1.00	Reference	1.00	Reference
2nd quartile	0.66	101	26.6	89	23.6	2.91	1.83-4.61	1.86	0.62-5.55
3rd quartile	0.83	114	30.0	76	20.2	3.82	2.41-6.04	4.65	1.05-20.65
4th quartile	1.07	113	29.7	76	20.2	3.80	2.40-6.01	5.40	1.13-25.78
Valine									
1st quartile	3.74	62	16.3	126	33.4	1.00	Reference	1.00	Reference
2nd quartile	4.89	83	21.8	107	28.4	1.73	1.12-2.67	2.01	0.70-5.80
3rd quartile	6.18	121	31.8	69	18.3	3.74	2.37-5.92	9.76	2.17-43.93
4th quartile	8.11	114	30.0	75	19.9	3.43	2.17-5.42	22.27	3.69-134.42

Table 4. Cont.

Amino acid	Median (g/day)	Cases		Controls		OR*	95% CI	OR†	95% CI
		No.	%	No.	%				
Overall		387		387					
NONESSENTIAL AMINO ACIDS									
Alanine									
1st quartile	3.03	57	15.0	132	35.0	1.00	Reference	1.00	Reference
2nd quartile	3.96	86	22.6	103	27.3	2.03	1.30-3.16	3.46	1.17-10.21
3rd quartile	4.99	129	33.9	61	16.2	4.69	2.95-7.47	10.16	2.59-39.89
4th quartile	6.60	108	28.4	81	21.5	3.24	2.06-5.09	9.98	2.03-49.05
Arginine									
1st quartile	3.63	52	13.7	137	36.3	1.00	Reference	1.00	Reference
2nd quartile	4.80	88	23.2	102	27.1	2.35	1.48-3.73	3.36	1.01-11.19
3rd quartile	6.11	131	34.5	58	15.4	5.89	3.62-9.59	27.53	5.13-147.67
4th quartile	8.08	109	28.7	80	21.2	3.79	2.36-6.09	12.77	2.45-66.69
Aspartic acid									
1st quartile	5.91	57	15.0	132	35.0	1.00	Reference	1.00	Reference
2nd quartile	7.77	85	22.4	104	27.6	1.99	1.28-3.08	2.85	0.97-8.38
3rd quartile	9.92	127	33.4	63	16.7	4.71	2.95-7.53	8.25	1.98-34.31
4th quartile	13.22	111	29.2	78	20.7	3.57	2.26-5.64	7.69	1.66-35.62
Cysteine									
1st quartile	0.80	48	12.6	141	37.4	1.00	Reference	1.00	Reference
2nd quartile	1.05	103	27.1	86	22.8	3.34	2.10-5.31	3.80	1.26-11.47
3rd quartile	1.29	124	32.6	66	17.5	5.39	3.34-8.77	9.43	2.17-40.89
4th quartile	1.69	105	27.6	84	22.3	3.69	2.30-5.93	6.63	1.45-30.25
Glutamic acid									
1st quartile	12.54	58	15.3	131	34.7	1.00	Reference	1.00	Reference
2nd quartile	16.06	92	24.2	97	25.7	2.19	1.41-3.40	1.24	0.48-3.20
3rd quartile	20.12	116	30.5	74	19.6	3.43	2.19-5.38	4.55	1.34-15.46
4th quartile	26.32	114	30.0	75	19.9	3.62	2.30-5.70	5.00	1.06-23.53
Glycine									
1st quartile	2.79	50	13.2	138	36.6	1.00	Reference	1.00	Reference
2nd quartile	3.69	99	26.1	91	24.1	3.10	1.93-4.99	2.67	0.92-7.74
3rd quartile	4.75	123	32.4	67	17.8	5.13	3.17-8.30	4.77	1.35-16.84
4th quartile	6.25	108	28.4	81	21.5	3.77	2.36-6.01	5.10	1.15-22.63
Proline									
1st quartile	4.22	65	17.1	124	32.9	1.00	Reference	1.00	Reference
2nd quartile	5.57	85	22.4	104	27.6	1.59	1.03-2.45	1.61	0.61-4.24
3rd quartile	6.88	114	30.0	76	20.2	2.86	1.84-4.44	2.91	0.89-9.48
4th quartile	9.23	116	30.5	73	19.4	3.17	2.02-4.96	3.68	0.88-15.49
Serine									
1st quartile	3.14	61	16.1	128	34.0	1.00	Reference	1.00	Reference
2nd quartile	4.11	85	22.4	105	27.9	1.76	1.14-2.73	2.75	0.85-8.87
3rd quartile	5.10	120	31.6	69	18.3	3.54	2.27-5.53	14.19	3.03-66.35
4th quartile	6.75	114	30.0	75	19.9	3.41	2.16-5.38	20.76	3.29-130.86
Tyrosine									
1st quartile	2.37	64	16.8	125	33.2	1.00	Reference	1.00	Reference
2nd quartile	3.11	80	21.1	109	28.9	1.54	0.99-2.38	1.69	0.60-4.76
3rd quartile	3.94	118	31.1	72	19.1	3.49	2.20-5.52	12.08	2.49-58.56
4th quartile	5.24	118	31.1	71	18.8	3.59	2.26-5.71	28.54	4.42-184.33

** ORs were estimated from conditional logistic regression models, conditioned on age and sex*

†Adjusted for education, history of asthma, history of dermatitis, allergy history in family members, and total fat intake.

Dietary antioxidants

We determined the daily intake of the following antioxidants: β-carotene, vitamin A, vitamin E, vitamin C, selenium and zinc. The association of allergic rhinitis with the intake of these antioxidants is shown in table 5. The strongest positive association for the highest quartile was observed for β-carotene (OR=5.12; 95% CI: 1.54-17.04). According to one pooled analysis of 500 000 women living in the USA, Canada, and some European countries, the average daily intake of β-carotene should be in the range 2000-7000 μg.[27] The mean intake of β-carotene in our study controls, that represent the general population, was 4839 μg/day, while that of cases was higher (6045 μg).

High vitamin A consumption was related to an elevated risk of allergic rhinitis in crude analysis before adjusting (OR= 2.87; 95% CI: 1.82-4.52 for 4th quartile). After adjustment, the effect remained high for the 3rd quartile only.

Vitamins E and C did not show any effect in the adjusted model while selenium and zinc, considered as antioxidants, showed a strong association, limited, however, to the 3rd quartile. (Table 5)

Table 5. Odds ratios of allergic rhinitis and antioxidants

Variable	Cases		Controls		OR*	95% CI	OR†	95% CI
	No.	%	No.	%				
β-carotene intake (median µg/day)								
1st quartile (1480.89)	70	18.4	119	31.6	1.00	Reference	1.00	Reference
2nd quartile (3178.22)	81	21.3	108	28.6	1.57	1.01-2.43	1.52	0.54-4.30
3rd quartile (5849.28)	116	30.5	74	19.6	2.86	1.83-4.48	2.70	0.90-8.07
4th quartile (9932.09)	113	29.7	76	20.2	**3.14**	**1.95-5.04**	**5.12**	**1.54-17.04**
Vitamin A intake (median µg Eq/day)								
1st quartile (695.83)	65	17.1	124	32.9	1.00	Reference	1.00	Reference
2nd quartile (1133.57)	88	23.2	101	26.8	1.79	1.14-2.81	1.08	0.42-2.80
3rd quartile (1534.79)	119	31.3	71	18.8	3.17	2.04-4.92	4.10	1.26-13.41
4th quartile (2261.91)	108	28.4	81	21.5	**2.87**	**1.82-4.52**	2.81	0.87-9.05
Vitamin E intake (median mg/day)								
1st quartile (8.44)	68	17.9	121	32.1	1.00	Reference	1.00	Reference
2nd quartile (11.51)	98	25.8	91	24.1	2.15	1.37-3.38	0.85	0.33-2.16
3rd quartile (14.83)	111	29.2	79	21.0	2.98	1.86-4.77	1.22	0.41-3.65
4th quartile (20.36)	103	27.1	86	22.8	**2.43**	**1.53-3.86**	2.09	0.57-7.73
Vitamin C intake (median mg/day)								
1st quartile (110.73)	78	20.5	111	29.4	1.00	Reference	1.00	Reference
2nd quartile (195.55)	79	20.8	110	29.2	1.01	0.66-1.56	0.82	0.30-2.21
3rd quartile (280.94)	114	30.0	76	20.2	2.12	1.39-3.24	1.04	0.39-2.81
4th quartile (425.12)	109	28.7	80	21.2	**2.10**	**1.34-3.27**	2.49	0.79-7.80
Selenium intake (median µg/day)								
1st quartile (77.78)	57	15.0	132	35.0	1.00	Reference	1.00	Reference
2nd quartile (103.18)	87	22.9	102	27.1	1.88	1.19-2.96	1.31	0.47-3.62
3rd quartile (130.66)	127	33.4	63	16.7	4.67	2.91-7.50	6.27	1.67-23.49
4th quartile (174.87)	109	28.7	80	21.2	3.24	2.04-5.14	3.96	0.90-17.31
Zinc intake (median mg/day)								
1st quartile (12.16)	63	16.6	126	33.4	1.00	Reference	1.00	Reference
2nd quartile (15.83)	88	23.2	101	26.8	1.74	1.12-2.70	2.36	0.77-7.19
3rd quartile (19.04)	122	32.1	68	18.0	3.34	2.14-5.21	5.78	1.44-23.22
4th quartile (24.08)	107	28.2	82	21.8	2.66	1.69-4.21	2.60	0.57-11.80
Fruit intake (median g/day)								
1st quartile (75.06)	65	17.1	124	32.9	1.00	Reference	1.00	Reference
2nd quartile (184.14)	92	24.2	97	25.7	1.88	1.20-2.94	1.70	0.62-4.62
3rd quartile (306.88)	106	27.9	84	22.3	2.46	1.59-3.81	3.19	1.07-9.51
4th quartile (519.93)	117	30.8	72	19.1	**3.12**	**2.00-4.87**	**5.11**	**1.67-15.63**
Vegetable intake (median g/day)								
1st quartile (173.52)	68	17.9	121	32.1	1.00	Reference	1.00	Reference
2nd quartile (312.23)	92	24.2	97	25.7	1.71	1.13-2.59	0.64	0.25-1.61
3rd quartile (445.24)	107	28.2	83	22.0	2.42	1.57-3.73	1.43	0.56-3.66
4th quartile (686.15)	113	29.7	76	20.2	**3.11**	**1.95-4.96**	2.51	0.83-7.58

* *Crude OR*

† *Adjusted for education, history of asthma, history of dermatitis, allergy history in family members, and intake of Kcal/day.*

Since fruits and vegetables are the main source of many antioxidants, they were also considered in this analysis as an important covariate. We introduced consumption of fruits and vegetables in to the crude and final adjusted analysis. The task was to verify if the effect of chosen vitamins and minerals with properties of antioxidant was actually attributable to that antioxidant or rather could be explained by the effect of the entire food group. Higher consumption of fruits showed a strong positive association before and after adjustment for confounding variables (OR=3.12; 95% CI: 2.00-4.87 and OR=5.11; 95% CI: 1.67-15.63 for highest quartiles respectively). Consumption of vegetables was related with allergic rhinitis only in the crude analysis (OR=3.11; 95% CI: 1.95-4.96 for highest quartile), however this relation was not statistically significant after adjustment. (Table 5)

Finally, we also carried out additional analyses introducing fruits and vegetables one by one as a confounding variable in to the final model established earlier. Results, which are displayed in table 6, show that consumption of β-carotene and fruit in general shows a strong effect on the development of allergic rhinitis. The effect of selenium and zinc has not changed substantially.

