EPIDEMIOLOGY OF WHEEZING IN INFANTS IN THE REGION OF PAMPLONA

Ismael Álvarez Álvarez

Department of Health Sciences

Public University of Navarre

2017

EPIDEMIOLOGY OF WHEEZING IN INFANTS IN THE REGION OF PAMPLONA

Ismael Álvarez Álvarez

Department of Health Sciences. Public University of Navarre.

Thesis supervised by:

Dr. Francisco Guillén Grima and Dr. Inés Aguinaga Ontoso.

April 2017

Francisco Guillén Grima, catedrático de Medicina preventiva y Salud Pública del Departamento de Ciencias de la salud de la Universidad Pública de Navarra, e Inés Aguinaga Ontoso, profesora titular de Medicina preventiva y Salud pública del Departamento de Ciencias de la salud de la Universidad Pública de Navarra, certifican:

Que la presente tesis doctoral, titulada "Epidemiology of wheezing in infants in the región of Pamplona", original de D. Ismael Álvarez Álvarez, ha sido realizada bajo mi dirección, y que a mi juicio reúne todos los requisitos de calidad y rigor científico para su defensa, con el fin de la obtención del título de Doctor y la mención de Doctor Internacional.

En Pamplona, a 6 de Abril de 2017.

Francisco Guillén Grima
Director de la tesis

Inés Aguinaga Ontoso
Directora de la tesis

A mi hermano.

Ella está en el horizonte.
Yo me acerco dos pasos y ella se aleja dos pasos.
Camino diez pasos y el horizonte se corre diez pasos más allá.
Por mucho que yo camine, nunca la alcanzaré.
¿Para qué sirve la utopía?
Para eso sirve, para caminar.

(Fernando Birri, Eduardo Galeano)

Acknowledgements

Al Dr. Francisco Guillén Grima y a la Dra. Inés Aguinaga Ontoso, por ofrecerme la oportunidad de haber podido realizar esta tesis doctoral, y por su guía y ayuda a lo largo de la realización de este trabajo.

A las familias participantes en el Estudio Internacional de Sibilancias en Lactantes en la comarca de Pamplona por su colaboración, y al personal sanitario que trabajó para hacerlo realidad. Sin su ayuda y compromiso, no existiría esta tesis doctoral.

A los trabajadores la Escuela de doctorado de Navarra (EDONA) y del Servicio de Préstamo Interbibliotecario de la Universidad Pública de Navarra, por su inestimable ayuda y trabajo en las numerosas ocasiones que fue necesario.

Al Institut de Santé Publique, d'Epidémiologie et de Développement (ISPED), por acogerme en mi estancia en Burdeos, y especialmente a Marielle Montoya, y a la Dra. Chantal Raherison, por facilitar mi estancia y por su tutela durante esos meses.

Al Departamento de Salud Pública y Medicina Preventiva de la Universidad de Navarra, por brindarme la oportunidad de poder trabajar en el proyecto SUN (Seguimiento Universidad de Navarra), y poder seguir aprendiendo y formándome.

A mi familia, por su apoyo y ayuda, sus consejos y ánimos. Y a mi compañera vital, a Hao, por su ayuda incluso cuando no era solicitada, su compañía, su preocupación, y dedicación. Sin estas personas a mi lado, no podría estar escribiendo estas líneas.

A mis compañeras y compañeros de fatigas *born and raised in the faculty*: Omar, María, Sole, Carlos, Benjamín, Rubén, Silvia, Saray, Pablo, Isabel, Laura, Sabrina. Vuestros ánimos, y el recuerdo de esos maravillosos años que vivimos, que me motiva a seguir trabajando. Esta tesis doctoral os pertenece.

Y por extensión, a todos mis amigas, amigos y familias, siempre unidos pese a la distancia y las circunstancias. Nombraros a todos sería injusto porque olvidaría algún nombre, pero sabed que os agradezco vuestro apoyo y ayuda en cada paso que he caminado. Este trabajo también es vuestro.

A todas y todos,

Gracias. Thank you. 谢谢. Merci.

Contents

Abstract, 1

Introduction, 2

Hypothesis and objectives, 19

Material and methods, 21

Results, 31

Discussion, 69

Conclusions, 90

References, 92

Appendices, 117

- Appendix 1. International Study of Wheezing in Infants questionnaire, 118
- Appendix 2. Publications, 127
- Appendix 3. Internship at the Institut de Santé Publique, d'Epidémiologie et de Développement, 151

Abstract

Background: wheezing in the first year of life affect both infant and parental quality of life. Risk factors as male gender, nursery attendance, presence of damp or mould stains at home, or family history of asthma and allergies, and protective factors such as breastfeeding more than six months have been previously described. The aim of this study was to investigate the prevalence and risk and protective factors for wheeze ever, recurrent wheeze and severe wheeze in infants in the region of Pamplona, Spain.

Material and methods: this cross-sectional study was part of the International Study of Wheezing in Infants (in Spanish, Estudio Internacional de Sibilancias en Lactantes, or EISL). Between 2006 and 2008, participating families answered a standardised validated questionnaire on demographic and anthropometric factors, respiratory and allergy symptoms, family background, environmental factors, and exposures during pregnancy and birth. Bivariate analyses (using chi-squared test or Student's t-test, as appropriate) were conducted, calculating odds ratios with 95% confidence intervals. Also, multivariate models were used to adjust for confounding variables. A p value lower than 0.05 was regarded as statistically significant.

Results: 1,065 questionnaires were answered. Prevalence of wheeze ever was 32.5%. Prevalences of recurrent and severe wheeze were 10.6% and 9.6%, respectively. Male gender, pneumonia in the first year of life, infant eczema, higher number of colds, prenatal exposure to tobacco smoke, nursery attendance and presence of pets in the household were some of the risk factors identified. Conversely, a longer exclusive breastfeeding was found as protective factor.

Conclusions: wheezing in infants is an important public health issue, that can lead to asthma in childhood. Prevalences found in this study were comparable to others found in European centres, but lower than those found in Latin American countries. Several preventable risk factors have been identified.

1. Introduction

1.1 Wheezing and asthma

Wheezing is a high-pitched whistling sound occurring during breathing, commonly during breathing out, coming from the bronchial tubes. Wheezing occurs when airways are narrowed or filled with mucus, due to several causes, like allergies, infections or irritation.

Wheezing is a common symptom in infants. The variety of responses of their lung to external influences is reduced from a clinical point of view, being two of the most typical responses contraction of the smooth muscle and inflammation of the bronchial mucosa. These responses, initiated by different stimuli, lead to the onset of wheezing (García-Marcos et al., 2009).

Recurrence is a common characteristic of wheezing, with approximately 30% of children who wheezed in the first six months of life also reporting wheezing at age three years (Sherriff et al., 2001).

Many infants suffer from recurrent wheeze transiently, disappearing the disease in the early childhood, but other children may develop asthma in the future, affecting their quality of life in the adolescence and adulthood.

Recurrent wheezing in the early life is a heterogeneous group of disorders with different pathophysiological mechanisms, but with a common symptom, the obstruction of the airway. This heterogeneity leads to a clinical variability which makes difficult to predict in a patient which will be the response to treatment and the long-term evolution.

Wheezing shows non-specific symptoms, and many diseases manifest wheezing during early life, with a similar clinical presentation, which makes very difficult to distinguish and diagnose wheezing in infants (Villa-Asensi, 2009).

The two more frequent causes of wheezing in children are bronchiolitis and asthma, but their diagnosis is difficult, which results in many children diagnosed as wheezers for the lack of a more precisely diagnosis. Other causes, although less frequent, include congenital anatomical abnormalities, aspiration of foreign bodies, other lung disorders as cystic fibrosis, and cardiac, immune and gastrointestinal disorders (Ducharme et al., 2014).

It has been observed that wheezing have a significant impact in infant's quality of life in the first years of life, affecting both the physical and mental functioning (Oostenbrink et al., 2006; Hafkamp-de Groen et al., 2013), quality of life in teenage years (Mohangoo et al., 2007), and also parental quality of life (Osman et al., 2001).

Asthma is defined as a common chronic disorder of the airways characterized by recurrent and variable symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. The interaction of these characteristics determines the clinical manifestations, severity of asthma and response to treatment.

The diagnosis of asthma should be determined by the presence of episodic symptoms of airflow obstruction, a partially reversible obstruction, and excluding other diagnoses. Other key indicators are the presence of wheezing, reporting a history of cough, recurrent wheezing, difficulties to breath or chest tightness, and the onset or worsening of symptoms upon exposure to dust, pollen or tobacco smoke (National Heart, Lung and Blood Institute, 2007).

Asthma and wheezing have a relevant economic impact. One study conducted in United Kingdom estimated the treatment cost in children between one to five years old was 52.75 million pounds, which represented the 0.15% of the National Health System expenditure (Stevens et al., 2003). Another study conducted in the United States described a significant upward trend in medical expenditure related to asthma in teenagers, with an annual growth rate of 2.5% in the period 2000-2009. Between years 2005-2009, medical expenditure for treatment of asthma in children under five years amounted to 2,500 million dollars, with approximately half of these costs related to hospitalizations (Jang et al., 2013).

1.2 Clinical phenotypes

Wheezing clinical phenotypes, helpful in taking therapeutic decisions, are more useful in medical practice than in epidemiological studies. A working group from the European Respiratory Society (ERS) defined two phenotypes according to the temporal pattern of wheeze (Brand et al., 2008).

Episodic viral wheeze

This phenotype is defined as wheeze in episodes, with the child not reporting wheezing between them. It is the most common phenotype in preschool age, although is not exclusive. Episodes of wheezing tend to occur seasonally.

According to clinical evidences, they are associated with viral respiratory tract infections, being rhinovirus, respiratory syncytial virus (RSV), coronavirus, human metapneumovirus, parainfluenza virus and adenovirus the most common agents.

Factors underlying the frequency and severity of episodes are not established yet, but severity of the first episode is related to atopy, exposure to tobacco smoke and prematurity at birth.

Episodic wheeze tends to decline over time, disappearing at age six years, although can remain as episodic wheeze in school age, disappearing at older ages, or change into another phenotype, multiple-trigger wheeze.

In contrast, other studies have shown evidence of children with severe episodic wheezing who had a higher risk of asthma at ages five to ten years, refuting that it can be considered a transient disease (Kappelle and Brand, 2012).

Treatment with inhaled corticosteroids in children with episodic wheezing is controversial. Some studies found that high doses of inhaled corticosteroids at the onset of the infection of the upper respiratory tract were an effective treatment for reducing severity and the need for oral corticosteroids, although the daily use of low doses did not show any clinical benefit (McKean and Ducharme, 2000).

On the other hand, other studies described a small benefit of inhaled steroids in preventing viral wheeze, and no effects in reducing symptoms of upper respiratory tract infections (Clavenna et al., 2014), nor the progression from episodic to persistent wheezing (Bisgaard et al., 2006).

The positive effects of daily treatment with leukotriene receptor antagonists (Montelukast) in reducing asthma exacerbations by approximately 30% were described in other study (Bisgaard et al., 2005).

Multiple-trigger wheeze

Contrary to episodic wheezing, this phenotype shows symptoms between episodes. Although viral respiratory tract infection is the main trigger of wheezing at early ages, some children also wheeze when they are exposed to other stimuli, such as tobacco smoke, laugh or exercise.

Multiple-trigger wheeze has been also associated with lung function abnormalities (Sonappa et al., 2010), or atopic sensitisation in the first year of life: food allergies to eggs or cow's milk, atopic dermatitis, or sensitisation to indoor allergens (Frey and von Mutius, 2009).

Cluster analyses defined two multiple-trigger wheeze phenotypes. Non-atopic uncontrolled wheezing was associated with nursery attendance and family history of asthma, and it was classified as moderate severe, whereas atopic multiple-trigger wheezing, which mostly affected boys, especially those who were atopic, was associated with the presence of mould or cockroaches, and overcrowded housing (Just et al., 2012).

Treatment for this phenotype with inhaled corticosteroids, or combined with long-acting β_2-agonist, was found effective, with a greater lung function improvement when both treatment were used jointly (Mäkelä et al., 2012).

Despite its therapeutic value, this clinical phenotypic classification has some drawbacks, such as the poor prediction in the patterns of wheezing in a year observation period (Schultz et al., 2010). Other disadvantages described were not allowing to difference wheezing by severity or frequency, or not predicting the future pattern, considering this classification into two phenotypes too simple, given the broad spectrum of recurrent wheeze disorders in preschool ages (Schultz and Brand, 2011).

In 2013, in the European Respiratory Society Annual Congress, this above-mentioned proposed classification was discussed, concluding that the distinction between episodic and multiple-trigger wheeze was not so clear in all patients as first suggested, and was a poor predictor of long-term results, considering better predictors the severity and frequency of the episodes.

As for treatment, in children with multiple-trigger wheeze, inhaled corticosteroids were considered the first therapeutic option, whilst in children who suffered episodic wheeze, treatment with inhaled corticosteroids or Montelukast was proposed if attacks were frequent, severe, or the doctor thought the symptoms were being underreported. The use or oral corticosteroids was limited to those children hospitalised with serious wheezing (Brand et al., 2014).

1.3 Epidemiological phenotypes

According to the duration of wheezing, several phenotypes have been defined, with no clinical value, but useful in epidemiological studies.

In the longitudinal Tucson Children's Respiratory Study, according to the history of wheezing, four categories were described: never wheezing (no lower tract respiratory illness in the first three years of life, and no wheezing at age six), transient early wheezing (at least one lower tract respiratory illness with wheezing in the first three years of life, but no wheezing at age six), late onset wheezing (no lower tract respiratory illness in the first three years of life, but wheezing at six years old), and persistent wheezing (at least one lower tract respiratory illness with wheezing during the first three years of life, and wheezing at age six).

Maternal history of asthma, smoking mother, rhinitis or eczema in the first year of life, male gender and Hispanic ethnic were factors associated with persistent wheezing, while only maternal smoking was associated with transient early wheezing.

Furthermore, at age six, 46% of children with persistent wheezing were diagnosed with asthma, compared to 22.5% who suffered from late onset wheezing, observing significant differences (Martinez et al., 1995).

Other studies confirmed the applicability of these phenotypes in other populations, finding that children with persistent wheeze at ten years showed a significantly impaired baseline lung function and required more medical care and drug treatment compared to children who never wheezed (Kurukulaaratchy et al., 2003).

In subsequent years, new analyses in the Tucson cohort led to characterise and define the following three new phenotypes of wheezing in childhood: transient wheezers, non-atopic wheezers, and atopic wheezers (Taussig et al., 2003).

Transient infant wheezers

Defined as children with sporadic wheezing during the first two or three years of life, who did not suffer from wheezing after age three. More than 80% of children with wheezing in the first year of life belonged to this group, as well as 60% who wheezed in the second year, and 30-40% who wheezed in the third year of life.

These children did not show a family history of asthma or atopic dermatitis, eosinophilia, high levels or immunoglobulin E (IgE), or markers of predisposition to allergies. The main risk factors were low levels of lung function before suffering from low tract respiratory infections, and have a young and/or smoking mother during pregnancy.

These children had a reduced lung function at birth, which will recover over time, although never will reach the level of those children who never wheezed in early life. There was no increased risk of wheeze at ages eleven and sixteen compared to children who did not wheeze in the first six years of life, but in the subsequent years they could show a higher risk of chronic obstructive pulmonary disease due to their smaller airways.

Non-atopic wheezers

Wheezing episodes began before three years, usually related to RSV infection or bronchiolitis, and continued after the third year of life. Approximately 20% of wheezing infants are classified in this heterogenic group, in which 60% of children at age 6 are atopic.

Children who suffered a lower tract respiratory infection caused by RSV showed three to five-fold higher risk of wheezing at six years, significantly decreasing the risk with age, and being non-significant at thirteen years. Although wheezing continued after three years, these children were not more likely to be atopic, being the main difference with children who did not suffer from RSV infection their lower levels of lung function at six and eleven years.

Children included in this group showed a good response to bronchodilators, without significant differences in lung function after its use compared to healthy children. These results suggested that non-atopic wheezers developed an acute respiratory obstruction due to viral infection, with an alteration in the control of airway tone, which determined the increased risk, decreasing this abnormality with age.

Atopic wheezers

Children in this group had symptoms in the first six years of life. Two subgroups were distinguished: early atopic wheezers, classified as children with persistent wheezing, whose symptoms began in the first three years of life, and late atopic wheezers, previously classified as having late onset wheezing, whose symptoms started after age three years.

Both groups were likely to be sensitized at age six to common allergens, but early atopic wheezers showed lower lung function levels and higher IgE levels at six and eleven years. Results showed that, during the first three years of life, an earlier onset of symptoms and earlier atopic sensitisation might be important risk factors in the development of severe diseases and deficits in lung function in people who suffer from recurrent episodes of airway obstruction.

In addition to these three phenotypes, Castro-Rodriguez and colleagues (2001) defined a fourth phenotype in this same cohort.

Girls overweight/obese and early menarche

Girls who started puberty before age eleven, and were overweight or obese, showed a higher prevalence of wheezing at eleven and thirteen years old. However, no differences in the prevalence were found in girls who started puberty after eleven years old, nor an increased risk of asthma symptoms in overweight or obese girls between six and eleven years old was found.

The proposed explanation was that obesity altered the production of female sex hormones, causing changes in the risk of asthma. Another explanation was that, due to increased susceptibility to allergens in overweight girls, they could show an increased risk for suffering asthma.

Although previous phenotypes were useful models, subsequent studies have helped to broaden the spectrum of phenotypes of wheezing in childhood. In the ALSPAC cohort six phenotypes from birth to age seven were defined, two of them not described previously (Henderson et al., 2008).

Never/infrequent wheeze

The 59% of children were included in this group, where 76.5% of children never wheezed, whilst 10% were wheezers at six months, with a decreasing prevalence from that age on.

Transient early wheeze

Prevalence of wheezing at eighteen months of life was between 50-60%, declining the prevalence at forty-two months of age.

Prolonged early wheeze

Prevalence of wheezing peaked at thirty months of age, declining to low prevalence at sixty-nine months.

Intermediate onset wheeze

Prevalence of wheezing was low until eighteen months, then rising rapidly to high prevalence at age forty-two months.

Late onset wheeze

Prevalence was 20% until forty-two months, increasing over 50% in the subsequent months.

Persistent wheeze

Prevalence of wheezing at six months of age was 65%, reaching approximately 90% in the subsequent months.

Intermediate onset, late onset and persistent wheeze showed a strong association with atopy, unlike other early-onset wheezing phenotypes. Maternal history of asthma and allergy were associated with all phenotypes when compared to infrequent wheeze, finding the strongest associations with persistent wheeze.

There were also associations between all phenotypes with diagnosed asthma at age ninety-one months, and with decrements of FEV_1 and FEF_{25-75} and increased airway responsiveness compared with the never/infrequent wheeze (Henderson et al., 2008).

1.4 Epidemiology

Estimating the prevalence of wheezing is complicated, due to bias which may lead to an underestimation of the true prevalence, either by parental ignorance of the term "wheezing", especially in adverse socioeconomic environments (Michel et al., 2006), or the wording of the question on wheezing in the questionnaires (Pescatore et al., 2015).

Despite this fact, several studies have ascertained the prevalence of wheezing symptoms in infancy and childhood. At the end of the 90s, in United Kingdom a significant increase in the prevalence of wheezing, from 12% to 26% in children aged under 5 years, was observed (Kuehni et al., 2001).

The prevalence of wheezing differed depending on the environment in which children were raised. Thus, several studies found that children exposed to a country environment showed lower prevalences than those living in urban environments (Genuneit, 2012; Horak et al., 2014).

In Europe, the prevalence of wheezing in preschool and school ages varied greatly among different countries. In Spain, 9.9% of children between six and seven years old had currently wheezed, with geographical differences, being the prevalence higher in Northern regions (Carvajal-Urueña et al., 2005).

In Portugal, the prevalence of wheezing in children aged three to five was 24.5% (Pereira et al., 2014), while in Italy, in the same age group, 12.1% of children had wheezed in the last twelve months (Peroni et al., 2009). In France, school age prevalence was 10.7%, also finding geographical differences, with an increasing gradient from Eastern to Western provinces (Delmas et al., 2012).

Also, in Germany, an increased prevalence of wheezing in school age children, especially in girls, was observed. The 12.0% of boys and 7.5% of girls wheezed in 1994-95, increasing to 13.6% and 12.7%, respectively, in 1999-2000 (Maziak et al., 2003). In addition, the same increasing trend was found in England, where the prevalence of wheezing in schoolchildren boys significantly increased from 21.0% to 27.6% in boys, and from 15.4% to 23.3% in girls (Shamssain, 2007).

Another study conducted by Bisgaard and Szefler (2007) found that prevalence of asthma symptoms in children between one to five years ranged from 29% in Northern European countries (Denmark, 23%; United Kingdom, 29%; Germany, 36%) to 48% in Southern European countries (Italy, 45%; Spain, 50%; France, 51%). There were also differences in the severity, with 19% of children showing persistent symptoms in the Nordic countries compared with the 30% in the South. Furthermore, in the United States the prevalence was 27%, not detecting any geographical gradient, and 23% of children reporting persistent symptoms.

In Latin America, the prevalence of wheezing was higher, and also differed among countries. In the Phase I of the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence of current wheeze in children aged six to seven years was 19.8%, ranging from 8.6% in Mexico to 32.1% in Costa Rica (Mallol et al., 2000). The third phase of this study found geographical differences, with higher prevalences in southern countries, attributing these differences to local ecological factors (Mallol et al., 2010).

In China, the prevalence of wheezing in preschool children ranged between 14% to 24%, with higher prevalences in Eastern cities, and an uprising trend of asthma prevalence in children in the last twenty years (Zhang et al., 2013; Huang et al., 2015). Furthermore, in Taiwan, the prevalence of wheezing in school age was 8.8%, also finding an increasing trend in the prevalence of wheeze ever (Wu et al., 2011).

In Japan, a nationwide study found that 19.9% of preschool children wheezed, being reported the disease more frequently in boys (Yoshida et al., 2009). In South Korea, the prevalence of asthma symptoms in the first three years of life was 16.5%, decreasing to 9.8% in older ages (Hong et al., 2012). In both countries, trends of prevalence levelled off in recent years (Yura et al., 2011; Kwon et al., 2011).

In addition to these above-mentioned cross-sectional studies, several studies have been conducted to determine the incidence of the disease.

A retrospective European study concluded that the incidence of asthma in men and women showed a different pattern. In childhood, girls show a lower risk of asthma, which increases during puberty and adulthood. On the contrary, incidence of wheezing in boys peaks during childhood, and decreases in the adolescence (de Marco et al., 2000). More recently, another study also showed similar findings. Incidence of asthma in boys was higher until age thirteen years, when female incidence increased. Further, an overall incidence rate of 6.71 per 1000 person-years in Dutch children and teenagers was observed (Engelkes et al., 2015).

In a Swedish hospitalised-population study, the incidence of wheezing was 3 cases per 1000 person-years in children between four months and four years old (Rylander et al., 1996), whilst asthma incidence rate in a nationwide prospective study in preschool children was 11 cases per 1000 person-years, observing a higher incidence in the first two years of life (Bröms et al., 2012).

In the United States, the incidence rate in children and teenagers was 12.5 per 1000 person years, with the highest rate in children aged up to 4 years, 23.4 per 1000 person-years (Winer et al., 2012).

1.5 Risk and protective factors

Several risk factors associated with wheezing in early life have been described in the literature. One of the most important are respiratory tract infections, which are responsible for more than 80% of asthma exacerbations in school age children (Johnston et al., 1995).

The most common agents in infections in children under six years old with wheezing were rhinovirus, RSV and bocavirus. The most common co infections were rhinovirus and RSV, rhinovirus and bocavirus, and RSV and human metapneumovirus (Chung et al., 2007).

A molecular epidemiological study conducted in Japanese children identified viral agents as RSV, rhinovirus, human metapneumovirus, parainfluenza virus, enterovirus, influenza virus, adenovirus and bocavirus. Among these virus, RSV was detected as the most frequent agent in those children without a history of wheezing or asthma, whereas rhinovirus was frequently found in children who had suffered from wheezing (Fujitsuka et al., 2011).

The role of RSV and rhinovirus as risk factors has been described in several studies. Kusel and colleagues (2007) found that lower tract respiratory infections caused by any of these agents in the first year of life increased the risk of recurrent wheeze and asthma in school age children sensitised in the first two years of life. Moreover, other studies concluded that severe respiratory diseases associated with rhinovirus were related to a significant increased risk of wheezing in the third year of life (Lemanske et al., 2005), and asthma at six years (Jackson et al., 2008). Likewise, RSV lower tract respiratory infections were associated with a higher risk of wheeze in early life (Stein et al., 1999). A relation between a high load of bocavirus with episodes of wheezing has also been described (Allander et al., 2007), as well as a direct correlation between viral load and duration of wheezing (Deng et al., 2012).

Viruses are not the only microorganisms which play an important role in the onset of wheezing. Colonization of the respiratory tract by *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, or a combination of these bacteria, was positively related to an increased risk of onset of wheezing and development of persistent wheezing and asthma in subsequent years (Bisgaard et al., 2007b).

Other bacteria, such as *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*, were also found associated with recurrent wheeze (Esposito et al., 2000).

Although some authors pointed to an independent effect of bacteria and virus (Bisgaard et al., 2010), other studies showed evidence of a link between bacterial colonization in virus-induced wheezing, which could aggravate the severity and persistence of the disease due to its impact on airways inflammation (Yu et al., 2010).

Other established major risk factor is allergic sensitisation at early ages. Sensitisation to allergens, as dust mites or animal allergens, was positively associated with persistent wheezing in subsequent ages, and chronicity of asthma (Illi et al., 2006; Llanora et al., 2012).

Parental history of asthma is another risk factor widely described in the literature. A review concluded that presence of asthmatics parents was associated with an increased risk of asthma in the offspring (Burke et al., 2003). Likewise, other studies also reported an increased risk of asthma and wheezing in schoolchildren whose father or mother were asthmatic, with a multiplicative effect if both parents were atopic or asthmatics (Bjerg et al., 2007).

Another well studied factor is the exposure to tobacco smoke. Smoking during pregnancy was found as a major risk factor for wheezing and asthma in childhood, whether or not children were postnatally exposed to tobacco smoke (Gilliland et al., 2001). On the other hand, an increased risk for recurrent wheezing and asthma in the first year of life in children exposed to tobacco smoke, independently of the prenatal exposure to tobacco smoke, has also been reported by several studies (Lannerö et al., 2006; Kanoh, 2012).

Other risk factors previously found as risk factors for wheeze in early life were male sex (Chong Neto et al., 2008), and overweight, this latter associated with a twice higher risk for the onset of wheezing in preschool age (Saldiva et al., 2007), while obesity was significantly related to the development of severe asthma, especially in girls (Garcia-Marcos et al., 2007).

Also, environmental factors, such as pollution, were positively related to the onset of infant wheeze. In a Danish prospective birth cohort study, a significant association was observed between wheezing in a population at risk and exposure to traffic-related (NO_2, NO_X, CO) and PM_{10} particles (Andersen et al., 2008). Furthermore, exposure to traffic, especially stop-and-go traffic, was found associated with higher prevalence and an increased risk for wheeze (Ryan et al., 2005).

Another environmental factor described in past investigations was the presence of mould and damp stains at home, found as risk factor for recurrent wheeze, and the most important factor in the development of severe wheeze in infants (Visser et al., 2010).

Conversely, protective factors against wheezing have also been described in the literature. One of the most studied was a longer breastfeeding period. An Australian study found that exclusive breastfeeding for at least four months reduced the risk of asthma at 6 years (Oddy et al., 1999). In the same cohort, breastfeeding less than six months was found significantly related to an increased risk of hospital admission for wheezing (Oddy et al., 2003).

1.6 Prediction of the epidemiological phenotype

Although there is no tool able to certainly predict whether infants will continue wheezing or will develop asthma, the identification of these symptomatic children may allow to develop a strategy for intervention that could change the natural course of the disease (Martinez, 1999). The combination of clinical data and information obtained in the laboratory could lead to the identification of children at high risk of further developing symptoms in the future.

The Asthma Predictive Index (API) was a tool used to identify the population at risk, based on the factors observed in the first three years of life. To allow a better classification of children with potential risk of asthma, two indexes and major and minor criteria were proposed.

Major criteria

- Parental medical diagnosis of asthma.
- Medical diagnosis of eczema.

Minor criteria

- Medical diagnosis of allergic rhinitis.
- Wheezing apart from colds.
- Eosinophilia ≥4%.

In the stringent index, if the infant suffered from recurrent wheeze in the first three years of life, and met at least one major criterion or two minor criteria, asthma prediction would be positive. On the other hand, if the loose index was used, an infant would suffer from asthma if met a major criterion or two minor criteria, although they did not wheeze repeatedly.

The stringent index showed low sensitivity, whilst its specificity, and both positive and negative predictive values were high. Sensitivity in the loose index decreased with age, whereas specificity remained around 80%. The positive predictive value showed high values, although lower than in the stringent index, whilst negative predictive value showed similar values.

One of the strengths of these indexes is its simplicity, which allows its use in clinical practice worldwide. The decision on which index should be used depends on the effectiveness and potential side effects of the preventive measures recommended for children at risk (Castro-Rodriguez et al., 2000; Castro-Rodriguez, 2010).

The API has been validated, considering that a positive score is a reliable predictor of asthma in wheezing children, being an objective test not subject to cultural differences. The main limitation is its low sensitivity, which make it unable to completely rule out a child who will not develop asthma in the future (Huffaker and Phipatanakul, 2014).

As the API did not evaluate allergic sensitisation to aeroallergens, milk, eggs or peanuts, reported as significant predictors for the development of asthma in children, a modified version (mAPI) was created. In this index, because the clinical diagnosis of allergic rhinitis without confirmed sensitisation in young children was uncertain, it was replaced by allergic sensitisation to inhalant allergens and food.

Major criteria

- Parental medical diagnosis of asthma.
- Parental medical diagnosis of atopic dermatitis.
- Allergic sensitisation ≥1 aeroallergen.

Minor criteria

- Allergic sensitisation to milk, eggs or peanuts.
- Wheezing apart from colds.
- Eosinophilia ≥4%.

Those children with at least four episodes of wheezing per year, who met at least one major criterion or at least two minor criteria, were considered at risk for developing asthma in the future. As the API, this modified version showed low sensitivity, but its specificity was very high, demonstrating its usefulness in the diagnosis of asthma in childhood (Guilbert et al., 2004; Chang et al., 2013).

1.7 The International Study of Asthma and Allergies in Childhood

The International Study of Asthma and Allergies in Childhood (ISAAC) was an international epidemiological research on asthma and allergies (rhinitis and eczema), developed from the merger of two projects which studied childhood asthma: an initiative in Auckland (New Zealand), which conducted an international comparative study of asthma severity, and another project in Bochum (Germany) which studied temporal trends and determinants of prevalence of asthma and allergies in children (Asher and Weiland, 1998).

The ISAAC study consisted in three Phases, each with its own objectives, methodology and study populations.

Phase I

In Phase I, the study population were children in two groups: six and seven years old (when asthma tends to be more prevalent and hospital admissions are higher), and thirteen and fourteen years old (when asthma mortality is higher).

The aims were to study the prevalence and severity of asthma, rhinitis and eczema in children from different centres, and make national and international comparisons, obtaining reference measurements for assessing future trends in the prevalence and severity, and providing a framework for further investigation of the role of lifestyle, environmental, genetic factors, and medical care in these diseases.

In this phase, one hundred and fifty-six centres in fifty-six countries participated, using written and video questionnaires designed to measure the prevalence and severity of asthma and allergic diseases, which were translated into different languages (Asher et al., 1995; Asher and Weiland, 1998).

Results from this first phase showed the highest prevalences of asthma symptoms in the United Kingdom, Ireland, Australia and New Zealand, and centres from North, Central and South America, while the lowest prevalences were found in Eastern Europe centres, Greece, China, Taiwan, Indonesia, India, Uzbekistan and Ethiopia.

In general, prevalence of allergic rhinoconjunctivitis and eczema was lower in those centres which reported lower prevalence of asthma, except in some Scandinavian and African centres (ISAAC Steering Committee, 1998).

Phase II

The objective of this phase was to identify the determinants of the observed differences in prevalence rates. The specific objectives were to assess the variation in the prevalence and severity of clinical symptoms and markers of asthma, allergic rhinitis and eczema, study the associations between potential determinants and the occurrence and severity of asthma and allergies, make comparisons between centres, and investigate associations between genotypes known or suspected to play a role in childhood asthma and allergies with the measured phenotypes, and to investigate gene-gene and gene-environment interactions.

Thirty centres in twenty-two countries, using a study population of children aged nine to eleven years, participated in this second phase. The study protocol included the use of standardized questionnaires and flexural dermatitis test, skin prick test and bronchial provocation test. For laboratory test, blood samples for IgE analyses were required, and dust samples were collected for the analyses of airborne allergens and endotoxins (Weiland et al., 2004).

In this phase, similar results were found in terms of international variation in the prevalence and severity of asthma symptoms, whereas a link between atopic sensitisation and asthma was only evidenced in affluent countries (Weinmayr et al., 2007).

Other remarkable results were the inverse association found between endotoxin levels and asthma symptoms, although there was no relation with allergic rhinitis (Gehring et al., 2008), and the discovery of four genes (*IL4R*, *TLR4*, *MS4A2*, *TLR9*) related to the onset of wheeze (Genuneit et al., 2009).

Phase III

This phase was developed to learn more about asthma, rhinoconjunctivitis and eczema etiologies. The aims of this phase were to examine time trends in the prevalence of asthma, allergic rhinoconjunctivitis and eczema in the centres participating in Phase I, describe the prevalence in those centres which did not participate in Phase I, and evaluate hypothesis proposed by the results obtained in that first phase.

As Phase III was a repetition of Phase I, study population was similar (children aged six and seven years, and thirteen and fourteen years). The period considered between two phases was at least five years, with identical data collection, which allowed to determine the temporal trends in the prevalence of the disease.

Over two hundred eighty centres in a hundred and six countries participated, which were classified as they had completed Phase I and participated in Phase III (one hundred sixteen centres), or had not participated in Phase I, but only in Phase III (one hundred sixty-eight centres) (Ellwood et al., 2005).

Results showed that prevalence of asthma symptoms in most of countries, especially English language countries, which reported higher prevalences in Phase I, had declined, whilst in countries which showed intermediate or low prevalences in the previous phase, it had increased (Pearce et al., 2007).

It can be considered the ISAAC study as an antecedent of the International Study of Wheezing in Infants, both for the outcome studied and its international nature, and the use of a similar methodology.

1.8 International Study of Wheezing in Infants

Definition and aims

The International Study of Wheezing in Infants (in Spanish, Estudio Internacional de Sibilancias en Lactantes, or EISL) is an international multicentre cross-sectional study, designed to assess the prevalence, severity and characteristics of wheezing in infants during the first year of life in European and Latin American countries.

The study began in 2005, with participating centres from Spain, Netherlands, Brazil, Chile, Mexico, Venezuela and Colombia. Figure 1 shows a map with the participating centres. More recently, centres from other Latin American countries (Honduras, El Salvador) have joined to the study.

Figure 1. Participating centres in the International Study of Wheezing in Infants.

The study was developed to determine the prevalence, severity and frequency of wheezing, and its relation with other respiratory diseases, such as pneumonia, and risk factors for wheezing in the first year of life.

The EISL study, as the ISAAC study, used standardized case definitions and methodology, which facilitated international collaboration and increased the value of the comparisons between centres.

The methodology was based on the one used by the ISAAC study, and participating centres were those which successfully participated in Phase I and III of ISAAC.

The main objectives of the International Study of Wheezing in Infants were:

1) To determine the prevalence and severity of wheezing in infants during the first year of life in different European and Latin American centres, and to make national and international comparisons.
2) To individually examine hypothesis that have been suggested by previous studies conducted in the past, and on the recommendation of international health institutions.
3) To study the relation between recurrent wheezing and pneumonia in different European and Latin American centres, and to make national and international comparisons.
4) To obtain reference measurements for assessing future trends in the prevalence and severity of the disease.
5) To build a network among participating centres for future studies, and provide a framework for further research of etiologic and pathologic factors.

Epidemiological and ecological factors examined in this study, focused on wheezing in the first year of life, have not been previously considered, so there were no international comparative studies which has used the same methodology, and therefore ensured comparisons validity. (Mallol and García-Marcos, 2006)

Importance of the study

Despite recurrent wheeze represent a public health problem, particularly in developing countries, information on the prevalence, characteristics and complications of wheezing disorders was scarce. There was no previous published information from international multicentre studies using a standardised methodology, about the true prevalence of wheeze and recurrent wheeze in the first year of life in infants who lived in Europe and Latin America, nor comparative studies including developed and developing countries.

Thus, the International Study of Wheezing in Infants offers a unique opportunity for scientific integration and creation of a network between participating centres, and its results provide valuable international epidemiological and ecological information on infant wheeze, its risk factors and complications (Mallol and García-Marcos, 2006).

International Study of Wheezing in Infants in Europe

In Spain, several centres in different cities participated in the study. In addition to Pamplona, other centres in cities such as Salamanca, Cartagena, Bilbao, Valencia, La Coruña or Madrid also participated in the EISL study (Mallol et al., 2010b; Pellegrini-Belinchón et al., 2012). Also, in the Netherlands, the study was conducted in the region of Zwolle (Visser et al., 2010).

In the region of Pamplona the study began in October 2006, following the methodology proposed in the international protocol. The participation in the EISL was an opportunity to work in a pioneer project studying a disease that, due to its prevalence and severity in infants and consequences in older ages, is considered an important public health issue.

2. Hypothesis and objectives

2.1 Hypothesis

The prevalence of wheezing in infants in the region of Pamplona is similar to others in European centres, but lower than in Latin American centres.

Risk factors previously described in the literature, as lower tract respiratory infections, smoking during pregnancy, parental history or asthma, or mould/damp stains at home, are risk factors for wheeze ever, recurrent wheeze and/or severe wheeze.

Exclusive breastfeeding more than six months is a protective factor for wheeze ever, recurrent wheeze and/or severe wheeze.

2.2 Main objective

To investigate the epidemiology and risk factors of wheezing in infants in the first year of life in the region of Pamplona, providing a framework for further research on the evolution of the prevalence and etiology of genetic, environmental, and lifestyle factors affecting the onset of wheeze.

2.3 Specific objectives

To describe the prevalence of wheeze ever, recurrent wheeze and severe wheeze in the first year of life in infants in the region of Pamplona.

To study risk factors associated with wheeze ever, recurrent wheeze, and severe wheeze, focusing in those related to history of respiratory and allergy symptoms, family history of asthma and allergies, exposure to tobacco smoke, or household and environmental factors, previously found as risk factors for wheeze.

To compare the results obtained with those from other centres where similar studies have been conducted following the protocol of the International Study of Wheezing in Infants.

3. Material and methods

3.1 Reference population

The region of Pamplona is an area in the centre of Navarre, a province in the North of Spain, which includes Pamplona city (capital of the province) and its metropolitan area. An urban area, more densely populated, and a surrounding rural periphery are distinguished.