Table 6. Odds ratios of allergic rhinitis and antioxidants adjusting for fruit and vegetable intake

Variable	OR*	95% CI	OR†	95% CI
β-carotene intake				
(median µg/day)				
1st quartile (1480.89)	1.00	Reference	1.00	Reference
2nd quartile (3178.22)	1.31	0.43-3.99	1.92	0.62-5.91
3rd quartile (5849.28)	1.87	0.56-6.25	3.04	0.81-11.36
4th quartile (9932.09)	**3.83**	**1.06-13.80**	4.51	0.84-24.25
Vitamin A intake				
(median µg Eq/day)				
1st quartile (695.83)	1.00	Reference	1.00	Reference
2nd quartile (1133.57)	1.05	0.38-2.91	0.94	0.34-2.65
3rd quartile (1534.79)	**4.97**	**1.37-17.97**	3.56	0.96-13.27
4th quartile (2261.91)	2.44	0.73-8.12	1.15	0.24-5.53
Vitamin E intake				
(median mg/day)				
1st quartile (8.44)	1.00	Reference	1.00	Reference
2nd quartile (11.51)	0.68	0.25-1.84	0.81	0.30-2.21
3rd quartile (14.83)	0.78	0.23-2.57	0.98	0.31-3.14
4th quartile (20.36)	1.23	0.28-5.40	1.29	0.27-6.19
Vitamin C intake				
(median mg/day)				
1st quartile (110.73)	1.00	Reference	1.00	Reference
2nd quartile (195.55)	0.43	0.14-1.36	0.80	0.28-2.29
3rd quartile (280.94)	0.36	0.10-1.31	0.63	0.19-2.11
4th quartile (425.12)	0.79	0.19-3.21	1.33	0.33-5.29
Selenium intake				
(median µg/day)				
1st quartile (77.78)	1.00	Reference	1.00	Reference
2nd quartile (103.18)	1.17	0.40-3.41	1.25	0.44-3.59
3rd quartile (130.66)	**5.86**	**1.41-24.32**	**5.06**	**1.29-19.89**
4th quartile (174.87)	3.27	0.67-15.89	3.09	0.64-14.94
Zinc intake				
(median mg/day)				
1st quartile (12.16)	1.00	Reference	1.00	Reference
2nd quartile (15.83)	2.14	0.66-6.95	2.27	0.69-7.46
3rd quartile (19.04)	**4.69**	**1.03-21.39**	**4.66**	**1.08-20.08**
4th quartile (24.08)	2.06	0.40-10.70	1.54	0.30-7.87
Fruit intake				
(median g/day)				
1st quartile (75.06)	---	---	1.00	Reference
2nd quartile (184.14)			1.47	0.52-4.15
3rd quartile (306.88)			2.59	0.81-8.26
4th quartile (519.93)			**4.43**	**1.37-14.37**
Vegetable intake				
(median g/day)				
1st quartile (173.52)	1.00	Reference	---	---
2nd quartile (312.23)	0.80	0.29-2.19		
3rd quartile (445.24)	1.36	0.50-3.69		
4th quartile (686.15)	2.50	0.79-7.96		

** Adjusted for education, history of asthma, history of dermatitis, allergy history in family members, and intake of Kcal/day and **additionally for Fruit consumption in g/day.***
*† Adjusted for education, history of asthma, history of dermatitis, allergy history in family members, and intake of Kcal/day and **additionally for Vegetables consumption in g/day**.*

Polyunsaturated fatty acids

Association of allergic rhinitis and consumption of omega-3 and omega-6 polyunsaturated fatty acids is displayed in table 7. Both types of polyunsaturated fatty acids were related with a tendency to decrease the risk of allergic rhinitis for the 4th quartile after adjustment, although this association was not statistically significant (OR=0.42; 95% CI: 0.13-1.38 for omega-3 and OR=0.55; 95% CI: 0.15-2.02 for omega-6). Forasmuch as main sources of omega-3 fatty acids are fish and other sea products, and omega-6 mainly comes from vegetable oils, we also took into account these food groups in this analysis. Seafood as independent variable showed slight increment in risk after adjusting for confounding variables although the relation was not statistically significant (OR=2.24; 95% CI: 0.76-6.58 for the 4th quartile). (Table 7)

Table 7. Odds ratios of allergic rhinitis and polyunsaturated fatty acids and seafood intake

Variable	Cases		Controls		OR*	95% CI	OR†	95% CI
	No.	%	No.	%				
Omega-3 intake (median g/day)								
1st quartile (2.28)	86	22.6	103	27.3	1.00	Reference	1.00	Reference
2nd quartile (3.65)	94	24.7	95	25.2	1.24	0.82-1.88	1.17	0.47-2.91
3rd quartile (4.78)	109	28.7	81	21.5	1.64	1.08-2.48	1.19	0.40-3.58
4th quartile (7.82)	91	23.9	98	26.0	1.16	0.76-1.77	**0.42**	**0.13-1.38**
Omega-6 intake (median g/day)								
1st quartile (7.61)	79	20.8	110	29.2	1.00	Reference	1.00	Reference
2nd quartile (10.57)	97	25.5	92	24.4	1.52	1.00-2.29	0.99	0.37-2.65
3rd quartile (13.99)	106	27.9	84	22.3	1.69	1.12-2.54	0.49	0.18-1.39
4th quartile (18.84)	98	25.8	91	24.1	1.55	1.00-2.39	**0.55**	**0.15-2.02**
Seafood intake (median g/day)								
1st quartile (51.51)	81	21.3	108	28.6	1.00	Reference	1.00	Reference
2nd quartile (82.41)	74	19.5	116	30.7	0.94	0.62-1.41	1.27	0.52-3.14
3rd quartile (121.90)	115	30.3	75	19.8	2.12	1.38-3.26	2.17	0.77-6.14
4th quartile (190.97)	110	28.9	79	20.9	1.80	1.19-2.72	2.24	0.76-6.58
Oil intake (median g/day)								
1st quartile (0.50)	84	22.1	105	27.8	1.00	Reference	1.00	Reference
2nd quartile (0.86)	123	32.4	81	21.4	1.90	1.25-2.88	3.75	1.38-10.18
3rd quartile (1.22)	81	21.3	76	20.1	1.33	0.86-2.06	0.71	0.26-1.96
4th quartile (1.79)	92	24.2	116	30.7	1.01	0.67-1.52	0.90	0.34-2.43

* *Crude OR*

† *Adjusted for education, history of asthma, history of dermatitis, allergy history in family members, and intake of Kcal/day.*

So as to ascertain that consumption of seafood and oil did not interact with the effect of polyunsaturated fatty acids, they were introduced in the final adjusted analysis. (Table 8) The results did not change substantially. One can observe, however, a statistically non-significant effect of omega-6 that follows a dose-response pattern. (Table 8)

Table 8. Odds ratios of allergic rhinitis and omega-3 and omega-6 polyunsaturated fatty acids additionally adjusting for seafood and oil intake

Variable	OR*	95% CI	OR†	95% CI
Omega-3 intake (median g/day)				
1st quartile (2.28)	1.00	Reference	1.00	Reference
2nd quartile (3.65)	1.10	0.43-2.78	1.42	0.54-3.78
3rd quartile (4.78)	1.03	0.33-3.21	1.26	0.38-4.20
4th quartile (7.82)	0.39	0.11-1.33	0.43	0.12-1.61
Omega-6 intake (median g/day)				
1st quartile (7.61)	1.00	Reference	1.00	Reference
2nd quartile (10.57)	0.80	0.28-2.27	0.70	0.24-2.02
3rd quartile (13.99)	0.39	0.13-1.18	0.47	0.15-1.46
4th quartile (18.84)	0.35	0.09-1.48	0.42	0.10-1.80

* *Adjusted for education, history of asthma, history of dermatitis, allergy history in family members, intake of Kcal/day* ***and additionally for seafood intake***

† *Adjusted for education, history of asthma, history of dermatitis, allergy history in family members, intake of Kcal/day* ***and additionally for oil intake***

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3.2.4. DISCUSSION

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The findings from this study provide strong evidence that a high intake of proteins is associated with increased risk of allergic rhinitis.

This association persisted after adjustment of lifestyle variables such as physical activity, smoking habits or alcohol consumption, as well as after control of education level, history of asthma, history of dermatitis and allergy history in family members. Energy intake and total fat intake were clearly associated with protein consumption. However, adjustment for these variables did not mitigate the effect of protein consumption on the risk of allergic rhinitis, but, on the contrary, increased it. Other variables that we did not measure in our study, or for which results are not available yet, may play the role of effect modifiers or confounders. These unmeasured variables include genetic factors, some of which were recently implicated in the etiology of the disease.[1]

As in any case-control study, memory and recall bias is a concern in our study. Differential recall between cases and controls would certainly introduce bias. However, in the present study, differential reporting, which leads cases to overestimate their protein, fruit, seafood or other nutrient intake, and controls to underestimate it, is unlikely as the questionnaire does not state the research question but only assesses food items and dishes. Measurement error in the assessment of these nutrients and food groups is likely to occur, but it is probably non differential with respect to disease status. If this bias exists, our results would then be biased towards the null value and our results would the underestimate the true effect.

Furthermore, despite the relatively high figures of sensitivity and specificity of our diagnosis of allergic rhinitis, misclassification of the outcome cannot be ruled out as symptoms of rhinitis are often mistaken with upper respiratory tract infections such as common cold or sinusitis.[6,7,24] However, this potential misclassification is unlikely to be differential with respect to exposure, and, again, our results would the underestimate the true effect.

Few studies related protein intake with the risk of allergic rhinitis. An ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) revealed a protective effect of high intakes of protein from cereal and nuts on allergic rhino-conjunctivitis. However, this study did not suggest any explanatory model and the association observed may be spurious.[28]

Possible explanations for the harmful effect of high intakes of protein may be advanced. Since the proportion of total energy, derived from protein, is relatively constant, protein intake may be considered as an indicator of total energy intake.[2] The risk increase among subjects with high intake of protein may then be mediated by the effect of energy intake. Our results show that a high energy intake is a risk factor of allergic rhinitis. Previous studies showed that caloric and protein restriction may boost cell-mediated immunity and antioxidant defenses, which inhibits oxidative damage and inflammation.[287] Excessive intake of protein and/or energy may then produce the opposite effect.

Other studies showed that low body mass, which could be conceptualized as a proxy for low energy intake, was associated with lower prevalence of atopic diseases such as asthma, while high energy intake was significantly associated with asthma.[30,31] Furthermore, other studies showed that obesity and overweight could be related to respiratory allergy through the inflammatory pathway, essentially through the increase of immune activity caused by adipokines, a specific type of cytokines secreted by adipose tissue.[32,33] Other cytokines, such as interleukin 10 (IL-10) and interferon gamma (IFN-γ) were also associated with excessive body weight and excessive consumption of nutrients.[34] It is remarkable that malnutrition was found to decrease the ability to produce cytokines.[35,36]

Other plausible explanations include the fact that a considerable proportion of the protein intake is due to meat products, which were associated with

increased inflammation status and increased risk of hay fever and asthma in previous studies.[37,38]

Furthermore, high amounts of protein are often associated with high quantities of sodium chloride, present in processed meat products. High levels of protein and sodium chloride in the diet increase the acidity of the blood and tissues.[39,40] Long-term metabolic acidosis consequences include systemic inflammation and impairment of the immune response.[40-42]

Finally, high intakes of protein are frequently associated with meat cooked at high temperatures. This kind of meat may contain high amounts of mutagens, such as polycyclic aromatic hydrocarbons and heterocyclic amines, formed during high-temperature cooking and grilling. Some of these mutagens were linked to respiratory disorders such as asthma,[37,43] as they interfere with membrane-bound β(2)-adrenergic receptors in the respiratory epithelium and trigger asthma attacks in asthmatics.[43] Allergic rhinitis and asthma share a common pathophysiology and similar risk factors and environmental triggers. Some authors think that both conditions are likely to be manifestations of the same systemic inflammatory disease as they often co-exist in the same patient and can predict the appearance of each other.[44-46]

The risk of allergic rhinitis increased with higher intake of most dietary antioxidants in our study population. Every antioxidant, including vitamin antioxidants which are obtained from food, is a redox (reduction-oxidation) agent, protecting against free radicals in some circumstances, but acting also as prooxidant and promoter of free radical under other conditions.[47] It was stated that excessive antioxidant action can adversely affect key physiological processes.[48] For example, large doses of vitamin E increase immune activity and may promote progression of immune and autoimmune diseases like asthma and allergies.[49] Furthermore, vitamin C is reported to have prooxidant properties in the presence of high body iron stores.[47]

Fruits and vegetables are the main source of antioxidants. While several studies found no effect of fruit on allergic rhinitis,[30,50-52] one study confirmed our results that show that a high or excessive intake of fruit could be a risk factor for allergic rhinitis.[37] Many fruits and vegetables contain high amounts of histamine and other biogenic amines that may produce symptoms such as sneezing, congestion and rhinorrhea.[37] These amines could then act as possible confounders of the relation fruit intake-allergic rhinitis.