The region of Pamplona includes the municipalities of Berrioplano, Ezcabarte, Berriozar, Ansoáin, Villava, Burlada, Huarte, Egüés, Pamplona, Orcoyen, Olza, Barañáin, Zizur Mayor, Aranguren, Noáin, Beriáin, Galar, Cizur, Tiebas-Muriarte de Reta, Zabalza, Echauri, Juluspeña and Olaibar.

Pamplona city is situated four hundred fifty-nine metres above sea level. Its climate is a transition between Mediterranean and Atlantic. The average annual temperature is 12.4ºC, ranging from the lowest average temperatures in January (1.1ºC) to the highest in August (21.7ºC). Total annual rainfall is 772.5 millimetres (Pamplona city council webpage).

In the region of Pamplona, population during the study was 315,988 in 2006, 319,208 in 2007, and 328,511 in 2008. The largest age groups in this period were both men and women aged thirty to thirty-four and thirty-five to thirty-nine years.

The foreign population ranged from 9.57% to 10.76% of the total population along the study period (2006-2008). European countries (Bulgaria and Romania) and Latin American countries (Colombia and Ecuador) were the most common countries of origin (Spanish Statistical Office webpage).

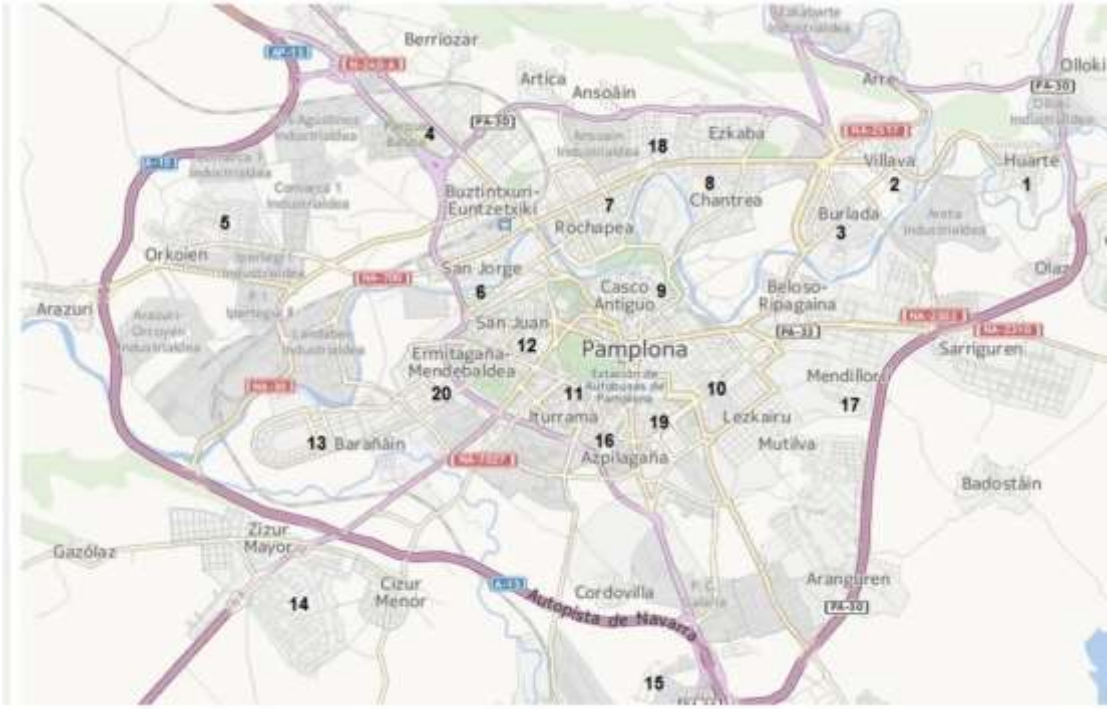
3.2 Study population

The study population were infants of the region of Pamplona who went to the healthcare centre for a health check-up at age fifteen months, within the Healthy Child Program (in Spanish, Programa del Niño Sano), to receive the correspondent vaccine. Sample size was 3,284 infants, divided into the twenty participating healthcare centres shown in Figure 2.

It was estimated that each EISL centre should have recruited a random sample between 1,000 and 3,000 infants aged between twelve and fifteen months, to facilitate comparisons between countries. In those centres where the infant population in this age range did not meet the required size allowed, the sample should have been similar to the general population of infants in the age range.

The study was conducted between December 2006 and June 2008. Random sampling was not carried out. Instead, every family who attended to the health check-up above mentioned was asked to participate. Infants whose parents did not complete the questionnaire were excluded from the study. Finally, from a sample of 3,284 infants, a total of 1,065 questionnaires (32.4%) were collected.

Figure 2. Participating healthcare centres in the region of Pamplona.



(1) Huarte; (2) Villava/Atarrabia; (3) Burlada; (4) Berriozar; (5) Orcoyen; (6) San Jorge; (7) Rochapea; (8) Chantrea; (9) Casco viejo; (10) II Ensanche; (11) Iturrama; (12) San Juan; (13) Barañáin; (14) Zizur-Echavacoiz; (15) Noáin; (16) Azpilagaña; (17) Mendillorri; (18) Ansoáin; (19) Milagrosa; (20) Ermitagaña.

3.3 Data collection

First, the Primary Care Management of Navarre's Health Service was informed about the project, and data from the paediatric nurses from the participating healthcare centres were required.

Appointments with the nurses were requested to explain the project, aims and methodology, what would be their role in it, and how it would be carried out in each healthcare centre. Nurses were informed that regular visits would be made or telephone contact would be maintained to resolve doubts that would arise or problems with the material, etcetera. It was emphasized that information about the project should be rigorous and complete, as the nurses were the spokespersons to the families.

The Public University of Navarre was asked to provide mugs with its logo, to thank the nurses for their cooperation, and pens as gifts to the families who participated, which were given with the questionnaire.

When families brought their children to the health revision at age fifteen months, as established in the Healthy Child Program (a set of activities carried out along the paediatric ages, aimed to the promotion of health and prevention of diseases), paediatric nurses gave them a covering letter explaining the study, and their collaboration was requested.

If families agreed to participate, after signing a full-informed written consent, instructions to complete the questionnaire were given. It was estimated a time between fifteen to twenty minutes to fill the questionnaire.

Families filled it at home, without the assistance of any health care professional, and could either hand it to the nurse in the same healthcare centre on the next visit, or mail it to the Public University of Navarre.

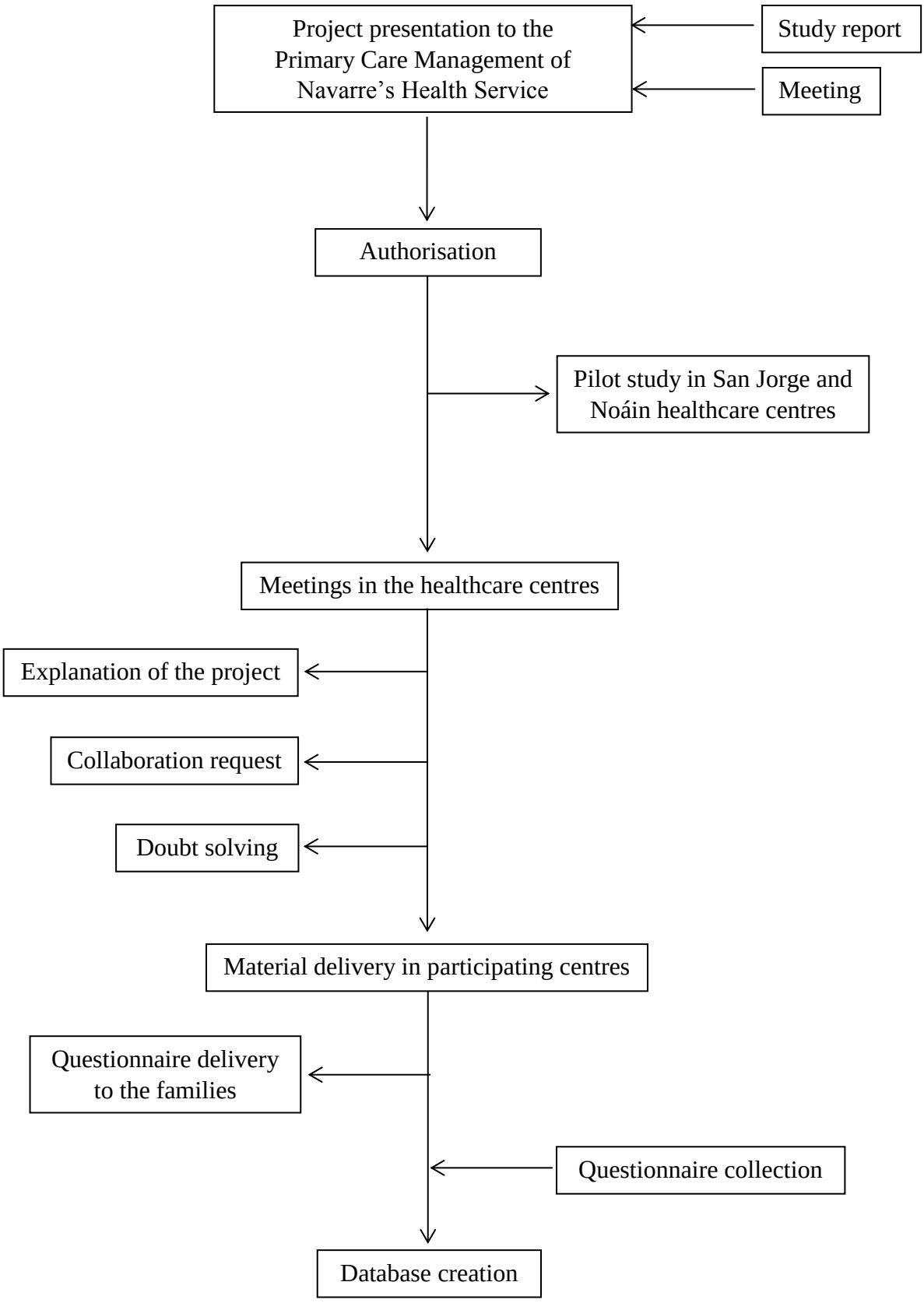
All questionnaires were kept by paediatric professionals and collected periodically or sent by mail to the Public University of Navarre (Table 1). In those healthcare centres with small infant population, questionnaires were sent to the Nursing Primary Care Department every month.

This study was approved by the Management of Primary Care of Navarre's Health Service and by the Scientific Ethic Committee of University of Murcia.

Table 1. Healthcare centres and questionnaires collection.

Healthcare centre (sample size)	Collection	Dates
Huarte (164)	Mail	-
Villava/Atarrabia (130)	Mail	-
Burlada (190)	Mail	-
Berriozar (196)	Mail/Collected in the centre	15/01/2007
Orcoyen (59)	Mail	-
San Jorge (218)	Mail/Collected in the centre	20/12/2006; 28/02/2007; 18/04/2007
Rochapea (389)	Mail	-
Chantrea (146)	Mail	-
Casco viejo (119)	Mail	-
II Ensanche (128)	Mail/Collected in the centre	19/01/2007; 12/04/2007
Iturrama (68)	Mail/Collected in the centre	10/01/2007; 7/03/2007; 15/05/2007
San Juan (151)	Mail/Collected in the centre	15/01/2007; 7/03/2007; 15/05/2007
Barañáin (195)	Mail	-
Zizur-Echavacoiz (291)	Mail/Collected in the centre	1/03/2007
Noáin (122)	Mail	-
Azpilagaña (63)	Mail	-
Mendillorri (251)	Mail	-
Ansoáin (185)	Mail/Collected in the centre	9/01/2007; 8/03/2007; 16/05/2007
Milagrosa (120)	Mail/Collected in the centre	12/04/2007; 20/04/2007
Ermitagaña (99)	Mail	-

3.4 Flow chart of the study



3.5 International Study of Wheezing in Infants timeline

In Figure 3, the steps followed in the International Study of Wheezing in Infants in the region of Pamplona between 2006 and 2008 are shown graphically.

May 2006

A report was sent to the Primary Care Management of Navarre's Health Service, and a meeting was scheduled to explain the project that would be carried out in the region.

July-August 2006

After obtaining the approval, a pilot study was conducted for two months in two healthcare centres (San Jorge and Noain), using the same methodology that would be followed in the subsequent months. These two healthcare centres continued in the study after this period.

October-November 2006

Once obtained satisfactory results in the pilot study, meetings with the paediatric nurses of the healthcare centres were scheduled to explain the project, request their collaboration and resolve doubts.

December 2006-June 2008

Once obtained the support of healthcare centres, materials (questionnaires and gifts) were delivered. Along a year and a half, questionnaires were given to the families who agreed to participate, and were collected by mail or in the centre, as previously explained.

September 2008

When all questionnaires were collected, they were read and a database was created in IBM SPSS v12 and STATA v7.

3.6 Questionnaires

The questionnaire used was the standard model of the International Study of Wheezing in Infants. As the region of Pamplona is a mixed language area, and most people speak both Spanish and Basque, it was decided to provide two models of the questionnaire in both languages.

The Spanish version was back translated to Basque by the Department of Euskera of the Public University of Navarre. Both questionnaire models are presented in Appendix 1. The questionnaire consisted of seventy-seven items with closed answer format, in four pages. The questions were dichotomous, categorized or numerical.

Figure 3. International Study of Wheezing in Infants timeline in the region of Pamplona.

Year	**2006**								**2007**	**2008**								
Months*	Ma	J	Jl	A	S	O	N	D		J	F	M	A	Ma	J	Jl	A	S
Meeting with the Management of Primary Care																		
Pilot study in San Jorge and Noáin healthcare centres																		
Meeting with paediatric nurses in healthcare centres																		
Delivery and collection of questionnaires																		
Database creation																		

*J: January; F: February; M: March; A: April; Ma: May; J: June; Jl: July; A: August; S: September; O: October; N: November; D: December.

The questionnaire gathered information about the infant (demographic and anthropometric data, respiratory/allergy symptoms, and treatment), wheezing (number of episodes, age of the first episode, characteristics and severity), family background (exposure to tobacco smoke, history of asthma or allergies, socioeconomic information), environmental factors (nursery attendance, household characteristics, feeding), and exposures throughout pregnancy (maternal diet, use of paracetamol, complications).

The questionnaire has been previously validated. It showed a high sensitivity and specificity, 86% and 91.8%, respectively, a predictive positive value of 76.8%, and a predictive negative value of 95.4% (Chong Neto et al., 2007), and was considered a valid tool to detect children with wheezing in the first year of life (Mallol et al., 2007).

Definitions

The dependent variable of the study was the presence or absence of wheezing in the first year of life. Wheeze ever was defined as a positive answer to the question: "Has your child had wheezing or whistling in the chest in the first 12 months of life?".

Recurrent wheeze was defined as three or more episodes of wheezing in the first year of life. Severe wheeze was defined as a positive answer to the question: "In the first 12 months of life, has your child experienced wheezing or whistling sounds in the chest that were so intense that he/she choked and had breathing difficulties?".

Infant eczema was defined as a positive response to the question: "Has your child had in the first 12 months of life red spots in the skin that itch and appear and disappear anywhere on the body, except around the mouth and nose, and in the area of the nappy?".

Colds were recorded when parents answered with a positive numerical response to the question: "How many colds (sneezing, cough, runny nose) has your child had in the first 12 months of life?"

Presence of mould/damp stains at home was assessed with a positive answer to the question: "Is there mould (fungi) or damp stains in the house where the child live?". Air pollution was ascertained with an affirmative answer to the question: "Do you consider your child live in an air polluted area?"

Mediterranean diet is characterised by frequent consumption of plant foods (fresh fruit, vegetables, legumes and nuts), low to moderate consumption of dairy products, fish and poultry, low consumption of red meats and sweets, low to moderate consumption of red wine (usually accompanying meals), and olive oil as the principal source of fat (Willett et al., 1995).

To assess the adherence to the Mediterranean diet during pregnancy, a score previously applied by Garcia-Marcos *et al.* (2007), based on the score used by Psaltopoulou *et al.* (2004), was developed.

As pro-Mediterranean diet components, white and oily fish, fruit, salads, fresh and cooked vegetables, legumes, cereals, pasta, rice, potatoes and nuts were included. Dairy products (milk and yogurt) were also presumed to be beneficial components as the involved population were pregnant women. Their consumption was scored with zero points in mothers who never consumed them during pregnancy, one point for those who occasionally consumed them (one-two times per week), and two points for those mothers who reported a usual consumption (three or more times a week).

Conversely, consumption of presumed non-Mediterranean diet components, as meat, fast food, high-fat dairy products (butter and margarine), snacks and pastries, was scored inversely, from two points if never consumed them during pregnancy, to zero points if was reported a usual consumption (three or more times a week). Alcohol consumption was excluded from the score. Therefore, a higher score indicated a better adherence to the Mediterranean dietary pattern.

In addition, as olive oil was not included in the food-frequency questionnaire, its consumption was ascertained by the question "Which is predominantly used to fry in the household where the infant lives?".

3.7 Database creation and statistical analysis

Questionnaires, both Spanish and Basque version, were designed by the Teleform Designer program. They were read with a Canon scanner DR30202, and the form processing application Teleform Reader 6.1 (Cardiff Software, USA). To avoid issues with processing personal data, according to the Organic Law 5/1992, regulating the automatic processing of personal data, no personal data were collected. Database was corrected removing abnormal values, and exported to a format compatible with IBM SPSS and STATA software. Analyses were performed with STATA version 13.0 (StataCorp, College Station, TX, USA).

Those infants with no information to the question "Has your child had wheezing or whistling in the chest in the first 12 months of life?" (eighteen subjects) were excluded from the analyses. Also, infants aged less than eleven months (five subjects), or those who had their first wheezing episode after twenty-four months of age (fifty-five subjects) were excluded. In those cases when parents did not answer the question about number of wheezing episodes, it was assumed they had healthy infants. Separate analyses were conducted for wheeze ever, recurrent wheeze and severe wheeze.

To allow detecting an estimated prevalence of wheezing of 34%, with an error of 2.5%, conducting a correction for a finite population of 3,284 newborns, a sample size of 972 subjects would be necessary.

To allow detecting prevalence odds ratios over two, with a 95% confidence, and a statistical power of 80%, assuming that prevalence of the exposition in healthy subjects was 10%, it would be necessary a sample size of 568 subjects. Calculations were conducted with OpenEpi program (Dean et al., 2013).

A descriptive analysis was performed, computing frequencies and percentages for categorical variables, and mean and standard deviation (±SD) for quantitative variables. Bivariate analyses were performed using the chi-squared test, or the Student's t-test, as appropriate, to study associations between factors and wheeze ever, recurrent wheeze and severe wheeze, calculating odds ratio (OR) with 95% confidence intervals (95% CI). In all analyses, a p value lower than 0.05 was regarded as statistically significant.

For each outcome of interest, multivariate models were used to adjust for confounding variables to obtain adjusted odds ratios (aOR). All the variables related to the outcome (p value<0.1) in the bivariate analysis were included in the model, and only retained if showed a statistically significant association (p value<0.05) or modified the association of interest by 15-20%.

This process resulted in the inclusion of the following covariates used for adjusting wheeze ever: sex, pneumonia, number of colds, maternal history of asthma, paternal history of atopic dermatitis, nursery attendance, number of siblings, and months of exclusive breastfeeding. Recurrent wheeze was adjusted by pneumonia, infant eczema, number of colds, smoking father, smoking during pregnancy, nursery attendance, hypertension during pregnancy, and prematurity at birth. Severe wheeze was adjusted by sex, number of colds, age of the first cold, colds in the first three months of life, history of atopic dermatitis in siblings, and months of exclusive breastfeeding.

The Hosmer-Lemeshow test for goodness of fit for logistic regression models was performed, being all models well calibrated (p value>0.1).

3.8 Funding

This study was funded by a research grant from the Carlos III Institute (Ministry of Health and Consumer Affairs, Ref. PI 050918), and a research grant from the Department of Health (Navarre Government, Ref. 6106).

4. Results

The study sample size in Pamplona was 3,284 infants. During the study 1,065 questionnaires were collected (participation rate: 32.4%). After exclusions, information from 987 infants was available for analysis.

4.1 Descriptive analysis

Demographic factors

Most questionnaires (80.1%) were filled by mothers, and 4.3% by fathers, while both parents completed the questionnaire in the 15.6% of cases.

Half of the sample, 50.8% of infants, were boys, and the mean age was 12.1 (±0.7) months.

The most common weight at birth (59.5% of infants) was between 2,500 and 3,499 grams and the mean height was 49.6 (±2.7) centimetres. When questionnaire was filled, mean weight and height were 9.5 (±1.2) kilograms, and 75.6 (±3.1) centimetres, respectively.

Almost every infant (97.0%) was white race and was born in Spain (99.7%). Likewise, most of fathers (91.1%) and mothers (91.9%) were also Spanish. (Table 2)

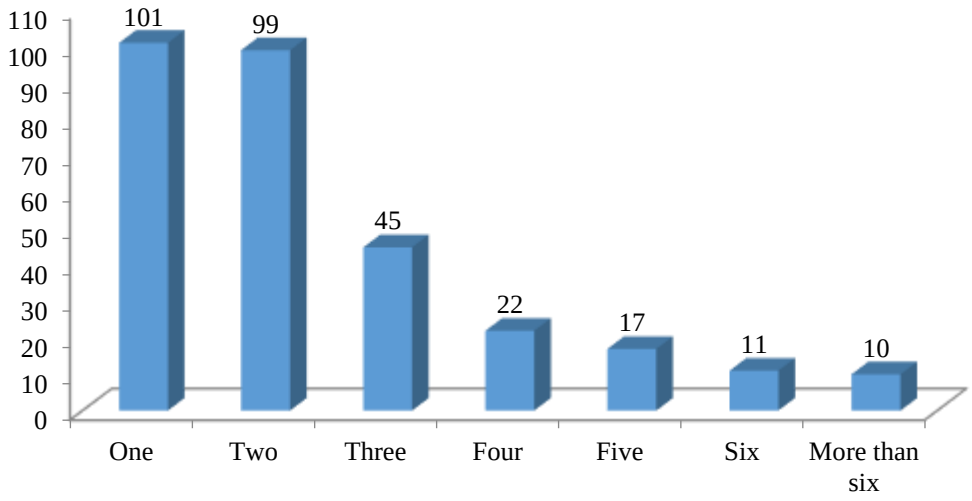
Table 2. Demographic and anthropometric factors.

	N (%)	$\bar{x}$±SD
Sex		
Boys	486 (50.8)	
Girls	470 (49.2)	
Age	969	12.1±0.7
Weight at birth		
Less than 1,500 grams	5 (0.5)	
1,500-1,999 grams	17 (1.7)	
2,000-2,499 grams	57 (5.8)	
2,499-3,499 grams	582 (59.5)	
More than 3,500 grams	318 (32.5)	
Weight (current)	951	9.5±1.2
Height at birth	939	49.6±2.7
Height (current)	925	75.6±3.1
Race		
White	951 (97.0)	
Gipsy	3 (0.3)	
Latin American	7 (0.7)	
Others (African, Asian,...)	19 (1.9)	

Wheezing, treatment and respiratory/allergy symptoms

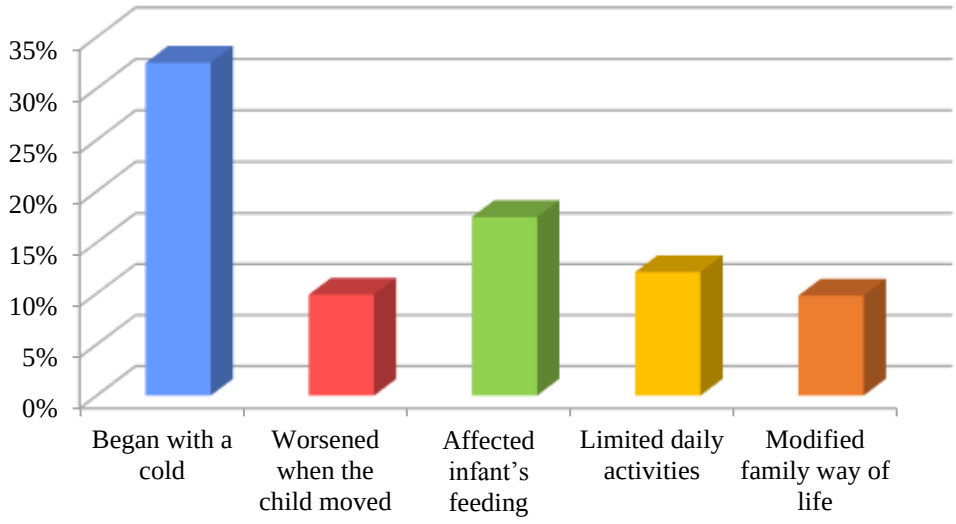
Of the total of infants in the study, 32.5% wheezed in the first year of life, 10.6% developed recurrent wheeze, and 9.6% suffered from severe wheeze. Figure 4 shows the number of episodes in the first year of life. The mean number of episodes was 2.7 (±3.9), and the mean age of the first episode was 6.5 (±3.0) months.

Figure 4. Number of wheezing episodes in the first year of life.



In the 32.5% of infants, wheezing began with a cold, and for the 9.9% worsened when they moved, or got angry, or laughed. Almost one fifth of parents reported that wheezing affected infant's feeding, and more than 10% had their daily activities limited. Family life was modified for this cause in the 9.8% of cases. (Figure 5)

Figure 5. Characteristics of wheezing in the infant.



A 22.1% of infants had received treatment with inhaled drugs, and 10.2% with inhaled corticosteroids. Frequencies of children treated with antileukotrienes or ketotifen were lower, the 3.6% and 0.6%, respectively, whereas the treatment with both drugs only was administered to one child (0.1%).

Parents were occasionally awakened by infant wheezing in the 15.2% of cases, and 4.2% were often awakened. A 13.8% of infants went to the Emergency Department due to the severity of wheezing. Hospitalisation was necessary once in twenty-six cases (2.8%), and three infants (0.3%) were hospitalised twice.

Only the 1.1% of infants were diagnosed with asthma by a physician, and a 4.1% had pneumonia or bronchopneumonia in the first year of life, being necessary the hospitalisation for this cause in 1.0% of the cases. The 13.9% of infants suffered from infant eczema. Mean number of colds in the first year of life was 3.5 (±3.7), and mean age of the first cold was 5.2 (±4.5) months. Two hundred forty infants (27.5%) had their first cold in the first three months of life. (Table 3)

Table 3. Wheezing, treatment and respiratory/allergy symptoms in the first year.

	N (%)	$\bar{x}$±SD
Wheezing		
Wheeze ever	321 (32.5)	
Recurrent wheeze	105 (10.6)	
Severe wheeze	95 (9.6)	
Wheezing episodes	305	2.7±3.9
Age of the first episode	320	6.5±3.0
Treatment		
Inhaled drugs	192 (22.1)	
Inhaled corticosteroids	85 (10.2)	
Awakened due to wheezing		
Never	535 (57.4)	
Rarely	216 (23.2)	
Occasionally	142 (15.2)	
Often	39 (4.2)	
Emergency Department	118 (13.8)	
Hospitalization due to wheezing		
Once	26 (2.8)	
Twice	3 (0.3)	
Diseases		
Asthma	10 (1.1)	
Pneumonia	38 (4.1)	
Hospitalization due to pneumonia	9 (1.0)	
Eczema	131 (13.9)	
Number of colds	983	3.5±3.7
Age of the first cold	976	5.2±4.5
First cold ≤ 3 months	240 (27.5)	

Family background

Two hundred and one mothers (20.7%) were smokers, and reported smoking a daily mean of 10.7 (±8.6) cigarettes. On the other hand, two hundred eighty-five fathers (29.9%) also smoked, a mean of 12.2 (±8.3) cigarettes per day. Furthermore, one hundred sixty-two mothers (16.7%) smoked during pregnancy. In the household, the mean number of smokers was 0.5 (±0.8) persons.

Forty-two fathers (4.3%), and fifty-two mothers (5.6%) were asthmatics, while only a 2.7% of siblings had asthma. One hundred and twenty-four fathers (13.0%), and one hundred thirty-two mothers (13.6%) had allergic rhinitis, whilst only the 2.1% of siblings were allergic. Thirty-seven fathers (3.9%), and fifty-seven mothers (6.0%) suffered from atopic dermatitis, as well as the 5.2% of siblings.

One hundred sixty-five fathers (17.4%) showed allergy in an allergy test, whereas the 5.9% had negative results. Similarly, one hundred sixty-eight mothers (17.7%) had positive allergy test results, against the 8.6% who did not show allergy. Among siblings, frequencies were lower, only twenty-five (2.8%) had allergy, whilst the 4.2% showed negative results in the allergy test.

Most mothers had a university degree (51.4%), or completed secondary education (40.1%). On the other hand, the 3.0% of mothers only had a basic school degree. One hundred eighty-nine fathers (19.9%) belonged to the professional social class, and three hundred sixty-four (38.4%) to skilled manual workers. Most of mothers (26.7%) were unemployed when the questionnaire was filled. Among those who worked, the 35.5% belonged to the managerial social class, and 16.0% to the professional. (Figure 6)

Mean age of mothers was 33.8 (±3.9) years. In Table 4 family background descriptive analysis results are summarized.

Figure 6. Frequencies of parental occupations.

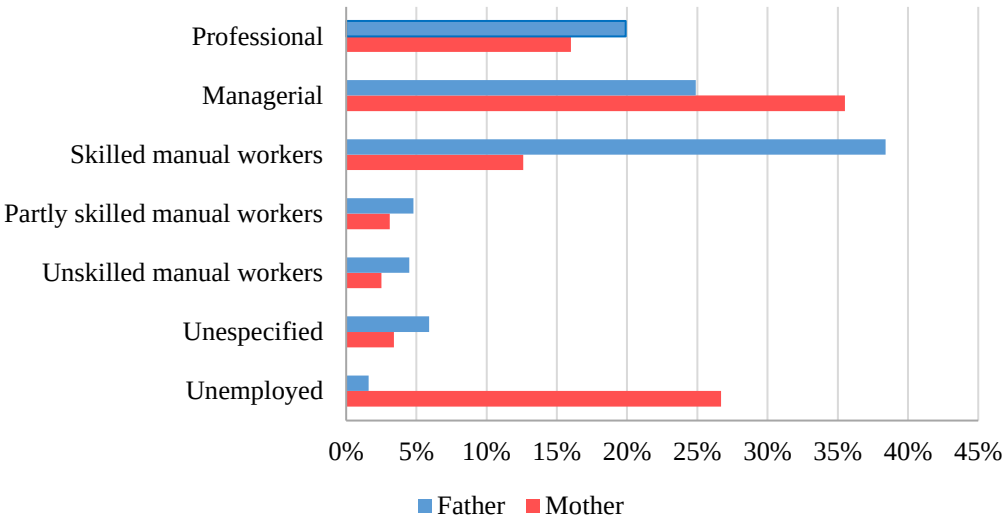


Table 4. Family background.

	N (%)	$\bar{x}$±SD
Smoking		
Smoking mother	201 (20.7)	
Daily smoked cigarettes	204	10.7±8.6
Smoking father	285 (29.9)	
Daily smoked cigarettes	283	12.2±8.3
Smoking during pregnancy	162 (16.7)	
First trimester	6 (14.0)	
Second trimester	1 (2.3)	
Third trimester	1 (2.3)	
Two trimesters	7 (16.3)	
Throughout pregnancy	28 (65.1)	
Number of smokers in the household	956	0.5±0.7
Asthma		
Father	42 (4.3)	
Mother	52 (5.6)	
Siblings	25 (2.7)	
Allergic rhinitis		
Father	124 (13.0)	
Mother	132 (13.6)	
Siblings	19 (2.1)	
Atopic dermatitis		
Father	37 (3.9)	
Mother	57 (6.0)	
Siblings	48 (5.2)	
Positive allergy test		
Father	165 (17.4)	
Mother	168 (17.7)	
Siblings	25 (2.8)	
Maternal education		
Basic school (≤8 years)	29 (3.0)	
Incomplete Secondary (9-11 years)	54 (5.5)	
Complete Secondary (≥12 years)	391 (40.1)	
University	502 (51.4)	
Mean age of mothers	983	33.8±3.9

Household and environmental factors

One third of infants (33.9%) attended to nursery in the first year of life. Children began attending to nursery at a mean age of 7.5 (±2.6) months.

When the baby was born, in most households (83.8%) there were no pets. Those families who had pets, usually had dogs (5.3%) and cats (3.0%). Likewise, when the questionnaire was filled, in most households there were no pets (82.9%), and those families who reported the presence of pets usually had dogs (4.7%), cats (3.2%) and other pets (3.5%).

The most common fuel used for heating was gas, in the 79.6% of households, and electricity was used for cooking by most families (90.4%).

Only fifty-eight dwellings (6.0%) had an air conditioning unit, and seventeen (1.8%) were carpeted. Almost every dwelling had a bathroom and kitchen inside the house, and phone at home (frequencies over 99% in all cases). Forty-one families (4.2%) reported the presence of mould or damp stains.

Over the 25% of families considered living in an air polluted area. Among them, more than a half (59.6%) reported a medium level of pollution, and only the 6.9% a high level.

Almost every child (98.6%) had complete immunisation schedule according to their age. Mean number of siblings was 0.6 (±0.8), and mean number of people living in the household was 3.4 (±1.0) persons.

Almost half of infants (43.2%) consumed industrial infant food every day over the first year of life, and 23.2% were fed with them once a week. On the contrary, the 22.7% of infants were not feed with industrial infant food in the first year of life.

Mean duration of exclusive breastfeeding was 4.2 (±3.1) months. Three hundred thirty-two mothers (34.0%) exclusively breastfed their infant six or more months. Duration of exclusive breastfeeding is shown in Figure 7.

Olive oil was the most frequent food used for frying (93.0%), while other oils were used by the 6.7% of families. In Table 5, household and environmental factors descriptive analysis results are presented.

Figure 7. Duration of exclusive breastfeeding (in months).

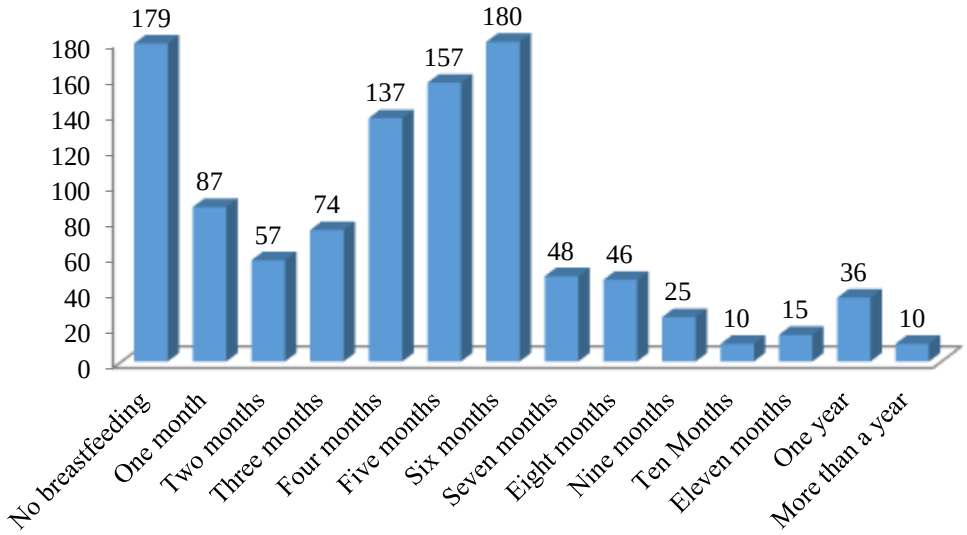


Table 5. Household and environmental factors.

	N (%)	$\bar{x}$±SD
Nursery		
Nursery attendance	330 (33.9)	
Age nursery attendance	352	7.5±2.6
Pets (birth)		
None	813 (83.8)	
Dog	51 (5.3)	
Cat	29 (3.0)	
Bird	21 (2.2)	
Rabbit/hamster	3 (0.3)	
Other pets	22 (2.3)	
More than one pet	31 (3.2)	
Pets (current)		
None	800 (82.9)	
Dog	45 (4.7)	
Cat	31 (3.2)	
Bird	22 (2.3)	
Rabbit/hamster	4 (0.4)	
Other pets	34 (3.5)	
More than one pet	29 (3.0)	
Household		
Air conditioning unit	58 (6.0)	
Carpet	17 (1.8)	
Bathroom inside the house	971 (99.2)	
Kitchen inside the house	961 (99.3)	
Telephone	967 (99.3)	
Mould or damp stains	41 (4.2)	
Air pollution	252 (25.6)	
High level	18 (6.9)	
Medium level	155 (59.6)	
Low level	87 (33.5)	
Complete immunisation schedule	952 (98.6)	
Number of siblings	986	0.6±0.8
Number of people at home	970	3.4±1.0
Industrial infant food		
Never	212 (22.7)	
Once a month	102 (10.9)	
Once a week	217 (23.2)	
Everyday	404 (43.2)	
Exclusive breastfeeding	976	4.2 ±3.1

Exposures during pregnancy and birth

The mean Mediterranean diet adherence score was 28.2 (±3.1) points, ranging between 17 and 36 points. Most women reported a frequent consumption of meat, fresh fruit and juices, fresh and cooked vegetables, salads, cereals, milk and yoghurt, and an occasional consumption of white and oily fish, legumes, pasta and rice, cooked potatoes, eggs, and industrial pastry. On the other hand, most pregnant women never consumed home-made hamburgers, fast food (precooked meals, fry-up), butter and margarine, nuts, snacks, or alcoholic beverages and soft drinks throughout pregnancy. (Figure 8)

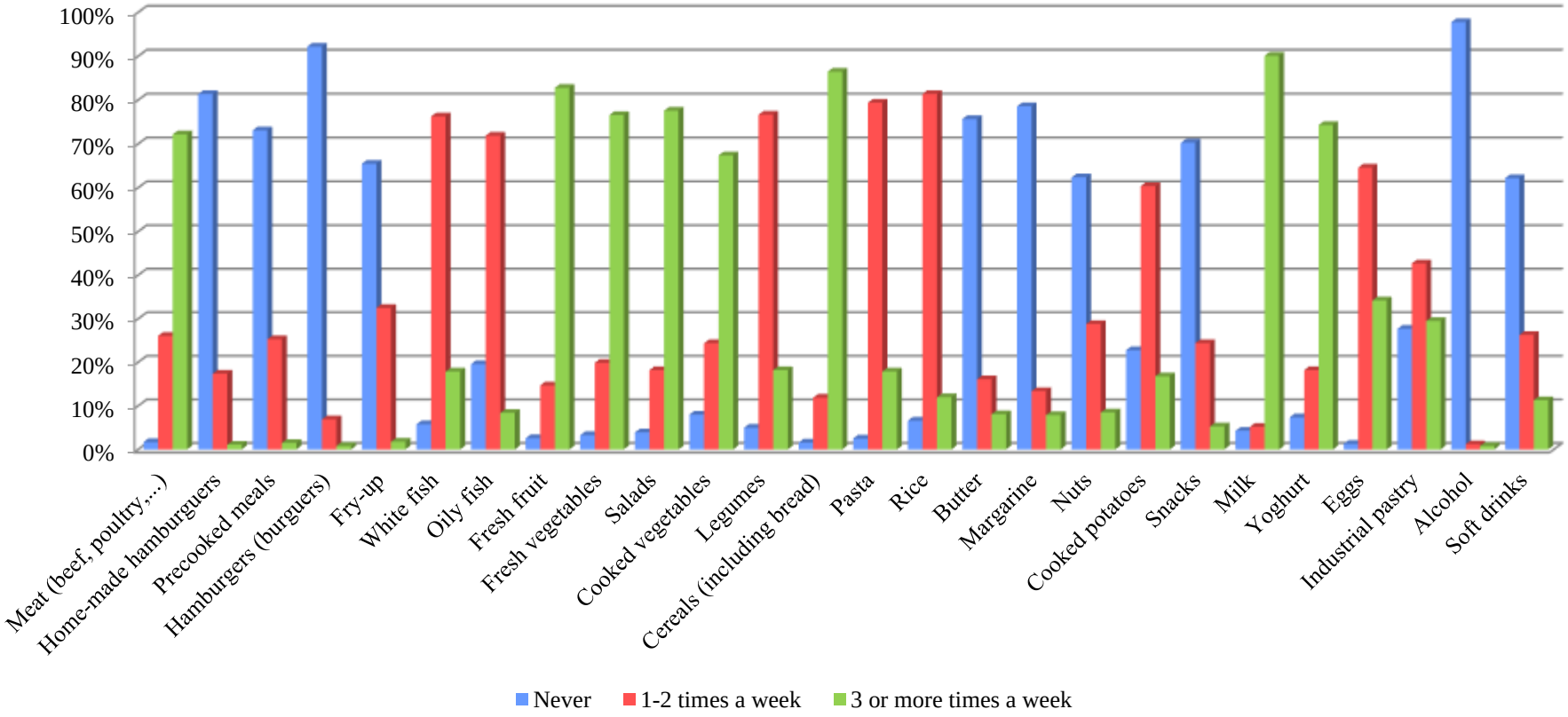
Over half of mothers (55.4%) never took oral contraceptives, whilst 15.8% did it between one and three years, and 13.4% more than six years. On the other hand, most women (82.7%) never or less than once a month took paracetamol during pregnancy, and 14.1% took it one to four times per month. The main causes for taking paracetamol were headaches (58.2%) and fever (14.5%).

The most frequent complications during pregnancy and birth were the use of forceps (21.5%), and caesarean section (17.5%). Other common complications were infections (13.7%) and nuchal cord (11.9%). (Table 6)

Table 6. Exposures during pregnancy and birth.

	N (%)	$\bar{x}$±SD
Mediterranean diet	668	32.3±3.4
Oral contraceptives		
Never	538 (55.4)	
Less than a year	59 (6.1)	
Between one to three years	154 (15.8)	
Between four to six years	91 (9.4)	
More than six years	130 (13.4)	
Paracetamol		
Never or less than once per month	805 (82.7)	
One to four times per month	137 (14.1)	
More than once per week	32 (3.3)	
Complication during pregnancy and birth		
Hypertension	77 (8.7)	
Threatened miscarriage	103 (11.6)	
Infections	122 (13.7)	
Gestational diabetes mellitus	66 (7.4)	
Malposition of the foetus	31 (3.6)	
Premature rupture of membranes	63 (7.2)	
Placenta problems	50 (5.7)	
Hypoxia	50 (5.8)	
Prematurity	78 (8.9)	
Nuchal cord or knots in umbilical cord	104 (11.9)	
Obstetric trauma	4 (0.5)	
Forceps/suction cup	191 (21.5)	
Caesarean section	158 (17.5)	

Figure 8. Frequencies of consumption of food groups during pregnancy.



After the descriptive analysis, we conducted bivariate and multivariate analyses to study the relation between factors and wheeze phenotypes. In the following sections, results from these analyses are shown.

4.2 Demographic factors

Wheeze ever

Of the total of infants who wheezed, 39.1% were boys, and 26.0% were girls, finding a significant association between infant gender and wheeze ever ($p<0.001$). Male gender was found positively associated with wheeze ever in the first year of life (aOR=1.82; 95% CI 1.33-2.51).

Mean age in children who wheezed was 12.2 (±0.9) months, while in healthy infants was 12.1 (±0.5) months, also showing statistical differences ($p=0.020$). However, non-significant higher odds for wheeze at older ages were observed (aOR=1.15; 95% CI 0.92-1.44).

The 39.2% of infants with low birth weight wheezed, compared to 31.9% with normal birth weight, not finding any significant association ($p=0.181$). In addition, no statistical differences were found when current weight (when the questionnaire was filled) was studied ($p=0.153$).

On the contrary, statistical differences were observed in height at birth ($p=0.037$). Mean height in wheezing infants was 49.4 (±2.5) centimetres, whilst healthy infants were taller, 49.8 (±2.8) centimetres. Although in the statistical limit, higher height at birth was found as a protective factor for wheeze ever (aOR=0.94; 95% CI 0.87-1.00).

Mean current height (when the questionnaire was filled) in wheezing infants was 75.4 (±3.0) centimetres, while healthy children were 75.7 (±3.1) centimetres tall. No statistical differences were observed ($p=0.178$), although higher height was also in the statistical borderline to be considered a protective factor (aOR=0.94; 95% CI 0.89-1.00).

No significant relations were detected between infant's race ($p=0.547$), nor place of birth ($p=1.000$) and wheeze ever. Moreover, no statistical relations were found between parental (father and mother) place of birth and wheeze in the offspring in the first year of life ($p=0.361$ and 0.841, respectively). (Table 7)

Recurrent wheeze

Of the 105 infants who wheezed repeatedly, 13.0% were boys and 8.7% were girls, detecting a significant association between infant gender and recurrent wheeze ($p=0.035$). Marginally significant increased odds for development of recurrent wheeze in male infants were found (aOR=1.62; 95% CI 0.98-2.68).

Mean age of recurrent wheezers was 12.1 (±0.5) months, whilst in healthy infants mean age was 12.1 (SD=±0.7) months, not observing statistical differences ($p=0.756$).

Table 7. Associations between demographic factors and wheeze ever.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex		<0.001		
Boys	190 (39.1)		1.83 (1.39-2.41)	1.82 (1.33-2.51)
Girls	122 (26.0)		1 (reference)	1 (reference)
Age		0.020		
Wheezers	12.2±0.9		1.27 (1.02-1.57)	1.15 (0.92-1.44)
Non-wheezers	12.1±0.5		1 (reference)	1 (reference)
Low weight at birth		0.181		
Low birth	31 (39.2)		1.38 (0.86-2.21)	1.37 (0.77-2.41)
Normal weight	287 (31.9)		1 (reference)	1 (reference)
Weight (current)		0.153		
Wheezers	9.6±1.2		1.09 (0.97-1.21)	1.03 (0.90-1.19)
Non-wheezers	9.5±1.2		1 (reference)	1 (reference)
Height at birth		0.037		
Wheezers	49.4±2.5		1 (reference)	1 (reference)
Non-wheezers	49.8±2.8		0.95 (0.90-1.00)	0.94 (0.87-1.00)
Height (current)		0.178		
Wheezers	75.4±3.0		1 (reference)	1 (reference)
Non-wheezers	75.7±3.1		0.97 (0.93-1.01)	0.94 (0.89-1.00)
Born in Spain		1.000		
Yes	316 (32.7)		1.03 (0.09-11.40)	2.62 (0.13-54.35)
No	1 (33.3)		1 (reference)	1 (reference)

The 13.9% of infants with low weight at birth, and 10.3% with normal weight, developed recurrent wheeze, not showing evidence of statistical differences (p=0.321). Also, no statistical differences in current weight were observed (p=0.161). Wheezing infants weighed 9.7 (±1.3) kilograms, against 9.5 (±1.2) kilograms in healthy infants.

When height at birth was studied, statistical differences were found (p=0.020). Wheezing infants were 49.0 (±3.3) centimetres tall, in contrast to 49.7 (±2.6) centimetres tall in healthy infants. However, higher height at birth was not inversely related to the development of recurrent wheeze (aOR=0.94; 95% CI 0.85-1.05).

Also, healthy infants were taller when current height (when the questionnaire was filled) was studied (75.6±3.1, against 75.3±2.9 in wheezing infants), but no statistical differences were observed (p=0.392).

No significant relations were observed between suffering from recurrent wheeze and infant's race (p=0.401), nor place of birth (p=1.000). In addition, neither father's (p=0.482) nor mother's place of birth (p=0.230) were significantly related to recurrent wheeze in the offspring. (Table 8)

Table 8. Associations between demographic factors and recurrent wheeze.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex		0.035		
Boys	63 (13.0)		1.56 (1.03-2.36)	1.62 (0.98-2.68)
Girls	41 (8.7)		1 (reference)	1 (reference)
Age		0.756		
Wheezers	12.1±0.5		0.96 (0.69-1.34)	0.94 (0.62-1.41)
Non-wheezers	12.1±0.7		1 (reference)	1 (reference)
Low weight at birth		0.321		
Low birth	11 (13.9)		1.40 (0.72-2.75)	0.99 (0.40-2.45)
Normal weight	93 (10.3)		1 (reference)	1 (reference)
Weight (current)		0.161		
Wheezers	9.7±1.3		1.13 (0.95-1.33)	1.20 (0.97-1.49)
Non-wheezers	9.5±1.2		1 (reference)	1 (reference)
Height at birth		0.020		
Wheezers	49.0±3.3		1 (reference)	1 (reference)
Non-wheezers	49.7±2.6		0.91 (0.84-0.98)	0.94 (0.85-1.05)
Height (current)		0.392		
Wheezers	75.3±2.9		1 (reference)	1 (reference)
Non-wheezers	75.6±3.1		0.97 (0.91-1.04)	1.01 (0.93-1.10)
Born in Spain		1.000		
Yes	102 (10.6)		-	-
No	0 (0.0)		-	-

Severe wheeze

Among infants who suffered from severe wheeze, 12.8% were boys, and 6.6% were girls, observing a significant association between severe wheeze and infant gender (p=0.001), and finding male gender as risk factor for severe wheeze (aOR=1.90; 95% CI 1.16-3.11).

Mean age in wheezing infants was 12.2 (±0.8) months, while in healthy infants was 12.1 (±0.7) months, not showing evidence of statistical differences (p=0.442).

The 8.9% of infants with low weight at birth, and 9.6% with normal weight, wheezed severely in the first year of life, not detecting a statistical relation (p=0.840). Conversely, statistical differences in infant's current weight (when the questionnaire was filled) were found (p=0.038). Mean weight in wheezing infants was 9.8 (±1.2) kilograms, compared to 9.5 (±1.2) kilograms in healthy infants. When weight rose, a non-significant increased risk for severe wheeze was observed (aOR=1.11; 95% CI 0.91-1.35).

On the other hand, no statistical differences were found when height at birth (p=0.172) nor current height (p=0.786) were studied. Infants who wheezed severely were smaller at birth than healthy infants (49.3±2.8 against 49.7±2.7), but were taller when the questionnaire was filled (75.6±3.1 and 75.5±3.0, respectively).

Neither children's race (p=0.254) nor place of birth (p=1.000) were significantly related to the development of severe wheeze in the first year of life. Moreover, no significant associations were found between severe wheeze in the offspring and parental (father and mother) place of birth (p=0.763 and p=0.521, respectively). (Table 9)

Table 9. Associations between demographic factors and severe wheeze.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex		0.001		
Boys	62 (12.8)		2.07 (1.32-3.25)	1.90 (1.16-3.11)
Girls	31 (6.6)		1 (reference)	1 (reference)
Age		0.442		
Wheezers	12.2±0.8		1.10 (0.85-1.43)	0.95 (0.61-1.48)
Non-wheezers	12.1±0.7		1 (reference)	1 (reference)
Low weight at birth		0.840		
Low birth	7 (8.9)		0.92 (0.41-2.06)	0.73 (0.29-1.81)
Normal weight	86 (9.6)		1 (reference)	1 (reference)
Weight (current)		0.038		
Wheezers	9.8±1.2		1.21 (1.01-1.44)	1.11 (0.91-1.35)
Non-wheezers	9.5±1.2		1 (reference)	1 (reference)
Height at birth		0.172		
Wheezers	49.3±2.8		1 (reference)	1 (reference)
Non-wheezers	49.7±2.7		0.94 (0.87-1.02)	0.92 (0.83-1.02)
Height (current)		0.786		
Wheezers	75.6±3.1		1.01 (0.94-1.08)	0.96 (0.88-1.05)
Non-wheezers	75.5±3.0		1 (reference)	1 (reference)
Born in Spain		1.000		
Yes	95 (9.8)		-	-
No	0 (0.0)		-	-

4.3 Treatment and respiratory/allergy symptoms

Wheeze ever

Most infants (89.1%) who had received treatment with inhaled drugs wheezed, against 20.4% who were not treated. Similarly, almost every child (95.3%) treated with inhaled corticosteroids wheezed in the first year of life, compared to 26.9% who did not receive treatment. In both cases, significant associations were found (p<0.001), and significant increased odds for wheeze ever in children who were treated were observed (aOR=35.90; 95% CI 18.75-68.76, and aOR=31.25; 95% CI 11.00-88.81, respectively).

Every child who had asthma diagnosed by a physician also wheezed in the first year of life, compared to 32.7% who were not asthmatic, also observing a significant association (p<0.001).

Most infants (84.2%) who suffered from pneumonia in the first year of life also wheezed, in contrast to 30.9% who did not have pneumonia, detecting a significant relation (p<0.001). A more than 8-fold significant higher risk for wheeze ever in children who had had pneumonia was shown (aOR=8.83; 95% CI 3.53-22.12). In addition, every infant hospitalised for pneumonia also wheezed, against 32.6% who were not hospitalised for this cause, also finding a statistically significant association (p<0.001).

The 43.5% of infants who had infant eczema, and 31.2% who did not, wheezed in the first year of life. A significant relation was observed (p=0.005), finding infant eczema in the statistical borderline to be considered risk factor for wheeze ever (aOR=1.54; 95% CI 0.97-2.43).

Mean number of colds in the first year of life in wheezing infants was 4.6 (±3.9) colds, and 2.9 (±3.5) colds in healthy infants, showing statistical differences (p<0.001). A significant higher risk for wheeze ever when number of colds rose was observed (aOR=1.17; 95% CI 1.10-1.25).

On the contrary, no statistical differences were detected when age of the first cold was studied (p=0.293). Wheezing infants had their first cold at a mean age of 5.0 (±4.7) months, and healthy infants at 5.3 (±4.4) months.

The 40.8% of children who had a cold in the first three months of life wheezed in the first year of life, compared to 32.1% who had their first cold at older ages. Although a significant association was found (p=0.015), no significant increased risk for wheeze ever in infants who had had a cold in early life was observed (aOR=1.01; 95% CI 0.69-1.47). (Table 10)

Recurrent wheeze

The 37.0% of infants treated with inhaled drugs wheezed repeatedly, compared to 4.9% who were not treated. On the other hand, 43.5% of children who were treated with inhaled corticosteroides developed recurrent wheeze, compared to 7.6% who were not treated. In both cases, significant associations between treatment and recurrent wheeze were found (p<0.001). Moreover, significant increased odds for recurrent wheeze when infants received any treatment were observed (aOR=8.44; 95% CI 4.89-14.58, and aOR=9.11; 95% CI 4.76-17.42, respectively).

Most asthmatic infants (70.0%) suffered from recurrent wheeze, compared to 10.2% who did not have asthma, detecting a statistical association (p<0.001). Also, an almost 20-fold significant increased risk for developing recurrent wheeze in asthmatic infants was observed (aOR=18.80; 95% CI 3.21-110.11).

The 39.5% of children who had pneumonia wheezed repeatedly, in contrast to 9.8% who did not suffer from pneumonia, showing evidence of a statistical association (p<0.001). Furthermore, a significant higher risk for recurrent wheeze in children who suffered from pneumonia was found (aOR=5.81; 95% CI 2.49-13.57).

Table 10. Associations between treatment and respiratory/allergy symptoms in the first year of life and wheeze ever.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Inhaled drugs		<0.001		
Yes	171 (89.1)		31.80 (19.48-51.93)	35.90 (18.75-68.76)
No	138 (20.4)		1 (reference)	1 (reference)
Inhaled corticosteroids		<0.001		
Yes	81 (95.3)		55.04 (19.91-152.13)	31.25 (11.00-88.81)
No	202 (26.9)		1 (reference)	1 (reference)
Asthma		<0.001		
Yes	10 (100)		-	-
No	308 (32.7)		-	-
Pneumonia		<0.001		
Yes	32 (84.2)		11.90 (4.92-28.80)	8.83 (3.53-22.12)
No	276 (30.9)		1 (reference)	1 (reference)
Hospital pneumonia		<0.001		
Yes	9 (100)		-	-
No	303 (32.6)		-	-
Eczema		0.005		
Yes	57 (43.5)		1.70 (1.17-2.48)	1.54 (0.97-2.43)
No	254 (31.2)		1 (reference)	1 (reference)
Number of colds		<0.001		
Wheezers	4.6±3.9		1.18 (1.12-1.24)	1.17 (1.10-1.25)
Non-wheezers	2.9±3.5		1 (reference)	1 (reference)
Age of the first cold		0.293		
Wheezers	5.0±4.7		1 (reference)	1 (reference)
Non-wheezers	5.3±4.4		0.98 (0.95-1.02)	1.00 (0.97-1.03)
Colds ≤ 3 months		0.015		
Yes	98 (40.8)		1.46 (1.08-1.99)	1.01 (0.69-1.47)
No	203 (32.1)		1 (reference)	1 (reference)

Most infants (77.8%) hospitalised for pneumonia had recurrent wheeze, against 10.2% who were not hospitalised for this cause, observing a significant relation (p<0.001). In addition, being hospitalised for pneumonia was positively related to the development of recurrent wheeze (OR=30.73; 95% CI 6.29-150.03).

The 19.1% of infants who had eczema, and 9.6% who did not, suffered from recurrent wheeze, showing statistical differences (p<0.001). More than twice increased odds for the onset of recurrent wheeze in infants who had infant eczema was observed (aOR=2.30; 95% CI 1.28-4.15).

Infants who wheezed repeatedly had a mean of 6.0 (±4.8) colds, whilst healthy infants reported a mean of 3.2 (±3.4) colds, detecting statistical differences (p<0.001). When number of colds rose, a 18% significant increased risk for recurrent wheeze was found (aOR=1.18; 95% CI 1.10-1.27).

Mean age of the first cold in infants who wheezed repeatedly was 4.6 (±4.3) months, while healthy children had their first cold at older ages, 5.3 (±4.5) months. However, no statistical differences were observed (p=0.121).

The 14.2% of infants who had their first cold in the first three months of life developed recurrent wheeze, compared to 10.1% who had their first cold at older ages, not finding any significant relation (p=0.090). (Table 11)

Table 11. Associations between treatment and respiratory/allergy symptoms in the first year of life and recurrent wheeze.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Inhaled drugs		<0.001		
Yes	71 (37.0)		11.45 (7.26-18.07)	8.44 (4.89-14.58)
No	33 (4.9)		1 (reference)	1 (reference)
Inhaled corticosteroids		<0.001		
Yes	37 (43.5)		9.39 (5.65-15.58)	9.11 (4.76-17.42)
No	57 (7.6)		1 (reference)	1 (reference)
Asthma		<0.001		
Yes	7 (70.0)		20.59 (5.24-80.93)	18.80 (3.21-110.11)
No	96 (10.2)		1 (reference)	1 (reference)
Pneumonia		<0.001		
Yes	15 (39.5)		6.03 (3.04-12.00)	5.81 (2.49-13.57)
No	87 (9.8)		1 (reference)	1 (reference)
Hospital pneumonia		<0.001		
Yes	7 (77.8)		30.73 (6.29-150.03)	-
No	95 (10.2)		1 (reference)	-
Eczema		0.001		
Yes	25 (19.1)		2.23 (1.36-3.65)	2.30 (1.28-4.15)
No	78 (9.6)		1 (reference)	1 (reference)
Number of colds		<0.001		
Wheezers	6.0±4.8		1.18 (1.11-1.24)	1.18 (1.10-1.27)
Non-wheezers	3.2±3.4		1 (reference)	1 (reference)
Age of the first cold		0.121		
Wheezers	4.6±4.3		1 (reference)	1 (reference)
Non-wheezers	5.3±4.5		0.95 (0.89-1.01)	0.97 (0.91-1.03)
Colds ≤ 3 months		0.090		
Yes	34 (14.2)		1.47 (0.94-2.29)	1.22 (0.68-2.20)
No	64 (10.1)		1 (reference)	1 (reference)

Severe wheeze

Many infants who were treated with inhaled drugs (39.1%) or corticosteroids (50.6%) wheezed severely in the first year of life, in contrast to those who were not treated (2.5% and 5.3%, respectively). In both cases, evidence of a significant relation was shown (p<0.001).

Furthermore, significant increased odds for severe wheeze in infants who had received any treatment were observed (aOR=16.65 95% CI 9.15-30.30, and aOR=13.07; 95% CI 7.13-23.98, respectively).

Over half of infants (60.0%) who had asthma diagnosed by a physician suffered from severe wheeze, compared to 9.4% who were not asthmatics, detecting a significant association ($p<0.001$). A more than 9-fold significant increased risk for severe wheeze in asthmatic infants was observed (aOR=9.29; 95% CI 2.13-40.47).

Almost half of infants (47.4%) who had pneumonia also suffered from severe wheeze, compared to 8.1% who did not have pneumonia, finding a significant relation ($p<0.001$). Moreover, pneumonia in the first year of life was positively related to the development of severe wheeze (aOR=6.93; 95% CI 3.11-15.44).

Similarly, most children (88.9%) who were hospitalised for pneumonia also wheezed severely, against 9.2% who were not hospitalised for this cause, finding statistical differences ($p<0.001$), and increased odds for severe wheeze in infants who required hospitalisation (OR=79.44; 95% CI 9.82-642.73).

The 16% of infants who had eczema, and 8.8% who did not report this condition, had severe wheeze, finding a statistically significant association ($p=0.010$). Furthermore, a positive relation between infant eczema and suffering from severe wheeze was observed (aOR=2.02; 95% CI 1.11-3.68).

In the first year of life, wheezing infants reported a mean of 5.6 (±5.2) colds, against 3.3 (±3.4) colds in healthy infants, showing statistical differences ($p<0.001$). When the number of colds rose, a 10% significant increased risk for the onset of severe wheeze was observed (aOR=1.10; 95% CI 1.03-1.18).

Also, statistical differences were found when studying the age of the first cold ($p=0.003$). Wheezing infants had their first cold at a mean age of 4.3 (±2.7) months, compared to 5.3 (±4.6) months in healthy infants. Having the first cold at older ages was found in the statistical borderline to be considered as protective factor for severe wheeze (aOR=0.86; 95% CI 0.74-1.00).

A 14.2% of infants who had a cold in the first three months of life suffered from severe wheeze, against 8.4% who had their first cold at older ages, detecting a statistical association ($p=0.011$). However, after adjustment, having a cold in the first three months of life was no longer found as risk factor for severe wheeze (aOR=0.67; 95% CI 0.30-1.48). (Table 12)

Table 12. Associations between treatment and respiratory/allergy symptoms in the first year of life and severe wheeze.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Inhaled drugs		<0.001		
Yes	75 (39.1)		24.89 (14.19-43.66)	16.65 (9.15-30.30)
No	17 (2.5)		1 (reference)	1 (reference)
Inhaled corticosteroids		<0.001		
Yes	43 (50.6)		18.20 (10.70-30.96)	13.07 (7.13-23.98)
No	40 (5.3)		1 (reference)	1 (reference)
Asthma		<0.001		
Yes	6 (60.0)		14.39 (3.99-51.97)	9.29 (2.13-40.47)
No	89 (9.4)		1 (reference)	1 (reference)
Pneumonia		<0.001		
Yes	18 (47.4)		10.25 (5.19-20.25)	6.93 (3.11-15.44)
No	72 (8.1)		1 (reference)	1 (reference)
Hospital pneumonia		<0.001		
Yes	8 (88.9)		79.44 (9.82-642.73)	-
No	85 (9.2)		1 (reference)	-
Eczema		0.010		
Yes	21 (16.0)		1.97 (1.16-3.33)	2.02 (1.11-3.68)
No	72 (8.8)		1 (reference)	1 (reference)
Number of colds		<0.001		
Wheezers	5.6±5.2		1.12 (1.07-1.19)	1.10 (1.03-1.18)
Non-wheezers	3.3±3.4		1 (reference)	1 (reference)
Age of the first cold		0.003		
Wheezers	4.3±2.7		1 (reference)	1 (reference)
Non-wheezers	5.3±4.6		0.92 (0.86-0.99)	0.86 (0.74-1.00)
Colds ≤ 3 months		0.011		
Yes	34 (14.2)		1.81 (1.14-2.86)	0.67 (0.30-1.48)
No	53 (8.4)		1 (reference)	1 (reference)

4.4 Family background

Wheeze ever

Among smoking mothers, 33.8% had a child who wheezed in the first year of life, against 30.9% who did not smoke, finding a statistically significant association (p=0.046), although no significant increased risk for wheeze ever in early life was observed (aOR=1.30; 95% CI 0.88-1.92).

Mothers who had wheezing offspring smoked a daily mean of 2.9 (±6.2) cigarettes, against 2.1 (±5.9) cigarettes smoked by mothers with healthy children. Statistical differences (p=0.046), and marginally significant higher odds for wheeze ever in infants when number of cigarettes smoked rose, were found (aOR=1.01; 95% CI 0.99-1.04).

On the other hand, among smoking fathers, 34.0% had a child who wheezed, compared to 31.8% who were non-smokers. No statistically significant association between paternal smoking status and wheeze in the first year of life was shown (p=0.497).

Fathers of wheezing children reported smoking a daily mean of 3.8 (±6.8) cigarettes, against 3.7 (±7.5) cigarettes smoked by fathers of healthy children, also not observing statistical differences (p=0.813).

Among smoking mothers during pregnancy, 40.1% had offspring who wheezed, in contrast to 31.2% who were non-smokers, detecting a significant association (p=0.028). Furthermore, prenatal exposure to tobacco smoke showed a marginally significant higher risk for wheeze ever in the offspring (aOR=1.43; 95% CI 0.95-2.15).

Wheezing infants lived with a mean of 0.6 (±0.9) smokers, while healthy children lived with 0.5 (±0.7) smokers, not finding statistical differences (p=0.144).

Almost half of asthmatic fathers (47.6%) had offspring who wheezed in the first year of life, compared to 31.7% who were not asthmatic, detecting a significant association (p=0.031). A non-significant increased risk for wheeze ever was observed in those infants with paternal history of asthma (aOR=1.70; 95% CI 0.83-3.48).

Also, a statistically significant relation was found when maternal history of asthma was assessed (p=0.019). Almost half of mothers with asthma (48.1%) had offspring who wheezed, compared to 32.3% who were not asthmatic. A marginally significant increased risk for wheeze ever in infants with positive history of maternal asthma was found (aOR=1.81; 95% CI 0.96-3.43).

Among allergic fathers, 29.8% had infants who wheezed, against 33.1% who did not report allergies. In addition, the 38.6% of allergic mothers had wheezing offspring, against 31.5% who were not allergic. In both cases, no significant relations between parental history of allergy and wheeze ever in the offspring were found (p=0.471 and p=0.104, respectively).

Over half of fathers (51.4%) who suffered from atopic dermatitis had wheezing children, against 32.0% who did not have eczema, finding statistical differences (p=0.014). Furthermore, paternal history of dermatitis was positively related to the onset of wheeze ever in the offspring (aOR=2.85; 95% CI 1.31-6.20).

On the contrary, 33.3% of mothers who suffered from atopic dermatitis had a child who wheezed, compared to 32.7% who did not report the condition, not detecting a statistically significant association (p=0.926).

Neither having asthmatic siblings (p=0.323), nor allergic (p=0.899), nor siblings with atopic dermatitis (p=0.522) was significantly related to the onset of wheeze in the first year of life.

When socioeconomic variables were studied, no statistically significant associations between maternal education (p=0.104), nor parental (father and mother) occupations (p=0.882 and p=0.110, respectively) and wheeze ever in the first year of life were observed.

Mean age of mothers who had a child who wheezed was 33.8 (±3.9) years, while mothers with healthy children had a mean age of 33.8 (±3.9) years, not detecting statistical differences (p=0.912). (Table 13)

Recurrent wheeze

Among smoking mothers, 13.4% had children who wheezed repeatedly, compared to 10.0% who were non-smokers, not finding a statistically significant association (p=0.161). In addition, no statistical differences were observed between daily number of cigarettes smoked and recurrent wheeze in the offspring (p=0.240).

On the other hand, among smoking fathers, 14.4% had offspring who developed recurrent wheeze, against 9.5% of non-smoking fathers, finding a significant relation (p=0.025). Moreover, having a smoking father significantly increased the risk of recurrent wheeze in the offspring (aOR=1.96; 95% CI 1.13-3.38). Conversely, no statistical differences were observed in the daily number of cigarettes smoked (p=0.104).

Among smoking mothers during pregnancy, 15.4% had a child who suffered from recurrent wheeze, in contrast to 9.6% who did not smoke, showing statistical differences (p=0.028), although a non-significant increased risk for recurrent wheeze in infancy was observed (aOR=1.28; 95% CI 0.68-2.40).

Infants who wheezed repeatedly lived with a mean of 0.6 (±0.8) smokers, whilst healthy infants lived with 0.5 (±0.8) smokers, not finding statistical differences (p=0.063).

The 16.7% of asthmatic fathers had a child who wheezed repeatedly, in contrast to 10.4% of non-asthmatic fathers, not finding a statistically significant association (p=0.194). Conversely, a significant association was found between positive maternal history of asthma and the development of recurrent wheeze in the offspring (p=0.013). Among asthmatic mothers, 21.2% had a child who wheezed repeatedly, compared to 10.2% of non-asthmatic mothers. However, after adjustment, having an asthmatic mother not significantly increased the risk of recurrent wheeze in the offspring (aOR=1.25; 95% CI 0.50-3.11).

A 10.5% of allergic fathers had offspring who wheezed repeatedly, compared to 10.8% of non-allergic fathers, not detecting a significant relation (p=0.929). On the other hand, among allergic mothers, 18.2% had wheezing offspring, compared to 9.6% who were not allergic, showing evidence of a statistically significant association (p=0.003). Non-significant increased odds for recurrent wheeze in those infants with allergic mothers were observed. (aOR=1.45; 95% CI 0.76-2.78).

Table 13. Associations between family background and wheeze ever.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Smoking mother		0.046		
Yes	77 (38.3)		1.39 (1.01-1.92)	1.30 (0.88-1.92)
No	238 (30.9)		1 (reference)	1 (reference)
Smoking father		0.497		
Yes	97 (34.0)		1.11 (0.83-1.49)	1.07 (0.75-1.51)
No	212 (31.8)		1 (reference)	1 (reference)
Smoking during pregnancy		0.028		
Yes	65 (40.1)		1.48 (1.04-2.09)	1.43 (0.95-2.15)
No	253 (31.2)		1 (reference)	1 (reference)
Smokers in the household		0.144		
Wheezers	0.6±0.9		1.14 (0.96-1.36)	1.13 (0.93-1.38)
Non-wheezers	0.5±0.7		1 (reference)	1 (reference)
Asthma				
Father		0.031		
Yes	20 (47.6)		1.96 (1.05-3.64)	1.70 (0.83-3.48)
No	294 (31.7)		1 (reference)	1 (reference)
Mother		0.019		
Yes	25 (48.1)		1.94 (1.11-3.40)	1.81 (0.96-3.43)
No	282 (32.3)		1 (reference)	1 (reference)
Allergic rhinitis				
Father		0.471		
Yes	37 (29.8)		0.86 (0.57-1.30)	0.74 (0.45-1.21)
No	274 (33.1)		1 (reference)	1 (reference)
Mother		0.104		
Yes	51 (38.6)		1.37 (0.94-2.00)	1.10 (0.67-1.81)
No	264 (31.5)		1 (reference)	1 (reference)
Atopic dermatitis				
Father		0.014		
Yes	19 (51.4)		2.24 (1.16-4.33)	2.85 (1.31-6.20)
No	294 (32.0)		1 (reference)	1 (reference)
Mother		0.926		
Yes	19 (33.3)		1.03 (0.58-1.81)	1.15 (0.58-2.26)
No	295 (32.7)		1 (reference)	1 (reference)
Maternal education		0.104		
Basic school	12 (41.4)		1 (reference)	1 (reference)
Incomplete Secondary	23 (42.6)		1.05 (0.42-2.62)	0.52 (0.16-1.64)
Complete Secondary	113 (28.9)		0.58 (0.27-1.24)	0.31 (0.12-0.85)
University	169 (33.7)		0.72 (0.34-1.54)	0.40 (0.15-1.05)
Mother's age		0.912		
Wheezers	33.8±3.9		1.00 (0.97-1.04)	1.01 (0.97-1.05)
Non-wheezers	33.8±3.9		1 (reference)	1 (reference)

The 16.2% of fathers with atopic dermatitis had wheezing offspring, in contrast to 10.4% who did not report the condition, not finding a statistically significant relation (p=0.255). Also, no significant association was found between maternal history of dermatitis and infant recurrent wheeze (p=0.955). The 10.5% of mothers who suffered from dermatitis had a child who wheezed repeatedly, compared to 10.7% of mothers who did not have eczema.

Neither having an asthmatic sibling (p=1.000), nor allergic siblings (p=0.440) nor siblings with atopic dermatitis (p=0.656) was significantly associated with recurrent wheeze in infants in the first year of life.

In addition, neither maternal education (p=0.305), nor parental (father and mother) occupations (p=0.806 and p=0.575, respectively) showed statistically significant associations with the development of recurrent wheeze.

Mean age of mothers whose offspring wheezed repeatedly was 33.8 (±3.4) years, whilst in mothers with healthy infants mean age was 33.8 (±4.0) years, not detecting statistical differences (p=0.829). (Table 14)

Severe wheeze

A 10.0% of smoking mothers had a child who suffered from severe wheeze, compared to 9.6% of mothers who did not smoke, not finding any statistically significant association (p=0.885). In addition, mothers who had wheezing offspring smoked a daily mean of 2.6±5.4 cigarettes, while mothers with healthy children smoked a daily mean of 2.3±6.1, also not showing statistical differences (p=0.653).

Among smoking fathers, 9.5% had a child who wheezed, against 9.6% who were not smokers, not finding a significant relation between paternal smoking status and severe wheeze in the offspring (p=0.953). Moreover, no statistical differences (p=0.722) were found between daily mean of cigarettes smoked by fathers whose offspring wheezed or was healthy (4.0±7.1 and 3.7±7.3, respectively).

Among smoking mothers during pregnancy, 13.6% had a child who wheezed severely, against 8.8% of mothers who did not smoke, nearly showing evidence of a statistically significant association between prenatal exposure to tobacco smoke and the onset of severe wheeze in the offspring (p=0.057). Furthermore, a non-significant increased risk for severe wheeze was shown (aOR=1.52; 95% 0.84-2.78)

Infants who wheezed severely lived with a mean of 0.6 (±0.9) smoking persons, in contrast to 0.5 (±0.8) smokers living with healthy children, not detecting statistical differences (p=0.354).

Table 14. Associations between family background and recurrent wheeze.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Smoking mother		0.161		
Yes	27 (13.4)		1.40 (0.87-2.23)	0.77 (0.33-1.82)
No	77 (10.0)		1 (reference)	1 (reference)
Smoking father		0.025		
Yes	41 (14.4)		1.61 (1.06-2.45)	1.96 (1.13-3.38)
No	63 (9.5)		1 (reference)	1 (reference)
Smoking during pregnancy		0.028		
Yes	25 (15.4)		1.71 (1.05-2.78)	1.28 (0.68-2.40)
No	78 (9.6)		1 (reference)	1 (reference)
Smokers in the household		0.063		
Wheezers	0.6±0.8		1.26 (0.99-1.60)	0.90 (0.54-1.51)
Non-wheezers	0.5±0.8		1 (reference)	1 (reference)
Asthma				
Father		0.194		
Yes	7 (16.7)		1.73 (0.75-4.00)	1.59 (0.54-4.70)
No	96 (10.4)		1 (reference)	1 (reference)
Mother		0.013		
Yes	11 (21.2)		2.36 (1.17-4.76)	1.25 (0.50-3.11)
No	89 (10.2)		1 (reference)	1 (reference)
Allergic rhinitis				
Father		0.929		
Yes	13 (10.5)		0.97 (0.53-1.80)	1.22 (0.60-2.47)
No	89 (10.8)		1 (reference)	1 (reference)
Mother		0.003		
Yes	24 (18.2)		2.11 (1.28-3.47)	1.45 (0.76-2.78)
No	80 (9.6)		1 (reference)	1 (reference)
Atopic dermatitis				
Father		0.255		
Yes	6 (16.2)		1.68 (0.68-4.12)	0.62 (0.16-2.48)
No	95 (10.4)		1 (reference)	1 (reference)
Mother		0.955		
Yes	6 (10.5)		0.98 (0.41-2.33)	0.68 (0.20-2.31)
No	97 (10.8)		1 (reference)	1 (reference)
Maternal education		0.305		
Basic school	5 (17.2)		1 (reference)	1 (reference)
Incomplete Secondary	7 (13.0)		0.71 (0.21-2.49)	0.66 (0.13-3.31)
Complete Secondary	34 (8.7)		0.46 (0.16-1.28)	0.52 (0.14-1.98)
University	58 (11.6)		0.63 (0.23-1.71)	0.67 (0.18-2.52)
Mother's age		0.829		
Wheezers	33.8±3.4		1.01 (0.95-1.06)	1.01 (0.94-1.08)
Non-wheezers	33.8±4.0		1 (reference)	1 (reference)

The 9.5% of asthmatic fathers had offspring who wheezed severely, in contrast to 9.4% of non-asthmatic, not observing any statistically significant association between paternal history of asthma and severe wheeze in the offspring (p=1.000).

In contrast, among asthmatic mothers, 19.2% had wheezing offspring, compared to 9.1% of non-asthmatic mothers, finding a significant relation (p=0.016), and a non-significant higher risk for severe wheeze in infants with a positive maternal history of asthma (aOR=1.79; 95% CI 0.71-4.52).

No statistical differences were found between paternal history of allergy and severe wheeze in the offspring (p=0.937). 9.7% of allergic fathers had a child who wheezed severely, compared to 9.9% of non-allergic fathers.

Among allergic mothers, 14.4% had a child who suffered from severe wheeze, against 9.0% of non-allergic mothers, finding a marginally significant association (p=0.049). However, non-significant increased odds for severe wheeze in infants with positive history of maternal allergy were found (aOR=1.37; 95% CI 0.73-2.59).

The 8.1% of fathers who had eczema also had wheezing offspring, against 9.9% who did not suffer from dermatitis. No statistically significant association between paternal history of atopic dermatitis and severe wheeze in the offspring was observed (p=1.000).

On the other hand, a significant relation between maternal history of dermatitis and severe wheeze in the offspring was detected (p=0.036). Among atopic mothers, 17.5% had a child who wheezed severely, compared to 9.1% of mothers who did not suffer from eczema. However, a non-significant increased risk for severe wheeze in infants with positive history of maternal dermatitis was found (aOR=1.38; 95% CI 0.57-3.32).