Several studies confirm our results showing that β-carotene may be a risk factor for allergic rhinitis.[50,52] Under specific circumstances, including presence of other antioxidants, such as vitamins E and C and other carotenoids, β-carotene may shift its antioxidant activity into prooxidant.[48,53]

The mechanism of ''anti-oxidative stress'' was also used recently to explain possible adverse effects of antioxidants.[54] This theory is based on the fact, that the susceptibility for allergic diseases may not only increase when Th2-type cytokines are over-produced but also when Th1-type cytokines, such as Interferon-c, are suppressed. High intakes of food rich in antioxidants may decrease Th1-type immunity and promote Th2-type immunity, which increases the susceptibility to allergic diseases when an allergen is incorporated.[54] The activation of the Th2-type immunity increases the production of specific IgE antibodies. These antibodies circulate in the peripheral blood and attach on the surface of all mast cells and basophils, including those of the nasal mucosa, thus producing acute nasal symptoms.[55,56]

In summary, an excessive intake of ''healthy food'' rich in antioxidants could increase the susceptibility to allergy via the anti-oxidative stress pathway. However, the most plausible explanation of our surprising result is reverse causality. Subjects with allergic rhinitis may increase their intake of fruit in order to promote general health and boost immunity. Theoretically, this should not occur in a case-control study with incident cases as ours, since exposure assessment precedes disease occurrence. However, we should bear in mind that

our cases may have been suffering from allergic rhinitis for a long period without being diagnosed and even without having sought medical advice. They may then have changed their diet pattern after the onset of disturbing symptoms.

In our study, high intakes of omega-3 and omega-6 polyunsaturated fatty acids were related with a tendency to decrease the risk of allergic rhinitis, although the association observed was not statistically significant. Polyunsaturated fatty acids are essential in ensuring the correct environment for membrane protein function, maintaining membrane fluidity and regulating cell signaling, gene expression and cellular function. It was suggested that through these actions polyunsaturated fatty acids can influence the functioning of immune cells and so, could have an impact on the development and manifestations of atopic diseases.[57] However, the information available on the role of each of the polyunsaturated fatty acids on the immune system is controversial.

While several studies have linked omega-6 polyunsaturated fatty acids with increased risk of allergic rhinitis,[58-63] and other studies have failed to find any relationship,[31,64-67] two studies confirmed our results that higher intake of omega-6 protects from allergic rhinitis.[50,68]

One the one hand, it is known that omega-6 polyunsaturated fatty acids participate in the production of prostaglandin E2, which shifts the Th1/Th2 balance in to the Th2 direction, a mechanism that favors, as we saw before, Th2-determined diseases such as allergies.[50] On the other hand, higher production of prostaglandins E2 was shown to inhibit allergen-induced inflammatory responses, which may then decrease the risk of allergic conditions such as rhinitis.[68] Biologically, both risk and prevention actions of omega-6 polyunsaturated fatty acids are then plausible.

The role of omega-3 polyunsaturated fatty acids is more straightforward. They were reported to decrease the production of inflammatory mediators and increase the level of anti-inflammatory mediators.[69] Dietary omega-3

polyunsaturated fatty acids decrease the level of arachidonic acid and increase eicosapentaenoic acid, which suppresses eicosanoids such as prostaglandin E2, a molecule associated with systemic inflammatory response as we saw before. This suppression yields to production of less biologically active 3-series prostaglandins (PG) and 5-series leukotrienes (LT), which decrease allergic reaction.[50,70] Also it was reported that omega-3 can alter gene expression, decreasing transcription factor activity such as nuclear factor-kB (NF-kB), which plays a role in activating inflammatory genes.[71]

Furthermore, omega-3 polyunsaturated fatty acids are reported to inhibit T-cell proliferation and production of IL-2 and IFNg, which are Th1-type cytokines. As mentioned before, this increases the susceptibility to allergic diseases.[72]

3.2.5. REFERENCES

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1. Barnes KC. Evidence for common genetic elements in allergic disease. J Allergy Clin Immunol. 2000;106:S192-200.
2. Tricon S, Willers S, Smit HA, Burney PG, Devereux G, Frew AJ. Nutrition and allergic disease. Clin Exp Allergy Rev. 2006; 6:117–88.
3. Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. Curr Opin Allergy Clin Immunol. 2005; 5:23-9.
4. Kilpeläinen M. Koskenvuo M, Helenius H, Terho EO. Stressful life asthma and atopic diseases. Clin Exp Allergy. 2002; 32:256-63.
5. Diet, Nutrition and the Prevention of Chronic Diseases. Joint WHO/FAO expert consultation report, Geneva, Switzerland, 2003.
6. Bousquet J, Khaltaev N, Cruz AA, Denburg J et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008; 63:8-160.
7. Bousquet J, Van Cauwenberge P, Khaltaev N. ARIA Workshop Group and World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001; 108:147–336.
8. Wallace DV, Dykewicz MS, Bernstein DI et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol. 2008; 122: 1-84.
9. Settipane RA. Demographics and epidemiology of allergic and nonallergic rhinitis. Allergy Asthma Proc. 2001; 22(4):185-9.
10. Mastin T. Recognizing and treating non-infectious rhinitis. J Am Acad Nurse Pract. 2003; 15(9):398-409.
11. Settipane RA, Lieberman P. Update on nonalergic rhinitis. Ann Allergy Asthma Immunol. 2001; 86:494-507.
12. Martin-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-Rodriguez JC, Salvini S et al. Development and validation of a food frequency questionnaire in Spain. Int J Epidemiol. 1993; 22(3):512-9.
13. Mataix Verdú José. Tabla de composición de alimentos. 4ª edición. 2003, Universidad de Granada. España

14. United States Department of Agriculture (USDA), Agricultural Research Service. Nutrient data. Available at: http://www.ars.usda.gov/Services/docs.htm?docid=22770 [Last access: 2014/04/03]
15. White JW Jr. Relative significance of dietary sources of nitrate and nitrite. J Agric Food Chem. 1975; 23(5):886-91.
16. Siciliano J, Krulick S, Heisler EG, Schwartz JH, White JW Jr. Nitrate and nitrite content of some fresh and processed market vegetables. J Agric Food Chem. 1975; 23(3):461-4.
17. The European Prospective Investigation into Cancer and Nutrition (EPIC) data bases. Available at: http://epic.iarc.fr/research/activitiesbyresearchfields/nutritionalresearch.php [Last access: 2014/04/03]
18. Hord NG, Tang Y, Bryan NS. Food sources of nitrates and nitrites: the physiologic context for potential health benefits. Am J Clin Nutr. 2009; 90(1):1-10.
19. Encuesta Nacional de Salud de España 2011/12 (ENSE 2011/12). Available at: http://www.msssi.gob.es/estadEstudios/estadisticas/encuestaNacional/encuesta2011.htm [Last access: 2014/04/03]
20. Vilain C. The evaluation and monitoring of public health action on tobacco. Smoke-free Europe: 3. Copenhagen, WHO Regional Office from Europe, 1987.
21. Greenland S, Robins JM. Confounding and misclassification. Am J Epidemiol. 1985; 122(3):495-506.
22. SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.
23. StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.
24. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J. 2004; 24:758-64.

25. 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.
26. Human energy requirements. Report of a Joint FAO/WHO/UNU Expert Consultation, Rome, Italy, 17-24 October 2001.
27. Koushik A, Hunter DJ, Spiegelman D, Anderson KE, Buring JE, Freudenheim JL et al. Intake of the major carotenoids and the risk of epithelial ovarian cancer in a pooled analysis of 10 cohort studies. Int J Cancer. 2006; 119(9):2148-54.
28. Ellwood P, Asher MI, Björkstén 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(3):436-43.
29. Ayala V, Naudí A, Sanz A, Caro P, Portero-Otin M, Barja G et al. Dietary protein restriction decreases oxidative protein damage, peroxidizability index, and mitochondrial complex I content in rat liver. J Gerontol A Biol Sci Med Sci. 2007; 62(4):352-360.
30. Huang SL, Lin KC, Pan WH. Dietary factors associated with physician-diagnosed asthma and allergic rhinitis in teenagers: analyses of the first Nutrition and Health Survey in Taiwan. Clin Exp Allergy. 2001; 31(2):259-64.
31. Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Dietary meat and fat intake and prevalence of rhinoconjunctivitis in pregnant Japanese women: baseline data from the Kyushu Okinawa Maternal and Child Health Study. Nutr J. 2012; 11:19.
32. Ciprandi G, Ricciardolo FL, Signori, Schiavetti I, Monardo M, Ferraro MR et al. Increased body mass index and bronchial impairment in allergic rhinitis. Am J Rhinol Allergy. 2013; 27:195-201.
33. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol. 2005; 115(5):911-919.

34. Sharabiani MT, Vermeulen R, Scoccianti C, Hosnijeh FS, Minelli L, Sacerdote C et al. Immunologic profile of excessive body weight. Biomarkers. 2011; 16(3):243-251.
35. Broide K, Lotz K, Cuomo AJ, Coburn DA, Federman EC, Wasserman SI. Cytokines in symptomatic asthma airways. J Allergy Clin Immunol. 1992; 89:958-67.
36. Grimble RF. Nutritional modulation of cytokine biology. Nutrition. 1998; 14(7-8):634-640.
37. Rosenkranz RR, Rosenkranz SK, Neessen KJ. Dietary factors associated with lifetime asthma or hayfever diagnosis in Australian middle-aged and older adults: a cross-sectional study. Nutr J. 2012; 11:84.
38. Fung TT, Schulze M, Manson JAE, Willett WC, Hu FB. Dietary patterns, meat intake, and the risk of type 2 diabetes in women. Arch Intern Med. 2004; 164:2235–2240.
39. Premji SS, Fenton TR, Sauve RS. Higher versus lower protein intake in formula-fed low birth weight infants. Cochrane Database Syst Rev. 2006; (1):CD003959.
40. Pizzorno J, Frassetto LA, Katzinger J. Diet-induced acidosis: is it real and clinically relevant? Br J Nut. 2010; 103(8):1185-1194.
41. Kalantar-Zadeh K, Mehrotra R, Fouque D, Kopple JD. Metabolic acidosis and malnutrition-inflammation complex syndrome in chronic renal failure. Semin Dial. 2004; 17(6):455-465.
42. Kraut JA, Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. Nat Rev Nephrol. 2010; 6(5):274-285.
43. Factor P, Akhmedov AT, McDonald JD, Qu A, Wu J, Jiang H et al. Polycyclic aromatic hydrocarbons impair 2AR function in airway epithelial and smooth muscle cells. Am J Respir Cell Mol Biol. 2011; 45(5):1045-1049.
44. Tan RA, Corren J. The relationship of rhinitis and asthma, sinusitis, food allergy, and eczema. Immunol Allergy Clin North Am. 2011; 31: 481–491.
45. Scadding GK, Bousquet J. Introduction: allergic rhinitis. Allergy. 2007; 85:3-5.

46. Mucci T, Govindraj S, Tversky J. Allergic rhinitis. Mt Sinai J Med. 2011; 78:634-644.
47. Herbert V. Prooxidant effects of antioxidant vitamins. Introduction. J Nutr. 1996; 126(4 Suppl):1197S-200S.
48. Herbert V, Shaw S, Jayatilleke E, Stopler-Kasdan T. Most free-radical injury is iron-related: it is promoted by iron, hemin, holoferritin and vitamin C, and inhibited by desferoxamine and apoferritin. Stem Cells. 1994; 12(3):289-303.
49. Herbert V. Vitamin E supplementation of elderly people. Am J Clin Nutr. 1991; 53(4):976-7.
50. Nagel G, Nieters A, Becker N, Linseisen J. The influence of the dietary intake of fatty acids and antioxidants on hay fever in adults. Allergy. 2003; 58:1277-84.
51. Farchi S, Forastiere F, Agabiti N, Corbo G, Pistelli R, Fortes C, et al. Dietary factors associated with wheezing and allergic rhinitis in children. Eur Respir J. 2003; 22:772-80.
52. Miyake Y, Sasaki S, Ohya Y, Miyamoto S, Matsunaga I, Yoshida T, et al.; Osaka Maternal And Child Health Study Group. Dietary intake of seaweed and minerals and prevalence of allergic rhinitis in Japanese pregnant females: baseline data from the Osaka Maternal and Child Health Study. Ann Epidemiol. 2006; 16(8):614-21.
53. Palozza P, Serini S, Di Nicuolo F, Piccioni E, Calviello G. Prooxidant effects of beta-carotene in cultured cells. Mol Aspects Med. 2003; 24(6):353-62.
54. Murr C, Schroecksnadel K, Winkler C, Ledochowski M, Fuchs D. Antioxidants may increase the probability of developing allergic diseases and asthma. Med Hypotheses. 2005; 64(5):973-7.
55. Broide DH. The pathophysiology of allergic rhinoconjunctivitis. Allergy Asthma Proc. 2007; 28(4):398-403.
56. Min YG. The pathophysiology, diagnosis and treatment of allergic rhinitis. Allergy Asthma Immunol Res. 2010; 2(2):65-76.