Neither having asthmatic (p=1.000), nor allergic siblings (p=0.105) was significantly related to the development of infant severe wheeze. However, infants whose siblings had eczema showed a more than 2-fold significantly increased risk for severe wheeze in the first year of life (aOR=2.57; 95% CI 1.14-5.80).

Maternal education was marginally associated with severe wheeze in the offspring (p=0.056). 8.8% of mothers with a University degree, and 9.2% with complete Secondary education, had a child who wheezed severely, compared to 20.7% who only attended to basic school. Higher maternal educational level was (although not reaching statistical significance) inversely related to suffer from severe wheeze.

Conversely, no significant associations were found between parental (father and mother) occupation and severe wheeze in the offspring in the first year of life (p=0.932 and p=0.076, respectively).

Mean age of mothers whose offspring had severe wheeze was 33.5 (±4.0) years, while mothers with healthy children had a mean age of 33.8 (±3.9) years, not showing statistical differences (p=0.458). (Table 15)

Table 15. Associations between family background and severe wheeze.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Smoking mother		0.885		
Yes	20 (10.0)		1.04 (0.62-1.75)	0.75 (0.40-1.41)
No	74 (9.6)		1 (reference)	1 (reference)
Smoking father		0.953		
Yes	27 (9.5)		0.99 (0.61-1.58)	0.86 (0.50-1.48)
No	64 (9.6)		1 (reference)	1 (reference)
Smoking during pregnancy		0.057		
Yes	22 (13.6)		1.64 (0.98-2.73)	1.52 (0.84-2.78)
No	71 (8.8)		1 (reference)	1 (reference)
Smokers in the household		0.354		
Wheezers	0.6±0.9		1.13 (0.87-1.48)	1.04 (0.75-1.42)
Non-wheezers	0.5±0.8		1 (reference)	1 (reference)
Asthma				
Father		1.000		
Yes	4 (9.5)		1.02 (0.35-2.91)	1.04 (0.30-3.55)
No	87 (9.4)		1 (reference)	1 (reference)
Mother		0.016		
Yes	10 (19.2)		2.39 (1.16-4.95)	1.79 (0.71-4.52)
No	79 (9.1)		1 (reference)	1 (reference)
Allergic rhinitis				
Father		0.937		
Yes	12 (9.7)		0.97 (0.52-1.84)	0.89 (0.43-1.83)
No	82 (9.9)		1 (reference)	1 (reference)
Mother		0.049		
Yes	19 (14.4)		1.71 (1.00-2.94)	1.37 (0.73-2.59)
No	75 (9.0)		1 (reference)	1 (reference)
Atopic dermatitis				
Father		1.000		
Yes	3 (8.1)		0.80 (0.24-2.66)	0.51 (0.11-2.34)
No	91 (9.9)		1 (reference)	1 (reference)
Mother		0.036		
Yes	10 (17.5)		2.13 (1.04-4.36)	1.38 (0.57-3.32)
No	82 (9.1)		1 (reference)	1 (reference)
Maternal education		0.056		
Basic school	6 (20.7)		1 (reference)	1 (reference)
Incomplete Secondary	9 (16.7)		0.77 (0.24-2.42)	2.02 (0.36-11.33)
Complete Secondary	36 (9.2)		0.39 (0.15-1.02)	0.85 (0.18-4.13)
University	44 (8.8)		0.37 (0.14-0.95)	0.75 (0.16-3.59)
Mother's age		0.458		
Wheezers	33.5±4.0		1 (reference)	1 (reference)
Non-wheezers	33.8±3.9		0.98 (0.93-1.03)	0.97 (0.91-1.04)

4.5 Household and environmental factors

Wheeze ever

Among infants who attended nursery, 41.8% wheezed, in contrast to 27.8% who did not attend, finding a significant association (p<0.001). Moreover, nursery attendance in the first year of life was positively related to wheeze ever in infants (aOR=1.39; 95% CI 0.99-1.95).

Infants who wheezed started attending nursery at a mean age of 3.5 (±5.9) months, whereas healthy infants began at 2.8 (±6.3) months, not detecting statistical differences (p=0.132).

In 40.1% of households with pets during pregnancy, infants wheezed in the first year of life, in contrast to 31.5% without pets. Similarly, when the questionnaire was filled, in 40.0% of households with pets, infants also wheezed, against 31.6% with no pets. In both cases, significant associations were observed (p=0.035 and p=0.037, respectively), although only those infants who currently lived with pets presented a marginally significant higher risk for wheeze ever in the first year of life (aOR=1.44; 95% CI 0.96-2.15).

No significant relations were found between fuel used for heating (p=0.474) nor for cooking (p=0.402) and wheeze ever. Also, no associations were detected between dwellings with an air conditioning unit or carpeted and wheeze ever (p=0.835 and p=0.768, respectively).

The 43.9% of families who reported presence of mould or damp stains in the walls had a child who wheezed, in contrast to 32.0% who did not report this issue in their dwellings, not finding a statistically significant association (p=0.110).

A 31.4% of families who considered living in a polluted area had wheezing offspring, against 32.7% who did not report this environmental issue, not finding a significant relation between air pollution and the onset of wheeze in infants (p=0.697).

Also, no significant association was observed when immunisation status was studied (p=0.567). Only three children (21.4%) who had a complete immunisation schedule wheezed, against 32.7% who did not complete the immunisation schedule.

The mean number of siblings of infants who wheezed was 0.7±0.7, whilst healthy children had a mean of 0.6 (±0.8) siblings, detecting statistical differences (p=0.048). When number of siblings rose, a 21% significant increased risk for wheeze ever was found (aOR=1.21; 95% CI 0.99-1.49).

Infants who wheezed lived with a mean of 3.5 (±1.0) persons, and healthy children lived with 3.3 (±1.1) persons, also showing statistical differences (p=0.035). When number of people in the same household rose, a non-significant higher risk for wheeze ever was observed (aOR=1.10; 95% CI 0.90-1.34).

The 34.9% of infants who consumed industrial infant food every day wheezed, compared to 31.3% who were fed with them once a week, and 30.2% who were not fed with industrial infant food in the first year of life, not detecting any significant relation (p=0.623).

Infants who wheezed were exclusively breastfed during a mean of 3.8 (±3.0) months, while healthy infants were breastfed for a longer period, 4.5 (±3.1) months, finding statistical differences (p=0.002). In addition, an exclusively longer breastfeeding was found as protective factor for wheeze ever (aOR=0.94; 95% CI 0.89-0.99).

No significant relation was detected between the food used for frying and the onset of wheezing in the first year of life (p=0.839). Table 16 summarizes the main associations between household and environmental factors and wheeze ever.

Recurrent wheeze

The 16.7% of infants who attended nursery in the first year of life developed recurrent wheeze, in contrast to 7.4% of children who did not attend, detecting a significant association (p<0.001). An almost 2-fold significant increased risk for recurrent wheeze in infants who attended nursery school was found (aOR=1.89; 95% CI 1.15-3.12).

Furthermore, statistical differences were also found in the age at which children began attending nursery school (p=0.039). Healthy infants attended at earlier ages than those who wheezed (2.9±6.1 and 4.2±6.6, respectively). However, after adjustment, no significant increased odds for recurrent wheeze were found (aOR=1.01; 95% CI 0.97-1.05).

In 14.7% of households where presence of pets during pregnancy was reported, infants wheezed repeatedly, against 10% of households with no pets, not detecting a significant association (p=0.082). Likewise, when the questionnaire was filled, in 14.6% of households with pets, children suffered from recurrent wheeze, compared to 10.0% of infants who lived in households with no pets, also not finding a significant relation (p=0.086).

Also, no statistically significant associations were found between fuel used for heating (p=0.933), nor for cooking (p=0.813), and the development of recurrent wheeze in the first year of life.

Only seven children (12.1%) who suffered from recurrent wheeze lived in dwellings with an air conditioning unit, and just one infant (5.9%) in a carpeted house, not detecting any significant association in either cases (p=0.664 and p=1.000, respectively).

Among families who had mould or damp stains at home, 9.8% had an infant who wheezed repeatedly, compared to 10.7% of families who did not report this issue in the dwelling, not finding a statistically significant relation between dampness and infant recurrent wheezing (p=1.000).

Table 16. Associations between household and environmental factors and wheeze ever.

	N (%) x̄±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Nursery attendance		<0.001		
Yes	138 (41.8)		1.87 (1.42-2.47)	1.39 (0.99-1.95)
No	179 (27.8)		1 (reference)	1 (reference)
Age nursery attendance		0.132		
Wheezers	3.5±5.9		1.02 (0.99-1.04)	1.01 (0.98-1.04)
Non-wheezers	2.8±6.3		1 (reference)	1 (reference)
Presence of pets (birth)		0.035		
Yes	63 (40.1)		1.46 (1.03-2.07)	1.37 (0.91-2.06)
No	256 (31.5)		1 (reference)	1 (reference)
None			1 (reference)	1 (reference)
Dog			1.29 (0.72-2.32)	1.29 (0.66-2.54)
Cat			1.33 (0.62-2.86)	0.96 (0.38-2.47)
Others			1.83 (1.00-3.33)	1.94 (0.96-3.93)
More than one			1.37 (0.66-2.87)	1.23 (0.55-2.76)
Presence of pets (current)		0.037		
Yes	66 (40.0)		1.44 (1.02-2.04)	1.44 (0.96-2.15)
No	253 (31.6)		1 (reference)	1 (reference)
None			1 (reference)	1 (reference)
Dogs			1.44 (0.78-2.67)	1.58 (0.78-3.20)
Cats			0.75 (0.33-1.70)	0.50 (0.17-1.44)
Others			1.89 (1.12-3.21)	1.86 (1.00-3.45)
More than one			1.53 (0.72-3.24)	1.80 (0.79-4.11)
Mould or damp stains		0.110		
Yes	18 (43.9)		1.67 (0.89-3.13)	1.55 (0.74-3.23)
No	296 (32.0)		1 (reference)	1 (reference)
Air pollution		0.697		
Yes	79 (31.4)		0.94 (0.69-1.28)	0.82 (0.57-1.18)
No	235 (32.7)		1 (reference)	1 (reference)
Number of siblings		0.048		
Wheezers	0.7±0.7		1.17 (0.99-1.38)	1.21 (0.99-1.49)
Non-wheezers	0.6±0.8		1 (reference)	1 (reference)
Number of people at home		0.035		
Wheezers	3.5±1.0		1.14 (1.01-1.29)	1.10 (0.90-1.34)
Non-wheezers	3.3±1.1		1 (reference)	1 (reference)
Exclusive breastfeeding		0.002		
Wheezers	3.8±3.0		1 (reference)	1 (reference)
Non-wheezers	4.5±3.1		0.93 (0.89-0.97)	0.94 (0.89-0.99)
<6 months			1 (reference)	1 (reference)
≥6 months			0.84 (0.63-1.12)	0.97 (0.69-1.36)

A 10.7% of families who considered living in an air polluted area had wheezing offspring, compared to 10.3% of families who did not report this issue, not finding any significant association (p=0.850).

Also, no statistical relation was shown between a complete immunization schedule and the onset of recurrent wheeze in the infant (p=0.384). Every child who wheezed repeatedly in the first year of life had been adequately vaccinated.

Infants who suffered from recurrent wheeze had a mean of 0.7 (±0.8) siblings, while healthy infants had 0.6 (±0.8) siblings, not showing statistical differences (p=0.340). Also, no statistical differences were found between the number of people who lived with the wheezing or healthy infants (3.5±1.0, and 3.4±1.1, respectively) and the development of recurrent wheeze in the first year of life (p=0.268).

The 13.1% of infants who wheezed repeatedly usually consumed industrial infant food, compared to 8.8% who consumed them once a week, and 10.9% who never were fed with industrial infant food, not finding a significant association (p=0.188).

Infants who suffered from recurrent wheeze exclusively breastfed for a mean of 3.9 (±3.1) months, in contrast to healthy children, who breastfed for a longer period, 4.3 (±3.1) months, although no statistical differences were observed (p=0.185).

Also, the food used for frying was not significantly related to the development of recurrent wheeze in infants in the first year of life (p=0.668). (Table 17)

Severe wheeze

Among infants who attended nursery in the first year of life, 10.3% suffered from severe wheeze, against 9.3% of infants who did not attend, not detecting any significant relation (p=0.616).

Furthermore, no statistical differences were observed between age of attendance to nursery school and infant severe wheeze (p=0.219). Wheezing infants began at a mean age of 2.6 (±3.6) months, while healthy children attended to nursery for the first time at older ages, 3.1 (±6.4) months.

Among families who reported presence of pets during pregnancy, 16.6% had a child who wheezed severely, compared to 8.5% who did have any pets, finding a statistically significant association (p=0.002). A 75% significant increased risk for severe wheeze in those infants whose families had contact with pets throughout pregnancy was observed (aOR=1.75; 95% CI 0.99-3.08).

Also, when the questionnaire was filled, a significant association was observed between the onset of severe wheeze and presence of pets (p=0.002). In 16.4% of households with pets, infants wheezed severely, in contrast to 8.5% who did not have any pets. Thus, presence of pets at home significantly increased the odds for suffering from severe wheeze (aOR=1.75; 95% CI 1.01-3.06).

Table 17. Associations between household and environmental factors and recurrent wheeze.

	N (%) x̄±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Nursery attendance		<0.001		
Yes	55 (16.7)		2.49 (1.65-3.76)	1.89 (1.15-3.12)
No	48 (7.4)		1 (reference)	1 (reference)
Age nursery attendance		0.039		
Wheezers	4.2±6.6		1.02 (1.00-1.05)	1.01 (0.97-1.05)
Non-wheezers	2.9±6.1		1 (reference)	1 (reference)
Presence of pets (birth)		0.082		
Yes	23 (14.7)		1.55 (0.94-2.55)	1.59 (0.86-2.93)
No	81 (10.0)		1 (reference)	1 (reference)
None			1 (reference)	1 (reference)
Dog			1.68 (0.76-3.70)	1.31 (0.50-3.41)
Cat			1.04 (0.31-3.52)	0.69 (0.13-3.63)
Others			1.62 (0.70-3.74)	1.77 (0.59-5.29)
More than one			1.74 (0.65-4.65)	3.44 (1.12-10.57)
Presence of pets (current)		0.086		
Yes	24 (14.6)		1.53 (0.94-2.50)	1.57 (0.86-2.86)
No	80 (10.0)		1 (reference)	1 (reference)
None			1 (reference)	1 (reference)
Dogs			1.66 (0.72-3.83)	1.43 (0.51-4.05)
Cats			0.96 (0.29-3.24)	1.15 (0.31-4.30)
Others			1.59 (0.75-3.35)	1.28 (0.46-3.51)
More than one			1.88 (0.70-5.05)	3.27 (1.07-9.99)
Mould or damp stains		1.000		
Yes	4 (9.8)		0.90 (0.32-2.59)	0.49 (0.12-2.03)
No	99 (10.7)		1 (reference)	1 (reference)
Air pollution		0.850		
Yes	27 (10.7)		1.05 (0.66-1.67)	1.24 (0.72-2.14)
No	74 (10.3)		1 (reference)	1 (reference)
Number of siblings		0.340		
Wheezers	0.7±0.8		1.12 (0.89-1.41)	1.10 (0.81-1.50)
Non-wheezers	0.6±0.8		1 (reference)	1 (reference)
Number of people at home		0.268		
Wheezers	3.5±1.0		1.11 (0.93-1.32)	1.06 (0.82-1.37)
Non-wheezers	3.4±1.1		1 (reference)	1 (reference)
Exclusive breastfeeding		0.185		
Wheezers	3.9±3.1		1 (reference)	1 (reference)
Non-wheezers	4.3±3.1		0.96 (0.89-1.02)	0.98 (0.90-1.07)
<6 months			1 (reference)	1 (reference)
≥6 months			0.74 (0.47-1.16)	0.73 (0.41-1.28)

Neither fuel used for heating nor for cooking were significantly related to severe wheeze in the first year of life (p=0.162 and p=0.731, respectively). In addition, neither having an air conditioning unit nor living in a carpeted house were significantly associated with infant severe wheeze (p=1.000 and p=0.396, respectively).

Only five families (12.2%) who reported having mould or damp stains at home had wheezing offspring, in contrast to 9.6% of families who did not report dampness in the dwelling, not finding any significant association (p=0.587).

Among families who reported living in an air polluted area, 9.9% had offspring who wheezed severely, compared to 9.0% who did not consider living in a polluted area, not detecting statistical differences (p=0.678).

Every child who wheezed severely in the first year of life had complete immunization schedule, not finding any statistically significant association between the immunisation status and the condition (p=0.219).

Wheezing infants had a mean of 0.8 (±0.7) siblings, whilst healthy children had 0.6 (±0.8) siblings, showing statistical differences (p=0.018). When number of siblings rose, a non-significant increased risk for severe wheeze was observed (aOR=1.15; 95% CI 0.86-1.53).

In contrast, no statistical differences were detected between the number of people in the household and infant severe wheeze (p=0.180). Wheezing infants lived with a mean of 3.5 (±1.0) persons, while healthy children lived with 3.4 (±1.1) persons.

The 12.6% of infants who consumed industrial infant food every day had severe wheezing, against only two children (2.0%) who were fed with them once a month, and 8.5% who never consumed industrial infant food in the first year of life, detecting statistical differences (p=0.004). Furthermore, a significant lower risk for severe wheeze in those infants who once a month were fed with industrial food was found (aOR=0.20; 95% CI 0.04-0.94).

Wheezing infants exclusively breastfed for a mean of 3.3 (±2.8) months, whereas healthy children breastfed for a longer period, 4.3 (±3.1) months, detecting statistical differences (p=0.001). In addition, a longer exclusively breastfeeding was inversely related to the onset of severe wheeze (aOR=0.90; 95% CI 0.82-0.98).

No statistically significant relation was found between food used for frying and suffering from severe wheeze in the first year of life (p=0.468). In Table 18, the associations between household and environmental factors and severe wheeze are summarized.

Table 18. Associations between household and environmental factors and severe wheeze.

	N (%) x̄±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Nursery attendance		0.616		
Yes	34 (10.3)		1.12 (0.72-1.74)	0.86 (0.51-1.44)
No	60 (9.3)		1 (reference)	1 (reference)
Age nursery attendance		0.219		
Wheezers	2.6±3.6		1 (reference)	1 (reference)
Non-wheezers	3.1±6.4		0.98 (0.94-1.03)	0.97 (0.92-1.03)
Presence of pets (birth)		0.002		
Yes	26 (16.6)		2.14 (1.31-3.49)	1.75 (0.99-3.08)
No	69 (8.5)		1 (reference)	1 (reference)
None			1 (reference)	1 (reference)
Dog			2.31 (1.08-4.95)	2.02 (0.87-4.72)
Cat			0.80 (0.19-3.43)	0.46 (0.06-3.55)
Other			3.00 (1.43-6.30)	2.11 (0.81-5.52)
More than one			2.07 (0.77-5.57)	2.06 (0.72-5.91)
Presence of pets (current)		0.002		
Yes	27 (16.4)		2.11 (1.30-3.41)	1.75 (1.01-3.06)
No	68 (8.5)		1 (reference)	1 (reference)
None			1 (reference)	1 (reference)
Dog			1.98 (0.85-4.61)	1.37 (0.54-3.51)
Cat			1.15 (0.34-3.89)	1.52 (0.43-5.39)
Other			2.69 (1.36-5.31)	1.82 (0.75-4.40)
More than one			2.24 (0.83-6.07)	2.80 (0.96-8.18)
Mould or damp stains		0.587		
Yes	5 (12.2)		1.31 (0.50-3.41)	1.17 (0.42-3.23)
No	89 (9.6)		1 (reference)	1 (reference)
Air pollution		0.678		
Yes	25 (9.9)		1.11 (0.68-1.80)	1.28 (0.75-2.18)
No	65 (9.0)		1 (reference)	1 (reference)
Number of siblings		0.018		
Wheezers	0.8±0.7		1.30 (1.04-1.62)	1.15 (0.86-1.53)
Non-wheezers	0.6±0.8		1 (reference)	1 (reference)
Number of people at home		0.180		
Wheezers	3.5±1.0		1.13 (0.94-1.36)	1.05 (0.83-1.32)
Non-wheezers	3.4±1.1		1 (reference)	1 (reference)
Exclusive breastfeeding		0.001		
Wheezers	3.3±2.8		1 (reference)	1 (reference)
Non-wheezers	4.3±3.1		0.89 (0.82-0.95)	0.90 (0.82-0.98)
<6 months			1 (reference)	1 (reference)
≥6 months			0.64 (0.39-1.04)	0.67 (0.39-1.15)

4.6 Exposures during pregnancy and birth

Wheeze ever

When maternal diet during pregnancy and its relation with wheeze ever was studied, only fresh fruit and cooked potatoes showed significant associations (p=0.039 and p=0.035, respectively).

However, neither usual (aOR=0.45; 95% CI 0.17-1.16) nor occasional consumption (aOR=0.45; 95% CI 0.16-1.24) of fresh fruit and natural juices during pregnancy were found inversely related to wheeze ever in the offspring.

Conversely, only those mothers who occasionally consumed cooked potatoes during pregnancy presented marginally higher odds for wheeze ever in the offspring (aOR=1.57; 95% 1.05-2.36).

No statistical differences were found between adherence to the Mediterranean diet during pregnancy and wheeze ever in the offspring (p=0.830). Mothers who had a child who wheezed scored a mean of 28.2 (±3.2) points, whereas in mothers with healthy infants the mean score was 28.2 (±3.0) points.

A 33.6% of mothers who never took oral contraceptives had a child who wheezed, compared to 31.2% and 30.8% who took them between one to three years, and four to six years, respectively, not finding any statistically significant association (p=0.395).

Among mothers who occasionally took paracetamol during pregnancy, 42.3% had wheezing offspring, in contrast to 31.1% who never or less than once a month took it, showing evidence of a statistically significant association (p=0.033). A 60% significant increased risk for wheeze ever in the offspring whose mothers reported an occasional consumption of paracetamol was observed (aOR=1.60; 95% CI 1.04-2.47).

When complications during pregnancy and birth were studied, gestational diabetes, malposition of the foetus and prematurity showed the highest, although non-significant, risks for wheeze ever in the offspring. (Table 19)

Recurrent wheeze

No significant associations were found between frequency of consumption of different food groups during pregnancy and development of recurrent wheeze in the offspring in the first year of life.

Furthermore, no statistical differences (p=0.598) were found between adherence to the Mediterranean dietary pattern during pregnancy and recurrent wheeze in the offspring. Mothers whose offspring wheezed repeatedly scored a mean of 28.0 (±3.2) points, whereas mothers with healthy children scored 28.2 (±3.1) points.

Table 19. Associations between exposures during pregnancy and birth and wheeze ever.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Mediterranean diet		0.897		
Wheezers	32.4±3.4		1.00 (0.96-1.05)	1.02 (0.97-1.08)
Non-wheezers	32.3±3.3		1 (reference)	1 (reference)
Oral contraceptives		0.395		
Never	181 (33.6)		1 (reference)	1 (reference)
Less than a year	23 (39.0)		1.26 (0.72-2.19)	1.39 (0.70-2.75)
One to three years	48 (31.2)		0.89 (0.61-1.31)	0.85 (0.54-1.34)
Four to six years	28 (30.8)		0.88 (0.54-1.42)	0.80 (0.45-1.44)
More than six years	34 (26.2)		0.70 (0.45-1.07)	0.66 (0.40-1.09)
Paracetamol		0.033		
Never/less than once a month	250 (31.1)		1 (reference)	1 (reference)
1-4 times a month	58 (42.3)		1.63 (1.13-2.36)	1.60 (1.04-2.47)
More than once a week	11 (34.4)		1.16 (0.55-2.45)	1.14 (0.46-2.81)
Complications				
None	-	-	1 (reference)	1 (reference)
Hypertension	28 (36.4)	0.427	1.22 (0.75-1.98)	1.22 (0.69-2.15)
Threatened miscarriage	38 (36.9)	0.304	1.25 (0.82-1.92)	1.31 (0.79-2.18)
Infections	40 (32.8)	0.875	1.03 (0.69-1.55)	0.88 (0.55-1.42)
Gestational diabetes	28 (42.4)	0.069	1.60 (0.96-2.66)	1.69 (0.90-3.14)
Malposition of the foetus	13 (41.9)	0.247	1.53 (0.74-3.18)	1.83 (0.79-4.28)
Premature rupture of membranes	19 (30.2)	0.745	0.91 (0.52-1.59)	1.19 (0.62-2.29)
Placenta problems	19 (38.0)	0.359	1.32 (0.73-2.37)	1.10 (0.54-2.22)
Hypoxia	18 (36.0)	0.551	1.20 (0.66-2.18)	1.03 (0.50-2.11)
Prematurity	32 (41.0)	0.091	1.50 (0.94-2.42)	1.47 (0.82-2.63)
Knots in umbilical cord	35 (33.7)	0.733	1.08 (0.70-1.66)	1.13 (0.69-1.85)
Obstetric trauma	1 (25.0)	1,000	0.70 (0.07-6.72)	-
Forceps/suction cup	53 (27.8)	0.100	0.74 (0.52-1.06)	0.81 (0.54-1.22)
Caesarean section	47 (29.8)	0.469	0.87 (0.60-1.27)	0.78 (0.50-1.23)

The 11.0% of mothers who never took oral contraceptives had a child with recurrent wheezing, in contrast to 9.1% of mothers who took them between one to three years, and 12.3% who took oral contraceptives for more than six years, not finding any significant relation between oral contraceptives use and recurrent wheeze in the offspring (p=0.873).

Also, no statistically significant association was found between paracetamol consumption during pregnancy and infant recurrent wheeze (p=0.110). The 16.1% of mothers who occasionally took paracetamol throughout pregnancy had wheezing offspring, in contrast to 9.9% who never or less than once a month took it.

When complications during pregnancy and birth were studied, only hypertension disorders during pregnancy and prematurity at birth were positively related to recurrent wheeze in the offspring.

Among mothers who reported hypertension during pregnancy, 16.7% had a child who wheezed repeatedly in the first year of life, compared to 10.3% who did not suffer from hypertension disorders, finding a more than 2-fold significant higher risk for recurrent wheeze in their children (aOR=2.18; 95% CI 1.04-4.55).

On the other hand, 21.8% of premature infants wheezed repeatedly, compared to 9.7% of infants born full term, finding an almost 3-fold significant increased risk for recurrent wheeze in premature infants (aOR=2.69; 95% CI 1.34-5.40). (Table 20)

Table 20. Associations between exposures during pregnancy and birth and recurrent wheeze.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Mediterranean diet		0.285		
Wheezers	31.9±3.5		1 (reference)	1 (reference)
Non-wheezers	32.4±3.4		0.96 (0.89-1.03)	0.99 (0.91-1.09)
Oral contraceptives		0.873		
Never	59 (11.0)		1 (reference)	1 (reference)
Less than a year	5 (8.5)		0.75 (0.29-1.95)	0.55 (0.15-1.96)
One to three years	14 (9.1)		0.81 (0.44-1.50)	0.92 (0.46-1.84)
Four to six years	8 (8.8)		0.78 (0.36-1.70)	0.94 (0.37-2.36)
More than six years	16 (12.3)		1.14 (0.63-2.05)	1.29 (0.63-2.62)
Paracetamol		0.110		
Never/less than once a month	80 (9.9)		1 (reference)	1 (reference)
1-4 times a month	22 (16.1)		1.73 (1.04-2.89)	1.56 (0.84-2.90)
More than once a week	3 (9.4)		0.94 (0.28-3.15)	0.49 (0.08-2.92)
Complications				
None	-	-	1 (reference)	1 (reference)
Hypertension	13 (16.9)	0.075	1.77 (0.94-3.36)	2.18 (1.04-4.55)
Threatened miscarriage	7 (6.8)	0.195	0.59 (0.27-1.32)	0.49 (0.19-1.22)
Infections	16 (13.1)	0.375	1.30 (0.73-2.30)	1.21 (0.61-2.39)
Gestational diabetes	10 (15.2)	0.239	1.53 (0.75-3.10)	0.81 (0.31-2.15)
Malposition of the foetus	6 (19.4)	0.134	1.99 (0.80-4.99)	2.24 (0.71-7.02)
Premature rupture of membranes	9 (14.3)	0.401	1.37 (0.65-2.87)	0.66 (0.24-1.85)
Placenta problems	7 (14.0)	0.450	1.37 (0.60-3.15)	1.26 (0.46-3.40)
Hypoxia	5 (10.0)	1.000	0.93 (0.36-2.40)	0.56 (0.16-1.91)
Prematurity	17 (21.8)	0.001	2.59 (1.44-4.65)	2.69 (1.34-5.40)
Knots in umbilical cord	7 (6.7)	0.178	0.58 (0.26-1.29)	0.63 (0.26-1.55)
Obstetric trauma	0 (0.0)	1,000	-	-
Forceps/suction cup	18 (9.4)	0.493	0.83 (0.48-1.42)	0.77 (0.41-1.44)
Caesarean section	18 (11.4)	0.767	1.09 (0.63-1.87)	0.63 (0.30-1.33)

Severe wheeze

Statistical differences were found in several food groups when their consumption during pregnancy was studied.

The 20.0% of mothers who usually consumed snacks during pregnancy had a child who wheezed severely, compared to 12.3% who reported an occasional consumption, and 7.8% of mothers who never consumed them throughout pregnancy (p=0.005). Non-significant increased risks for severe wheeze in the offspring in those mothers who occasionally or frequently consumed snacks were observed (aOR=1.40; 95% CI 0.80-2.44, and aOR=2.17; 95% CI 0.86-5.49, respectively).

Moreover, although eggs consumption did not show statistical differences (p=0.081), both occasional and usual eggs consumption during pregnancy were found inversely related to infant severe wheeze (aOR=0.16; 95% CI 0.03-0.73, and aOR=0.11; 95% CI 0.02-0.52, respectively).

Adherence to the Mediterranean diet during pregnancy did not show statistical differences (p=0.208). Mothers who had children who wheezed severely scored a mean of 27.8 (±3.5) points, whereas those with healthy children scored 28.3 (±3.0) points.

The 8.9% of mothers who never took oral contraceptives had a child who wheezed severely, compared to 9.7% of mothers who took them between one to three years, and 7.7% who took them more than 6 years, not showing evidence of any statistically significant relation between oral contraceptives use and infant severe wheeze (p=0.555).

On the contrary, a significant association was detected between paracetamol consumption during pregnancy and severe wheeze in the offspring (p=0.011). The 8.5% of mothers who never (or less than once a month) took paracetamol had a child who wheezed severely, against 16.8% who occasionally took it, and three mothers (9.4%) who took paracetamol more than once a week. Marginally significant increased odds for severe wheeze in those infants whose mothers occasionally had paracetamol during pregnancy were observed (aOR=1.78; 95% CI 0.99-3.22).

When complications during pregnancy and birth were studied, no statistically significant associations were detected between any of the complications during pregnancy and birth and the onset of severe wheeze in the first year of life. Gestational diabetes, malposition of the foetus and prematurity showed the highest (although non-significant) odds for the onset of severe wheeze in the offspring.

In Table 21, the associations between exposures during pregnancy and birth and severe wheeze in the infant are shown.

Table 21. Associations between exposures during pregnancy and birth and severe wheeze.

	N (%) $\bar{x}$±SD	p value	Crude OR (95% CI)	Adjusted OR (95% CI)
Mediterranean diet		0.027		
Wheezers	31.4±4.0		1 (reference)	1 (reference)
Non-wheezers	32.4±3.3		0.92 (0.86-0.99)	0.99 (0.91-1.08)
Oral contraceptives		0.555		
Never	48 (8.9)		1 (reference)	1 (reference)
Less than a year	9 (15.3)		1.84 (0.85-3.97)	2.06 (0.90-4.71)
One to three years	15 (9.7)		1.10 (0.60-2.03)	0.97 (0.49-1.92)
Four to six years	9 (9.9)		1.12 (0.53-2.37)	1.40 (0.60-3.28)
More than six years	10 (7.7)		0.85 (0.42-1.73)	0.69 (0.30-1.62)
Paracetamol		0.011		
Never/less than once a month	68 (8.5)		1 (reference)	1 (reference)
One to four times a month	23 (16.8)		2.19 (1.31-3.65)	1.78 (0.99-3.22)
More than once a week	3 (9.4)		1.12 (0.33-3.78)	0.92 (0.22-3.76)
Complications				
None	-	-	1 (reference)	1 (reference)
Hypertension	8 (10.4)	0.807	1.10 (0.51-2.37)	1.04 (0.44-2.44)
Threatened miscarriage	10 (9.7)	0.960	1.02 (0.51-2.04)	1.16 (0.55-2.42)
Infections	13 (10.7)	0.693	1.13 (0.61-2.12)	1.04 (0.52-2.07)
Gestational diabetes	10 (15.2)	0.119	1.75 (0.86-3.57)	1.78 (0.78-4.10)
Malposition of the foetus	4 (12.9)	0.525	1.44 (0.49-4.23)	1.53 (0.46-5.06)
Premature rupture of membranes	6 (9.5)	0.991	1.00 (0.42-2.41)	0.98 (0.36-2.63)
Placenta problems	3 (6.0)	0.617	0.59 (0.18-1.94)	0.59 (0.16-2.09)
Hypoxia	2 (4.0)	0.218	0.37 (0.09-1.56)	0.38 (0.08-1.71)
Prematurity	11 (14.1)	0.163	1.62 (0.82-3.20)	1.52 (0.70-3.28)
Knots in umbilical cord	8 (7.7)	0.526	0.78 (0.37-1.67)	0.83 (0.37-1.87)
Obstetric trauma	0 (0.0)	1.000	-	-
Forceps/suction cup	12 (6.3)	0.083	0.57 (0.31-1.08)	0.60 (0.29-1.24)
Caesarean section	11 (7.0)	0.267	0.69 (0.36-1.33)	0.70 (0.34-1.46)

5. Discussion

The present study aimed to study the epidemiology of wheezing in infants in the region of Pamplona, a Spanish Northern city. Almost one third of infants in the sample wheezed in the first year of life, and nearly 10% wheezed repeatedly or suffered from severe wheeze. Male gender, pneumonia in the first year of life, infant eczema, higher number of colds, prenatal and postnatal exposure to tobacco smoke, presence of pets in the household, or nursery attendance, have been found as main risk factors for these wheeze phenotypes.

Prevalence

Prevalences of wheeze ever and recurrent wheeze in infants in the first year of life in the region of Pamplona were 32.5% and 10.6%, respectively. These figures are similar to others found in EISL Spanish centres. In Salamanca, the prevalence of wheeze ever was 32.3%, and 11.9% for recurrent wheeze (Pellegrini-Belinchon et al., 2012). In Cantabria, also a Northern region, 32.7% of infants wheezed in the first year of life, and 14.3% developed recurrent wheeze (Bercedo-Sanz et al., 2015).

In Northern coastal cities, as La Coruña or Bilbao, prevalences of wheeze ever were higher, 34.8% and 38.9%, respectively, while in Southern cities, the prevalence ranged from 28.7% in Valencia to 39.1% in Cartagena (Mallol et al., 2010b). These results, except for Valencia, are in line with a study that found outdoor relative humidity as risk factor in coastal cities (Garcia-Marcos et al., 2009).

Prevalence of severe wheeze in the region of Pamplona was 9.6%, lower than in Cartagena (16.2%), but similar to other centres, e.g., Cantabria (9.8%), Bilbao (10.3%) or La Coruña (11.3%) (Mallol et al., 2010b; Bercedo-Sanz et al., 2015).

The other European EISL centre, in Netherlands, found prevalences of wheeze ever and recurrent wheeze of 28.5% and 14.5%, respectively, also comparable with ours. However, prevalence of severe wheeze (15.4%) was higher than what was found in the region of Pamplona (Visser et al., 2010).

In Latin America, past studies found that 47.3% of infants had wheezed in the first year of life, 21.4% wheezed repeatedly, and 23.6% suffered severe wheezing episodes (Mallol et al., 2010b). More recently, a pooled analysis showed that the prevalence of wheezing in the first year of life in Latin American countries was 39.9%, with 16.6% of infants who wheezed repeatedly, and 17.6% suffering severe wheezing episodes (Mallol et al., 2016). In Argentina, 39% of infants had at least one wheezing episode in the first year of life, and of these, 33.0% were classified as recurrent wheezers (Teijeiro et al., 2016).

The above-cited evidence shows that prevalence of the disease in Latin America is higher than in Europe, and this could be due to several factors. One of the causes hypothesised to explain these differences were the multifactorial environment-gene interactions, distinctive in each region, which modulate airway responses from early life (Mallol et al., 2010b).

Also, differences in the prevalences could be attributed to socioeconomic factors. Garcia-Marcos *et al.* (2010) observed that low socioeconomic conditions had an important role in the higher prevalence of recurrent wheeze found in Latin America compared to Europe. In the same line, several studies showed evidence that children in low-income households had a higher risk for suffering from wheezing (Hafkamp-de Groen et al., 2013b), or a 2-fold increased risk of asthma in childhood (Kozyrskyj et al., 2010).

Other authors also found a relation between poverty and dirt, as household rodent infestation and infrequent cleaning of the house, and exposure to community violence, and an increased risk for wheezing (Barreto et al., 2010; Alves et al, 2012), sustaining the hypothesis that worse socioeconomic conditions might be one of the causes explaining the higher prevalence observed in Latin American countries.

Another possible reason could be the parasitic infection, which was positively related to the onset of wheeze in Brazilian children (Alcântara-Neves et al., 2010). Nevertheless, results are conflictive (Leonardi-Bee et al., 2006), and further studies are necessary to confirm this hypothesis.

Male gender

Our results showed significant differences in the prevalence of wheeze between boys and girls, showing evidence that male gender was a risk factor for all wheeze phenotypes. These findings agree with other studies in preschool populations, which also found male gender as a risk factor for wheeze in infants (Chong Neto et al., 2008; Venero-Fernandez et al., 2013). In a Dutch study, van Merode *et al.* (2007) observed gender differences, finding that boys significantly suffered more wheezing episodes, and more often presented for medical consultations.

One possible explanation for these gender differences could be genetic factors. Previous studies have described interactions between male sex and heredity of a family allergic disease, influencing in the appearance of wheezing at early ages (Melén et al., 2004). In addition, another study identified polymorphisms in the *IFGN* gene, which increased the risk of asthma in children, especially in those who had suffered from wheezing, while it was a protective factor in girls (Loisel et al., 2011).

Another reason for the higher prevalence of wheeze in boys could be the physiological differences in airways. Young *et al.* (2000) found in a healthy cohort that, in the first years of life, boys had lower airway flows than girls, with a significant gender influence. These findings are consistent with previous investigations finding differences in the lung function between boys and girls, with the latter having larger airways relative to their lungs than boys (Tepper et al., 1986).

Weight and height

In this study, low birth weight did not show any significant association with any wheeze outcome, in contrast to findings from several previous investigations. One of them described the relationship between low birth weight and wheezing, cough and respiratory infections, being significant between ages two and five, and showing the highest risk at four years old (Caudri et al., 2007).

A meta-analysis conducted by Mebrathu *et al.* (2015) also found low birth weight as a risk factor for wheeze, although no significant relation between the disease and high birth weight was detected.