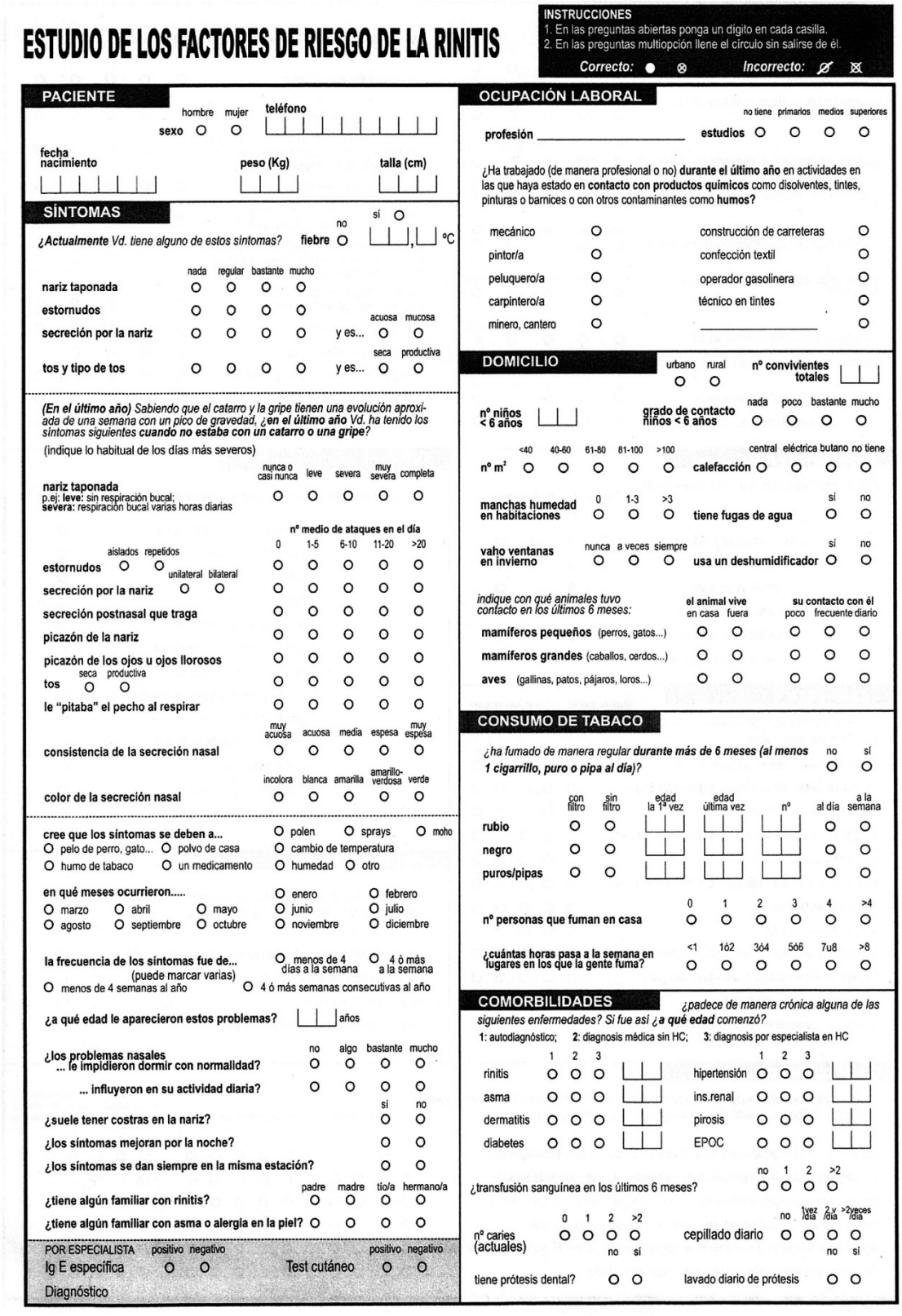
57. Calder PC, Kremmyda LS, Vlachava M, Noakes PS, Miles EA. Is there a role for fatty acids in early life programming of the immune system? Proc Nutr Soc 2010; 69(3):373-80.
58. Chatzi L, Apostolaki G, Bibakis I, Skypala I, Bibaki-Liakou V, Tzanakis N et al. Protective effect of fruits, vegetables and the Mediterranean diet on asthma and allergies among children in Crete. Thorax. 2007; 62:677-83.
59. Wakai K, Okamoto K, Tamakoshi A, Lin Y, Nakayama T, Ohno Y. Seasonal allergic rhinoconjunctivitis and fatty acid intake: a cross-sectional study in Japan. Ann Epidemiol. 2001; 11(1):59-64.
60. Lowe AJ, Thien FC, Stoney RM, Bennett CM, Hosking CS, Hill DJ et al. Associations between fatty acids in colostrum and breast milk and risk of allergic disease. Clin Exp Allergy. 2008; 38(11):1745-51.
61. Trak-Fellermeier MA, Brasche S, Winkler G, Koletzko B, Heinrich J. Food and fatty acid intake and atopic disease in adults. Eur Respir J. 2004; 23:575-82.
62. Bolte G, Frye C, Hoelsher B, Meyer I, Wjst M, Heinrich J. Margarine consumption and allergy in children. Am J Respir Crit Care Med. 2001; 163:277-9.
63. Kompauer I, Demmelmair H, Koletzko B, Bolte G, Linseisen J, Heinrich J. Association of fatty acids in serum phospholipids with hay fever, specific and total immunoglobulin E. Br J Nutr. 2005; 93:529-35.
64. Miyake Y, Sasaki S, Tanaka K, et al. Fish and fat intake and prevalence of allergic rhinitis in Japanese females: the Osaka Maternal and Child Health Study. J Am Coll Nutr 2007; 26:279-87.
65. Hoff S, Seiler H, Heinrich J, Kompauer I, Nieters A, Becker N et al. Allergic sensitization and allergic rhinitis are associated with n-3 polyunsaturated fatty acids in the diet and in red blood cell membranes. Eu.r J. Clin. Nutr. 2005; 59:1071-80.
66. Bolte G, Winkler G, Hölscher B, Thefeld W, Weiland SK, Heinrich J. Margarine consumption, asthma, and allergy in young adults: results of the German National Health Survey 1998. Ann Epidemiol. 2005; 15(3):207-13.

67. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. Allergy. 2009; 64(6):840-8.
68. Miyake Y, Tanaka K, Sasaki S, Arakawa M. Polyunsaturated fatty acid intake and prevalence of eczema and rhinoconjunctivitis in Japanese children: the Ryukyus Child Health Study. BMC Public Health. 2011; 11:358.
69. Wendell SG, Baffi C, Holguin F. Fatty acids, inflammation, and asthma. J Allergy Clin Immunol. 2014; 133:1255-64.
70. Grimm H, Mayer K, Mayser P, Eigenbrodt E. Regulatory potential of (n-3) fatty acids in immunological and inflammatory processes. Br J Nutr. 2002; 87: Suppl 1:S59–67.
71. Gottrand F. Long-chain polyunsaturated fatty acids influence the immune system of infants. J Nutr. 2008; 138(9):1807S-1812S.
72. Calder PC, Yaqoob P, Thies F, Wallace FA, Miles EA. Fatty acids and lymphocyte functions. Br J Nutr. 2002; 87:S31–48.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

3.2.6. ANNEXES

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA



ESTUDIO DE LOS FACTORES DE RIESGO DE LA RINITIS

INSTRUCCIONES
1. En las preguntas abiertas ponga un dígito en cada casilla.
2. En las preguntas multiopción llene el círculo sin salirse de él.

Correcto: ● ⊗ *Incorrecto:* ⊘ ⊠

PACIENTE

sexo: hombre ○ mujer ○ — teléfono

fecha nacimiento — peso (Kg) — talla (cm)

SÍNTOMAS

¿Actualmente Vd. tiene alguno de estos síntomas? fiebre: no ○ sí ○ __,__ °C

	nada	regular	bastante	mucho	
nariz taponada	○	○	○	○	
estornudos	○	○	○	○	
secreción por la nariz	○	○	○	○	y es... acuosa ○ mucosa ○
tos y tipo de tos	○	○	○	○	y es... seca ○ productiva ○

(En el último año) *Sabiendo que el catarro y la gripe tienen una evolución aproximada de una semana con un pico de gravedad, ¿**en el último año** Vd. ha tenido los síntomas siguientes **cuando no estaba con un catarro o una gripe**?*

(indique lo habitual de los días más severos)

	nunca o casi nunca	leve	severa	muy severa	completa
nariz taponada p.ej: **leve:** sin respiración bucal; **severa:** respiración bucal varias horas diarias	○	○	○	○	○

	nº medio de ataques en el día: 0	1-5	6-10	11-20	>20
estornudos aislados ○ repetidos ○	○	○	○	○	○
secreción por la nariz unilateral ○ bilateral ○	○	○	○	○	○
secreción postnasal que traga	○	○	○	○	○
picazón de la nariz	○	○	○	○	○
picazón de los ojos u ojos llorosos	○	○	○	○	○
tos seca ○ productiva ○	○	○	○	○	○
le "pitaba" el pecho al respirar	○	○	○	○	○

	muy acuosa	acuosa	media	espesa	muy espesa
consistencia de la secreción nasal	○	○	○	○	○

	incolora	blanca	amarilla	amarillo-verdosa	verde
color de la secreción nasal	○	○	○	○	○

cree que los síntomas se deben a...
○ pelo de perro, gato... ○ polvo de casa ○ humo de tabaco ○ un medicamento ○ polen ○ sprays ○ moho ○ cambio de temperatura ○ humedad ○ otro

en qué meses ocurrieron.....
○ marzo ○ abril ○ mayo ○ junio ○ julio ○ agosto ○ septiembre ○ octubre ○ noviembre ○ diciembre ○ enero ○ febrero ○ diciembre

la frecuencia de los síntomas fue de... (puede marcar varias)
○ menos de 4 días a la semana ○ 4 ó más a la semana ○ menos de 4 semanas al año ○ 4 ó más semanas consecutivas al año

¿a qué edad le aparecieron estos problemas? __ años

	no	algo	bastante	mucho
¿los problemas nasales ... le impidieron dormir con normalidad?	○	○	○	○
... influyeron en su actividad diaria?	○	○	○	○

	sí	no
¿suele tener costras en la nariz?	○	○
¿los síntomas mejoran por la noche?	○	○
¿los síntomas se dan siempre en la misma estación?	○	○

	padre	madre	tío/a	hermano/a
¿tiene algún familiar con rinitis?	○	○	○	○
¿tiene algún familiar con asma o alergia en la piel?	○	○	○	○

POR ESPECIALISTA
Ig E específica: positivo ○ negativo ○ — Test cutáneo: positivo ○ negativo ○
Diagnóstico

OCUPACIÓN LABORAL

profesión _____ **estudios:** no tiene ○ primarios ○ medios ○ superiores ○

¿Ha trabajado (de manera profesional o no) **durante el último año** en actividades en las que haya estado en **contacto con productos químicos** como disolventes, tintes, pinturas o barnices o con otros contaminantes como **humos?**

mecánico	○	construcción de carreteras	○
pintor/a	○	confección textil	○
peluquero/a	○	operador gasolinera	○
carpintero/a	○	técnico en tintes	○
minero, cantero	○	_____	○

DOMICILIO

urbano ○ rural ○ — **nº convivientes totales** __

nº niños < 6 años __ — **grado de contacto niños < 6 años:** nada ○ poco ○ bastante ○ mucho ○

	<40	40-60	61-80	81-100	>100		central	eléctrica	butano	no tiene
nº m²	○	○	○	○	○	**calefacción**	○	○	○	○

	0	1-3	>3		sí	no
manchas humedad en habitaciones	○	○	○	**tiene fugas de agua**	○	○

	nunca	a veces	siempre		sí	no
vaho ventanas en invierno	○	○	○	**usa un deshumidificador**	○	○

indique con qué animales tuvo contacto en los últimos 6 meses:	**el animal vive** en casa	fuera	**su contacto con él** poco	frecuente	diario
mamíferos pequeños (perros, gatos...)	○	○	○	○	○
mamíferos grandes (caballos, cerdos...)	○	○	○	○	○
aves (gallinas, patos, pájaros, loros...)	○	○	○	○	○