The foetal origin hypothesis postulated that inadequate nutrition of the foetus determined the predisposition to suffer diseases in the future (Barker, 1990). In the same way, lung function in infants with low birth weight was significantly lower compared to infants with normal birth weight (Dezateux et al., 2004). It could be speculated that low weight at birth was related to an incorrect lung development, with consequences in the childhood.

When high weight at birth (infants who weighed more than 3,500 grams) was considered, no significant associations with any wheeze phenotypes were observed (data not shown), differing from the findings of a meta-analysis which found high birth weight as risk factor of asthma in infants (Flasherman and Rutherford, 2006). However, results are conflicting, with other studies describing a weak decrease in the risk of asthma and wheeze in children who weighed more than four kilograms at birth (Mebrathu et al., 2015b).

When weight gain (assessed as current weight) was studied, only statistical differences, but a non-significant increased risk for severe wheeze, were observed, contrasting to previous literature.

Results from a meta-analysis showed evidence that a major gain of weight was related to the onset of wheezing in preschool age, and with asthma in subsequent ages (Sonnenschein-van der Voort et al., 2014). Also, van der Gugten *et al.* (2012) found that a higher gain of weight in the first three months of life was associated with wheezing and worse lung function in childhood, independently of weight at birth. In a longitudinal study, a positive relation between weight and adiposity gain in the first year of life and wheeze in the first years of life was also observed (Pike et al., 2010).

Several studies have described higher adiposity, overweight and obesity in the first year of life as a risk factor for wheeze and recurrent wheeze (Taveras et al., 2008; Mebrathu et al., 2015c). According to child growth standards proposed by the World Health Organization, infant's weight in our sample was near the median, which might explain why overweight was not found associated with any wheeze disorders.

Higher height at birth and when the questionnaire was filled were in the statistical borderline to be considered as protective factors for wheeze ever. These findings seem to be in line with other studies describing a lower risk of wheeze at age three years in children with higher height growth rates (de Korte-de Boer et al., 2015), suggesting a relation between infant height and lung development.

Race

Neither race or ethnic group, nor offspring's or parental place of birth, were significantly associated with any wheeze phenotype. The lack of significant relations contrasts with previous findings. Panico and colleagues (2007) detected differences in a cohort study conducted in the United Kingdom. In their study, black race was found as risk factor for asthma and wheeze, while Bangladeshi children were less prone to these conditions than white race children at age three years.

Another English study found a significant lower prevalence and risk for wheeze in south Asian children in the first year of life compared to white race children, although between age two to four, the risk for wheeze was inverted (Kuehni et al., 2007). In the United States, differences were also observed in prevalence and severity of wheeze in black and Hispanics children and adolescents, as well as hospitalizations for this cause, higher in these ethnic groups compared to white children (Jones et al., 2008).

These differences could be attributed to several factors. Some studies have suggested a genetic role in racial differences, especially in people with African ancestry (Flores et al., 2012), whilst other authors pointed to an adverse socioeconomic environment as the main reason for the disparities (Smith et al., 2005; Cope et al., 2008; Beck et al., 2014).

When we analysed parental occupation and place of birth, statistical differences were detected. Most of foreign parents had low qualified jobs, with presumably lower salaries, which could lead to socioeconomic differences between Spanish and immigrant families (data not shown). Nonetheless, in this study, low participation of immigrant population could have biased our results. Therefore, it could be thought that higher number of participating immigrant families may had helped to minimize the probable existing sampling bias.

Quality of life

Our results showed that wheeze affected not only infant's, but also parental quality of life. Several studies agree with these observations. In the Generation R study, lower scores for quality of life in infants aged twelve months with asthma-like symptoms and their families were observed, especially if these were severe, concluding that infants with severe symptoms had a higher risk for low quality of life (Mohangoo et al., 2012). Furthermore, Hafkamp-de Groen *et al.* (2013) also found lower quality of life at four years old in children who reported wheeze, especially those who had persistent wheeze.

In schoolchildren, asthma severity was also related to lower quality of life, affecting both emotional function and activity limitation (Halterman et al., 2004). These findings support the hypothesis that wheeze and asthma not only were associated with lower quality of life, but also suggested that severity play a main role in children's and parental conditions of life.

Treatment

Although treatment with inhaled drugs and corticosteroids was strongly associated with every wheeze disorders, these results should be interpreted carefully. It could be thought that reverse causation led to these findings. Although the study's cross-sectional design not allow to confirm this hypothesis, it seem plausible to think that infants were treated because of their condition, and not that treatment led to the onset of wheeze.

Past studies have described the prevalence of use and effects of treatment in infancy. In two Brazilian EISL centres, the prevalences of use of inhaled corticosteroids were 18.5% and 24.3% (Alvim et al., 2011; Chong Neto et al., 2007b), higher than what was found in our study, possibly due to the higher prevalence of the disease in Latin American infants.

The use and efficacy of corticosteroids in the treatment of wheezing is still controversial. Some studies described a beneficial effect in children with asthma symptoms, with an increase of days with no symptoms (Roorda et al., 2001), and reduction in wheezing and asthma exacerbations, especially in asthmatic children (Castro-Rodriguez and Rodrigo, 2009).

Conversely, other studies did not found any effect in the progression from episodic to persistent wheezing, or in the natural course of asthma in children at high risk (Bisgaard et al., 2006; Guilbert et al., 2006), and a recent meta-analysis showed evidence that corticosteroids administration did not lead to lower hospital admissions, less need for additional systemic corticoids courses, shorter hospital length of stay, nor less unscheduled emergency department visits for asthma symptoms (Castro-Rodriguez et al., 2016).

On the other hand, although the questionnaire did not address antibiotic treatment, several authors have described a significant association between antibiotic treatment and risk for wheeze (Alm et al., 2008; Verhulst et al., 2008). Changes in the intestinal microflora due to antibiotics use could be the underlying cause of this increased risk (Verhulst et al., 2008).

Respiratory/allergy symptoms in the first year of life

Our findings showed that every asthmatic child had wheezed in the first year of life. Moreover, most of the children who were diagnosed with asthma by a physician had wheezed repeatedly or severely.

Wheeze is one of the manifestations of asthma. Thus, although a significant association have been detected, reverse causation should not be discarded. Asthma would not be a risk factor for wheeze, but the onset of wheeze would increase the risk of developing asthma.

Prior studies have assessed the association between wheezing and asthma. Among children with a parental history of asthma or allergy, frequent early wheezing (before three years) was strongly associated with asthma at age seven years (Ly et al., 2006). Kappelle and Brand (2012) found a higher risk for childhood asthma in children with severe episodic viral wheeze who needed hospitalization and had a family history of asthma.

Martinez *et al.* (1995) also suggested a relation between early wheezing episodes and predisposition to asthma in childhood. In the same Tucson Children's Respiratory Study, suffering from wheeze at six years of age (late onset wheezing and persistent wheezing) was found related to asthma in adolescence and early adulthood (Morgan et al., 2005; Stern et al., 2008).

Two factors were proposed to explain the connection between infant wheeze and asthma: viral respiratory tract infections and allergic sensitisation. The inflammatory responses to these agents may alter the structure and function of lung and airway tissues, leading to asthma (Holt and Sly, 2002; Holt et al., 2004).

Viral respiratory tract infections have been described as one of the major risk factors for wheeze in infants and preschool children, with convincing evidence supporting this relation (Busse et al., 2010).

Kusel *et al.* (2006) found rhinovirus as the most common respiratory pathogen, describing a higher risk for both upper and lower respiratory tract infections than RSV. In a Japanese study in children aged up to three years old hospitalised with lower respiratory tract infections, RSV and rhinovirus were detected in a higher percentage in patients who wheezed than in those without the condition, concluding these viruses were associated with wheeze in infants (Takeyama et al., 2014). Moreover, another prospective study described rhinovirus infection as the most important risk factor for recurrent wheeze among infants who had been hospitalised for bronchiolitis (Midulla et al., 2012).

Mommers *et al.* (2010), in the KOALA study, observed that infection-like symptoms in the first three months of life, including having a cold episode in early life, were related to wheezing in the first two years of life. Further evidence also described a higher risk of asthma at school ages in those children who suffered from virus-induced wheezing in infancy (Kotaniemi-Syrjänen et al., 2003; Puig et al., 2010).

In this study, pneumonia and higher number of colds were significantly related to the onset of wheeze ever, recurrent and severe wheeze, in line with the above-mentioned findings.

Some of the mechanisms suggested to explain the relationship between viral infections and the onset of wheeze and asthma were genetic factors (Caliskan et al., 2013), diminished neonatal lung function (van der Zalm et al., 2011), or immunologic factors, as imbalanced Th1/2 responses (Message et al., 2008).

In addition, a review by Gern and coworkers (2005) concluded that viral infections, due to viral damage and pro inflammatory responses, led to impairment in lung function, which could play causative role in the onset of wheeze.

On the other hand, only in those children who reported severe wheeze episodes, an older age of the first cold episode was found as protective factor. Previous studies described an age-dependent adaptive immune response, biased to Th2 response in children aged up to three months (Kristjansson et al., 2005). Thus, changes in the immune response at older ages seem to be a reasonable explanation to this finding.

Infant eczema was also found positively associated with every wheeze phenotype, being our findings consistent with previous literature. Several investigations have described a higher risk for wheeze, and 2-fold increased risk of asthma at school age, in infants who suffered from atopic dermatitis in the first months of life (Sangsupawanich et al., 2007; Saunes et al., 2012; Neuman et al., 2014).

Venero-Fernandez and coworkers (2013) found infant eczema as the largest risk factor for wheezing in a cohort of Cuban infants. Moreover, eczema was recently found in European EISL centres, but not in Latin American, related to a shorter period to the first wheeze episode (Pacheco-Gonzalez et al., 2016).

Several explanations could be proposed. Past studies showed evidence of higher IgE levels in children with atopic dermatitis (Perkin et al., 2004), strongly associated with airway responsiveness (Sears et al., 1991). Therefore, an IgE-mediated mechanism could be involved in the increased risk of wheeze in children who had eczema.

Other possible explanation could be the role of the atopic march, defined as the progression from atopic dermatitis to other allergic diseases, such as asthma (Zheng et al., 2011; Dharmage et al., 2014). In this progression, the occurrence of wheezing could be considered as the onset of early asthmatic symptoms. Nevertheless, in a study conducted by Illi *et al.* (2004), the atopic march was discarded when a co manifestation of early atopic dermatitis and wheezing, instead of the above-cited progression, was observed.

Exposure to tobacco smoke

Exposure to tobacco smoke has been described as a major risk factor for wheeze by many studies. Murray *et al.* (2004) found that both maternal smoking during pregnancy and postnatal exposure to tobacco smoke, increased the risk of wheezing in the first year of life. In the same line, in the Generation R study, conducted in Dutch children aged up to four years, Duijts and colleagues (2012) described a higher risk for wheeze in preschool ages in children exposed to tobacco smoke during pregnancy.

Also, a recent meta-analysis showed that prenatal maternal smoking was associated with a 40% significant increased risk of wheeze in the first two years of life, and postnatal maternal smoking, but not paternal, was significantly related to the onset of wheeze in early life (Burke et al., 2012).

In our study, smoking throughout pregnancy was marginally associated with wheeze ever, in accordance with previous findings, and non-significant higher risks were observed for recurrent and severe wheeze. In contrast, maternal postnatal smoking was not significantly associated with any wheeze outcome.

Several studies have found that in utero exposure to tobacco smoke affects lung growth and development, and is associated with reduced lung function (Gilliland et al., 2000; Wang et al., 2008). The greatest effect of smoking during pregnancy could therefore minimise the effect of postnatal maternal smoking, explaining the non-significant higher risk for wheeze in children whose mothers continued smoking after giving birth.

On the other hand, paternal smoking only showed a statistically significant association with the development of recurrent wheeze. This finding contrasts to other Spanish study underlining the influence of maternal postnatal smoking compared to paternal smoking on the development of respiratory symptoms (wheezing, cough) in children aged three to six years (Jurado et al., 2005).

Higher number of smokers in the household showed non-significant increased risks for both wheeze ever and severe wheeze, in contrast to other studies in which household environmental tobacco smoke was described as risk factor for wheezing (Tsai et al., 2010; Hunt et al., 2011).

Nonetheless, some inconsistencies in the data that may altered our results should be noted. Fifty parents (twenty mothers and thirty fathers) who reported being current smokers did not account themselves as smokers in the household. Although it might be a possible scenario, it could be thought that inconsistencies removal would reinforce the association between number of smokers in the household and the outcomes of interest.

Furthermore, although similar estimates in the assessment of environmental tobacco smoke risk for recurrent wheezing either using biomarkers or questionnaires were observed (Carlsten et al., 2012), it is worth mentioning that our data source were written questionnaires, and no biomarkers, as cotinine (Benowitz, 1999), were used to ascertain the exposure to environmental tobacco smoke, which could have provided more reliable information.

Family history of asthma and allergies

Many authors have described the link between parental history of asthma and allergies and the onset of wheeze and asthma in the offspring. In a prospective study in infants aged up to eighteen months, a parental history of asthma was positively associated with the incidence of lower respiratory tract illnesses with wheezing (Bosken et al., 2000).

In the same line, Pérez-Yarza *et al.* (2015), in a Spanish cohort of moderate-to-late preterm infants, also showed evidence that history of asthma in either parent was a risk factor for developing recurrent wheeze in the first year of life.

These findings contrast with ours, where only maternal history of asthma was found positively related to wheeze ever, and neither maternal nor paternal history of asthma were significantly associated with the development of recurrent nor severe wheeze, although non-significant increased risks were observed.

In a Swedish study conducted in schoolchildren, Bjerg *et al.* (2007) observed that both maternal and paternal history of asthma showed an increased risk for wheeze in childhood, and the greatest risk if both parents were asthmatics. Unfortunately, in our study only two infants had a parental history of asthma, and joint effect (maternal and paternal) could not be studied.

On the other hand, paternal and siblings' history of dermatitis were found as risks factor for wheeze ever and severe wheeze, respectively. Results from other EISL studies seem to be, at least partially, in line with our findings. Bessa *et al.* (2014) found a parental history of asthma as risk factor for occasional and recurrent wheezing, and history of dermatitis only for occasional wheezing. However, they evaluated the joint effect of parental history of atopy, whilst we studied maternal and paternal relations individually.

In this study, maternal history of asthma seemed to show a greater effect in the onset of wheeze ever and severe wheeze than paternal history. Prior studies also described a stronger association between maternal asthma and childhood asthma, especially in preschool children (Litonjua et al., 1998). More recently, a meta-analysis confirmed these findings, asserting that maternal asthma was a greater contributor for risk of asthma in the offspring than paternal asthma (Lim et al., 2010).

The results presented suggest the existence of a hereditary mechanism in the onset of wheeze and asthma in the offspring, corroborated by other investigations (Willemsen et al., 2008; Cantani and Micera, 2011). Further, several mechanisms have been proposed to explain the role of family history of asthma in the development of the disease in the offspring.

A review concluded that the influence of an allergic mother in the transition from a Th2 skewed immune response in the offspring during pregnancy to a non-allergic Th1 response after birth might play an important role, apart from other factors, such as environmental stimuli or breast milk factors, which also might contribute to the shaping of the newborn immune response (Barrett, 2008). Another described mechanism were epigenetic alterations due to maternal asthma, as DNA methylations of certain genes with potential importance in the development of asthma in the infant (Gunawardhana et al., 2014).

It is worth noting that in this study prevalences of asthma and rhinitis among parents were nearly 6% and 15%, respectively. These figures were lower than others observed in Spanish EISL centres, where asthma and rhinitis prevalences were above 10%, and nearly or over 20%, respectively (Garcia-Marcos et al., 2010). Although our findings showed a tendency towards significant increased risks, especially in the parental history of asthma, lower prevalences may suggest that these results underestimate the effect of family history of allergic diseases, and therefore should be interpreted with caution.

Socioeconomic factors

Socioeconomic determinants have a proven influence in the onset and evolution of diseases (Marmot, 2005). In this study, factors considered to be indicators of the socioeconomic background were maternal educational level and parental occupation, which showed a major impact in children's health related quality of life and risk of developing asthma in childhood (von Rueden et al., 2006; Kozyrskyj et al., 2010).

Conflictive results have been found in previous studies assessing the relationship between educational level and the onset of wheezing. On one hand, several authors have described a significant protective effect against wheeze and recurrent wheeze in infants and schoolchildren whose parents had a higher educational level (Dom et al., 2009; de Meer et al., 2010). In the UK Millenium Cohort Study, Taylor-Robinson *et al.* (2016) observed that lower maternal educational level was positively related to early and persistent wheeze in the crude analyses, but after adjustment, statistical significance was not reached.

On the contrary, Miyake and coworkers (2012) described a 2.4-fold increased risk for wheeze in Japanese schoolchildren whose mothers had fifteen or more years of education compared with those whose mothers studied for less than thirteen years.

In this study, only infants whose mothers studied twelve or more years but did not have a University degree showed lower risk for wheeze ever. Although declining trends were observed when maternal education level was higher, we could not detect the protective effects of maternal education described in other studies.

Nonetheless, when we recategorised maternal education level into two categories (low: <12 years; high: ≥12 years), significantly lower risk for wheeze ever and severe wheeze were observed when higher maternal educational level was reported (data not shown), in line with the positive role previously mentioned.

Our results did not show any significant association between parental occupation and any of the outcomes of interest. Moreover, when we recategorised occupations into three categories (white collar worker: executive, graduate, administrative assistant; blue collar worker: manual skilled, semi-skilled, non-skilled workers; others: other cases, not working), non-significant relations were also found (data not shown).

These findings contrast with other studies describing a significant association between parental occupations and (increased or decreased) risk of diagnosis of asthma in childhood (Li et al., 2009).

Other authors remarked the role of prenatal and/or postnatal maternal exposure to sensitisers, as latex, biocides or fungicides, which increased the likelihood of suffering from wheeze and asthma in childhood (Tagiyeva et al., 2010). Unfortunately, in the questionnaire, occupational categories were not accurate enough to determine parental jobs, therefore not enabling to evaluate possible exposures or risks which might be related to the development of infant wheeze.

It also could be thought that the lack of significant associations observed could be due to the existence of a universal access to medical care in those years, which could have attenuated the presumed negative effect in low income families.

Furthermore, none of the outcomes were significantly related to maternal age, in contrast to other studies, which described the protective role of having an older mother against the onset of asthma symptoms in the offspring (Ruijsbroek et al., 2011), whereas another Spanish study found in a cohort of newborns that younger maternal age was inversely associated with wheeze in the offspring in the first six months of age (Pérez-Tarazona et al., 2010).

In this sample, over 90% of mothers were older than twenty-eight years old. Although younger maternal age is likely to be associated with worse lifestyle habits associated with wheeze disorders in the offspring, the fact that most of the women were near or in their thirties could explain why maternal age showed a diminished role.

Nursery attendance

Nursery attendance was found as risk factor for both wheeze ever and recurrent wheeze in the first year of life. These findings are supported by some previously published investigations, although role of nursery attendance in the onset of the disease is still conflictive.

In a Swedish study in children aged one to six years old, current wheeze was significantly related to nursery attendance, especially in the first years of life (Hagerhed-Engman et al., 2006). Moreover, other prospective longitudinal studies found similar results. Celedón *et al.* (2002) showed evidence of an increased risk for wheeze associated with nursery attendance only in the first year of life, which became non-significant in subsequent years, while in the PIAMA birth cohort study, early nursery attendance was positively associated with wheeze in the first year of life, observing a decreasing risk trend with age (Caudri et al., 2009).

Conversely, in the Tucson Children's Respiratory Study, Ball *et al.* (2000) only found attending nursery during the first six months of life positively related to the development of frequent wheeze at two years of age, whereas in older ages it was a protective factor for the onset of asthma.

In the same line, more recent research has also shown evidence that nursery attendance was associated with a reduced risk of current wheeze at age five years among British children (Nicolau et al., 2008).

The exposure to an infectious environment and the contact with other children could be the reasons of the increased risk observed in our study. Several investigations have found that children attending to nursery were at high risk for suffering from respiratory tract infections (Marbury et al., 1997; Sun and Sundell, 2011), previously stated as a main risk factor for wheeze. This assertion contrast with the "hygiene hypothesis", which stated that early life infections might confer protection against allergies (Strachan, 1989).

Only among those infants who developed recurrent wheeze, age of entry to nursery showed statistical differences, observing a non-significant increased risk in those children who started attending nursery at older ages. These findings seem to be in line with other investigation which found older age at entry to nursery as risk factor for atopic outcomes during childhood (Krämer et al., 1999), due to protection conferred by early infections against allergies in older ages.

However, in this latter study, the reference age of entry was 6 to 11 months, and was compared to children who began attending at ages 12-23 months and 24 months and older, differing substantially from our study, where mean age for both wheezing and healthy infants was below six months of age, thus a hypothetical harmful effect of older age of entry may have been diminished.

Pet ownership

Overall, our findings seem to show higher odds for the onset of wheeze disorders when families reported presence of pets in the household, both during pregnancy and when the questionnaire was filled, although significant associations were only detected for wheeze ever and severe wheeze. Presence of dogs or cats, the most common pets, were not significantly related to the development of any wheeze phenotype. Unexpectedly, despite the lack of significant associations, having more than one pet showed more than 3-fold increased risk for recurrent wheeze.

When the literature was revised, inconsistencies when assessing the effect of pets keeping in wheeze and asthma outcomes in childhood were observed. In Mexican American children, in utero exposure to cats, dogs and birds was found positively related to wheeze and asthma in infancy and adolescence (Eldeirawi et al., 2016).

On the other hand, in a systematic review conducted by Apelberg and colleagues (2001), they concluded that exposure to pets showed a non-significant protective effect for wheeze and asthma at younger ages, but increased risk in older children. More recently, another meta-analysis did not find any significant association between any type of pet ownership during the first two years of life and asthma in schoolchildren (Lodrup Carlsen et al., 2012).

In a Canadian prospective study, Carlsten *et al.* (2011) showed evidence that early exposure to dog, along with elevated indoor pollution or exposure to tobacco smoke, also increased the risk for asthma in infancy in a high-risk birth cohort.

Presence of dogs, rabbits or birds during pregnancy and any pet ownership in early life was found positively associated with wheeze only in the first months of life, but not at subsequent ages, in an UK birth cohort (Collin et al., 2015).

In this latter study, rabbit and rodent ownership showed an overall higher risk for wheeze, whereas presence of cats was a protective factor, in line with other studies (Celedón et al., 2002b). On the other hand, in the Tucson Chidren's Respiratory Study, Remes *et al.* (2001) found an inverse association between dog exposure in infancy, but not cat, and risk of suffering from frequent wheeze.

This great inconsistency was attributed to the questions used to assess self-reported pet exposure in questionnaires, which showed a great variation across studies (Apfelbacher et al., 2016).

As stated before, overall, our findings suggest a higher risk for wheeze in those children exposed to pets. Sensitisation to animal allergens has been described by several studies as one major risk factor for asthma (Rönmark et al., 2003; Korppi et al., 2008; Uddenfeldt et al., 2013; Bjerg et al., 2015). Therefore, one reasonable explanation could be that presence of pets in the household increased indoor pet allergens, leading to infant's sensitisation to those allergens, who consequently showed an increased risk for developing wheeze disorders.

It also should be noted the probable existence of bias resultant of avoidance of pet ownership in families with history of asthma or allergies, or whose children wheezed in the first months of life, which might have underestimated the effects of presence of pets.

Household environmental conditions

To assess the effect of household indoor air quality, fuel used for heating and cooking were studied. The exposure to fume emitting heaters in the first year of life has been found consistently associated with wheeze and asthma in schoolchildren (Phoa et al., 2004). In addition, improving home heating (to non-polluting heating) led to a reduction of asthma symptoms and was associated with improved children wellbeing (Howden-Chapman et al., 2008). These findings contrast with ours, which did not show any significant relation between any wheeze outcome and domestic heating.

On the other hand, some investigations showed evidence that use of gas and a gas hob for cooking was positively related to an increased risk for childhood wheeze (de Bilderling et al., 2005), whilst others did not find any association neither with wheeze nor asthma (Willers et al., 2006). More recently, in a meta-analysis, Lin *et al.* (2013) concluded that only increased indoor dioxide of nitrogen levels was associated with higher risk for wheeze, but no increased risk in children who had been exposed to gas cooking was observed.

In our study, no statistical associations were detected, in line with these latter findings. The fact that most of the families in our sample had central heating in their dwellings, and used electricity for cooking, could be the reason of the lack of statistical associations found.

The presence of infants in dwellings with carpeted floor was very limited in our study sample. In contrast to our findings, where no significant relation was detected, other authors described an almost 40% increased risk for wheeze and severe wheeze in infants living in dwellings with carpet covered floor, due to higher exposure to house-dust mites or chemical-mediated mechanisms (Herr et al., 2012).

Likewise, dampness and mould stains did not show significant associations with any wheeze phenotype, contrasting with previous findings. A meta-analysis including eight European birth cohorts concluded that infants exposed to mould and/or dampness were at significant increased risk of asthma at preschool ages (Tischer et al., 2011). In the CCHH study conducted in Shanghai (China), a positive relation between wheeze and dampness exposure was also observed, showing a clear dose-response relationship between dampness indicators and airway symptoms (Hu et al., 2014).

Furthermore, Visser *et al.* (2010), in the European EISL study conducted in Netherlands also found a strong association between damp housing and each wheeze phenotype, especially severe wheeze (defined in that study as wheezing which needed hospitalization). Nevertheless, the lower number of families reporting damp or mould stains in our sample compared to these studies could have masked a significant association with the outcomes of interest.

Air pollution has also been described as risk factor for wheeze in the preschool ages. Oxidative stress or the promotion of inflammatory responses were some of the mechanisms proposed as causes of the adverse health effects (Bernstein et al., 2004).

In a prospective birth cohort study, infants exposed to either moving or stop-and-go traffic showed an increased risk for wheeze in the first year of life compared to those unexposed (Ryan et al., 2007). In the same study, higher risk persisted at three years of age, and accentuation of the effect of exposure to traffic-related particles in children coexposed to high levels of endotoxin in the home, was observed (Ryan et al., 2009).

Also, Sonnenschein-van der Voort and colleagues (2012) described a significant relation between exposure to higher traffic-related air pollutants and wheeze in the first years of life, although only in those children exposed to tobacco smoke during fetal and infant life.

In contrast with previously published, in this study no significant associations between air pollution and any wheeze phenotype have been observed. However, in the questionnaire, families were asked for their personal perception of living in an air polluted area, and no objective measurements were conducted.

Therefore, it is plausible to think that the lack of mechanisms to measure air quality might have led to reporting bias, thus our results should be interpreted carefully.

Presence of older siblings was significantly related to the onset of wheeze ever and severe wheeze, although only the first showed a marginally increased risk. These findings contrast with previous investigations which did not show evidence of any relation between sibship size or birth order and asthma, although this condition seemed to be less prevalent in families with more children (Bernsen et al., 2003). Recently, Wu *et al.* (2016) also found a 15% significant decrease in risk for asthma in preschool children with every additional sibling at home. These investigations considered the hygiene hypothesis (Strachan, 1989) explained the lower risk observed. Conversely, in a French birth cohort study, presence of siblings was significantly associated with an increased risk for mild and severe wheeze (Herr et al., 2012).

The contradictions among previous findings could be due to differences in the outcome studied and the age of the sample. Presence of siblings could be related to higher odds for suffering respiratory infections, triggering wheeze in the first months of life. However, in most children, wheezing at early ages is a transient condition, and in subsequent ages, this exposure to pathogens might confer protection against asthma.

On the other hand, only wheeze ever was found significantly associated with living in a crowded household, although non-significant increased risk after adjustment was observed. In contrast to our findings, Cardoso *et al.* (2004) described a strong reduction in the incidence of asthma in crowded houses, in line with the above-mentioned hygiene hypothesis.

Nonetheless, some facts should be considered. In our study, less than 10% of infants lived with five or more people, and only ten families could be considered as living in crowded households (seven or more people), which may have led to underestimate the effect of crowding.

Breastfeeding

The role of breastfeeding in relation to wheeze and asthma-related symptoms has not been completely elucidated. While some authors reported an increased risk in those children who were longer breastfed (Wright et al., 2001), others did not find any relation between breastfeeding duration and onset of wheeze or asthma or being hospitalised for these conditions (Miyake et al., 2008; Leung et al., 2016).

Nonetheless, there is sufficient evidence supporting the protective effects of longer breastfeeding in wheeze disorders. Compared to longer exclusive breastfeeding or breastfeeding for more than six months, shorter periods of exclusive breastfeeding and never breastfeeding were positively associated with risk of asthma symptoms (Sonnenschein-van der Voort et al., 2012b). More recently, Dogaru *et al.* (2014) conducted a meta-analysis including one hundred thirteen studies, concluding that breastfeeding was strongly associated with lower risk of developing asthma.

In this line, our findings also showed a decreased risk for both wheeze ever and severe wheeze, and a non-significant lower risk for recurrent wheeze. When we dichotomised the variable into breastfeeding at least six months or less than six months, infants who were breastfed for a longer period showed a decreased risk, although did not reach statistical significance for any wheeze outcome.

Discrepancies found in the literature may be related to a widely proven protective effect of longer breastfeeding in early childhood, which gradually disappear in subsequent years. Supporting this statement, Guibas *et al.* (2013), in two studies with preschoolers and preadolescents, only observed a protective effect in younger children.

Several investigations described a protective role of breast milk against the development of respiratory tract infections (Duijts et al., 2010; Tarrant et al., 2010; Yamakawa et al., 2015), a well-established risk factor for wheeze in early life, possibly via its antimicrobial properties and promoting infant's immune system development and maturation (Hanson et al., 2002; Field, 2005), which could explain the lower risk observed in infants who breastfed for a longer period.

Further, when industrial infant food consumption frequency was studied, interpreting it as a weaning assessment, only a significant relation with severe wheeze was observed, although the lower risk observed in those infants who consumed industrial infant food once a month seem to be related to the small number of subjects in this group, thus this finding should be interpreted carefully. When consumption frequencies were dichotomised (never and once a month versus once a week and everyday), a non-significant increased risk in those children who often consumed industrial infant foods in the first year of life was observed (data not shown). Overall, these findings stressed the importance of longer breastfeeding.

Diet and adherence to the Mediterranean diet during pregnancy

When dietary components were studied individually, statistical differences in fruit, potatoes, snacks and eggs intake were observed. Frequent consumption of fruit was related to non-significant decreased risks for wheeze ever and recurrent wheeze, whilst higher intake of eggs during pregnancy was inversely associated with severe wheeze. Conversely, both frequent intake of potatoes and snacks were related to higher, although non-significant, risks for wheeze ever and severe wheeze, respectively.

Several past studies have assessed the role of maternal diet during pregnancy in offspring respiratory outcomes. Miyake *et al.* (2010) did not find a protective role for infant wheeze in higher intake of fruit and vegetables, in agreement with our findings, although an inverse relationship with vitamin E intake was described. Oily fish, especially in non-breastfed children, have been inversely associated with atopic and persistent wheeze in childhood (Romieu et al., 2007), whereas in another Spanish EISL centre, occasional meat consumption and avoiding eating pasta during pregnancy were also protective factors for wheeze in the first years of life (Castro-Rodriguez et al., 2016b). However, none of these latter findings were shown in our study.

In this questionnaire, potatoes food group also included chips (French fries), which could be considered as an unhealthy dietary component (as well as the snacks group), explaining the increased risks observed.

On the other hand, frequent eggs intake during pregnancy was associated with decreased risk for severe wheeze in the offspring. This finding, due to be a well-known allergenic food, seems contradictory, and thus this result should be interpreted with caution.

The health benefits of the Mediterranean dietary pattern have been widely studied, reporting a nearly 50% decreased risk for wheeze in preschool children who greatly adhered to the Mediterranean diet (Castro-Rodriguez et al., 2008). However, better adherence to this diet in pregnant women showed non-conclusive findings. While some studies found higher adherence to the Mediterranean diet not significantly associated with wheeze in the first year of life (Chatzi et al., 2013), supporting our findings, others showed evidence of a protective effect against persistent wheeze in childhood (Chatzi et al., 2008).

In contrast to previous research finding olive oil use for cooking or dressing salads during pregnancy as protective factor (Castro-Rodriguez et al., 2010b), in this study no statistical relation was observed, even when the variable was recategorised into olive oil as main source versus other oils and butter/margarine (data not shown).

Assessment of the adherence to the Mediterranean diet had some limitations, and in this regard, some facts should be noted. First, recall bias should not be excluded. Secondly, the food-frequency questionnaire used only allowed a gross estimation, as only the frequency, but not the portion sizes, were ascertained, and no further adjustments (e.g., energy intake) were conducted. Thirdly, the variability in scores used to measure adherence could be another reason of the differences observed with other studies (Milà-Villaroel et al., 2011).

Moreover, in this study sample, maternal education, occupation and maternal age were found as factors which influence the adherence to the Mediterranean diet during pregnancy (Álvarez-Álvarez et al., 2015). However, no significant differences in these factors were observed, explaining the lack of statistical differences in the adherence to the Mediterranean dietary pattern.

Oral contraceptives and paracetamol

When oral contraceptive pills use before pregnancy was examined, no significant associations were observed for any wheeze phenotype. In line with these findings, in a large Norwegian pregnant cohort, Hancock *et al.* (2011) neither found statistical associations between oral contraceptive pills use and respiratory outcomes, including lower tract respiratory infections, wheezing, or asthma.

In the same line, inconclusive findings were shown in another study describing a slightly higher risk for asthma if oral contraceptives were used within six months before pregnancy, but non-significant risk if use was within the two years before conception (Osman et al., 2009).

On the contrary, recently, in a Japanese study, maternal use of oral contraceptive pills, especially for more than three months, was positively associated with infant wheeze (Yamamoto-Hanada et al., 2016). Therefore, the role of oral contraceptives during pregnancy and its relation with wheeze outcomes remains controversial.

Further, underlying mechanisms remain unclear. Some authors hypothesised that predisposition to asthma in the offspring could be due to immunomodulatory mechanisms during pregnancy (Wjst and Dold, 1997), whereas epigenetic causes, via DNA methylation of specific genes, were recently proposed as a plausible cause (Guthikonda et al., 2014).

The effect of prenatal paracetamol exposure and wheeze in early life has also been studied by several studies. Shaheen *et al.* (2002), in the ALSPAC study, reported an increased risk of persistent wheezing when paracetamol use during early pregnancy was frequent. Also, prenatal exposure to paracetamol was found positively associated with infant wheeze in other European cohorts in more recent studies (Rebordosa et al., 2008; Goksör et al., 2011).

Interestingly, Garcia-Marcos *et al.* (2009b), when investigated the effect of paracetamol during pregnancy stratifying for maternal asthma, only found a significant increased risk of wheezing in offspring of non-asthmatic mothers. Overall, our findings, showing an increased risk for wheeze and severe wheeze in infants whose mothers occasionally took paracetamol during pregnancy, seem to be in line with the literature.

The harmful effect of paracetamol use could be mediated by oxidative damage due to the impairment of respiratory antioxidant defences (reduced gutathione) (Nuttall et al., 2003), or by modulating glutathione levels on Th1-Th2 cytokine response patterns (Dimova et al., 2005). Other studies have proposed confounding as an explanation of the association between paracetamol use in pregnancy and wheezing in infants (Migliore et al., 2015). Nevertheless, in this study we adjusted for a wide range of confounders, thus, although it should not be discarded, this latter hypothesis does not seem very plausible.

Complications during pregnancy

Gestational diabetes, maternal hypertension, malposition of the foetus and prematurity were the complications throughout pregnancy which showed the highest odds for wheeze disorders in infants.

In agreement with our findings, Zugna and colleagues (2015), in a pooled analysis of fourteen birth cohorts, showed that hypertensive disorders, and particularly preeclampsia, were related to an increased risk of developing recurrent wheeze, while diabetes showed a non-significant increased risk.

Hypertension was also related to transient, late-onset and persistent wheezing in childhood in an Italian study, whereas diabetes showed a marginally increased risk for persistent wheezing, and urinary tract infections during pregnancy were positively associated with transient wheezing, differing these latter findings with ours (Rusconi et al., 2007). In the ALSPAC study, gestational hypertension was not related to wheeze at eighteen months of life, whilst preeclampsia showed a weak association with early wheezing (Shaheen et al., 2016).

It should be mentioned that, in the questionnaire, it was not specified if hypertension term included other related disorders, as preeclampsia, and this fact should be considered when interpreting the results.

In our study, prematurity showed increased risks for all wheeze disorders, although only reached statistical significance for recurrent wheeze. Previous evidence seems to be in line with these findings (Kumar et al., 2008; Robison et al., 2012). Abnormalities of the small airways in prematurely born infants may explain the link with the onset of wheeze in the first months of life (Broughton et al., 2007).

In a longitudinal prospective study, Annesi-Maesano *et al.* (2001) showed evidence of the relation between malpresentation of the foetus at birth and a significant increase of asthma in the child. Although in this study malposition showed higher odds for both wheeze ever and recurrent wheeze, no statistical significance was reached, and wide confidence intervals were shown, probably due to the small number of mothers who reported this complication.

Delivery via caesarean section showed a non-significant decreased risk for all wheeze phenotypes, contrasting to prior evidence. Caesarean delivery was found positively associated with development of asthma in the first years of life (Davidson et al., 2010; Magnus et al., 2011).

Some studies have proposed that exposure to vaginal bacteria lead to colonization by bacteria from the mother's birth canal and perianal region, instead of bacteria from hospital environment, conducting to different immune system maturation (Huurre et al.,2008; Cho and Norman, 2013), explaining the higher risk observed in children delivered by cesarean section, although it was not reflected in our results.

Strengths and limitations

One of the strengths of this study was the large number of variables studied (demographic, environmental or family background, among others), which guarantee a wide focus on studying wheeze disorders. In addition, a validated questionnaire, a well-recognised tool, was used.

Another strength was the fact that, as part of the EISL multicentre project, the results obtained enable to make national and international comparisons with other European and Latin American centres, providing a framework for future research.

However, several limitations should be addressed. The main limitation of the study is its low participation rate. Nearly one third of the families participated in the study (32.4%). Compared to other EISL centres, in Zwolle (Netherlands) the participation rate was 81% (Visser et al., 2010), and in most Spanish centres was over 70% (Garcia-Marcos et al., 2010). This low participation rate may have led to a sampling bias, and its consequences should be acknowledged.

One of the possible reasons of this participation rate could be the low participation of foreign population. More than 90% of parents had born in Spain. However, according to the data from the Navarre Statistical Office (Navarre Statistical Office webpage), between 2006 and 2008, about 20% of births in Navarre were from foreign mothers, thus their low participation had a notable effect.

Another possible cause was the inability to make phone calls or send reminder letters to participants, to obey the data protection law and authorizations, which could have helped increasing the participation rate.

In this study, self-reported information was used, although is prone to reporting bias. Nevertheless, questionnaires were filled when infants aged 12-15 months, and a diminished impact of reporting bias should be expected. Finally, the cross-sectional study design not allowed studying causality, and should also be pointed out as a weakness.

6. Conclusions

1. Prevalence of wheeze ever in infants in the region of Pamplona was 32.5%. Prevalences of recurrent wheeze and severe wheeze in the first year of life were 10.6% and 9.6%, respectively.