CONSUMO DE TABACO

*¿ha fumado de manera regular **durante más de 6 meses (al menos 1 cigarrillo, puro o pipa al día)**?* no ○ sí ○

	con filtro	sin filtro	edad la 1ª vez	edad última vez	nº	al día	a la semana
rubio	○	○	__	__	__	○	○
negro	○	○	__	__	__	○	○
puros/pipas	○	○	__	__	__	○	○

	0	1	2	3	4	>4
nº personas que fuman en casa	○	○	○	○	○	○

	<1	1&2	3&4	5&6	7u8	>8
¿cuántas horas pasa a la semana en lugares en los que la gente fuma?	○	○	○	○	○	○

COMORBILIDADES

*¿padece de manera crónica alguna de las siguientes enfermedades? Si fue así ¿**a qué edad** comenzó?*

1: autodiagnóstico; **2**: diagnosis médica sin HC; **3**: diagnosis por especialista en HC

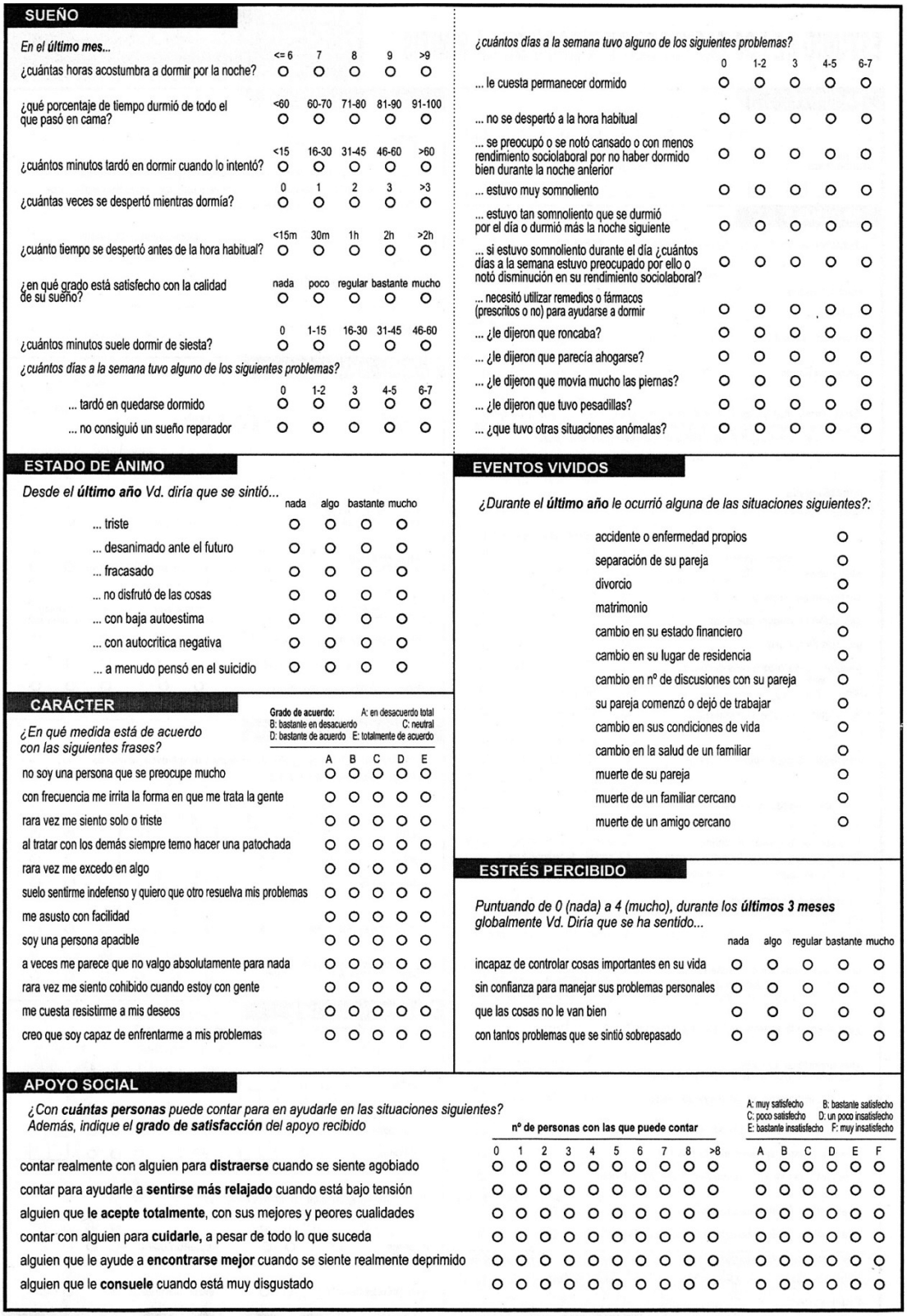
	1	2	3			1	2	3	
rinitis	○	○	○	__	hipertensión	○	○	○	__
asma	○	○	○	__	ins.renal	○	○	○	__
dermatitis	○	○	○	__	pirosis	○	○	○	__
diabetes	○	○	○	__	EPOC	○	○	○	__

	no	1	2	>2
¿transfusión sanguínea en los últimos 6 meses?	○	○	○	○

	0	1	2	>2		no	1vez /día	2 v /día	>2veces /día
nº caries (actuales)	○	○	○	○	cepillado diario	○	○	○	○

	no	sí		no	sí
tiene prótesis dental?	○	○	lavado diario de prótesis	○	○

Annex I (side A). Data collection questionnaire.



SUEÑO

*En el **último mes**...*

¿cuántas horas acostumbra a dormir por la noche?	<= 6	7	8	9	>9
¿qué porcentaje de tiempo durmió de todo el que pasó en cama?	<60	60-70	71-80	81-90	91-100
¿cuántos minutos tardó en dormir cuando lo intentó?	<15	16-30	31-45	46-60	>60
¿cuántas veces se despertó mientras dormía?	0	1	2	3	>3
¿cuánto tiempo se despertó antes de la hora habitual?	<15m	30m	1h	2h	>2h
¿en qué grado está satisfecho con la calidad de su sueño?	nada	poco	regular	bastante	mucho
¿cuántos minutos suele dormir de siesta?	0	1-15	16-30	31-45	46-60

¿cuántos días a la semana tuvo alguno de los siguientes problemas?

	0	1-2	3	4-5	6-7
... tardó en quedarse dormido					
... no consiguió un sueño reparador					

¿cuántos días a la semana tuvo alguno de los siguientes problemas?

	0	1-2	3	4-5	6-7
... le cuesta permanecer dormido					
... no se despertó a la hora habitual					
... se preocupó o se notó cansado o con menos rendimiento sociolaboral por no haber dormido bien durante la noche anterior					
... estuvo muy somnoliento					
... estuvo tan somnoliento que se durmió por el día o durmió más la noche siguiente					
... si estuvo somnoliento durante el día ¿cuántos días a la semana estuvo preocupado por ello o notó disminución en su rendimiento sociolaboral?					
... necesitó utilizar remedios o fármacos (prescritos o no) para ayudarse a dormir					
... ¿le dijeron que roncaba?					
... ¿le dijeron que parecía ahogarse?					
... ¿le dijeron que movía mucho las piernas?					
... ¿le dijeron que tuvo pesadillas?					
... ¿que tuvo otras situaciones anómalas?					

ESTADO DE ÁNIMO

*Desde el **último año** Vd. diría que se sintió...*

	nada	algo	bastante	mucho
... triste				
... desanimado ante el futuro				
... fracasado				
... no disfrutó de las cosas				
... con baja autoestima				
... con autocritica negativa				
... a menudo pensó en el suicidio				

CARÁCTER

Grado de acuerdo: A: en desacuerdo total B: bastante en desacuerdo C: neutral D: bastante de acuerdo E: totalmente de acuerdo

¿En qué medida está de acuerdo con las siguientes frases?

	A	B	C	D	E
no soy una persona que se preocupe mucho					
con frecuencia me irrita la forma en que me trata la gente					
rara vez me siento solo o triste					
al tratar con los demás siempre temo hacer una patochada					
rara vez me excedo en algo					
suelo sentirme indefenso y quiero que otro resuelva mis problemas					
me asusto con facilidad					
soy una persona apacible					
a veces me parece que no valgo absolutamente para nada					
rara vez me siento cohibido cuando estoy con gente					
me cuesta resistirme a mis deseos					
creo que soy capaz de enfrentarme a mis problemas					

EVENTOS VIVIDOS

*¿Durante el **último año** le ocurrió alguna de las situaciones siguientes?:*

accidente o enfermedad propios	
separación de su pareja	
divorcio	
matrimonio	
cambio en su estado financiero	
cambio en su lugar de residencia	
cambio en nº de discusiones con su pareja	
su pareja comenzó o dejó de trabajar	
cambio en sus condiciones de vida	
cambio en la salud de un familiar	
muerte de su pareja	
muerte de un familiar cercano	
muerte de un amigo cercano	

ESTRÉS PERCIBIDO

*Puntuando de 0 (nada) a 4 (mucho), durante los **últimos 3 meses** globalmente Vd. Diría que se ha sentido...*

	nada	algo	regular	bastante	mucho
incapaz de controlar cosas importantes en su vida					
sin confianza para manejar sus problemas personales					
que las cosas no le van bien					
con tantos problemas que se sintió sobrepasado					

APOYO SOCIAL

*¿Con **cuántas personas** puede contar para en ayudarle en las situaciones siguientes? Además, indique el **grado de satisfacción** del apoyo recibido*

nº de personas con las que puede contar

A: muy satisfecho B: bastante satisfecho C: poco satisfecho D: un poco insatisfecho E: bastante insatisfecho F: muy insatisfecho

	0	1	2	3	4	5	6	7	8	>8	A	B	C	D	E	F
contar realmente con alguien para **distraerse** cuando se siente agobiado																
contar para ayudarle a **sentirse más relajado** cuando está bajo tensión																
alguien que **le acepte totalmente**, con sus mejores y peores cualidades																
contar con alguien para **cuidarle,** a pesar de todo lo que suceda																
alguien que le ayude a **encontrarse mejor** cuando se siente realmente deprimido																
alguien que le **consuele** cuando está muy disgustado																

Annex I (side B). Data collection questionnaire.

CONSUMO MEDIO DE ALIMENTOS DURANTE EL ÚLTIMO AÑO

INSTRUCCIONES
1. Las preguntas se refieren a la media de consumo durante el último año.
2. En las preguntas multiopción llene el círculo sin salirse de él.

Correcto: ● ⊗ Incorrecto: ⊘ ⊠

Bebidas (unidad: vaso o botellín)	nunca ó <1/mes	1-3/mes	1/sem.	2-4/sem.	5-6/sem.	1/día	2-3/día	>3/día
refrescos de cola con cafeína y azúcar (coca-cola, pepsi...)	O	O	O	O	O	O	O	O
...ídem sin azúcar (coca-cola, ...)	O	O	O	O	O	O	O	O
refrescos sin cafeína con azúcar (coca-cola, kas, tónicas...)	O	O	O	O	O	O	O	O
refrescos sin cafeína ni azúcar (coca-cola, fanta, ...)	O	O	O	O	O	O	O	O
refrescos energéticos con cafeína y azúcar (red bull, burn...)	O	O	O	O	O	O	O	O
refrescos energéticos sin cafeína (aquarius, gatorade...)	O	O	O	O	O	O	O	O
zumos de naranja o cítricos exprimidos (recientes o envasados)	O	O	O	O	O	O	O	O
zumos de naranja o cítricos a partir de concentrado (envasados)	O	O	O	O	O	O	O	O
otros zumos recién hechos	O	O	O	O	O	O	O	O
bebidas de chocolate (cacaolat, cola-cao, nesquik...)	O	O	O	O	O	O	O	O
té, bebidas de té (nestea, lipton...)	O	O	O	O	O	O	O	O
café (no descafeinado), soluble o de cafetera (con o sin leche)	O	O	O	O	O	O	O	O

agua ___ vasos al día — cerveza ___ jarras o botellín /día O /sem O

vino tinto ___ copas o vasos /día O /sem O — vino blanco ___ copas o vasos O O

licores (solos o incluyendo los combinados con refrescos) ___ copas o vasos O O

Aceites	nunca ó <1/mes	1-3/mes	1/sem.	2-4/sem.	5-6/sem.	1/día	2-3/día	>3/día
veces de uso de aceite de oliva para aliñar	O	O	O	O	O	O	O	O
veces de uso de otro aceite distinto al de oliva para aliñar	O	O	O	O	O	O	O	O
raciones de alimentos fritos en aceite de oliva	O	O	O	O	O	O	O	O
raciones de alimentos fritos en otro aceite distinto al de oliva	O	O	O	O	O	O	O	O

Carnes y Pescados	nunca ó <1/mes	1-3/mes	1/sem.	2-4/sem.	5-6/sem.	1/día	2-3/día	>3/día
carne de cerdo (ración)	O	O	O	O	O	O	O	O
bacon/panceta (ración)	O	O	O	O	O	O	O	O
carne de ternera (ración)	O	O	O	O	O	O	O	O
hígado (ternera o cerdo) (ración)	O	O	O	O	O	O	O	O
carne de pollo (ración)	O	O	O	O	O	O	O	O
hamburguesa (unidad)	O	O	O	O	O	O	O	O
jamón/lomo (ración)	O	O	O	O	O	O	O	O
otros embutidos (ración)	O	O	O	O	O	O	O	O
atún o bonito (ración)	O	O	O	O	O	O	O	O
bacalao (ración)	O	O	O	O	O	O	O	O
salmón (ración)	O	O	O	O	O	O	O	O
sardinas, boquerones (2 ó 3)	O	O	O	O	O	O	O	O
anchoas, arenques (2 ó 3)	O	O	O	O	O	O	O	O
anguilas/angulas (ración)	O	O	O	O	O	O	O	O
jurel (ración)	O	O	O	O	O	O	O	O
caballa (ración)	O	O	O	O	O	O	O	O
otros pescados (ración)	O	O	O	O	O	O	O	O
mejillones, almejas (ración)	O	O	O	O	O	O	O	O
crustáceos (ración)	O	O	O	O	O	O	O	O
pulpo (ración)	O	O	O	O	O	O	O	O

Vegetales	nunca ó <1/mes	1-3/mes	1/sem.	2-4/sem.	5-6/sem.	1/día	2-3/día	>3/día
zanahorias (1 unidad)	O	O	O	O	O	O	O	O
remolachas (1 unidad)	O	O	O	O	O	O	O	O
cebolla (media)	O	O	O	O	O	O	O	O
berenjena (media)	O	O	O	O	O	O	O	O
calabacín/calabaza (ración)	O	O	O	O	O	O	O	O
espárragos (1 unidad)	O	O	O	O	O	O	O	O
espinacas, acelgas (ración)	O	O	O	O	O	O	O	O
puerros (ración)	O	O	O	O	O	O	O	O
tomate (uno) o salsa ídem (ración)	O	O	O	O	O	O	O	O
lechuga, escarola (ración)	O	O	O	O	O	O	O	O
pimientos (ración)	O	O	O	O	O	O	O	O
col, grelos, repollo (ración)	O	O	O	O	O	O	O	O
judías,guisantes (ración)	O	O	O	O	O	O	O	O
patatas (ración)	O	O	O	O	O	O	O	O

Frutas *(no en zumo)*	nunca ó <1/mes	1-3/mes	1/sem.	2-4/sem.	5-6/sem.	1/día	2-3/día	>3/día
aguacate (1 porción)	O	O	O	O	O	O	O	O
naranja o pomelo (1 unidad), mandarinas (2 unidades)	O	O	O	O	O	O	O	O
manzana, pera (unidad)	O	O	O	O	O	O	O	O
plátano (unidad)	O	O	O	O	O	O	O	O
melocotón (1 unidad), albaricoque, ciruelas (2 unidades), cerezas (taza)	O	O	O	O	O	O	O	O
fresas (taza)	O	O	O	O	O	O	O	O
kiwi (unidad)	O	O	O	O	O	O	O	O
melón/sandía (ración)	O	O	O	O	O	O	O	O
piña (ración)	O	O	O	O	O	O	O	O
aceitunas verdes (ración)	O	O	O	O	O	O	O	O

Cereales	nunca ó <1/mes	1-3/mes	1/sem.	2-4/sem.	5-6/sem.	1/día	2-3/día	>3/día
pan blanco (ración)	O	O	O	O	O	O	O	O
pan integral (ración)	O	O	O	O	O	O	O	O
cereales desayuno (ración)	O	O	O	O	O	O	O	O
pasta, arroz (ración)	O	O	O	O	O	O	O	O
lentejas, habas (ración)	O	O	O	O	O	O	O	O
pizza (ración)	O	O	O	O	O	O	O	O
croissants, donuts (unidad)	O	O	O	O	O	O	O	O
sopa o consomé (plato)	O	O	O	O	O	O	O	O

Lácteos y Chocolates	nunca ó <1/mes	1-3/mes	1/sem.	2-4/sem.	5-6/sem.	1/día	2-3/día	>3/día
leche (un vaso)	O	O	O	O	O	O	O	O
leche enriquecida con w3 (vaso)	O	O	O	O	O	O	O	O
yogures sólidos o líquidos (con o sin frutas)	O	O	O	O	O	O	O	O
mantequilla, margarina (porción)	O	O	O	O	O	O	O	O
queso azul (porción)	O	O	O	O	O	O	O	O
queso blanco o fresco (porción)	O	O	O	O	O	O	O	O
otros quesos (porción)	O	O	O	O	O	O	O	O
chocolate o bombones (3 ó 4 ó 1 taza)	O	O	O	O	O	O	O	O

Otros	nunca ó <1/mes	1-3/mes	1/sem.	2-4/sem.	5-6/sem.	1/día	2-3/día	>3/día
champiñones, setas (ración)	O	O	O	O	O	O	O	O
frutos secos (1 bolsa)	O	O	O	O	O	O	O	O
mayonesa industrial (ración)	O	O	O	O	O	O	O	O
huevos (2) (no en tortilla de patatas)	O	O	O	O	O	O	O	O
tortilla de patatas (ración)	O	O	O	O	O	O	O	O

Annex I (side C). Data collection questionnaire.

ACTIVIDAD DIARIA

Instrucciones:
1. Conteste a las siguientes preguntas de acuerdo con sus preferencias y no según las directrices que le pueda imponer su trabajo o su horario escolar.
2. Para cada pregunta piense en lo que hace la mayoría de las personas.
3. Piense en su sueño nocturno y no en sus posibles períodos de sueño durante el día.

*¿Suponiendo que **fuese totalmente libre** para elegir y **comparando con la mayoría de la gente**, cuándo preferiría hacer las siguientes actividades?*

¿cuándo preferiría...

1: **mucho más temprano** que la mayoría de la gente
2: **un poco más temprano...**
3: **igual...**
4: **un poco más tarde...**
5: **mucho más tarde** que la mayoría de la gente

	1	2	3	4	5
...levantarse?	O	O	O	O	O
...acostarse?	O	O	O	O	O
...hacer un examen importante de 3 horas?	O	O	O	O	O
...levantarse si tuviera 8 horas de trabajo por hacer?	O	O	O	O	O
...levantarse si tuviera un día libre y nada que hacer?	O	O	O	O	O
...hacer un trabajo mental que requiere gran concentración?	O	O	O	O	O
...hacer alguna actividad social en un día libre?	O	O	O	O	O
...desayunar?	O	O	O	O	O
...comer?	O	O	O	O	O
...empezar a trabajar cada día?	O	O	O	O	O
...hacer ejercicio o deporte fuerte?	O	O	O	O	O
...hacer una entrevista importante en la que necesitara estar en su mejor momento?	O	O	O	O	O

EJERCICIO FÍSICO

Por favor, indique el grado habitual de su actividad física:

	mucho menor	menor	igual	mayor	mucho mayor
su actividad física comparando con otras personas de su misma edad es...	O	O	O	O	O

	<5	6-15	16-30	31-45	>45
¿cuántos minutos dedica al día a caminar o ir en bicicleta al trabajo o de compras?	O	O	O	O	O

en su tiempo libre...	nunca	raras veces	a veces	a menudo	muy a menudo
... pasea en bicicleta	O	O	O	O	O
... practica un deporte	O	O	O	O	O
... ve la televisión	O	O	O	O	O
... pasea caminando	O	O	O	O	O
... suele hacer algo que le haga sudar	O	O	O	O	O

si suele practicar algunos deportes o ir al gimnasio, indique la intensidad que requieren y el tiempo que les dedica:

	pequeña	media	grande
intensidad (1er deporte)	O	O	O
intensidad (2º deporte)	O	O	O

pequeña: andar; media: ciclismo, gimnasia, natación; grande: fútbol

nº horas semanales que dedica a 1er deporte |_|_| ...a 2º deporte |_|_|

nº meses al año que dedica a 1er deporte |_|_| ...a 2º deporte |_|_|

MEDICAMENTOS

*¿durante los últimos 6 meses Vd. ha tomado al menos **3 veces por semana** algún medicamento?* (incluidos complejos vitamínicos)

	dosis	día	sem.	mes	nº meses
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|
____________	|_|_|	O	O	O	|_|_|

EVOLUCIÓN DE SÍNTOMAS (desde hace 5 días)

fiebre no O sí O ¿cuánta? |_|_|,|_| ºC

	mucho menor	menor	igual	mayor	mucho mayor
taponamiento de la nariz	O	O	O	O	O
frecuencia y severidad de los estornudos	O	O	O	O	O
secreción por la nariz	O	O	O	O	O
picazón de los ojos u ojos llorosos	O	O	O	O	O
tos	O	O	O	O	O
secreción postnasal que traga	O	O	O	O	O

	sí	no
la secreción por la nariz se ha vuelto más mucosa	O	O
la secreción por la nariz se ha vuelto más verdosa	O	O
se produce expectoración al toser	O	O
la secreción bronquial (flemas) es más verdosa	O	O

	no existió 5 días antes	mucho menor	menor	igual	mayor	mucho mayor
malestar general	O	O	O	O	O	O
dolor de garganta	O	O	O	O	O	O
dolor de cabeza	O	O	O	O	O	O
otros ____________	O	O	O	O	O	O
____________	O	O	O	O	O	O
____________	O	O	O	O	O	O
____________	O	O	O	O	O	O

Annex I (side D). Data collection questionnaire.

Antihistamines		Corticosteroids	AR	AR & Asthma	Asthma	noAR
Aerius	Tavegil	Acetato de cortisona	Aerius	Cetirizina	Alvesco	Atrovent nasal
Afluón	Telfast	Beclometasona	Afluon	Dezacor	Anasma	Avamys
Alastina	Variargil	Betametasona	Colyrio	Flixonase	Atrovent	Budesonida nasal
Alercina	Velodan	Budesonida	Alergoliber	Idasal	Budesonida	Flixonase
Alergoflat	Viternum	Clobetasol	Atrovent nasal	Respibien	Dacortin	Idasal
Alergoliber	Xazal	Clobetasona	Avamys	Rinobactil	Foradil	Rino-Ebastel
Alerlisin	Zaditen	Desoximetasona	Azomyr	Telfast	Formodual	
Alerrid	Zasten	Dexametasona	Bilina	Vispring colirio	Formoterol	
Alersol	Zolistan	Diclorisona	Budesonida nasal	Zasten	Foster	
Atarax	Zyrtec	Diflorasona	Clarityne		Inaladuo	
Azaron		Diflucortolona	Ebastina		Pectox Lisina	
Azomyr		Fluclorolona	Evastel		Plusvent	
Bactil		Flumetasona	Flixonase		Pulmicort	
Benadryl		Fluocinolona	Grazax (vacuna)		Ribujet	
Bilaxten		Fluocinónido	Levocetirizina		Rilast	
Bilina		Fluocortina	Loratadina		Salbutamol	
Biodramina		Flupamesona	Mizolen		Seretide	
Cetimerck		Fluticasona	Mometasona		Symbicort forte	
Cetineu		Halcinónido	Muntel		Terbasmin	
Cetirizina EFG		Halometasona	Nasacort		Terbutalina	
Chiclida		Hidrocortisona	Nasonex		Urbason	
Cinfamar		Metilprednisolona	Rhinocort		Ventolin	
Clarytine		Metilprednisona	Rhinomer			
Cliveran		Mometasona	Rhinomer			
Cobiona		Prednicarbato	Rhinospray			
Corifina		Prednisolona	Rinelon			
Coulergin		Prednisona	Rinocorin			
Dormidina		Triamcinolona	Rino-Ebastel			
Dramine			Rupafin			
Ebastel			Singulair			
Ebastina EFG			Talforte (vacuna)			
Fenergan			Xazal			
Fenistil			Dimetane			
Fexofenadina EFG			Chlor-Trimeton			
Fluidasal			Tavist			
Frinova			Benadryl			
Ibis			Claritin			
Ketasma			Zyrtec			
Klarvitina			Optimine			
Livocab			Allegra			
Loratidina EFG			Atarax			
Mircol			Vistaril			
Mizolen						
Muntel						
Navicalm						
Obalix						
Olopatanol (colirio)						
Oxatokey						
Periactin						
Polaramine						
Ratioalerg						
Reactine						
Relestat (colirio)						
Rinialer						
Rupafin						
Soñodor						
Stopcold Virtlix						

AR – allergic rhinitis
noAR – non-allergic rhinitis

Annex II. List of medicines commonly used for treating symptoms of allergic rhinitis, non-allergic rhinitis and asthma.