2. Prevalences found in this study were comparable to those in other EISL European centres, but were lower than those observed in Latin American centres.

3. Male gender, pneumonia, infant eczema, higher number of colds, smoking during pregnancy, maternal history of asthma, or paternal history of dermatitis, were identified as risk factors for wheeze ever in the first year of life.

4. Also, nursery attendance, presence of pets in the household when the questionnaire was filled, higher number of siblings, and paracetamol consumption during pregnancy were found as risk factors for wheeze ever in infants.

5. Male gender, pneumonia, infant eczema, higher number of colds, smoking father, nursery attendance, hypertension during pregnancy and prematurity were risk factors for recurrent wheeze in infants.

6. Male gender, pneumonia, infant eczema, higher number of colds, history of dermatitis in siblings, presence of pets during pregnancy and when the questionnaire was filled, and paracetamol consumption during pregnancy were risk factors for severe wheeze.

7. Higher height at birth, and longer exclusive breastfeeding were identified as protective factors for wheeze ever. Older age when suffering the first cold, and longer exclusive breastfeeding were protective factors for severe wheeze. No protective factors were found for recurrent wheeze.

8. This study reflects that wheezing in infants is a common disease which affects both infant and parental quality of life, and can lead to asthma in subsequent ages. Several preventable risk factors, such as household and environmental factors, have been identified.

7. References

Alcântara-Neves NM, Badaró SJ, dos Santos MC, Pontes-de-Carvalho L, Barreto ML. (2010). The presence of serum anti-*Ascaris lumbricoides* IgE antibodies and of *Trichuris trichiura* infection are risk factors for wheezing and/or atopy in preschool-aged Brazilian children. *Respir Res*, 11, 114.

Allander T, Jartti T, Gupta S, Niesters HG, Lehtinen P, Österback R, et al. (2007). Human bocavirus and acute wheezing in children. *Clin Infect Dis*, 44(7), 904-910.

Alm B, Erdes L, Möllborg P, Pettersson R, Norvenius SG, Aberg N, et al. (2008). Neonatal antibiotic treatment is a risk factor for early wheezing. *Pediatrics*, 121(4), 697-702.

Álvarez Álvarez I, Aguinaga Ontoso I, Marín Fernández B, Guillén Grima F, Niu H. (2015). Estudio transversal de los factores que influyen en la adhesión a la dieta mediterránea en el embarazo. *Nutr Hosp*, 31(4), 1845-1852.

Alves G da C, Santos DN, Feitosa CA, Barreto ML. (2012). Community violence and childhood asthma prevalence in peripheral neighborhoods in Salvador, Bahia State, Brazil. *Cad Saude Publica*, 28(1), 86-94.

Alvim CG, Nunes S, Fernandes S, Camargos P, Fontes MJ. (2011). Oral and inhaled corticoid treatment for wheezing in the first year of life. *J Pediatr (Rio J)*, 87(4), 314-318.

Andersen ZJ, Loft S, Ketzel M, Stage M, Scheike T, Hermansen MN, et al. (2008). Ambient air pollution triggers wheezing symptoms in infants. *Thorax*, 63(8), 710-716.

Annesi-Maesano I, Moreau D, Strachan D. (2001). In utero and perinatal complications preceding asthma. *Allergy*, 56(6), 491-497.

Apelberg BJ, Aoki Y, Jaakkola JJ. (2001). Systematic review: exposure to pets and risk of asthma and asthma-like symptoms. *J Allergy Clin Immunol*, 107(3), 455-460.

Apfelbacher C, Frew E, Xiang A, Apfel A, Smith H. (2016). Assessment of pet exposure by self-report in epidemiological studies of allergy and asthma: a systematic review. *J Asthma*, 53(4), 363-373.

Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. (1995). International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*, 8(3), 483-491.

Asher MI, Weiland SK. (1998). The International Study of Asthma and Allergies in Childhood (ISAAC). *Clin Exp Allergy*, 28(Suppl 5), 52-66.

Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. (2000). Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med*, 343(8), 538-543.

Barker DJ. (1990). The fetal and infant origins of adult disease. *BMJ*, 301(6761), 1111.

Barreto ML, Cunha SS, Fiaccone R, Esquivel R, Amorim LD, Alvim S, et al. (2010). Poverty, dirt, infections and non-atopic wheezing in children from a Brazilian urban center. *Respir Res*, 11, 167.

Barrett, EG. (2008). Maternal influence in the transmission of asthma susceptibility. *Pulm Pharmacol Ther*, 21(3), 474-484.

Beck AF, Huang B, Simmons JM, Moncrief T, Sauers HS, Chen C, et al. (2014). Role of financial and social hardships in asthma racial disparities. *Pediatrics*, 133(3), 431-439.

Benowitz NL. (1999). Biomarkers of environmental tobacco smoke exposure. *Environ Health Perspect*, 107(Suppl 2), 349-355.

Bercedo-Sanz A, Lastra-Martínez L, Pellegrini-Belinchón J, Vicente-Galindo E, Lorente-Toledano E, García-Marcos L. (2015). Wheezing and risk factors in the first year of life in Cantabria, Spain. The EISL study. *Allergol Immunopathol (Madr)*, 43(6), 543-552.

Bernsen RM, de Jongste JC, van der Wouden JC. (2003). Birth order and sibship size as independent risk factors for asthma, allergy, and eczema. *Pediatr Allergy Immunol*, 14(6), 464-469.

Bernstein JA, Alexis N, Barnes C, Bernstein IL, Bernstein JA, Nel A, et al. (2004). Health effects of air pollution. *J Allergy Clin Immunol*, 114(5), 1116-1123.

Bessa OA, Leite AJ, Solé D, Mallol J. (2014). Prevalence and risk factors associated with wheezing in the first year of life. *J Pediatr (Rio J)*, 90(2), 190-196.

Bisgaard H, Hermansen MN, Bonnelykke K, Stokholm J, Baty F, Skytt NL, et al. (2010). Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. *BMJ*, 341, c4978.

Bisgaard H, Hermansen MN, Buchvald F, Loland L, Halkjaer LB, Bonnelykke K, et al. (2007). Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med*, 357(15), 1487-1495.

Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. (2006). Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med*, 354(19), 1998-2005.

Bisgaard H, Szefler S. (2007). Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol*, 42(8), 723-728.

Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, et al. (2005). Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med*, 171(4), 315-322.

Bjerg A, Hedman L, Perzanowski MS, Platts-Mills T, Lundbäck B, Rönmark E. (2007). Family history of asthma and atopy: in-depth analyses of the impact on asthma and wheeze in 7- to 8-year-old children. *Pediatrics*, 120(4), 741-748.

Bjerg A, Winberg A, Berthold M, Mattsson L, Borres MP, Rönmark E. (2015). A population-based study of animal component sensitization, asthma, and rhinitis in schoolchildren. *Pediatr Allergy Immunol*, 26(6), 557-563.

Bosken CH, Hunt WC, Lambert WE, Samet JM. (2000). A parental history of asthma is a risk factor for wheezing and nonwheezing respiratory illnesses in infants younger than 18 months of age. *Am J Respir Crit Care Med*, 161(6), 1810-1815.

Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. (2008). Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J*, 32(4), 1096-1110.

Brand PL, Caudri D, Eber E, Gaillard EA, Garcia-Marcos L, Hedlin G, et al. (2014). Classification and pharmacological treatment of preschool wheezing: changes since 2008. *Eur Respir J*, 43(4), 1172-1177.

Bröms K, Norbäck D, Sundelin C, Eriksson M, Svärdsudd K. (2012). A nationwide study of asthma incidence rate and its determinants in Swedish pre-school children. *Eur J Epidemiol*, 27(9), 695-703.

Broughton S, Thomas MR, Marston L, Calvert SA, Marlow N, Peacock JL, et al. (2007). Very prematurely born infants wheezing at follow-up: lung function and risk factors. *Arch Dis Child*, 92(9), 776-780.

Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. (2012). Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics*, 129(4), 735-744.

Burke W, Fesinmeyer M, Reed K, Hampton L, Carlsten C. (2003). Family history as a predictor of asthma risk. *Am J Prev Med*, 24(2), 160-169.

Busse WW, Lemansje RF Jr, Gern JE. (2010). Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet*, 376(9743), 826-834.

Caliskan M, Bochkov YA, Kreiner-Moller E, Bonnelykke K, Stein MM, Du G, et al. (2013). Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med*, 368(15), 1398-1407.

Cantani A, Micera M. (2011). A study on 300 asthmatic children, 300 controls and their parents confirms the genetic transmission of allergy and asthma. *Eur Rev Med Pharmacol Sci*, 15(9), 1051-1056.

Cardoso MR, Cousens SN, de Góes Siqueira LF, Alves FM, D'Angelo LA. (2004). Crowding: risk factor or protective factor for lower respiratory disease in young children? *BMC Public Health*, 4, 19.

Carlsten C, Brauer M, Dimich-Ward H, Dybuncio A, Becker AB, Chan-Yeung M. (2011). Combined exposure to dog and indoor pollution: incident asthma in a high-risk birth cohort. *Eur Respir J*, 37(2), 324-330.

Carlsten C, Dimich-Ward H, DyBuncio A, Becker AB, Chan-Yeung M. (2012). Cotinine versus questionnaire: early-life environmental tobacco smoke exposure and incident asthma. *BMC Pediatr*, 12, 187.

Carvajal-Urueña I, García-Marcos L, Busquets-Monge R, Suárez-Varela MM, García de Andoin N, Batlles-Garrido J, et al. (2005). Geographic variation in the prevalence of asthma symptoms in Spanish children and adolescents. International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3, Spain. *Arch Bronconeumol*, 41(12), 659-666.

Castro-Rodriguez JA, Beckhaus AA, Forno E. (2016). Efficacy of oral corticosteroids in the treatment of acute wheezing episodes in asthmatic preschoolers: systematic review with meta-analysis. *Pediatr Pulmonol*, 51(8), 868-876.

Castro-Rodriguez JA, Garcia-Marcos L, Alfonseda Rojas JD, Valverde-Molina J, Sanchez-Solis M. (2008). Mediterranean diet as a protective factor for wheezing in preschool children. *J Pediatr*, 152(6), 823-828.

Castro-Rodriguez JA, Garcia-Marcos L, Sanchez-Solis M, Pérez-Fernández V, Martinez-Torres A, Mallol J. (2010). Olive oil during pregnancy is associated with reduced wheezing during the first year of life of the offspring. *Pediatr Pulmonol*, 45(4), 395-402.

Castro-Rodríguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. (2001). Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med*, 163(6), 1344-1349.

Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. (2000). A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*, 162(4Pt1), 1403-1406.

Castro-Rodriguez JA, Ramirez-Hernandez M, Padilla O, Pacheco-Gonzalez RM, Pérez-Fernández V, Garcia-Marcos L. (2016). Effect of foods and Mediterranean diet during pregnancy and first years of life on wheezing, rhinitis and dermatitis in preschoolers. *Allergol Immunopathol (Madr)*, 44(5), 400-409.

Castro-Rodriguez JA, Rodrigo GJ. (2009). Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics*, 123(3), e519-e525.

Castro-Rodriguez JA. (2010). The Asthma Predictive Index: a very useful tool for predicting asthma in young children. *J Allergy Clin Immunol*, 126(2), 212-216.

Caudri D, Wijga A, Gehring U, Smit HA, Brunekreef B, Kerkhof M, et al. (2007). Respiratory symptoms in the first 7 years of life and birth weight at term: the PIAMA Birth Cohort. *Am J Respir Crit Care Med*, 175(10), 1078-1085.

Caudri D, Wijga A, Scholtens S, Kerkhof M, Gerritsen J, Ruskamp JM, et al. (2009). Early daycare is associated with an increase in airway symptoms in early childhood but is no protection against asthma or atopy at 8 years. *Am J Respir Crit Care Med*, 180(6), 491-498.

Celedón JC, Litonjua AA, Ryan L, Platts-Mills T, Weiss ST, Gold DR. (2002). Exposure to cat allergen, maternal history of asthma, and wheezing in first 5 years of life. *Lancet*, 360(9335), 781-782.

Celedón JC, Litonjua AA, Ryan L, Weiss ST, Gold DR. (2002). Day care attendance, respiratory tract illnesses, wheezing, asthma, and total serum IgE level in early childhood. *Arch Pediatr Adolesc Med*, 156(3), 241-245.

Chang TS, Lemanske RF Jr, Guilbert TW, Gern JE, Coen MH, Evans MD, et al. (2013). Evaluation of the Modified Asthma Predictive Index in high-risk preschool children. *J Allergy Clin Immunol Pract*, 1(2), 152-156.

Chatzi L, Garcia R, Roumeliotaki T, Basterrechea M, Begiristain H, Iñiguez C, et al. (2013). Mediterranean diet adherence during pregnancy and risk of wheeze and eczema in the first year of life: INMA (Spain) and RHEA (Greece) mother-child cohort studies. *Br J Nutr*, 110(11), 2058-2068.

Chatzi L, Torrent M, Romieu I, Garcia-Esteban R, Ferrer C, Vioque J, et al. (2008). Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax*, 63(6), 507-513.

Cho CE, Norman M. (2013). Cesarean section and development of the immune system in the offspring. *Am J Obstet Gynecol*, 208(4), 249-254.

Chong Neto HJ, Rosario N, Dela Bianca AC, Solé D, Mallol J. (2007). Validation of a questionnaire for epidemiologic studies of wheezing in infants. *Pediatr Allergy Immunol*, 18(1), 86-87.

Chong Neto HJ, Rosário NA, Grupo EISL Curitiba. (2008). Risk factors for wheezing in the first year of life. *J Pediatr (Rio J)*, 84(6), 495-502.

Chong Neto HJ, Rosário NA, Solé D, Mallol J. (2007). Prevalence of recurrent wheezing in infants. *J Pediatr (Rio J)*, 83(4), 357-362.

Chung JY, Han TH, Kim SW, Kim CK, Hwang ES. (2007). Detection of viruses identified recently in children with acute wheezing. *J Med Virol*, 79(8), 1238-1243.

Clavenna A, Sequi M, Cartabia M, Fortinguerra F, Borgui M, Bonati M, et al. (2014). Effectiveness of nebulized beclomethasone in preventing viral wheezing: an RCT. *Pediatrics*, 133(3), e505-512.

Collin SM, Granell R, Westgarth C, Murray J, Paul ES, Sterne JA, et al. (2015). Associations of pet ownership with wheezing and lung function in childhood: findings from a UK birth cohort. *PLoS One*, 10(6), e0127756.

Cope SF, Ungar WJ, Glazier RH. (2008). Socioeconomic factors and asthma control in children. *Pediatr Pulmonol*, 43(8), 745-752.

Davidson R, Roberts SE, Wotton CJ, Goldacre MJ. (2010). Influence of maternal and perinatal factors on subsequent hospitalisation for asthma in children: evidence from the Oxford record linkage study. *BMC Pulm Med*, 10, 14.

de Bilderling G, Chauhan AJ, Jeffs JA, Withers N, Johnston SL, Holgate ST, et al. (2005). Gas cooking and smoking habits and the risk of childhood and adolescent wheeze. *Am J Epidemiol*, 162(6), 513-522.

de Korte-de Boer D, Mommers M, Thijs C, Jaminon M, Jansen M, Mujakovic S, et al. (2015). Early life growth and the development of preschool wheeze, independent from overweight: the LucKi Birth Cohort Study. *J Pediatr*, 166(2), 343-349.e1.

De Marco R, Locatelli F, Sunyer J, Burney P. (2000). Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med*, 162(1), 68-74.

de Meer G, Reijneveld SA, Brunekreef B. (2010). Wheeze in children: the impact of parental education on atopic and non-atopic symptoms. *Pediatr Allergy Immunol*, 21(5), 823-830.

Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health. Accessed 24/03/2017. From: www.OpenEpi.com

Delmas MC, Guignon N, Leynaert B, Annesi-Maesano I, Com-Ruelle L, Gonzalez L, et al. (2012). Prévalence et contrôle de l'asthme chez le jeune enfant en France. *Rev Mal Respir*, 29(5), 688-696.

Deng Y, Gu X, Zhao X, Luo J, Luo Z, Wang L, et al. (2012). High viral load of human bocavirus correlates with duration of wheezing in children with severe lower respiratory tract infection. *PLoS One*, 7(3), e34353.

Dezateux C, Lum S, Hoo AF, Hawdon J, Costeloe K, Stocks J. (2004). Low birth weight for gestation and airway function in infancy: exploring the fetal origins hypothesis. *Thorax*, 59(1), 60-66.

Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. (2014). Atopic dermatitis and the atopic march revisited. *Allergy*, 69(1), 17-27.

Dimova S, Hoet PH, Dinsdale D, Nemery B. (2005). Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *Int J Biochem Cell Biol*, 37(8), 1727-1737.

Dogaru CM, Nyffenegger D, Pescatore AM, Spycher BD, Kuehni CE. (2014). Breastfeeding and childhood asthma: systematic review and meta-analysis. *Am J Epidemiol*, 179(10), 1153-1167.

Dom S, Droste JH, Sariachvili MA, Hagendorens MM, Bridts CH, Stevens WJ, et al. (2009). The influence of parental educational level on the development of atopic sensitization, wheezing and eczema during the first year of life. *Pediatr Allergy Immunol*, 20(5), 438-447.

Ducharme FM, Tse SM, Chauhan B. (2014). Diagnosis, management, and prognosis of preschool wheeze. *Lancet*, 383(9928), 1593-1604.

Duijts L, Jaddoe VW, Hofman A, Moll HA. (2010). Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. *Pediatrics*, 126(1), e18-25.

Duijts L, Jaddoe VW, van der Valk RJ, Henderson JA, Hofman A, Raat H, et al. (2012). Fetal exposure to maternal and paternal smoking and the risks of wheezing in preschool children: the Generation R Study. *Chest*, 141(4), 876-885.

Eldeirawi K, Kunzweiler C, Combs AM, Persky VW. (2016). In utero exposure to pets is associated with asthma and wheezing in Mexican American children. *J Asthma*, 53(4), 374-381.

Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW, the ISAAC Steering Committee. (2005). The International Study of Asthma and Allergies in Childhood (ISAAC): Phase Three Rationale and Methods. *Int J Tuberc Lung Dis*, 9(1), 10-16.

Engelkes M, Janssens HM, de Ridder MA, de Jongste JC, Sturkenboom MC, Verhamme KM. (2015). Time trends in the incidence, prevalence and age at diagnosis of asthma in children. *Pediatr Allergy Immunol*, 26(4), 367-374.

Esposito S, Blasi F, Arosio C, Fioravanti L, Fagetti L, Droghetti R, et al. (2000). Importance of acute Mycoplasma pneumoniae and Chlamydia pneumoniae infections in children with wheezing. *Eur Respir J*, 16(6), 1142-1146.

Field CJ. (2005). The immunological components of human milk and their effect on immune development in infants. *J Nutr*, 135(1), 1-4.

Flasherman V, Rutherford GW. (2006). A meta-analysis of the effect of high weight on asthma. *Arch Dis Child*, 91(4), 334-339.

Flores C, Ma SF, Pino-Yanes M, Wade MS, Pérez-Méndez L, Kittles RA, et al. (2012). African ancestry is associated with asthma risk in African Americans. *PLoS One*, 7(1), e26807.

Frey U, von Mutius E. (2009). The challenge of managing wheezing in infants. *N Engl J Med*, 360(20), 2130-2133.

Fujitsuka A, Tsukagoshi H, Arakawa M, Goto-Sugai K, Ryo A, Okayama Y, et al. (2011). A molecular epidemiological study of respiratory viruses detected in Japanese children with acute wheezing illness. *BMC Infect Dis*, 11, 168.

García-Marcos L, Batllés-Garrido J, Blanco-Quirós A, García-Hernández G, Guillén-Grima F, González-Díaz C, et al. (2009). Influence of two different geo-climatic zones on the prevalence and time trends of asthma symptoms among Spanish adolescents and schoolchildren. *Int J Biometeorol*, 53(1), 53-60.

Garcia-Marcos L, Canflanca IM, Garrido JB, Varela AL, Garcia-Hernandez G, Guillen Grima F, et al. (2007). Relationship of asthma and rhinoconjunctivitis with obesity, exercise and Mediterranean diet in Spanish schoolchildren. *Thorax*, 62(6), 503-508.

Garcia-Marcos L, Mallol J, Solé D, Brand PL, the EISL Group. (2010). International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life. *Pediatr Allergy Immunol*, 21(5), 878-888.

García-Marcos L, Sánchez-Solís de Querol M, Bosch Giménez V. (2009). Epidemiología e historia natural de las sibilancias en el lactante. In: *Sibilancias en el lactante 2009*. Villa Asensi JR, Madrid: Luzan 5, 11-26.

Garcia-Marcos L, Sanchez-Solis M, Perez-Fernandez V, Pastor-Vivero MD, Mondejar-Lopez P, Valverde-Molina J. (2009). Is the effect of prenatal paracetamol exposure on wheezing in preschool children modified by asthma in the mother? *Int Arch Allergy Immunol*, 149(1), 33-37.

Gehring U, Strikwold M, Schram-Bijkerk D, Weinmayr G, Genuneit J, Nagel G, et al. (2008). Asthma and allergic symptoms in relation to house dust endotoxin: Phase Two of the International Study of Asthma and Allergies in Childhood (ISAAC II). *Clin Exp Allergy*, 38(12), 1911-1920.

Genuneit J, Cantelmo JL, Weinmayr G, Wong GW, Cooper PJ, Riikjärv MA, et al. (2009). A multi-centre study of candidate genes for wheeze and allergy: the International Study of Asthma and Allergies in Childhood Phase 2. *Clin Exp Allergy*, 39(12), 1875-1888.

Genuneit J. (2012). Exposure to farming environments in childhood and asthma and wheeze in rural populations: a systematic review with meta-analysis. *Pediatr Allergy Immunol*, 23(6), 509-518.

Gern JE, Rosenthal LA, Sorkness RL, Lemanske RF Jr. (2005). Effects of viral respiratory infections on lung development and childhood asthma. *J Allergy Clin Immunol*, 115(4), 668-674.

Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, et al. (2000). Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax*, 55(4), 271-276.

Gilliland FD, Li YF, Peters JM. (2001). Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med*, 163(2), 429-436.

Goksör E, Thengilsdottir H, Alm B, Norvenius G, Wennergren G. (2011). Prenatal paracetamol exposure and risk of wheeze at preschool age. *Acta Paediatr*, 100(12), 1567-1571.

Guibas GV, Xepapadaki P, Moschonis G, Douladiris N, Filippou A, Tsirigoti L, et al. (2013). Breastfeeding and wheeze prevalence in pre-schoolers and pre-adolescents: the Genesis and Healthy Growth studies. *Pediatr Allergy Immunol*, 24(8), 772-781.

Guilbert TW, Morgan WJ, Krawiec M, Lemanske RF Jr, Sorkness C, Szefler SJ, et al. (2004). The prevention of early asthma in Kids study: design, rationale and methods for the Childhood Asthma Research and Education network. *Control Clin Trials*, 25(3), 286-310.

Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, et al. (2006). Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med*, 354(19), 1985-1997.

Gunawardhana LP, Baines KJ, Mattes J, Murphy VE, Simpson JL, Gibson PG. (2014). Differential DNA methylation profiles of infants exposed to maternal asthma during pregnancy. *Pediatr Pulmonol*, 49(9), 852-862.

Guthikonda K, Zhang H, Nolan VG, Soto-Ramírez N, Ziyab AH, Ewart S, et al. (2014). Oral contraceptives modify the effect of GATA3 polymorphisms on the risk of asthma at the age of 18 years via DNA methylation. *Clin Epigenetics*, 6(1), 17.

Hafkamp-de Groen E, Mohangoo AD, Landgraf JM, de Jongste JC, Duijts L, Moll HA, et al. (2013). The impact of preschool wheezing patterns on health-related quality of life at age 4 years. *Eur Respir J*, 41(4), 952-959.

Hafkamp-de Groen E, Sonnenschein-van der Voort AM, Mackenbach JP, Duijts L, Jaddoe VW, Moll HA, et al. (2013). Socioeconomic and sociodemographic factors associated with asthma related outcomes in early childhood: the Generation R Study. *PLoS One*, 8(11), e78266.

Hagerhed-Engman L, Bornehag CG, Sundell J, Aberg N. (2006). Day-care attendance and increased risk for respiratory and allergic symptoms in preschool age. *Allergy*, 61(4), 447-453.

Halterman JS, Yoos HL, Conn KM, Callahan PM, Montes G, Neely TL, et al. (2004). The impact of childhood asthma on parental quality of life. *J Asthma*, 41(6), 645-653.

Hancock DB, Haberg SE, Furu K, Whitworth KW, Nafstad P, Nystad W, et al. (2011). Oral contraceptive pill use before pregnancy and respiratory outcomes in early childhood. *Pediatr Allergy Immunol*, 22(5), 528-536.

Hanson LA, Korotkova M, Haversen L, Mattsby-Baltzer I, Hahn-Zoric M, Silfverdal SA, et al. (2002). Breast-feeding, a complex support system for the offspring. *Pediatr Int*, 44(4), 347-352.

Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, et al. (2008). Associations of wheezing phenotypes in the first six years of life with atopy, lung function and airway responsiveness in mid childhood. *Thorax*, 63(11), 974-980.

Herr M, Just J, Nikasinovic L, Foucault C, Le Marec AM, Giordanella JP, et al. (2012). Influence of host and environmental factors on wheezing severity in infants: findings from the PARIS birth cohort. *Clin Exp Allergy*, 42(2), 275-283.

Holt PG, Sly PD, Martinez FD, Weiss ST, Björkstén B, von Mutius E, et al. (2004). Drug development strategies for asthma: in search of a new paradigm. *Nat Immunol*, 5(7), 695-698.

Holt PG, Sly PD. (2002). Interactions between respiratory tract infections and atopy in the aetiology of asthma. *Eur Respir J*, 19(3), 538-545.

Hong S, Son DK, Lim WR, Kim SH, Kim H, Yum HY, et al. (2012). The prevalence of atopic dermatitis, asthma, and allergic rhinitis and the comorbidity of allergic diseases in children. *Environ Health Toxicol*, 27, e2012006.

Horak E, Morass B, Ulmer H, Genuneit J, Braun-Fahrländer C, von Mutius E, et al. (2014). Prevalence of wheezing and atopic diseases in Austrian schoolchildren in conjunction with urban, rural or farm residence. *Wien Klin Wochenschr*, 126(17-18), 532-536.

Howden-Chapman P, Pierse N, Nicholls S, Gillespie-Bennett J, Viggers H, Cunningham M, et al. (2008). Effects of improved home heating on asthma in community dwelling children: randomised controlled trial. *BMJ*, 337, a1411.

Hu Y, Liu W, Huang C, Zou ZJ, Zhao ZH, Shen L, et al. (2014). Home dampness, childhood asthma, hay fever, and airway symptoms in Shanghai, China: associations, dose-response relationships, and lifestyle's influences. *Indoor Air*, 24(5), 450-463.

Huang C, Liu W, Hu Y, Zou Z, Zhao Z, Shen L, et al. (2015). Updated prevalences of asthma, allergy, and airway symptoms, and a systematic review of trends over time for childhood asthma in Shanghai, China. *PLoS One*, 10(4), e0121577.

Huffaker MF, Phipatanakul W. (2014). Utility of the Asthma Predictive Index in predicting childhood asthma and identifying disease-modifying interventions. *Ann Allergy Asthma Immunol*, 112(3), 188-190.

Hunt A, Crawford JA, Rosenbaum PF, Abraham JL. (2011). Levels of household particulate matter and environmental tobacco smoke exposure in the first year of life for a cohort at risk for asthma in urban Syracuse, NY. *Environ Int*, 37(7), 1196-1205.

Huurre A, Kalliomäki M, Rautava S, Rinne M, Salminen S, Isolauri E. (2008). Mode of delivery – effects on gut microbiota and humoral immunity. *Neonatology*, 93(4), 236-240.

Illi S, von Mutius E, Lau S, Nickel R, Grüber C, Niggemann B, et al. (2004). The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol*, 113(5), 925-931.

Illi S, von Mutius E, Lau S, Niggemann B, Grüber C, Wahn U, et al. (2006). Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet*, 368(9537), 763-770.

Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. (2008). Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*, 178(7), 667-672.

Jang J, Gary Chan KC, Huang H, Sullivan SD. (2013). Trends in cost and outcomes among adult and pediatric patients with asthma: 2000-2009. *Ann Allergy Asthma Immunol*, 111(6), 516-522.

Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. (1995). Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ*, 310(6989), 1225-1229.

Jones R, Lin S, Munsie JP, Radigan M, Hwang SA. (2008). Racial/ethnic differences in asthma-related emergency department visits and hospitalizations among children with wheeze in Buffalo, New York. *J Asthma*, 45(10), 916-922.

Jurado D, Muñoz C, Luna J de D, Muñoz-Hoyos A. (2005). Is maternal smoking more determinant than paternal smoking on the respiratory symptoms of young children? *Respir Med*, 99(9), 1138-1144.

Just J, Gouvis-Echraghi R, Couderc R, Guillemot-Lambert N, Saint-Pierre P. (2012). Novel severe wheezy young children phenotypes: boys atopic multipple-trigger and girls nonatopic uncontrolled wheeze. *J Allergy Clin Immunol*, 130(1), 103-110.

Kanoh M, Kaneita Y, Hara M, Harada S, Gon Y, Kanamaru H, et al. (2012). Longitudinal study of parental smoking habits and development of asthma in early childhood. *Prev Med*, 54(1), 94-96.

Kappelle L, Brand PL. (2012). Severe episodic viral wheeze in preschool children: high risk of asthma at age 5-10 years. *Eur J Pediatr*, 171(6), 947-954.

Korppi M, Hyvärinen M, Kotaniemi-Syrjänen A, Piippo-Savolainen E, Reijonen T. (2008). Early exposure and sensitization to cat and dog: different effects on asthma risk after wheezing in infancy. *Pediatr Allergy Immunol*, 19(8), 696-701.

Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. (2003). Rhinovirus-induced wheezing in infancy – the first sign of childhood asthma? *J Allergy Clin Immunol*, 111(1), 66-71.

Kozyrskyj AL, Kendall GE, Jacoby P, Sly PD, Zubrick SR. (2010). Association between socioeconomic status and the development of asthma: analyses of income trajectories. *Am J Public Health*, 100(3), 540-546.

Krämer U, Heinrich J, Wjst M, Wichmann HE. (1999). Age of entry to day nursery and allergy in later childhood. *Lancet*, 353(9151), 450.454.

Kristjansson S, Bjarnarson SP, Wennergren G, Palsdottir AH, Arnadottir T, Haraldsson A, et al. (2005). Respiratory syncytial virus and other respiratory viruses during the first 3 months of life promote a local TH2-like response. *J Allergy Clin Immunol*, 116(4), 805-811.

Kuehni CE, Davis A, Brooke AM, Silverman M. (2001). Are all wheezing disorders in very young (preschool) children increasing in prevalence? *Lancet*, 357(9271), 1821-1825.

Kuehni CE, Strippoli MP, Low N, Brooke AM, Silverman M. (2007). Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. *Clin Exp Allergy*, 37(12), 1738-1746.

Kumar R, Yu Y, Story RE, Pongracic JA, Gupta R, Pearson C, et al. (2008). Prematurity, chorioamnionitis, and the development of recurrent wheezing: a prospective birth cohort study. *J Allergy Clin Immunol*, 121(4), 878-884.e6.

Kurukulaaratchy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH. (2003). Characterization of wheezing phenotypes in the first 10 years of life. *Clin Exp Allergy*, 33(5), 573-578.

Kusel MM, de Klerk NH, Holt PG, Kebadze T, Johnston SL, Sly PD. (2006). Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: a birth cohort study. *Pediatr Infect Dis J*, 25(8), 680-686.

Kusel MM, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, et al. (2007). Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol*, 119(5), 1105-1110.

Kwon JW, Kim BJ, Song Y, Seo JH, Kim TH, Yu J, et al. (2011). Changes in the prevalence of childhood asthma in Seoul from 1995 to 2008 and its risk factors. *Allergy Asthma Immunol Res*, 3(1), 27-33.

Lannerö E, Wickman M, Pershagen G, Nordvall L. (2006). Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). *Respir Res*, 7, 3.

Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, et al. (2005). Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol*, 116(3), 571-577.

Leonardi-Bee J, Pritchard D, Britton J. (2006). Asthma and current intestinal parasite infection: systematic review and meta-analysis. *Am J Respir Crit Care Med*, 174(5), 514-523.

Leung JY, Kwok MK, Leung GM, Schooling CM. (2016). Breastfeeding and childhood hospitalizations for asthma and other wheezing disorders. *Ann Epidemiol*, 26(1), 21-27.e1-3.

Li X, Sundquist K, Sundquist J. (2009). Parental occupation and risk of hospitalization for asthma in children and adolescents. *J Asthma*, 46(8), 815-821.

Lim RH, Kobzik L, Dahl M. (2010). Risk for asthma in offspring of asthmatic mothers versus fathers: a meta-analysis. *PLoS One*, 5(4), e10134.

Lin W, Brunekreef B, Gehring U. (2013). Meta-analysis of the effects of indoor nitrogen dioxide and gas cooking on asthma and wheeze in children. *Int J Epidemiol*, 42(6), 1724-1737.

Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. (1998). Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med*, 158(1), 176-181.

Llanora GV, Ming LJ, Wei LM, van Bever HP. (2012). House dust mite sensitization in toddlers predict persistent wheeze in children between eight to fourteen years old. *Asia Pac Allergy*, 2(3), 181-186.

Lodrup Carlsen KC, Roll S, Carlsen KH, Mowinckel P, Wijga AH, Brunekreef B, et al. (2012). Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. *PLoS One*, 7(8), e43214.

Loisel DA, Tan Z, Tisler CJ, Evans MD, Gangnon RE, Jackson DJ, et al. (2011). *IFNG* genotype and sex interact to influence the risk of childhood asthma. *J Allergy Clin Immunol*, 128(3), 524-531.

Ly NP, Gold DR, Weiss ST, Celedón JC. (2006). Recurrent wheeze in early childhood and asthma among children at risk for atopy. *Pediatrics*, 117(6), e1132-e1138.

Magnus MC, Haberg SE, Stigum H, Nafstad P, London SJ, Vangen S, et al. (2011). Delivery by cesarean section and early childhood respiratory symptoms and disorders: the Norwegian mother and child cohort study. *Am J Epidemiol*, 174(11), 1275-1285.

Mäkelä MJ, Malmberg LP, Csonka P, Klemola T, Kajosaari M, Pelkonen AS. (2012). Salmeterol and fluticasone in young children with multiple-trigger wheeze. *Ann Allergy Asthma Immunol*, 109(1), 65-70.

Mallol J, García-Marcos L, Aguirre V, Martinez-Torres A, Perez-Fernández V, Gallardo A, et al. (2007). The International Study of Wheezing in Infants: questionnaire validation. *Int Arch Allergy Immunol*, 144(1), 44-50.

Mallol J, García-Marcos L, Solé D, Brand P, the EISL Study Group. (2010). International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources. *Thorax*, 65(11), 1004-1009.

Mallol J, García-Marcos L. (2006). Estudio Internacional de Sibilancias en Lactantes (EISL). *Respirar*, 1-6.

Mallol J, Solé D, Asher I, Clayton T, Stein R, Soto-Quiroz M. (2000). Prevalence of asthma symptoms in Latin America: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Pulmonol*, 30(6), 439-444.

Mallol J, Solé D, Baeza-Bacab M, Aguirre-Camposano V, Soto-Quiros M, Baena-Cagnani C, et al. (2010). Regional variation in asthma symptom prevalence in Latin American children. *J Asthma*, 47(6), 644-650.

Mallol J, Solé D, Garcia-Marcos L, Rosario N, Aguirre V, Chong H, et al. (2016). Prevalence, severity, and treatment of recurrent wheezing during the first year of life: a cross-sectional study of 12,405 Latin American infants. *Allergy Asthma Immunol Res*, 8(1), 22-31.

Marbury MC, Maldonado G, Waller L. (1997). Lower respiratory illness, recurrent wheezing, and day care attendance. *Am J Respir Crit Care Med*, 155(1), 156-161.

Marmot M. (2005). Social determinants of health inequalities. *Lancet*, 365(9464), 1099-1104.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, et al. (1995). Asthma and wheezing in the first six years of life. *N Engl J Med*, 332(3), 133-138.

Martinez FD. (1999). Present and future treatment of asthma in infants and young children. *J Allergy Clin Immunol*, 104(4Pt2), 169-174.

Maziak W, Behrens T, Brasky TM, Duhme H, Rzehak P, Weiland SK, et al. (2003). Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and III surveys in Münster, Germany. *Allergy*, 58(7), 572-579.

McKean MC, Ducharme F. (2000). Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database Syst Rev*, (2), CD001107.

Mebrahtu TF, Feltbower RG, Greenwood DC, Parslow RC. (2015). Birth weight and childhood wheezing disorders: a systematic review and meta-analysis. *J Epidemiol Community Health*, 69(5), 500-508.

Mebrahtu TF, Feltbower RG, Greenwood DC, Parslow RC. (2015). Childhood body mass index and wheezing disorders: a systematic review and meta-analysis. *Pediatr Allergy Immunol*, 26(1), 62-72.

Mebrahtu TF, Feltbower RG, Parslow RC. (2015). Effects of birth weight and growth on childhood wheezing disorders: findings from the Born in Bradford Cohort. *BMJ Open*, 5(11), e009553.

Melén E, Kere J, Pershagen G, Svartengren M, Wickman M. (2004). Influence of male sex and parental allergic disease on childhood wheezing: role of interactions. *Clin Exp Allergy*, 34(6), 839-844.

Message SD, Laza-Stanca V, Mallia P, Parker HL, Zhu J, Kebadze T, et al. (2008). Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production. *Proc Natl Acad Sci USA*, 105(36), 13562-13567.

Michel G, Silverman M, Strippoli M-PF, Zwahlen M, Brooke AM, Grigg J, et al. (2006). Parental understanding of wheeze and its impact on asthma prevalence estimates. *Eur Respir J*, 28(6), 1124-1130.

Midulla F, Pierangeli A, Cangiano G, Bonci E, Salvadei S, Scagnolari C, et al. (2012). Rhinovirus bronchiolitis and recurrent wheezing: 1-year follow-up. *Eur Respir J*, 39(2), 396-402.

Migliore E, Zugna D, Galassi C, Merletti F, Gagliardi L, Rasero L, et al. (2015). Prenatal paracetamol exposure and wheezing in childhood: causation or confounding? *PLoS One*, 10(8), e0135775.

Milà-Villarroel R, Bach-Faig A, Puig J, Puchal A, Farran A, Serra-Majem L, et al. (2011). Comparison and evaluation of the reliability of indexes of adherence to the Mediterranean diet. *Public Health Nutr*, 14(12A), 2338-2345.

Miyake Y, Sasaki S, Tanaka K, Hirota Y. (2010). Consumption of vegetables, fruit, and antioxidants during pregnancy and wheeze and eczema in infants. *Allergy*, 65(6), 758-765.

Miyake Y, Tanaka K, Sasaki S, Hirota Y. (2012). Parental employment, income, education and allergic disorders in children: a prebirth cohort study in Japan. *Int J Tuberc Lung Dis*, 16(6), 756-761.

Miyake Y, Tanaka K, Sasaki S, Kiyohara C, Ohya Y, Fukushima W, et al. (2008). Breastfeeding and the risk of wheeze and asthma in Japanese infants: the Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol*, 19(6), 490-496.

Mohangoo AD, de Koning HJ, de Jongste JC, Landgraf JM, van der Wouden JC, Jaddoe VW, et al. (2012). Asthma-like symptoms in the first year of life and health-related quality of life at age 12 months: the Generation R study. *Qual Life Res*, 21(3), 545-554.

Mohangoo AD, de Koning HJ, Mangunkusumo RT, Raat H. (2007). Health-related quality of life in adolescents with wheezing attacks. *J Adolesc Health*, 41(5), 464-471.

Mommers M, Thijs C, Stelma F, Penders J, Reimerink J, van Ree R, et al. (2010). Timing of infection and development of wheeze, eczema, and atopic sensitization during the first 2 yr of life: the KOALA Birth Cohort Study. *Pediatr Allergy Immunol*, 21(6), 983-989.

Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. (2005). Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med*, 172(10), 1253-1258.

Murray CS, Woodcock A, Smillie FI, Cain G, Kissen P, Custovic A, et al. (2004). Tobacco smoke exposure, wheeze and atopy. *Pediatr Pulmonol*, 37(6), 492-496.

National Heart, Lung, and Blood Institute. (2007). Expert panel report 3: Guidelines for the diagnosis and management of asthma. US Department of Health and Human Services.

Navarre Statistical Office (Instituto de Estadística de Navarra). Accessed 23/11/2016. From: http://www.navarra.es/AppsExt/GN.InstitutoEstadistica.Web/InformacionEstadistica.aspx?R=1&E=1

Neuman A, Bergström A, Gustafsson P, Thunqvist P, Andersson N, Nordvall L, et al. (2014). Infant wheeze, comorbidities and school age asthma. *Pediatr Allergy Immunol*, 25(4), 380-386.

Nicolaou NC, Simpson A, Lowe LA, Murray CS, Woodcock A, Custovic A. (2008). Day-care attendance, position in sibship, and early childhood wheezing: a population-based birth cohort study. *J Allergy Clin Immunol*, 122(3), 500-506.e5.

Nutall SL, Williams J, Kendall MJ. (2003). Does paracetamol cause asthma? *J Clin Pharm Ther*, 28(4), 251-257.

Oddy WH, Holt PG, Sly PD, Read AW, Landau LI, Stanley FJ, et al. (1999). Association between breast feeding and asthma in 6 year old children: findings from a prospective study. *BMJ*, 319(7213), 815-819.

Oddy WH, Sly PD, de Klerk NH, Landau LI, Kendall GE, Holt PG, et al. (2003). Breast feeding and respiratory morbidity in infancy: a birth cohort study. *Arch Dis Child*, 88(3), 224-228.

Oostenbrink R, Jansingh-Piepers EM, Raat H, Nuijsink M, Landgraf JM, Essink-Bot ML, et al. (2006). Health-related quality of life of pre-school children with wheezing illness. *Pediatr Pulmonol*, 41(10), 993-1000.

Osman LM, Baxter-Jones ADG, Helms PJ, on behalf of the EASE study group. (2001). Parents' quality of life and respiratory symptoms in young children with mild wheeze. *Eur Respir J*, 17(2), 254-258.

Osman MF, Black C, Jick S, Hannaford P. (2009). Previous maternal oral contraception and the risk among subsequent offspring of asthma diagnosis in early childhood. *Paediatr Perinat Epidemiol*, 23(6), 567-573.

Pacheco-Gonzalez RM, Mallol J, Solé D, Brand PL, Perez-Fernandez V, Sanchez-Solis M, et al. (2016). Factors associated with the time to the first wheezing episode in infants: a cross-sectional study from the International Study of Wheezing in Infants (EISL). *NPJ Prim Care Respir Med*, 26, 15077.

Pamplona city council. Conoce Pamplona. Accesed 25/01/2016. From: http://www.pamplona.es/verPagina.asp?idPag=263&idioma=1

Panico L, Bartley M, Marmot M, Nazroo JY, Sacker A, Kelly YJ. (2007). Ethnic variation in childhood asthma and wheezing illnesses: findings from the Millennium Cohort Study. *Int J Epidemiol*, 36(5), 1093-1102.

Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. (2007). Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*, 62(9), 758-766.

Pellegrini-Belinchón J, Miguel-Miguel G, De Dios-Martín B, Vicente-Galindo E, Lorente-Toledano F, García-Marcos L. (2012). Study of wheezing and its risk factors in the first year of life in the Province of Salamanca, Spain. The EISL Study. *Allergol Immunopathol (Madr)*, 40(3), 164-171.

Pereira AM, Morais-Almeida M, Santos N, Nunes C, Fonseca JA. (2014). Wheezing in preschool children in Portugal: prevalence, characterization and association with rhinitis. *Rev Port Imunoalergologia*, 22(3), 215-226.

Pérez Tarazona S, Alfonso Diego J, Amat Madramany A, Chofre Escrihuela L, Lucas Sáez E, Bou Monterde R. (2010). Incidencia y factores de riesgo de bronquitis sibilantes en los primeros 6 meses de vida en una cohorte de Alzira (Valencia). *An Pediatr (Barc)*, 72(1), 19-29.

Pérez-Yarza EG, Moreno-Galdó A, Ramilo O, Rubí T, Escribano A, Torres A, et al. (2015). Risk factors for bronchiolitis, recurrent wheezing, and related hospitalization in preterm infants during the first year of life. *Pediatr Allergy Immunol*, 26(8), 797-804.

Perkin MR, Strachan DP, Williams HC, Kennedy CT, Golding J, the ALSPAC Study Team. (2004). Natural history of atopic dermatitis and its relationship to serum total immunoglobulin E in a population-based birth cohort study. *Pediatr Allergy Immunol*, 15(3), 221-229.

Peroni DG, Piacentini GL, Bodini A, Boner AL. (2009). Preschool asthma in Italy: prevalence, risk factors and health resource utilization. *Respir Med*, 103(1), 104-108.

Pescatore AM, Spycher BD, Beardsmore CS, Kuehni CE. (2015). "Attacks" or "Whistling": impact of questionnaire wording on wheeze prevalence estimates. *PLoS One*, 10(6), e0131618.

Phoa LL, Toelle BG, Ng K, Marks GB. (2004). Effects of gas and other fume emitting heaters on the development of asthma during childhood. *Thorax*, 59(9), 741-745.

Pike KC, Crozier SR, Lucas JS, Inskip HM, Robinson S, the Southampton Women's Survey Study Group, et al. (2010). Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. *Thorax*, 65(12), 1099-1106.

Psaltopoulou T, Naska A, Orfanos P, Trichopoulos D, Mountokalakis T, Trichopoulou A. (2004). Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr*, 80(4), 1012-1018.

Puig C, Fríguls B, Gómez M, García-Algar O, Sunyer J, Vall O. (2010). Relación entre las infecciones respiratorias de vías bajas durante el primer año de vida y el desarrollo de asma y sibilancias en niños. *Arch Bronconeumol*, 46(10), 514-521.

Rebordosa C, Kogevinas M, Sorensen HT, Olsen J. (2008). Pre-natal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. *Int J Epidemiol*, 37(3), 583-590.

Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. (2001). Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol*, 108(4), 509-515.

Robison RG, Kumar R, Arguelles LM, Hong X, Wang G, Apollon S, et al. (2012). Maternal smoking during pregnancy, prematurity and recurrent wheezing in early childhood. *Pediatr Pulmonol*, 47(7), 666-673.

Romieu I, Torrent M, Garcia-Esteban R, Ferrer C, Ribas-Fitó N, Antó JM, et al. (2007). Maternal fish intake during pregnancy and atopy and asthma in infancy. *Clin Exp Allergy*, 37(4), 518-525.

Rönmark E, Perzanowski M, Platts-Mills T, Lundbäck B. (2003). Different sensitization profile for asthma, rhinitis, and eczema among 7-8-year-old children: report from the Obstructive Lung Disease in Northern Sweden studies. *Pediatr Allergy Immunol*, 14(2), 91-99.

Roorda RJ, Mezei G, Bisgaard H, Madsen C. (2001). Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol*, 108(4), 540-546.

Ruijsbroek A, Wijga AH, Kerkhof M, Koppelman GH, Smit HA, Droomers M. (2011). The development of socio-economic health differences in childhood: results of the Dutch longitudinal PIAMA birth cohort. *BMC Public Health*, 11, 225.

Rusconi F, Galassi C, Forastiere F, Bellasio M, De Sario M, Ciccone G, et al. (2007). Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. *Am J Respir Crit Care Med*, 175(1), 16-21.

Ryan PH, Bernstein DI, Lockey J, Reponen T, Levin L, Grinshpun S, et al. (2009). Exposure to traffic-related particles and endotoxin during infancy is associated with wheezing at age 3 years. *Am J Respir Crit Care Med*, 180(11), 1068-1075.

Ryan PH, LeMasters G, Biagini J, Bernstein D, Grinshpun SA, Shukla R, et al. (2005). Is it traffic type, volume, or distance? Wheezing in infants living near truck and bus traffic. *J Allergy Clin Immunol*, 116(2), 279-284.

Ryan PH, LeMasters GK, Biswas P, Levin L, Hu S, Lindsey M, et al. (2007). A comparison of proximity and land use regression traffic exposure models and wheezing in infants. *Environ Health Perspect*, 115(2), 278-284.

Rylander E, Eriksson M, Pershagen G, Nordvall L, Ehrnst A, Ziegler T. (1996). Wheezing bronchitis in children. Incidence, viral infections, and other risk factors in a defined population. *Pediatr Allergy Immunol*, 7(1), 6-11.

Saldiva SR, Escuder MM, Venâncio SI, Benicio MH, Assis AM, Oliveira LP, et al. (2007). Is overweight a risk factor for wheezing in pre-school children? A study in 14 Brazilian communities. *Public Health Nutr*, 10(9), 878-882.

Sangsupawanich P, Chongsuvivatwong V, Mo-Suwan L, Choprapawon C. (2007). Relationship between atopic dermatitis and wheeze in the first year of life: analysis of a prospective cohort of Thai children. *J Investig Allergol Clin Immunol*, 17(5), 292-296.

Saunes M, Oien T, Dotterud CK, Romundstad PR, Storro O, Holmen TL, et al. (2012). Early eczema and the risk of childhood asthma: a prospective, population-based study. *BMC Pediatr*, 12, 168.

Schultz A, Brand PL. (2011). Episodic viral wheeze and multiple trigger wheeze in preschool children: a useful distinction for clinicians? *Paediatr Respir Rev*, 12(3), 160-164.

Schultz A, Devadason SG, Savenije OEM, Sly PD, Le Souëf PN, Brand PL. (2010). The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr*, 99(1), 56-60.

Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. (1991). Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med*, 325(15), 1067-1071.

Shaheen SO, Macdonald-Wallis C, Lawlor DA, Henderson AJ. (2016). Hypertensive disorders of pregnancy, respiratory outcomes and atopy in childhood. *Eur Respir J*, 47(1), 156-165.

Shaheen SO, Newson RB, Sherriff A, Henderson AJ, Heron JE, Burney PG, et al. (2002). Paracetamol use in pregnancy and wheezing in early childhood. *Thorax*, 57(11), 958-963.

Shamssain M. (2007). Trends in the prevalence and severity of asthma, rhinitis and atopic eczema in 6- to 7- and 13- to 14-yr-old children from the north-east of England. *Pediatr Allergy Immunol*, 18(2), 149-153.

Sherriff A, Peters TJ, Henderson J, Strachan D, the ALSPAC Study Team. (2001). Risk factor associations with wheezing patterns in children followed longitudinally from birth to 3 ½ years. *Int J Epidemiol*, 30(6), 1473-1484.

Smith LA, Hatcher-Ross JL, Wertheimer R, Kahn RS. (2005). Rethinking race/ethnicity, income, and childhood asthma: racial/ethnic disparities concentrated among the very poor. *Public Health Rep*, 120(2), 109-116.

Sonnappa S, Bastardo CM, Wade A, Saglani S, McKenzie SA, Bush A, et al. (2010). Symptom-pattern phenotype and pulmonary function in preschool wheezers. *J Allergy Clin Immunol*, 126(3), 519-526.

Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, Annesi-Maesano I, Arshad SH, Barros H, et al. (2014). Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. *J Allergy Clin Immunol*, 133(5), 1317-1329.

Sonnenschein-van der Voort AM, de Kluizenaar Y, Jaddoe VW, Gabriele C, Raat H, Moll HA, et al. (2012). Air pollution, fetal and infant tobacco smoke exposure, and wheezing in preschool children: a population-based prospective birth cohort. *Environ Health*, 11, 91.

Sonnenschein-van der Voort AM, Jaddoe VW, van der Valk RJ, Willemsen SP, Hofman A, Moll HA, et al. (2012). Duration and exclusiveness of breastfeeding and childhood asthma-related symptoms. *Eur Respir J*, 39(1), 81-89.

Spanish Statistical Office (Instituto Nacional de Estadística, INE). Accessed 30/01/2016. From: http://www.ine.es/dyngs/INEbase/es/categoria.htm?c=Estadistica_P&cid=1254734710990

Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. (1999). Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*, 354(9178), 541-545.

Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. (2008). Wheezing and hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet*, 372(9643), 1058-1064.

Stevens CA, Turner D, Kuehni CE, Couriel JM, Silverman M. (2003). The economic impact of preschool asthma and wheeze. *Eur Respir J*, 21(6), 1000-1006.

Strachan DP. (1989). Hay fever, hygiene, and household size. *BMJ*, 299(6710), 1259-1260.

Sun Y, Sundell J. (2011). Early daycare attendance increase the risk for respiratory infections and asthma of children. *J Asthma*, 48(8), 790-796.

Tagiyeva N, Devereux G, Semple S, Sherriff A, Henderson J, Elias P, et al. (2010). Parental occupation is a risk factor for childhood wheeze and asthma. *Eur Respir J*, 35(5), 987-993.

Takeyama A, Hashimoto K, Sato M, Sato T, Tomita Y, Maeda R, et al. (2014). Clinical and epidemiologic factors related to subsequent wheezing after virus-induced lower respiratory tract infections in hospitalized pediatric patients younger than 3 years. *Eur J Pediatr*, 173(7), 959-966.

Tarrant M, Kwok MK, Lam TH, Leung GM, Schooling CM. (2010). Breast-feeding and childhood hospitalizations for infections. *Epidemiology*, 21(6), 847-854.

Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. (2003). Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol*, 111(4), 661-675.

Taveras EM, Rifas-Shiman SL, Camargo CA Jr, Gold DR, Litonjua AA, Oken E, et al. (2008). Higher adiposity in infancy associated with recurrent wheeze in a prospective cohort of children. *J Allergy Clin Immunol*, 121(5), 1161-1166.e3.

Taylor-Robinson DC, Pearce A, Whitehead M, Smyth R, Law C. (2016). Social inequalities in wheezing in children: findings from the UK Millennium Cohort Study. *Eur Respir J*, 47(3), 818-828.

Teijeiro A, Badellino H, Raiden MG, Cuello MN, Kevorkof G, Gatti C, et al. (2016). Risk factors for recurrent wheezing in the first year of life in the city of Cordoba, Argentina. *Allergol Immunopathol (Madr)*, doi: 10.1016/j.aller.2016.08.009.

Tepper RS, Morgan WJ, Cota K, Wright A, Taussig LM. (1986). Physiologic growth and development of the lung during the first year of life. *Am Rev Respir Dis*, 134(3), 513-519.

The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. (1998). Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet*, 351(9111), 1225-1232.

Tischer CG, Hohmann C, Thiering E, Herbarth O, Müller A, Henderson J, et al. (2011). Meta-analysis of mould and dampness exposure on asthma and allergy in eight European birth cohorts: the ENRIECO initiative. *Allergy*, 66(12), 1570-1579.

Tsai CH, Huang JH, Hwang BF, Lee YL. (2010). Household environmental tobacco smoke and risks of asthma, wheeze and bronchitic symptoms among children in Taiwan. *Respir Res*, 11, 11.

Uddenfeldt M, Janson C, Lampa E, Rask-Andersen A. (2013). Sensitization to pets is a major determinant of persistent asthma and new asthma onset in Sweden. *Ups J Med Sci*, 118(2), 111-121.

van der Gugten AC, Koopman M, Evelein AM, Verheij TJ, Uiterwaal CS, van der Ent CK. (2012). Rapid early weight gain is associated with wheeze and reduced lung function in childhood. *Eur Respir J*, 39(2), 403-410.

van der Zalm MM, Uiterwaal CS, Wilbrink B, Koopman M, Verheij TJ, van der Ent CK. (2011). The influence of neonatal lung function on rhinovirus-associated wheeze. *Am J Respir Crit Care Med*, 183(2), 262-267.

van Merode T, Maas T, Twellaar M, Kester A, van Schayck CP. (2007). Gender-specific differences in the prevention of asthma-like symptoms in high-risk infants. *Pediatr Allergy Immunol*, 18(3), 196-200.

Venero-Fernández SJ, Suárez-Medina R, Mora-Faife EC, García-García G, Valle-Infante I, Gómez-Marrero L, et al. (2013). Risk factors for wheezing in infants born in Cuba. *QJM*, 106(11), 1023-1029.

Verhulst SL, Vael C, Beunckens C, Nelen V, Goossens H, Desager K. (2008). A longitudinal analysis on the association between antibiotic use, intestinal microflora, and wheezing during the first year of life. *J Asthma*, 45(9), 828-832.

Villa Asensi JR. (2009) Clínica y diagnóstico diferencial de las sibilancias en el lactante. In: *Sibilancias en el lactante 2009*. Villa Asensi JR, Madrid: Luzan 5, 43-58.

Visser CA, Garcia-Marcos L, Eggink J, Brand PL. (2010). Prevalence and risk factors of wheeze in Dutch infants in their first year of life. *Pediatr Pulmonol*, 45(2), 149-156.

von Rueden U, Gosch A, Rajmil L, Bisegger C, Ravens-Sieberer U. (2006). Socioeconomic determinants of health related quality of life in childhood and adolescence: results from a European study. *J Epidemiol Community Health*, 60(2), 130-135.

Wang L, Pinkerton KE. (2008). Detrimental effects of tobacco smoke exposure during development on postnatal lung function and asthma. *Birth Defects Res C Embryo Today*, 84(1), 54-60.

Weiland SK, Björkstén B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP, et al. (2004). Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J*, 24(3), 406-412.

Weinmayr G, Weiland SK, Björkstén B, Brunekreef B, Büchele G, Cookson WO, et al. (2007). Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Crit Care Med*, 176(6), 565-574.

Willemsen G, van Beijsterveldt TC, van Baal CG, Postma D, Boomsma DI. (2008). Heritability of self-reported asthma and allergy: a study in adult Dutch twins, siblings and parents. *Twin Res Hum Genet*, 11(2), 132-142.

Willers SM, Brunekreef B, Oldenwening M, Smit HA, Kerkhof M, De Vries H, et al. (2006). Gas cooking, kitchen ventilation, and asthma, allergic symptoms and sensitization in young children – the PIAMA study. *Allergy*, 61(5), 563-568.

Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, et al. (1995). Mediterranean diet pyramid: a cultural model for healthy eating. *Am J Clin Nutr*, 61(6 Suppl), 1402S-1406S.

Winer RA, Qin X, Harrington T, Moorman J, Zahran H. (2012). Asthma incidence among children and adults: findings from the Behavioral Risk Factor Surveillance System Asthma Call-back Survey – United States, 2006-2008. *J Asthma*, 49(1), 16-22.

Wjst M, Dold S. (1997). Is asthma an endocrine disease? *Pediatr Allergy Immunol*, 8(4), 200-204.

Wright AL, Holberg CJ, Taussig LM, Martinez FD. (2001). Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax*, 56(3), 192-197.

Wu P, Feldman AS, Rosas-Salazar C, James K, Escobar G, Gebretsadik T, et al. (2016). Relative importance and additive effects of maternal and infant risk factors on childhood asthma. *PLoS One*, 11(3), e0151705.

Wu WF, Wan KS, Wang SJ, Yang W, Liu WL. (2011). Prevalence, severity, and time trends of allergic conditions in 6-to-7-year-old schoolchildren in Taipei. *J Investig Allergol Clin Immunol*, 21(7), 556-562.

Yamakawa M, Yorifuji T, Kato T, Inoue S, Tokinobu A, Tsuda T, et al. (2015). Long-term effects of breastfeeding on children's hospitalization for respiratory tract infections and diarrhea in early childhood in Japan. *Matern Child Health J*, 19(9), 1956-1965.

Yamamoto-Hanada K, Futamura M, Yang L, Shoda T, Narita M, Kobayashi F, et al. (2016). Preconceptional exposure to oral contraceptive pills and the risk of wheeze, asthma and rhinitis in children. *Allergol Int*, 65(3), 327-331.

Yoshida K, Horimukai K, Gocho N, Oishi T, Akashi M, Watanabe H, et al. (2009). Nation-wide prevalence of wheezing by using ISAAC questionnaire from pre-school children to adolescents in Japan. *J Allergy Clin Immunol*, 123(2 Suppl), S218.

Young S, Sherrill DL, Arnott J, Diepeveen D, LeSouëf PN, Landau LI. (2000). Parental factors affecting respiratory function during the first year of life. *Pediatr Pulmonol*, 29(5), 331-340.

Yu D, Wei L, Zhengxiu L, Jian L, Lijia W, Wei L, et al. (2010). Impact of bacterial colonization on the severity, and accompanying airway inflammation, of virus-induced wheezing in children. *Clin Microbiol Infect*, 16(9), 1399-1404.

Yura A, Kouda K, Iki M, Shimizu T. (2011). Trends of allergic symptoms in school-children: large-scale long term consecutive cross-sectional studies in Osaka Prefecture, Japan. *Pediatr Allergy Immunol*, 22(6), 631-637.

Zhang YP, Li BZ, Huang C, Yang X, Qian H, Deng QH, et al. (2013). Ten cities cross-sectional questionnaire survey of children asthma and other allergies in China. *Chin Sci Bull*, 58(34), 4182-4189.

Zheng T, Yu J, Oh MH, Zhu Z. (2011). The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res*, 3(2), 67-73.

Zugna D, Galassi C, Annesi-Maesano I, Baïz N, Barros H, Basterrechea M, et al. (2015). Maternal complications in pregnancy and wheezing in early childhood: a pooled analysis of 14 birth cohorts. *Int J Epidemiol*, 44(1), 199-208.

8. Appendices

Appendix 1

International Study of Wheezing in Infants questionnaire

Proyecto Salud Respiratoria durante el primer año de vida

46266

1. Fecha de hoy dia ☐☐ mes ☐☐ año ☐☐☐☐

2. Fecha de nacimiento del niño/a dia ☐☐ mes ☐☐ año ☐☐☐☐

4. Sexo de su hijo/a ☐ niño ☐ niña

5. Edad de su hijo/a (en meses) ☐☐

3. Persona que rellena la encuesta ☐ Madre ☐ Padre ☐ Otra ☐ Padre y Madre

6. ¿Cuánto pesó su hijo/a al nacer?

☐ menos de 1500 gramos ☐ 1500 a 1999 gr ☐ 2000 a 2499 gr ☐ 2500 a 3499 gr ☐ más de 3500 gr ☐ no lo recuerdo

7. ¿Cuánto pesa su hijo/a actualmente? (en kilos) ☐☐ **8. ¿Cuánto midió su hijo/a al nacer? (en centímetros,)** ☐☐

9. ¿Cuánto mide su hijo/a actualmente?(en centímetros) ☐☐

10. Raza o etnia de su hijo/a

☐ blanca ☐ gitana ☐ norteafricana ☐ subsahariana ☐ india hispanoamericana ☐ asiática ☐ otra

11. ¿Nació su hijo/a en España? ☐ Si ☐ No

11.1. Si ha respondido "NO", ¿en qué país nació su hijo/a?

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

12. Lugar de nacimiento del padre

☐ España ☐ Europa excepto España ☐ África ☐ Norteamerica ☐ Sudamerica y CentroA ☐ Asia ☐ Australia ☐ Australia Oceanía

13. Lugar de nacimiento de la madre

☐ España ☐ Europa excepto España ☐ África ☐ Norteamerica ☐ Sudamerica y CentroA ☐ Asia ☐ Australia

14. ¿Ha tenido su hijo/a silbidos o pitos en el pecho en sus primeros 12 meses de vida? ☐ Si ☐ No

15. ¿Cuantos episodios de silbidos o pitos en el pecho ha tenido su hijo en sus primeros12 meses de vida ☐☐

16. ¿A qué edad tuvo su hijo/a el primer episodio de silbidos o pitos en el pecho? ☐☐ **meses**

17. Cuando su hijo/a tiene pitos en el pecho ¿Suele comenzar por un resfriado normal? ☐ Si ☐ No ☐ nunca ha tenido pitos

18. ¿Se le han desencadenado o empeorado a su hijo/a los pitos en el pecho al moverse más (gatear, correr..) o al enfadarse o reir? ☐ Si ☐ No ☐ nunca ha tenido pitos

19. Los pitos en el pecho de su hijo/a ¿afectan a la alimentación del niño/a? ☐ Si ☐ No ☐ nunca ha tenido pitos

20. Los pitos en el pecho de su hijo ¿limitan las actividades diarias de los padres del niño ☐ Si ☐ No ☐ nunca ha tenido pitos

21. Los pitos en el pecho de su hijo/a ¿han modificado la vida familiar? ☐ Si ☐ No ☐ nunca ha tenido pitos

22. ¿Ha recibido su hijo/a tratamiento con medicamentos inhalados para dilatarle los bronquio ☐ Si ☐ No ☐ Ns/NC

23. ¿Ha recibido su hijo/a tratamiento con corticoides inhalados? Ejemplo: Flixotide, Becloasma ☐ Si ☐ No ☐ Ns/NC
Pulmicort, Fluinol, Inhalacor, Budesonida, Becotide, Pulmictan, Ribujet, etc.

24. ¿Ha recibido su hijo/a tratamiento con otros medicamentos como antileucotrienos (Singulair)o ketotifeno (Zasten, Ketasma)?

☐ sí, tomó antileucotrienos ☐ sí, tomó ketotifeno ☐ sí, tomó ambos medicamentos ☐ no ☐ no sabe

25. En los primeros 12 meses de vida ¿cuántas veces se ha despertado usted por la noche debido a la tos con ahogos o silbidos/pitos en el pecho de su hijo/a?

☐ nunca ☐ raras veces (menos 1 vez /mes) ☐ algunas veces (algunas semanas en algunos meses) ☐ frecuentemente (2 o más noches / semana, casi todos los meses)

26. En los primeros 12 meses de vida, ¿han sido las sibilancias o silbidos/pitos en el pecho tan importantes como para tener que llevarlo a un Servicio de Urgencias? ☐ Si ☐ No

27. En los primeros 12 meses de vida, ¿han sido las sibilancias o silbidos/pitos en el pecho tan importantes que usted notara que su hijo/a tenía mucha dificultad para respirar y se ahogaba? ☐ Si ☐ No

46266

28. ¿Ha estado su hijo/a hospitalizado por pitos, silbidos o ahogos en el pecho en sus primeros 12 meses de vida?

☐ no ☐ 1 vez ☐ 2 veces ☐ 3 veces ☐ 4 veces ☐ 5 veces ☐ 6 veces ☐ 7 veces ☐ 8 veces ☐ 9 o más veces

29. ¿Le ha dicho un médico alguna vez que su hijo/a tiene asma ? ☐ Si ☐ No

30. ¿Ha tenido su hijo/a neumonía o bronconeumonía en sus primeros 12 meses de vida? ☐ Si ☐ No

31. ¿Ha estado su hijo/a hospitalizado por neumonía o bronconeumonía en sus primero ☐ Si ☐ No

32. ¿Ha tenido su hijo/a, en sus primeros 12 meses de vida, manchas rojas en la piel que pican y que aparecen y desaparecen en cualquier parte del cuerpo, excepto alrededor de la boca y la nariz y excepto en el área del pañal? ☐ Si ☐ No

33. ¿Fuma la madre (o tutora) del niño/a actualmente? ☐ Si ☐ No

33.1. ¿Cuántos cigarrillos al día fuma la madre (o tutora) del niño/a? (Si no fuma marque "00" ☐☐

34. ¿Fuma el padre (o tutor) del niño/a actualmente? ☐ Si ☐ No

34.1. ¿Cuántos cigarrillos al día fuma el padre (o tutor) del niño/a? (Si no fuma marque "00" ☐☐

35 ¿Fumó la madre del niño durante el embarazo del niño/a? ☐ Si ☐ No

35.1. Si responde "SÍ" marque en qué trimestre, puede marcar varias respuestas

☐ 1º trimestre ☐ 2º trimestre ☐ 3º trimestre

36. ¿Cuántos de los que viven en la casa fuman cigarrillos, incluyendo a los padres? ☐

37 ¿Tiene asma el padre del niño/a? ☐ Si ☐ No **38. ¿Tiene asma la madre del niño/a?** ☐ Si ☐ No

39. ¿Tiene asma algún hermano/a del niño/a? ☐ Si ☐ No

40. ¿Tiene alergia nasal (rinitis alérgica, fiebre del heno) el padre del niño/a? ☐ Si ☐ No

41. ¿Tiene alergia nasal (rinitis alérgica, fiebre del heno) la madre del niño/a? ☐ Si ☐ No

42. ¿Tiene alergia nasal (rinitis alérgica, fiebre del heno) algún hermano/a del niño/a? ☐ Si ☐ No

43. ¿Tiene alergia en la piel (dermatitis alérgica) el padre del niño/a, excluyendo dermatitis alérgica de contacto? ☐ Si ☐ No

44. ¿Tiene alergia en la piel (dermatitis alérgica) la madre del niño/a, excluyendo dermatitis alérgica de contacto? ☐ Si ☐ No

45. ¿Tiene alergia en la piel (dermatitis alérgica) algún hermano del niño/a, excluyendo dermatitis alérgica de contacto? ☐ Si ☐ No

46. ¿Se le han realizado al padre del niño/a, alguna vez, pruebas de alergia en piel o en sangre?

☐ no ☐ sí, y mostró alergia ☐ sí, pero no mostró alergia

47. ¿Se le han realizado a la madre del niño/a, alguna vez, pruebas de alergia en piel o en sangre?

☐ no ☐ sí, y mostró alergia ☐ sí, pero no mostró alergia

48. ¿Se le han realizado algún hermano/a del niño/a, alguna vez, pruebas de alergia en piel o en sangre?

☐ no ☐ sí, y mostró alergia ☐ sí, pero no mostró alergia

49. ¿Ha ido su hijo/a a la guardería en sus primeros 12 meses de vida? ☐ Si ☐ No

50. ¿A qué edad comenzó su hijo/a a ir a la guardería? (en meses,Si no ha ido todavía a una guardería marque "00" ☐☐ m

51. ¿Con qué frecuencia ha ingerido su hijo/a cualquiera de los siguientes productos (NO elaborados en casa) durante sus primeros 12 meses de vida?: yogur, flan, natillas, petit suisse, patatas fritas envasadas, mermeladas, chocolate, refrescos, zumos de sobre, en sobre, en brick o botella, néctar, etc..

☐ nunca ☐ una vez al mes ☐ una vez por semana ☐ todos los días de la semana

52. En la casa que vive el niño/a, ¿qué tipo de combustible se usa, predominantemente, para la calefacción?

☐ electricidad ☐ gas central ☐ estufa de gas ☐ queroseno ☐ carbón ☐ madera ☐ otra

53. En la casa que vive el niño/a, ¿qué tipo de combustible se usa, predominantemente, para cocinar?

☐ electricidad ☐ gas ☐ queroseno ☐ carbón ☐ madera ☐ otra

54. ¿Tiene aire acondicionado en la casa que vive el niño/a? ☐ Si ☐ No

55. De las siguientes mascotas, marque las que tenía en su casa cuando nació su hijo/a

☐ no tenía mascotas ☐ perro ☐ gato ☐ aves ☐ conejo/hamster ☐ otra

56. De las siguientes mascotas, marque las que tiene actualmente en la casa que vive el niño/a

☐ no tenía mascotas ☐ perro ☐ gato ☐ aves ☐ conejo/hamster ☐ otra

57. La casa en la que vive el niño/a, ¿está enmoquetada? ☐ Si ☐ No

58. La casa en la que vive el niño/a, ¿tiene baño completo (lavabo, inodoro, ducha/bañera) en el interior ☐ Si ☐ No

59. La cocina de la casa en la que vive el niño/a (el lugar dónde se prepara la comida)¿está dentro de la casa ☐ Si ☐ No

60. ¿Tiene teléfono (fijo o móvil) en la casa en la que vive el niño/a? ☐ Si ☐ No

61. Marque, por favor, el nivel de educación alcanzado por la madre del niño/a

☐ educación básica, primaria o ninguna (8 años o menos)

☐ educación media o secundaria incompleta (9-11 años)

☐ educación media o secundaria completa y superior (12 y más años)

☐ educación universitaria

62. ¿Cuántos meses alimentó a su hijo/a exclusivamente con leche materna (sin leches adaptadas, cereales, zumo zumos de frutas u otros alimentos como papillas, etc.. ?(en meses, Si no le dió leche materna marque "00"**)** ☐☐

63. ¿Cuántos resfriados (estornudos, tos, moquillo nasal como agua, con o sin fiebre) ha tenido su hijo/ en sus primeros 12 meses de vida? (Si no ha tenido resfriados marque "00"**)** ☐☐ r

64 ¿Cuántos meses tenía su hijo/a cuando se resfrió por primera vez? Si no ha tenido resfriados marque "00 ☐☐

65 ¿Considera usted que su hijo/a vive en una zona con contaminación atmosférica? ☐ Si ☐ No
(humos de fábricas, tráfico intenso de vehículos, etc..)

65.1 Si ha respondido "SI", marque lo que considere oportuno ☐ mucho ☐ moderado ☐ poco

66. ¿Hay moho (hongos) o manchas de humedad en la casa que vive el niño/a? ☐ Si ☐ No

67. ¿Tiene su hijo/a las vacunas correspondientes a su edad completas? ☐ Si ☐ No

68. Número de hermanos/as que tiene su hijo/a Si no tiene hermanos marque "00" ☐☐
0

69. ¿Cuántas personas, adultos y niños, viven en total en la casa en la que vive el niño/a actualmente ☐☐

70. Ocupación del padre

☐ directivos, administradores, licenciados

☐ otros directivos téc. medios, diplomados

☐ cuadros intermedios, administrativos

☐ trabajadores manuales cualificados

☐ trabajadores manuales semicualificados

☐ trabajadores no cualificados

☐ otros casos,mal especificados

☐ actualmente no trabaja

71. Ocupación de la madre

☐ directivos, administradores, licenciados

☐ otros directivos téc. medios, diplomados

☐ cuadros intermedios, administrativos

☐ trabajadores manuales cualificados

☐ trabajadores manuales semicualificados

☐ trabajadores no cualificados

☐ otros casos,mal especificados

☐ actualmente no trabaja

72. Edad de la madre del niño (en años) ☐☐

73. ¿Qué se utiliza, predominantemente, en la cocina de la casa en la que vive el niño/a para freir?

☐ aceite de oliva ☐ mantequilla ☐ margarina ☐ otro tipo de aceite

46266

74. Durante el embarazo de su hijo/a, ¿con qué frecuencia comió o bebió lo siguiente?
(nunca u ocasionalmente, una o dos veces por semana , tres o más veces por semana, no lo comió por intolerancia o alergia, no sabe)

Carne (ternera, pollo, cordero, conejo, cerdo, ...)	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Hamburguesas cocinadas en casa	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Comida rápida: **Pizzas precocinadas, platos precocinados**	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Hamburguesas en burgers, perritos, etc..	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Frituras: croquetas, palitos merluza, etc..	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Pescado blanco	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Pescado azul	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Fruta fresca/zumo natural	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Verdura fresca	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Ensaladas	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Verdura cocinada	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Legumbres	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Cereales, incluido pan	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Pasta	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Arroz	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Mantequilla	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Margarina	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Frutos secos, o mantequilla de cacahuete/avellana	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Patatas cocinadas en casa (incluidas patatas fritas)	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Patatas fritas de bolsa y snacks (gusanitos, fritos, etc...)	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Leche	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Yogur	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Huevos	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Bollería industrial, galletas	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Bebidas con alcohol	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS
Bebidas gaseosas	☐ nunca Ocasion	☐ 1-2 veces sem	☐ 3 ó mas	☐ Alergia	☐ NS

75. ¿Durante cuánto tiempo en total tomó la madre del niño/a anticonceptivos orales antes de quedarse embarazada del niño/a al que se refiere este cuestionario? ☐ nunca ☐ menos de 1 año ☐ de 1 a 3 años ☐ de 4 a 6 años ☐ más de 6 años

76. Durante el embarazo del niño/a al que se refiere esta encuesta, ¿con qué frecuencia tomó la madre del niño paracetamol (termalgin, gelocatil, etc..)? ☐ nunca o menos de 1 vez al mes ☐ de 1 a 4 veces al mes ☐ más de 1 vez a la semana

Si tomó alguna vez paracetamol durante el embarazo ¿porqué causa lo hizo?

☐ cefalea/migraña ☐ fiebre ☐ dolor muscular ☐ otra causa

77. Durante el embarazo y parto del niño/a al que se refiere esta encuesta, ¿tuvo alguna de las siguientes complicaciones?

Hipertensión ..... ☐ Si ☐ No
Amenaza de aborto ..... ☐ Si ☐ No
Infecciones ..... ☐ Si ☐ No
Diabetes gestacional ..... ☐ Si ☐ No
Mala presentación ..... ☐ Si ☐ No
Rotura prematura de aguas. ☐ Si ☐ No
Problemas de la placenta .... ☐ Si ☐ No
Sufrimiento fetal, hipoxia.. ☐ Si ☐ No
Prematuridad ..... ☐ Si ☐ No
Vueltas de cordón ..... ☐ Si ☐ No
Trauma obstétrico en el niño ..... ☐ Si ☐ No
Forceps, ventosa ..... ☐ Si ☐ No
Cesárea ..... ☐ Si ☐ No

IKERKETA, BIZITZAKO LEHEN URTEKO ARNAS OSASUNARI

5657

1. Gaurko eguna Eguna ☐☐ Hila ☐☐ Urtea ☐☐☐☐

2. Haurraren jaioteguna Eguna ☐☐ Hila ☐☐ Urtea ☐☐☐☐

3. Inkesta betetzen ari den pertsona

☐ ama ☐ aita ☐ beste bat ☐ gurasoak

4. Semearen/alabaren sexua ☐ mutikoa ☐ neskatoa

5. Haurraren adina ☐☐ hilabete

6. Zenbat pisatu zuen jaoitzean?

☐ menos 1500 gr ☐ 1500 a 1999 gr ☐ 2000 a 2499 gr ☐ 2500 a 3499 gr ☐ 3500 gramo baino gehiago ☐ ez dut gogoan

7. Zenbat pisatzen du zure haurrak orain? (kg) ☐☐

8. Zer neurri izan zuen jaoitzean? (cm) ☐☐

9 Zer neurri du zure haurrak orain? (cm) ☐☐

Zure semearen arraza edo etnia

☐ zuria ☐ ijitoa ☐ iparafrikarra ☐ azpisahararra ☐ hispanoamerikar indiarra ☐ asiarra ☐ besteren bat

11. Zure semea/alaba Espainian jaio al zen? ☐ Bai ☐ ez

11.1. "EZ" erantzun baduzu, zein herrialdetan jaio zen zure semea/alaba?