ÁREA DE MEDICINA PREVENTIVA

Facultad de Medicina

ESTUDIO DE FACTORES DE RINITIS

La rinitis es una enfermedad muy frecuente en el mundo entero. Poco se sabe sobre factores de exposición que aumenten o prevengan esta enfermedad. Por ello, desde la Facultad de Medicina de la Universidad de Santiago y el Complejo Hospitalario de Pontevedra queremos proceder al estudio de dichos factores por medio de un cuestionario sencillo dirigido a usuarios de farmacias. Nuestro objetivo es que se conozca mejor esta enfermedad y que se sepa prevenir.

EN QUÉ CONSISTE SU COLABORACIÓN EN EL ESTUDIO

Pedimos su participación a fin de que Vd. sea incluido en el grupo de personas que padecen la enfermedad o en el de las personas sanas que van a ser comparadas com aquéllas. Ud. deberá **contestar a las preguntas** contenidas en un cuestionario estándar, algo que lleva unos 20 minutos. Estas preguntas informan sobre su alimentación, su pauta de sueño, y el nível de estrés al que está sometido. Le llamaremos por teléfono una semana después de esta entrevista para hacerle algunas preguntas durante 2 minutos sobre síntomas de alergia. A mayores, le pediremos tambien que moje en saliva un trozo de papel filtro estéril que servirá para conocer si las características genéticas del individuo pueden influir en desarrollar la enfermedad.

Confidencialidad: Garantizamos que los cuestionarios serán exclusivamente utilizados para los objetivos mencionados y que el equipo de investigación mantendrá confidencialidad absoluta. El estudio ES TOTALMENTE ANÓNIMO. Sólo conoceremos su teléfono.

Para cualquier duda puede Ud. comunicarse con los responsables del estudio, Dr. **Carlos Regueira** en el teléfono **981-951194**, del CIBER de Epidemiología (Hospital Clínico Universitario. Primer piso) o con el Dr **Bahi Takkouche** en el teléfono **981-581237** del Área de Medicina Preventiva de la Facultad de Medicina.

Participación voluntaria: Su participación en el estudio es totalmente voluntaria, por lo que puede rechazar tomar parte en el estudio y podrá abandonarlo en cualquier momento.

FORMULARIO DE ACEPTACIÓN DEL ESTUDIO DE FACTORES DE LAS RINITIS

Yo, D(a). _____ declaro bajo mi responsabilidad que,

- recibí suficiente información sobre el estudio.
- pude hacer preguntas sobre el mismo.
- fui informado por **Jurgita Saulyte**

- entiendo que mi participación es voluntaria.
- entiendo que puedo retirarme del estudio: 1. cuando quiera.
  2. sin tener que dar explicaciones.

Pontevedra, a .....de.....de.....

Firma del participante: Firma del investigador:

Annex III. Informed consent model used

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4. GENERAL CONCLUSIONS

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1. In our meta-analysis, there is evidence of a weak association between exposure to tobacco smoke and allergic rhinitis among adults.

2. Among children and adolescents, both active and passive exposure to tobacco smoking are associated with a moderate increase of the risk of allergic rhinitis.

3. The findings of the prospective case control study provide strong evidence that a high intake of proteins is associated with increased risk of allergic rhinitis.

4. Proteins of animal origin exert a stronger effect on allergic rhinitis than proteins of vegetable origin.

5. High intakes of the amino acids leucine, tyrosine, valine and serine are associated with an increase in the risk of allergic rhinitis in a dose-response fashion.

6. High intakes of β-carotene increase the risk of developing allergic rhinitis.

7. High consumption of fruits shows strong positive association with allergic rhinitis, while that of vegetables is weakly associated with this disease. However, these associations may be due to reverse causality.

8. High intakes of omega-3 and omega-6 polyunsaturated fatty acids showe a tendency to decrease the risk of allergic rhinitis.

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5. RESUMEN DE LA TESIS DOCTORAL

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La rinitis alérgica se describe como la inflamación de la membrana de la mucosa nasal, mediada por la producción de inmunoglobulina-E (IgE). Normalmente se presenta con secreción nasal, obstrucción y picor nasal y estornudos. Los síntomas son reversibles y están provocados por la exposición a alérgenos u otros factores ambientales de presencia continua o estacional, por lo que la rinitis alérgica se clasifica en *estacional* o *perenne*. Últimamente también se ha propuesto una clasificación nueva según la gravedad y duración de los síntomas: rinitis alérgica intermitente o persistente.

La rinitis alérgica es una de las enfermedades alérgicas con mayor prevalencia que, por su elevada incidencia, impacto sustancial en la calidad de vida y alto coste económico, tiene una importancia que se ha infravalorado hasta ahora en la investigación epidemiológica. Se ha estimado que la rinitis alérgica afecta a más de 600 millones de personas en todo el mundo y esta cifra sigue incrementándose, especialmente en los países más desarrollados. Dado que esta enfermedad a menudo puede ser trivializada por el paciente o no reconocida por el médico, produciéndose, así, un control inadecuado de los síntomas, esta cifra, probablemente, subestima la verdadera magnitud de la enfermedad lo que la convierte en un problema de Salud Pública importante en este siglo.

Según la literatura más reciente, las interacciones genético-ambientales son los factores de riesgo más importantes de las enfermedades atópicas tales como la rinitis alérgica. Así mismo, la causa más plausible del aumento de la prevalencia en las últimas décadas puede estar relacionada con los cambios en los factores de riesgo asociados con el medio ambiente y el estilo de vida: la dieta, el estrés, la contaminación, las vacunas y los patrones de infección en la infancia. La "hipótesis de la higiene", asociada con la considerable mejoría del saneamiento, está ganando credibilidad. Esta teoría afirma que la exposición temprana a los agentes infecciosos influye en el desarrollo del sistema inmunológico reduciendo la probabilidad de desarrollar enfermedades atópicas, mientras un exceso de higiene aumenta la probabilidad de desarrollar

las enfermedades tales como la rinitis alérgica y el asma más adelante en la vida del niño.

Los hábitos de estilo de vida son unos de los pocos factores que se pueden manipular con el fin de prevenir una enfermedad. La nutrición es uno de los componentes más importantes entre los que tienen una influencia considerable en la salud de los seres humanos.

La identificación de los factores modificables de la rinitis alérgica tiene implicaciones importantes en la calidad de vida de los pacientes, así como en la reducción de los gastos directos e indirectos de esta enfermedad. Los cambios de estilo de vida, tales como el hábito dietético y el hábito de fumar, pueden ser unos de los factores esenciales y por ello hemos decidido llevar a cabo un metaanálisis y un estudio de casos y controles con los siguientes objetivos:

1. Determinar el efecto de consumo de tabaco sobre el desarrollo de rinitis alérgica según los estudios realizados: realizar una revisión sistemática y un metaanálisis de los artículos publicados hasta el momento acerca de los hábitos de fumar y riesgo de rinitis alérgica.

2. Determinar el efecto del consumo alto de la proteína en la dieta diaria sobre el desarrollo de la rinitis alérgica.

3. Determinar el efecto del consumo alto de los antioxidantes: ß-caroteno, vitamina A, vitamina E, vitamina C, selenio y zinc en la dieta diaria sobre el desarrollo de la rinitis alérgica.

4. Determinar el efecto del consumo alto de los ácidos grasos poliinsaturados omega-3 y omega-6 en la dieta diaria sobre el desarrollo de la rinitis alérgica.

El tabaquismo es uno de los factores potenciales para las enfermedades atópicas como la rinitis alérgica, pero hasta ahora los resultados de los estudios individuales han sido contradictorios. El objetivo del metaanálisis que hemos realizado fue examinar las evidencias de las asociaciones entre el hábito de fumar activo o la exposición pasiva al humo de tabaco y la rinitis alérgica.

Para ello, hemos recuperado los estudios publicados en cualquier idioma hasta el 30 de junio de 2013 mediante la búsqueda sistemática en Medline, Embase, las cinco bases de datos bibliográficas regionales de la Organización Mundial de la Salud y las bases de datos ISI-Proceedings; examinando manualmente las referencias de los artículos originales y de las revisiones recuperadas, y mediante el establecimiento de contacto personal con investigadores clínicos. Hemos incluido estudios de cohortes, de casos y controles, y transversales que presentaban estimaciones de odds ratio (OR) o riesgos relativos (RR) así como intervalos de confianza para los hábitos de fumar y rinitis alérgica, primero entre la población general y luego entre los niños.

Para calcular los riesgos relativos agrupados, con sus intervalos de confianza de 95%, hemos ponderado los odds ratios de los estudios transversales y de casos y controles, y los riesgos relativos de los estudios de cohortes, ponderándolos por el inverso de su varianza. Para cada estudio, se utilizó la estimación de la medida de efecto que se ajustó por el mayor número de factores de confusión. Cuando había heterogeneidad se utilizó el modelo de efectos aleatorios, y cuando esta estaba ausente, el modelo de efectos fijos.

Para comprobar la heterogeneidad, hemos utilizado una versión de la prueba de DerSimonian y Laird Q, adaptada a muestras pequeñas. La hipótesis nula de esta prueba es la ausencia de la heterogeneidad. Para cuantificar esta heterogeneidad se calculó la proporción de la varianza total debida a variación entre estudios (estadístico Ri). Además, hemos explorado el origen de la heterogeneidad estratificando nuestro análisis según varias variables tales

como diseño, tipo de exposición (tabaquismo activo o pasivo) y edad de los participantes (niños/adolescentes o adultos).

Se evaluó el sesgo de la publicación visualmente, utilizando los gráficos en embudo, y después, más formalmente, mediante el test de Egger. Todos los análisis se realizaron con el software HEpiMA® versión 2.1.3 Y STATA versión 12.

Hemos conseguido 97 estudios de rinitis alérgica y hábitos de fumar que sirvieron para ser incluidos en nuestro metaanálisis. Al analizar todos los estudios juntos la rinitis alérgica no se asoció con el tabaquismo activo (RR agrupado, 1.02; 95% CI: 0.92–1.15), pero se asoció con el tabaquismo pasivo (RR agrupado 1.10; 95% CI: 1.06–1.15). Entre los niños y adolescentes, tanto el tabaquismo activo como pasivo se asociaron con un aumento moderado del riesgo de la rinitis alérgica: para los fumadores activos el RR agrupado fue 1.40; 95% CI: 1.24–1.59 y para los fumadores pasivos el RR agrupado fue 1.09; 95% CI: 1.04–1.14. Las asociaciones del tabaquismo y la rinitis alérgica en los adultos fueron muy moderadas.

Se han observado asociaciones modestas entre el tabaquismo y la rinitis alérgica en los adultos. Los resultados están limitados por el potencial de la confusión y el sesgo dado que la mayoría de los estudios utilizó un diseño transversal. Además, los estudios mostraron un alto grado de heterogeneidad y las medidas de la exposición y la enfermedad se evaluaron bajo auto-informe, lo que puede incrementar la posibilidad de errores de clasificación.

Los presentes hallazgos sugieren que, en los países donde fuman muchas personas, el 14% de la rinitis alérgica en los niños puede ser atribuible al tabaquismo activo. Por lo tanto, la eliminación del tabaquismo activo entre los niños y adolescentes podría prevenir uno de cada siete casos de rinitis alérgica.

La segunda parte de nuestro trabajo consistía en realizar un estudio de casos y controles para determinar el efecto del consumo alto de proteína, antioxidantes

y ácidos grasos poliinsaturados en la dieta sobre el desarrollo de la rinitis alérgica.

Con el propósito de encontrar los factores de riesgo dietéticos de la rinitis alérgica, hemos llevado a cabo un estudio de casos y controles entre enero de 2011 y octubre 2013. Se incorporaron 387 casos y 387 controles de 6 farmacias en 2 ciudades del noroeste de España y de las unidades de neumología, alergología y de urgencias de 2 hospitales principales de las mismas ciudades: Santiago de Compostela y Pontevedra. En cada ubicación (farmacia o unidad hospitalaria), los controles fueron emparejados por edad y sexo.

La participación en el estudio fue voluntaria y anónima, informando del estudio que se estaba llevando a cabo y ofreciendo la participación en él. Dicha participación consistió en la cumplimentación de un cuestionario de 4 páginas, a partir de cuyas preguntas se conformaron las variables de exposición y de enfermedad, referentes al año anterior a la fecha de la encuesta. El cuestionario consistió en una serie de preguntas sobre síntomas de rinitis, antecedentes médicos, frecuencia de consumo de alimentos (Food Frequency Questionnaire (FFQ)) y preguntas sobre otras variables de estilo de vida que podrían ser posibles factores de confusión de la relación entre la dieta y la rinitis alérgica. Previamente, los participantes firmaban un documento mediante el cual otorgaban su consentimiento a participar en el estudio admitiendo que habían sido informados de sus características.

Para determinar los casos de rinitis alérgica, hemos utilizado el cuestionario elaborado por "The Allergic Rhinitis and its Impact on Asthma" (ARIA), junto con los criterios propuestos por "The Joint Task Force on Practice Parameters". Se pidió a los participantes que registrasen la presencia habitual de seis síntomas principales de la rinitis en los días más severos, evaluando su frecuencia de 0 (ningún ataque en el día) a 4 (más de 20 ataques en el día). Estos síntomas fueron: nariz taponada, estornudos, secreción nasal, secreción postnasal, picazón de la nariz y picazón de los ojos u ojos llorosos. También se

les pedía evaluar la consistencia de la secreción nasal, de 0 (muy acuosa) a 4 (muy espesa), y el color, de 0 (incolora) a 4 (verde).

El desafío principal de nuestro diagnóstico era separar los casos de rinitis alérgica de los casos de rinitis no alérgica, ya que los síntomas típicos suelen ser similares en ambas enfermedades. Además, otras enfermedades tales como el catarro común o la sinusitis también pueden llevar a un diagnóstico erróneo de rinitis alérgica ya que provocan obstrucción nasal y bloquean los senos paranasales. Por lo tanto, al mismo tiempo que el estudio principal, se realizó un estudio de validación destinado a documentar la validez de nuestro diagnóstico de la rinitis alérgica. Para ello, se utilizó como *estándar de oro* una muestra de 255 personas seleccionadas al azar entre nuestros sujetos hospitalarios que previamente habían sido diagnosticados de rinitis alérgica, de rinitis no alérgica y de los en que se confirmó la ausencia de rinitis. Más precisamente, hemos seleccionado 70 pacientes con el diagnóstico de rinitis alérgica confirmado por a) examen clínico, b) pruebas cutáneas positivas a los alérgenos inhalados comunes y/o presencia de IgE específicas en el suero c) ausencia de medicación previa de rinitis. También, hemos seleccionado 25 sujetos con diagnóstico confirmado de la rinitis no alérgica, que fue establecido por examen clínico y confirmado por pruebas cutáneas negativas y niveles de IgE en suero normales. Los sujetos con rinitis no alérgica también tenían que confirmar que no habían tomado ningún tipo de medicación para los síntomas de rinitis durante el último año. Por último, se incluyeron 160 sujetos que fueron confirmados como libres de rinitis alérgica y no alérgica, así como de cátaro común y sinusitis. Estos sujetos tenían que cumplir los siguientes criterios: 1) puntuación de síntomas de rinitis ≤ 3 sobre 12, (2) ausencia de cualquier sospecha subjetiva y de diagnóstico confirmado previamente de rinitis, (3) no estar tomando ningún medicamento que podría ocultar posibles síntomas de rinitis. Se les pidió a estos sujetos completar nuestro cuestionario de enfermedad y se calculó la sensibilidad y especificidad de nuestro diagnóstico, utilizando diferentes puntos de corte para las puntuaciones de los síntomas. Las cifras finales para el diagnóstico de rinitis alérgica fueron las

siguientes: sensibilidad 0.74 y especificidad 0.92. Estas cifras se alcanzaron utilizando el corte de 4 puntos o más sobre 12 en la puntuación total de síntomas.

Después de la validación de caso, hemos establecido cuatro criterios que fueron necesarios para el diagnóstico de la rinitis alérgica mediante nuestro cuestionario: (1) puntuación mínima de 4 sobre 12 puntos en la puntuación total de los tres síntomas principales de rinitis (nariz taponada, estornudos y secreción por la nariz), (2) consistencia de la secreción nasal muy acuosa, acuosa o media, (3) color de la secreción nasal incolora o blanca, y (4) por lo menos uno de los alérgenos que provocan las síntomas de la rinitis tenía que ser polen, polvo doméstico o pelo de animales.

Para evaluar el consumo diario de los macro y micronutrientes, junto con el consumo diario de energía de la dieta regular y obtener la ingesta diaria de macro y micronutrientes, se utilizó un cuestionario de frecuencia alimentaria de 86 ítems elaborado a partir de un cuestionario de frecuencia alimentaria (FFQ) validado en España. A los participantes se les pidió que indicasen la frecuencia media de consumo de cada uno de los alimentos en porciones o unidades al día o a la semana durante el último año. El consumo de cada alimento fue recodificado en una escala con un rango de 8 categorías: de "nunca" a "más de tres veces al día."

Para calcular el contenido de macro y micronutrientes para cada alimento se utilizó la Base de Datos de Composición de Alimentos Española, ampliada con fuentes europeas y estadounidenses cuando algunos datos no estaban disponibles en las fuentes españolas.

La variable de ingesta diaria de proteínas fue creada calculando el contenido real de la proteína en cada uno de los alimentos del cuestionario. La misma metodología se aplicó para el cálculo de la ingesta diaria de otros macro y micronutrientes.

La ingesta diaria de los antioxidantes de cada participante se calculó a partir de todos los productos alimenticios, calculando su contenido de β-caroteno, vitamina A, vitamina E, vitamina C, selenio y zinc. Lo mismo se repitió para el cálculo de la ingesta de los ácidos grasos poliinsaturados omega-3 y omega-6. La variable del consumo diario de pescado y marisco se calculó sumando cualquier tipo de pescado y otros mariscos tales como mejillones, crustáceos y pulpo. La ingesta de aceite se calculó a partir del consumo promedio de aceite de oliva o cualquier otro tipo de aceite vegetal, que se utilizaba para cocinar o para aliñar.

El consumo de tabaco fue determinado según las normas de un cuestionario estándar elaborado por la Organización Mundial de Salud.

Para el análisis de datos se utilizaron los paquetes estadísticos SPSS (*Statistical Packagefor Social Sciences*) versión 18.0 y STATA versión 12.0 (StataCorp LP, College Station, Texas). Se examinaron las distribuciones de las variables y en aquellas que no seguían una distribución normal se procedió a realizar una conversión logarítmica para aproximarse a la normalidad. El diseño del estudio nos permitió calcular los odds ratio (OR) y sus intervalos de confianza del 95% para cada factor de riesgo. El análisis consistió en un modelo multivariado de regresión logística condicional sobre los factores edad y sexo, ajustado por variables potencialmente confusoras. Se consideraron como variables de confusión o modificadoras de efecto todas aquellas que ejercieron efecto en el análisis univariante, modificando el efecto de la variable principal en más de un 10%. Al final 5 variables de confusión principales fueron seleccionada para su inclusión en el modelo final: nivel de estudios, antecedentes personales de asma, antecedentes personales de dermatitis alérgica, antecedentes familiares de alergias e ingesta total de grasas. La ingesta total de kilocalorías también fue considerada en algunos modelos finales como variable potencial de confusión.

La muestra definitiva de este estudio consistió de 774 sujetos, de los cuales 387 eran casos de rinitis alérgica y 387 eran controles, pareados por edad y sexo. La

tasa de la respuesta global fue 72.5%. La edad media de los participantes fue 34.5 años, con un rango de 18 a 77. La muestra consistió en 129 hombres (33%) y 258 (67%) mujeres en en cada grupo.

El dato más relevante de este trabajo es el hallazgo de que un alto consumo de proteínas aumenta el riesgo de la rinitis alérgica (OR = 3.79; IC del 95%: 2.40 a 5.97 para el último cuartil de la ingesta). La asociación fue mayor después de ajustar por los factores de confusión (OR = 9.07; IC del 95%: 1.92 a 42.83 para el 4º cuartil). La ingesta total de energía y la ingesta total de grasa también se asociaron con el consumo de proteínas. Sin embargo, al ajustar por estas variables el efecto del consumo de proteínas sobre el riesgo de la rinitis alérgica no se redujo, sino que se observó un incremento. Las proteínas de origen animal parecen ejercer mayor efecto que las proteínas de origen vegetal, aunque ambas mostraron un incremento en el efecto para el cuartil más alto después del ajuste por las variables confusoras. En el análisis de los aminoácidos por separado, el consumo elevado de leucina, tirosina, valina y serina se asocia con un aumento del riesgo y un efecto dosis-respuesta.

Los resultados obtenidos para la mayoría de los aminoácidos analizados (ß-caroteno, vitamina A, vitamina E, vitamina C, selenio y zinc) indican la existencia de una importante asociación entre estas variables y el desarrollo de la rinitis alérgica. La asociación positiva más fuerte se observó entre la ingesta alta de β-caroteno y rinitis alérgica, que aumento aún más después de ajustar por las variables de confusión (OR = 5.12; IC del 95%: 1.54-17.04 para 4º cuartil). El consumo alto de la vitamina A fue relacionado con un aumento en el riesgo sólo antes de ajustar por otras variables (OR= 2.87; 95% CI: 1.82-4.52 para 4º cuartil). Las vitaminas E y C no han tenido efecto apreciable en el modelo ajustado, mientras que los minerales selenio y zinc mostraron efecto, limitado, sin embargo, para el 3er cuartil. El mayor consumo de frutas fue significativamente relacionado con el riesgo de la rinitis alérgica antes y después de ajustar por las variables de confusión (OR=3.12; 95% CI: 2.00-4.87 y OR=5.11; 95% CI: 1.67-15.63 para los últimos cuartiles, respectivamente). El

consumo de verduras se relacionó con la enfermedad sólo en el análisis crudo (OR=3.11; 95% CI: 1.95-4.96 para 4º cuartil), sin embargo, esta relación pierde significación después de ajuste.

Los valores altos de los ácidos grasos poliinsaturados en la dieta diaria mostraron tendencia a disminuir el riesgo de la rinitis alérgica para el último cuartil del consumo después de ajustar por otras variables de confusión, aunque la asociación no fue estadísticamente significativa (OR=0.42; 95% CI: 0.13-1.38 para omega-3 y OR=0.55; 95% CI: 0.15-2.02 para omega-6). Puesto que las fuentes principales de los ácidos grasos omega-3 son pescado y marisco, y de los ácidos grasos omega-6 aceites vegetales, estas variables también fueron consideradas en el análisis. Sin embargo, Los resultados no cambiaron sustancialmente después de incluir el consumo de estos grupos de alimentos en el modelo.

Como en cualquier estudio de casos y controles, el sesgo de la memoria es una de las debilidades de este estudio. También existe la posibilidad de medición errónea de los valores de macro y micronutrientes, pero es más probable que eso no sea diferencial respecto al estado de la enfermedad. Por otra parte, a pesar de las cifras relativamente altas de sensibilidad y especificidad de nuestro diagnóstico de la rinitis alérgica, la clasificación errónea de caso no se puede descartar, puesto que los síntomas de la rinitis se confunden a menudo con infecciones de las vías respiratorias superiores, como el catarro común o la sinusitis.

Los resultados de ambas partes de este trabajo confirman que los factores ambientales modificables, tales como tabaquismo y alimentación, influyen en la aparición de rinitis alérgica. Se ha demostrado que había una asociación entre la exposición al humo del tabaco y la rinitis alérgica, esencialmente en niños.

Por otra parte, la alimentación también parece sobre la aparición de rinitis. Los resultados de este estudio confirman que un consumo excesivo de proteínas y de algunos antioxidantes, tales como ß-caroteno, puede aumentar el riesgo de

rinitis alérgica. Al contrario, el consumo alto de ácidos grasos poliinsaturados omega-6 y omega-3 ejerce un efecto protector sobre la enfermedad.

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