☐☐☐☐☐☐☐☐☐☐☐☐☐☐

12. Aitaren jaioterria

☐ Espainia ☐ Europa, Espainia kenduta ☐ Afrika ☐ Iparramerik ☐ Hegoamerika eta ErtA ☐ Asia ☐ Australia/Ozeania

13 Amaren jaioterria

☐ Espainia ☐ Europa, Espainia kenduta ☐ Afrika ☐ Iparramerik ☐ Hegoamerika eta ErtA ☐ Asia ☐ Australia/Ozeania

14. Izan al du zure semeak/alabak txistu-hotsa edo soinua bularrean, bere bizitzaren aurreneko 12 hilabeteetan? ☐ Bai ☐ ez

15. Zenbat alditan izan du txistu-hotsa edo soinua bularrean bere bizitzaren aurreneko 12 hilabeteetan ☐☐
(Behin ere ez badu izan txistu-hotsik markatu 00)

16. Zein adinetan izan zuen zure semeak/alabak txistu-hotsa edo soinua bularrean lehen aldiz ☐☐ **hil.**

17. Zure semeak/alabak bularrean txistu-hotsak dituenean, hoztura arrunt batekin hasten dira?

☐ bai ☐ No ☐ ez du txistu-hotsik izan inoiz

18. ¿Gehiago mugitzean (lau-oinean iblitzean,haserretzean, laster edo barre egitean) sortu edo okerragotu al zaizkio zure semeari/alabari txistu-hotsak? ☐ bai ☐ No ☐ ez du txistu-hotsik izan inoiz

19. Zure semearen/alabaren bularreko txistu-hotsek eragiten al diote elikaduran? ☐ Bai ☐ ez ☐ ez du txistu-hotsik izan inoiz

20. Zure semearen/alabaren bularreko txistu-hotsek eragozpenak jartzen dizkizuete gurasoei eguneko jardueretan?

☐ Si ☐ ez ☐ ez du txistu-hotsik izan inoiz

21. Zure semearen/alabaren bularreko txistu-hotsek aldatu al dute familiaren bizimodua?

☐ ba ☐ ez ☐ ez du txistu-hotsik izan inoiz

22. Zure semeak/alabak izan al du bronkioak zabaltzeko botiken (bronkiodilatadoreen) tratamenduren bat nebulizazioetan edo inhalazioetan?Adibidez: Ventolín, Terbasmín, Berodual,Berotec, eta abar. ☐ bai ☐ ez ☐ ez dakit/ez dut erantzungo

23. Zure semeak/alabak izan al du kortikoide inhalatuen tratamenduren bat? Adibidez: Flixotide, Becloasma, Pulmicort, Fluinol, Inhalacor, Budesonida, Becotide, Pulmictan, Ribujet, eta abar.

☐ bai ☐ ez ☐ ez dakit/ez dut erantzungo

24. Zure semeak/alabak izan al du beste botika batzuen tratamenduren bat, adibidez antileukotrienoena (Singulair)? edo ketotifenoarena (Zasten, Ketasma)?

☐ bai, antileukotrienoak hartu zituen ☐ ketotifenoa hartu zuen ☐ bai, bi botika horiek hartu zituen ☐ ez ☐ ez dakit

25. Haurraren bizitzaren aurreneko 12 hilabeteetan zenbat alditan iratzarri zara gauean zure semeak/alabak itolarria edo bularrean txistu-hotsak izan

☐ inoiz ez ☐ inoiz edo behin (hilean behin baino ☐ noizbait (aste batzuetan hil batzuetan zehar) ☐ maiz (bi gauetan edo gehiagotan astean, ia hilero)

26. Haurraren bizitzaren aurreneko 12 hilabeteetan, bularreko txistu-hotsak edo soinuak eraman behar izan baituzue? ☐ bai ☐ ez

27. Haurraren bizitzaren aurreneko 12 hilabeteetan, bularreko txistu-hotsak edo soinuak hain garrantzitsuak izan dira, ezen zure semeak/alabak zailtasun handia baitzuen arnas hartzeko eta itotzen baitzen?

☐ Bai ☐ Ez

5657

28. Zure semea/alaba ospitalean egon al da, bere bizitzaren aurreneko 12 hilabeteetan, bularreko txistu-hotsak edo soinuak zeuzkalako?

☐ ez ☐ behin ☐ bi aldiz ☐ 3 aldiz ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 aldiz edo gehiagoz

29. Medikuren batek esan al dizu zure semeak/alabak asma daukala? ☐ Bai ☐ Ez

30. Izan al du zure semeak/alabak pneumonia edo bronkopneumonia, bere bizitzaren hasierako 12 hilabeteetan? ☐ bai ☐ ez

31. Zure semea/alaba ospitalean egon al da, bere bizitzaren aurreneko 12 hilabeteetan, pneumonia edo bronkopneumonia zeukalako?

☐ Bai ☐ ez

32. Izan al ditu zure semeak/alabak gorrituak azalean, azkura eman, eta agertu eta desagertzen direnak,gorputzeko edozein ataletan, alde batera utzita ahoaren ingurua, sudurra eta haur-ohialak hartzen duen aldea? ☐ bai ☐ ez

33. Erretzen al du haurraren amak (edo tutoreak) orain? ☐ Bai ☐ ez

33.1. Zenbat zigarro erretzen ditu egunean haurraren amak (edo tutoreak)? ☐☐ **zig** Erretzen ez badu, markatu "00"

34. Erretzen al du haurraren aitak (edo tutoreak) orain? ☐ bai ☐ ez

34.1. Zenbat zigarro erretzen ditu egunean haurraren aitak (edo tutoreak)? ☐☐ **zig** Erretzen ez badu, markatu "00"

35. Erre al zuen haurraren amak haurdunaldian? ☐ bai ☐ ez

35.1. "Bai" erantzun baduzu, markatu zein hiruhilekotan; erantzun bat baino gehiago marka dezakezu

☐ 1. lauhilekoan ☐ 2. lauhilekoan ☐ 3.lauhilekoan

36. Etxean bizi direnetan zenbatek erretzen ditu zigarroak, gurasoak barne direla? ☐

37. Haurraren aitak asma dauka? ☐ bai ☐ ez

38. Haurraren amak asma dauka? ☐ bai ☐ ez

39. Haurraren anaia , arreba edo ahizparen batek asma dauka? ☐ bai ☐ ez

40. Haurraren aitak ba al du sudur alergia (errinitis alergikoa, belar onduaren sukarra? ☐ bai ☐ ez

41. Haurraren amak a al du sudur alergia (errinitis alergikoa, belar onduaren sukarra? ☐ bai ☐ ez

42. Haurraren anaia , arreba edo ahizparren+ batek ba al du sudur alergia (errinitis alergikoa, belar onduaren sukarra ☐ bai ☐ ez

43. Haurraren aitak ba al du azaleko alergia (dermatitis alergikoa), alde batera utzita kontaktuzko dermatitis alergikoa ☐ bai ☐ ez

44. Haurraren amak ba al du azaleko alergia (dermatitis alergikoa), alde batera utzita kontaktuzko dermatitis alergikoa ☐ bai ☐ ez

45. Haurraren anaia , arreba edo ahizparen batek ba al du azaleko alergia (dermatitis alergikoa), alde batera utzita kontaktuzko dermatitis alergikoa?

☐ bai ☐ ez

46. Haurraren aitari egin al dizkiote alergiaren probak larruazalean edo odolean?

☐ ez ☐ bai eta alergia bazuen ☐ bai, baina ez zuen alergiarik

47. Haurraren amari egin al dizkiote alergiaren probak larruazalean edo odolean?

☐ ez ☐ bai eta alergia bazuen ☐ bai, baina ez zuen alergiarik

48. Haurraren anaia , arreba edo ahizparren+ bati egin al dizkiote alergiaren probak larruazalean edo odolean?

☐ ez ☐ bai eta alergia bazuen ☐ bai, baina ez zuen alergiarik

49. Joan al da zure semea/alaba haurtzaindegira, bere bizitzaren hasierako 12 hilabeteetan? ☐ bai ☐ ez

50. Zein adinetan hasi zen zure semea/alaba haurtzaindegian? ☐☐ **hil** . Oraindik joan ez bada, markatu "00"

51. Zenbatetan hartu ditu zure semeak/alabak produktu hauek (etxean egiten EZ direnak),bere bizitzaren aurreneko 12 hilabeteetan? Jogurta, budina petit suisse, patata frijitu ontziratuak mermeladak, txokolatea, freskagarriak, zukuak hautsetan, brickean edo botilan, nektarra, eta abarrak?

☐ behin ere ez ☐ hilean behin ☐ astean behin ☐ asteko egun guztietan

52. Haurra bizi den etxean, zein da berokuntzan gehienbat erabiltzen den erregaia?

☐ elektrizitatea ☐ gas zentrala ☐ gas estufa ☐ kerosenoa ☐ ikatza ☐ egurra ☐ besteren bat

53. Haurra bizi den etxean, zein da sukaldean gehienbat erabiltzen den erregaia?

☐ elektrizitatea ☐ gas zentrala ☐ gas estufa ☐ kerosenoa ☐ ikatza ☐ egurra ☐ besteren bat

54. Aire girotua al dago haurra bizi den etxean? ☐ Bai ☐ ez

55. Hurrengo maskotetatik zein dira haurrak etxean zituenak jaio zenean?

☐ ez zuen maskotarik ☐ txakurra ☐ katua ☐ hegaztiak ☐ untxia/hamsterra ☐ beste bat

56. Hurrengo maskotetatik zein dira haurrak etxean dituenak?

☐ ez zuen maskotarik ☐ txakurra ☐ katua ☐ hegaztiak ☐ untxia/hamsterra ☐ beste bat

57. Haurra bizi den etxeak moketa al dauka? ☐ bai ☐ ez

58. Haurra bizi den etxeak ba al dauka barnean bainugela osoa (konketa, komuna, dutxa/bainu-ontzia) ☐ bai ☐ ez

59. Haurra bizi den etxeko sukaldea (janaria prestatzeko tokia) etxearen barnean al dago? ☐ Bai ☐ ez

60. Haurra bizi den etxean ba al dago telefonoa (finkoa edo sakelakoa)? ☐ Bai ☐ ez

61. Markatu, mesedez, zein hezkuntza mailatara iritsi den haurraren ama

☐ oinarrizko hezkuntza, lehen hezkuntza edo bat ere ez (8 urtera edo gutxiagora arte)

☐ maila ertaineko hezkuntza, edo bigarren hezkuntza bukatu gabe (9-11 urte bitartean)

☐ maila ertaineko hezkuntza, edo bigarren osoa eta goi mailako hezkuntza (12 urtetik aurrera)

☐ unibertsitate hezkuntza

62. Zenbat hilabetetan zehar eman zenion haurrari ama-esnea bakar-bakarrik (ez esne egokituak, zerealak ☐☐

63. Zenbat hoztura (dominstikuak, eztula, ura bezalako mukia, sukarrarekin edo gabe) izan du zure semeak/alaba ☐☐ hozt

64. Zenbat hilabete zeuzkan zure semeak/alabak lehenbizikoz hotz hartu zuenean? ☐☐ hilabete

65 Semea/alaba atmosferaren kutsadura handia duen alderdian bizi al da, zure ustez? ☐ bai ☐ ez
(fabriketako keak, ibilgailuen trafiko handia, eta abar))

65.1 "Bai" erantzun baduzu, markatu egoki iruditzen zaizuna ☐ askokoa ☐ neurrikoa ☐ gutxikoa

66. Lizuna (onddoak) edo hezetasun orbanak al daude haurra bizi den etxean? ☐ Bai ☐ Ez

67. Bere adinari dagozkion txerto guztiak dauzka zure semeak/alabak? ☐ Bai ☐ ez

68. Zenbat anaia-arreba dauzka zure semeak/alabak? ☐☐ anai-arreba

69. Zenbat lagun bizi da, guztira, helduak eta haurrak hartuta, haurra bizi den etxean? ☐☐

70. Aitaren lana

☐ zuzendaria, administrtzailea, lizentziaduna
☐ bestelako zuzendari tekniko ertaina, diplomaduna
☐ erdiko buruak+, administrariak
☐ esku langile kualifikatuak
☐ esku langile erdikualifikatuak
☐ kualifikaziorik gabeko langileak
☐ gaizki zehaztutako beste kasu batzuk
☐ orain ez dago lanean

71. Amaren lana

☐ zuzendaria, administrtzailea, lizentziaduna
☐ bestelako zuzendari tekniko ertaina, diplomaduna
☐ koadro ertainak, administrariak
☐ esku langile kualifikatuak
☐ esku langile erdikualifikatuak
☐ kualifikaziorik gabeko langileak
☐ gaizki zehaztutako beste kasu batzuk
☐ orain ez dago lanean

72. Haurraren amaren adina ☐☐ urte

73. Zer erabiltzen da gehienbat, haurra bizi den etxeko sukaldean frijitzeko?

☐ oliba olioa ☐ gurina ☐ margarina ☐ beste olio mota bat

5657

74. Haurdunaldian, zure semeak/alabak, zenbatetan jan edo edan zituen honako hauek?noiz edo oso gutxitan / astean behin edo bitan / astean hirutan edo gehiagotan/, ez zuen jan intolerantzia edo alergiagatik/ , ez dakit /

Haragia (txahala, oilaskoa, axuria, untxia, txerria..)	☐ inoiz edo oso	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Etxean prestatutako hanburgesak	☐ inoiz edo oso	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED

Janari lasterra

Pizza aurrekozinatuak, plater aurrekozinatuak	☐ inoiz edo oso	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Hanburgesak burgerretan, hot dogak eta abarrak	☐ inoiz edo oso	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Frijituak: kroketak, legatz-taketak, eta abar.	☐ inoiz edo oso	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED

Arrain zuria	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Arrain urdina	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Fruta/zuku naturalak	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Berdura freskoa	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Entsaladak	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Berdura kozinatua	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Lekaleak	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Zerealak, ogia barne	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Pasta	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Arroza	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Gurina	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Margarina	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Fruitu lehorrak edo kakahuete edota hur manteka	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Etxean prestatutako patatak (frijituak barne)	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Poltsako patata frijituak eta snackak (gusanitoak, frijituak eta abarrak)	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Esnea	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Jogurta	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Arrautzak	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Industria opilak, gailetak	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Edari alkoholdunak	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED
Edari gasdunak	☐ inoiz edo oso gutxitan	☐ behin edo bitan	☐ hirutan edo gehiagotan	☐ alergiagatik	☐ ED

75. Zenbat denboran hartu zituen haurraren amak ahozko antisorgailuak galdera-zerrenda honetako haurrarekin haurdun gelditu baino

☐ behin ere ez ☐ urte bat baino gutxiago ☐ 1etik 3ra urte bitartean ☐ 4tik 6ra urte bitartean ☐ 6 urte edo gehiagotan

76. Galdera-zerrenda honetako haurraren haurdunaldian, zenbatetan hartu zituen haurraren amak parazetamola (termalgin, gelocatil, e.a..)?

☐ behin ere ez edo hilean behin baino utxiagotan ☐ hilean gutxienez behin edo gehienez ☐ astean behin baino gehiagotan

76.1. Haurdunaldian parazetamola hartu bazenuen, zergatik hartu zenuen?

☐ buruko mina/migraña ☐ sukarra ☐ muskuluetako mina ☐ beste zerbaitengatik

77. Galdera-zerrenda honetako haurraren haurdunaldian edo erditzerakoan, izan al zenuen konplikazio hauetakoren bat?
Mesedez, erantzun "Bai" edo "Ez" kasu bakoitzean

Hipertentsioa	☐ Bai	☐ Ez	**Sufrimendu fetala, hipoxia**	☐ Bai	☐ Ez
Umea galtzeko arriskua	☐ Bai	☐ Ez	**Prematuroa**	☐ Bai	☐ Ez
Infektzioak	☐ Bai	☐ Ez	**Zilbor-hestearen bueltak**	☐ Bai	☐ Ez
Haurdunaldiko diabetesa	☐ Bai	☐ Ez	**Trauma obstetrikoa haurrarengan**	☐ Bai	☐ Ez
Gaizki heldu zela	☐ Bai	☐ Ez	**Fortzeps, bentosa**	☐ Bai	☐ Ez
Garaia baino lehenago urak botatzea	☐ Bai	☐ Ez	**Zesarea**	☐ Bai	☐ Ez
Arazoak plazentarekin	☐ Bai	☐ Ez			

Appendix 2

Publications

Nutrición Hospitalaria

Nutr Hosp. 2015;31(4):1845-1852
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original/*Otros*

Estudio transversal de los factores que influyen en la adhesión a la dieta mediterránea en el embarazo

Ismael Álvarez Álvarez, Inés Aguinaga Ontoso, Blanca Marín Fernández, Francisco Guillén Grima y Hao Niu

Departamento de Ciencias de la Salud, Universidad Pública de Navarra. Pamplona. Navarra. España.

Resumen

Introducción: **La dieta mediterránea es un estilo de vida con efectos beneficiosos contrastados en el embarazo, tanto para la madre como para su descendencia. Sin embargo, se desconocen los factores que influyen en la adhesión a esta dieta.**

Objetivo: **Investigar los factores (nivel educativo, ocupación, lugar de nacimiento, número de hijos previo y edad) que influyen en la adhesión a la dieta mediterránea en mujeres embarazadas de la comarca de Pamplona.**

Material y métodos: **Utilizando los datos del Estudio Internacional de Sibilancias en Lactantes (EISL) en la comarca de Pamplona, se analizaron las asociaciones entre los alimentos y los factores. Se estableció una puntuación de dieta mediterránea y se estudiaron las puntuaciones de acuerdo a los factores.**

Resultados: **Se encontraron diferencias significativas en la puntuación de dieta mediterránea según el nivel de estudios (p=<0,001), la ocupación (p=0,015) y la edad (p=<0,001).**

Conclusión: **Mujeres con mejor nivel educativo, mejor ocupación y mayor edad muestran una mayor afinidad a la dieta mediterránea durante el embarazo.**

(*Nutr Hosp*. 2015;31:1845-1852)

DOI: 10.3305/nh.2015.31.4.8420

Palabras clave: *Embarazo. Dieta mediterránea.*

CROSS-SECTIONAL STUDY OF FACTORS INFLUENCING ADHERENCE TO THE MEDITERRANEAN DIET IN PREGNANCY

Abstract

Introduction: **Mediterranean diet is a lifestyle with contrasted beneficial effects on pregnancy, for both the mother and her offspring. However, factors influencing adherence to this diet are unknown.**

Objective: **To investigate the factors (educational level, occupation, place of birth, number of previous children and age) that influence adherence to the Mediterranean diet in pregnant women in the region of Pamplona.**

Material and methods: **Using the data from the Estudio Internacional de Sibilancias en Lactantes (EISL) in the region of Pamplona, associations between food and factors were analysed. A score of Mediterranean diet was established and the scores according to the factors were studied.**

Results: **Significant differences in the Mediterranean diet score by level of education (p=<0,001), occupation (p=0,015) and age (p=<0,001) were found.**

Conclusion: **Women with better education, better occupation and older show a greater affinity to the Mediterranean diet during pregnancy.**

(*Nutr Hosp*. 2015;31:1845-1852)

DOI: 10.3305/nh.2015.31.4.8420

Key words: *Pregnancy. Mediterranean Diet.*

Introducción

La alimentación materna durante el embarazo influye tanto en la madre como en los recién nacidos, con efectos tales como riesgo de un parto prematuro[1] y pre eclampsia[2], o el riesgo de padecer enfermedades alérgicas en la infancia[3].

La dieta mediterránea se caracteriza por el consumo abundante de alimentos vegetales (frutas, verduras, cereales, legumbres,…), un consumo moderado de productos lácteos, pescados y carne de aves, y un bajo consumo de carnes rojas, siendo el aceite de oliva la principal fuente de grasas[4].

Los beneficios de esta dieta durante el embarazo han sido previamente estudiados, tanto para las madres, que experimentan un menor incremento de peso durante el embarazo[5], como para la descendencia, siendo un factor protector de síntomas de asma y atopía[6], con efectos positivos en la talla y peso al nacer[7-9], y disminuyendo el riesgo de espina bífida[10] y gastrosquisis[11].

No obstante, a pesar de conocerse los numerosos beneficios asociados a una alimentación saludable, no exis-

Correspondencia: Ismael Álvarez Álvarez.
Facultad de Ciencias de la Salud.
Universidad Pública de Navarra.
Avenida de Barañain s/n. 31008 Pamplona.
E-mail: alvarez.80114@e.unavarra.es

Recibido: 26-XI-2014.
Aceptado: 20-XII-2014.

ten estudios sobre qué factores influyen en la alimentación durante el embarazo en las mujeres españolas.

El objetivo de este estudio transversal ha sido investigar qué factores (nivel de educación, ocupación, lugar de nacimiento, número de hijos previos y edad) influyen en la adhesión a la dieta mediterránea en mujeres embarazadas en la comarca de Pamplona.

Material y métodos

Población del estudio

La población del estudio son las madres de los lactantes incluidos en el Estudio Internacional de Sibilancias en Lactantes (EISL)[12] en la comarca de Pamplona. Este estudio observacional transversal multicéntrico se llevó a cabo entre los años 2006 y 2008, y en él participaron 20 centros de salud.

Las familias participantes eran aquellas que acudían con su hijo/a a la revisión de los 15 meses de edad, según establecía el Programa de Niño Sano, y quisieron participar en el estudio.

Recolección de datos

Cuando las familias con su hijo/a acudían al centro de salud a la revisión de los 15 meses, una enfermera de pediatría les entregaba una carta de presentación del estudio, les solicitaba su colaboración y se les indicaba las instrucciones para rellenar el cuestionario.

Los cuestionarios se podían entregar en la siguiente visita, o remitirlos por correo a la Universidad Pública de Navarra. La recogida de cuestionarios desde los centros de salud se hizo por correo, y en ocasiones puntuales se hizo una recogida en el propio centro.

Con el fin de evitar problemas con el tratamiento de datos personales derivados de la Ley Orgánica 5/1992, de Regulación del Tratamiento Automatizado de los Datos de Carácter Personal, no se recogieron datos personales.

El cuestionario utilizado fue el modelo estándar utilizado en el EISL, utilizando una versión en castellano y otra en euskera. Este cuestionario ha sido validado[13].

Se utilizaron preguntas que hacen referencia a la madre: "Lugar de nacimiento de la madre", "Nivel de educación alcanzado por la madre del niño/a", "Ocupación de la madre", "Edad de la madre", y al número de hijos previos con la pregunta: "Número de hermanos que tiene su hijo/a".

En el cuestionario se incluye un apartado dedicado a la alimentación materna en el embarazo, que consta de 26 ítems que incluyen diferentes grupos de alimentos: carne, comida rápida, pescado, fruta, verduras y ensaladas, legumbres, cereales, pasta, arroz, mantequilla y margarina, frutos secos, patatas, snacks, leche, yogur, huevos, bollería industrial y bebidas alcohólicas y gaseosas.

Se preguntó la frecuencia con la que se consumieron los alimentos, siendo las posibles respuestas: "Nunca", "1-2 veces por semana", "3 o más veces por semana", "Alergia" y "No sabe".

Se desarrolló una puntuación de la dieta mediterránea en base a la clasificación usada por García-Marcos et al.[14]. Como alimentos de una dieta mediterránea se incluyeron: pescado (blanco y azul), fruta, verdura fresca y cocinada, ensaladas, legumbres, cereales, pasta, arroz, patatas y frutos secos, valorando su consumo con una puntuación entre 0 (Nunca), 1 (1-2 veces por semana), y 2 (3 o más veces por semana). Los alimentos considerados no adecuados en la dieta mediterránea fueron: carne, comida rápida, leche y snacks, puntuando su consumo entre 2 (Nunca), 1 (1-2 veces por semana), y 0 (3 o más veces por semana).

Se excluyeron del estudio aquellas mujeres que no habían contestado la frecuencia de consumo de más de seis alimentos incluidos en la encuesta.

Análisis estadístico

Se utilizó el test chi cuadrado de independencia con el método Montecarlo para cada alimento, con un intervalo de confianza del 95%, según el nivel de educación, la ocupación y el lugar de nacimiento de la madre. Para la diferencia entre las medias según el número de hermanos y la edad de la madre se utilizó un test ANOVA.

En la puntuación de la dieta mediterránea se calculó la media y la desviación típica, y la puntuación mínima y máxima de cada grupo, y se estudiaron las diferencias mediante un test ANOVA.

El nivel de significación estadística se estableció en $\alpha<0,05$.

Todos los cálculos se hicieron con el software IBM SPSS Statistics versión 20 (Chicago, Illinois, EEUU).

Resultados

El número total de participantes en el EISL fue 1065 mujeres. De ellas, 1051 (98,69%) cumplieron con los requisitos y fueron la muestra de este estudio.

En ninguno de los factores estudiados existieron diferencias significativas en el consumo de carne, yogur y huevos.

Las mujeres con un menor nivel de estudios comían más platos precocinados, hamburguesas de burguers, frituras, y snacks. Por el contrario, el consumo de pescado azul, verdura fresca y cocinada, y cereales fue mayor en mujeres con un nivel más alto de estudios (Tabla I).

El consumo de hamburguesas caseras y en burguers fue mayor en mujeres con una peor ocupación. La misma tendencia se observó en el caso de las frituras, ensaladas, verdura fresca y cocinada, y margarina. Por otro lado, son las mujeres con mejores ocupaciones las que comían significativamente menos arroz (tabla I).

Tabla I
Asociación entre la frecuencia de consumo de alimentos y el nivel de estudios, ocupación y lugar de nacimiento de la madre

	Nivel de estudios			*Ocupación*			*Lugar de nacimiento*		
	N	*p*	*IC 95%*	*N*	*p*	*IC 95%*	*N*	*p*	*IC 95%*
Carne	1029	0,069	0,064-0,074	1012	0,370	0,360-0,379	1030	0,368	0,358-0,377
Hamburguesas caseras	1005	0,101	0,095-0,107	988	0,001	<0,001-0,001	1006	0,012	0,010-0,014
Platos precocinados	989	0,001	<0,001-0,002	973	0,082	0,077-0,088	992	0,006	0,004-0,007
Hamburguesas burguers	977	0,002	0,001-0,003	964	0,002	0,001-0,003	979	0,003	0,002-0,004
Frituras	986	<0,001	<0,001-<0,001	969	<0,001	<0,001-<0,001	989	0,001	<0,001-0,001
Pescado blanco	1027	0,511	0,501-0,520	1011	0,208	0,200-0,216	1027	0,001	<0,001-0,001
Pescado azul	998	0,006	0,004-0,007	980	0,244	0,236-0,253	998	0,014	0,012-0,016
Fruta fresca	1038	0,138	0,131-0,145	1021	0,422	0,412-0,431	1039	0,768	0,760-0,776
Verdura fresca	1035	0,012	0,010-0,014	1018	0,032	0,028-0,035	1035	0,147	0,140-0,153
Ensalada	1026	0,149	0,142-0,156	1018	0,036	0,032-0,040	1036	0,817	0,810-0,825
Verdura cocinada	1027	0,006	0,004-0,007	1010	0,013	0,011-0,015	1028	0,160	0,153-0,167
Legumbres	1033	0,378	0,368-0,388	1016	0,435	0,425-0,445	1033	0,002	0,001-0,003
Cereales	1020	0,039	0,035-0,043	1002	0,854	0,847-0,861	1018	0,027	0,024-0,030
Pasta	1024	0,204	0,196-0,212	1005	0,596	0,586-0,605	1024	0,036	0,033-0,040
Arroz	1021	0,190	0,183-0,198	1003	0,007	0,005-0,009	1021	<0,001	<0,001-<0,001
Mantequilla	1003	0,685	0,676-0,694	987	0,052	0,047-0,056	1004	<0,001	<0,001-<0,001
Margarina	994	0,171	0,164-0,179	980	0,045	0,041-0,049	995	0,024	0,021-0,027
Frutos secos	1010	0,137	0,130-0,143	994	1,000	0,999-1,000	1009	0,938	0,934-0,943
Patatas	1014	0,164	0,156-0,171	999	0,062	0,057-0,066	1015	0,040	0,036-0,043
Snacks	998	0,026	0,023-0,029	984	0,260	0,251-0,269	1001	0,266	0,257-0,275
Leche	1031	0,217	0,209-0,225	1014	0,522	0,512-0,531	1031	0,008	0,006-0,010
Yogur	1038	0,086	0,080-0,091	1020	0,631	0,622-0,640	1038	0,277	0,268-0,285
Huevos	1023	0,619	0,610-0,629	1006	0,195	0,187-0,203	1024	0,294	0,285-0,303
al	1021	0,188	0,180-0,195	1004	0,255	0,247-0,264	1023	0,853	0,846-0,860
Bebidas alcohólicas	1028	0,345	0,336-0,354	1011	0,411	0,401-0,420	1028	0,040	0,036-0,044
Bebidas gaseosas	1024	0,089	0,083-0,094	1008	0,165	0,157-0,172	1023	0,049	0,045-0,054

Según el lugar de nacimiento, existieron diferencias significativas en el consumo de hamburguesas caseras y de burguers, platos precocinados, frituras, pescado blanco y azul, legumbres, cereales, pasta, arroz, mantequilla y margarina, patatas, leche, y bebidas alcohólicas y gaseosas (Tabla I).

En la tabla II se exponen los resultados que muestran que aquellas mujeres que tuvieron más hijos comieron significativamente más hamburguesas caseras, frituras, mantequilla y margarina. Asimismo, son estas mujeres las que más frecuentemente comían pescado blanco durante el embarazo.

Las embarazadas más jóvenes consumieron significativamente más platos precocinados y hamburguesas en burguers, arroz, y bebidas gaseosas. Por el contrario, aquellas mujeres de más edad, durante el embarazo, comieron más pescado blanco y azul, fruta fresca, ensaladas, verdura fresca y cocinada, cereales, margarina, y frutos secos (Tabla III).

En la tabla IV se exponen las puntuaciones de la dieta mediterránea, que muestran diferencias significativas en el nivel de estudios (p=<0,001), la ocupación (p=0,015), y la edad de la madre (p=<0,001). No se encontraron diferencias significativas según el lugar de nacimiento de la madre o el número previo de hijos.

Discusión

En este estudio los resultados sugieren que la adhesión a la dieta mediterránea por parte de mujeres embarazadas es significativamente mayor en aquellas que poseen un mejor nivel educativo, una ocupación de más nivel, y en mujeres con mayor edad.

Las mujeres embarazadas con un mejor nivel educativo presentaron una mayor adherencia a la dieta mediterránea, una afirmación refrendada por otros estudios[15,16]. Esto puede ser debido a que un mayor nivel educativo puede indicar un mayor autoconocimiento de la salud y cuidado personal, lo que puede influir en adoptar una dieta saludable, más aún en el embarazo. El hecho de poseer conocimientos sobre nutrición está asociado a la adhesión a la dieta mediterránea[17], pudiendo estar este hecho relacionado con un mayor nivel educativo.

Aquellas mujeres con unos mayores ingresos, medidos por su ocupación, mostraron una mayor adherencia a la dieta mediterránea, un resultado concordante con otros estudios[16,18]. Un mayor poder adquisitivo permite comprar una variedad mayor de alimentos. Además, una parte de los alimentos que forman parte de la dieta mediterránea tienen precios altos (frutas, pescados), lo que puede dificultar el acceso para alguna gente con ingresos más bajos, que seleccionará productos más baratos, pese a que no se adapten a los estándares de la dieta mediterránea.

La edad es otro factor que muestra diferencias significativas, siendo las mujeres de mayor edad las que muestran una mayor adhesión a la dieta mediterránea, algo que también se encontró en otros estudios[19]. Una posible explicación es que las mujeres más mayores suelen tener mayor conciencia de su salud y tienden a cuidarse más, como sucede en este caso, con la elección de una dieta más saludable.

No obstante, hay estudios que con resultados contrarios a los encontrados. Un estudio en población marroquí[20] no encontró ninguna asociación entre la adhesión a la dieta mediterránea y la edad, los ingresos o el nivel educativo. Un posible motivo que explique este hecho puede venir de las diferencias culturales que existen entre Marruecos y los países europeos, existiendo en Marruecos estándares dietéticos adecuados y asumidos por la población, sin importar los factores que sí influyen en las dietas de otros países.

Los resultados de otro estudio portugués[21] mostraron que las familias con un mejor nivel socioeconómico tienen una dieta más pobre. Esto está motivado, según dicho estudio por cambios en los patrones de alimentación al cambiar el estilo de vida (la vida urbana y mayores ingresos conducen a consumir otro tipo de alimentos menos saludables que las personas que viven en áreas rurales y mantienen una dieta más saludable). En nuestro estudio no se ha tenido en cuenta el entorno donde viven las familias, pero los resultados hallados indicaron que las mujeres con mayor nivel socioeconómico, al contrario de lo encontrado en este estudio, mostraron una mayor adhesión.

Las fortalezas de este estudio son la amplia muestra estudiada, más aun tratándose de una población de tamaño pequeño como es la comarca de Pamplona, y que el estudio haya sido dirigido a estudiar patrones de alimentación en mujeres embarazadas, un colectivo sobre el que apenas existe bibliografía en relación a este tema.

Las debilidades serían el hecho de no disponer de un cuestionario más detallado para este tipo de estudios, ya que el modelo utilizado, si bien ha sido validado, fue concebido inicialmente para estudios de otra índole. Otra de las debilidades es el posible sesgo de recuerdo que pueda existir, ya que las madres respondían al cuestionario cuando su hijo acudía a una revisión a los 15 meses de edad.

Los resultados obtenidos según el factor de lugar de nacimiento de la madre pueden ser confusos, ya que la población extranjera participante en el estudio fue muy minoritaria. Otros estudios centrados estos colectivos sería útil para hallar resultados más sólidos.

En conclusión, aquellas mujeres con un mayor nivel educativo, una mejor ocupación y mayor edad muestran una mayor adhesión a la dieta mediterránea, un estilo de vida con beneficios contrastados, tanto para la madre como para su descendencia.

Sería conveniente realizar más estudios sobre este tema, con cuestionarios más amplios y específicos, a fin de contrastar si los resultados obtenidos en este estudio son acordes, y en ese caso, plantear políticas para la promoción de la dieta mediterránea entre aquellas mujeres embarazadas que muestren adhesiones más bajas, vistos los numerosos beneficios que conlleva una alimentación saludable, tanto para la madre como para el recién nacido.

Tabla II
Diferencias en la frecuencia de consumo de alimentos y el número de hijos previos

	Nunca			*1-2 veces/semana*			*3 o más veces/semana*			
	N	*Media*	*Desv. típica*	*N*	*Media*	*Desv. típica*	*N*	*Media*	*Desv. típica*	*p*
Carne	18	0,50	0,618	273	0,54	0,652	748	0,63	0,848	0,267
Hamburguesas caseras	828	0,59	0,753	177	0,66	0,988	10	1,30	1,418	0,014
Platos precocinados	730	0,63	0,850	254	0,53	0,639	14	0,79	1,051	0,171
Hamburguesas burguers	912	0,59	0,787	68	0,53	0,634	7	1,14	1,345	0,143
Frituras	658	0,55	0,816	321	0,67	0,677	17	1,53	1,841	<0,001
Pescado blanco	63	0,43	0,560	791	0,59	0,799	184	0,76	0,905	0,008
Pescado azul	195	0,59	0,790	728	0,63	0,801	84	0,55	0,782	0,627
Fruta fresca	26	0,65	0,629	151	0,61	0,766	872	0,61	0,811	0,963
Verdura fresca	33	0,70	0,770	211	0,57	0,786	801	0,62	0,812	0,594
Ensalada	42	0,48	0,634	187	0,58	0,678	817	0,63	0,842	0,389
Verdura cocinada	81	0,51	0,654	255	0,56	0,801	702	0,64	0,821	0,171
Legumbres	54	0,59	1,091	796	0,60	0,764	193	0,65	0,896	0,787
Cereales	15	0,27	0,458	125	0,51	0,643	889	0,63	0,834	0,080
Pasta	25	0,4	0,500	828	0,60	0,788	181	0,70	0,902	0,140
Arroz	69	0,67	0,634	838	0,60	0,795	123	0,68	0,986	0,481
Mantequilla	775	0,58	0,726	160	0,58	0,723	77	0,88	1,386	0,006
Margarina	797	0,60	0,773	130	0,58	0,735	77	0,84	1,247	0,034
Frutos secos	640	0,59	0,756	292	0,64	0,864	87	0,77	1,020	0,119
Patatas	231	0,57	0,693	621	0,61	0,835	172	0,66	0,860	0,534
Snacks	711	0,60	0,848	246	0,62	0,651	51	0,73	0,896	0,522
Leche	45	0,58	0,621	54	0,48	0,606	941	0,62	0,827	0,477
Yogur	75	0,57	0,888	189	0,55	0,687	785	0,63	0,827	0,467
Huevos	13	0,69	0,855	671	0,58	0,744	349	0,64	0,871	0,456
Bollería industrial	291	0,64	0,942	438	0,57	0,651	303	0,63	0,871	0,441
Bebidas alcohólicas	1015	0,61	0,811	15	0,60	0,507	8	1,00	1,069	0,399
Bebidas gaseosas	648	0,58	0,699	271	0,65	1,032	115	0,70	0,794	0,203

Tabla III
Diferencias en la frecuencia de consumo de alimentos y la edad de la madre

	Nunca			*1-2 veces/semana*			*3 o más veces/semana*			
	N	*Media*	*Desv. típica*	*N*	*Media*	*Desv. típica*	*N*	*Media*	*Desv. típica*	*p*
Carne	17	32,47	4,446	271	33,71	4,000	747	33,83	3,855	0,350
Hamburguesas caseras	828	33,87	3,915	176	33,52	3,752	10	33,70	5,376	0,555
Platos precocinados	729	34,11	3,882	253	33,36	3,699	14	31,64	5,401	0,003
Hamburguesas burguers	911	33,89	3,789	68	32,41	4,382	7	31,71	7,158	0,004
Frituras	656	33,96	3,845	320	33,79	3,652	17	31,71	6,263	0,053
Pescado blanco	63	31,89	5,150	787	33,85	3,683	184	34,34	4,010	<0,001
Pescado azul	196	32,92	4,074	725	34,14	3,720	83	33,83	4,480	<0,001
Fruta fresca	26	32,96	5,378	149	33,20	3,615	870	33,98	3,855	0,037
Verdura fresca	33	33,27	4,618	210	32,85	4,195	800	34,11	3,727	<0,001
Ensalada	40	32,25	4,205	187	33,37	4,014	815	33,98	3,856	0,006
Verdura cocinada	80	33,39	4,759	254	32,82	3,864	701	34,26	3,715	<0,001
Legumbres	53	33,79	3,800	796	33,85	3,784	191	33,81	4,167	0,990
Cereales	15	30,40	5,654	121	33,21	3,998	889	33,91	3,829	0,001
Pasta	25	32,40	4,010	826	33,88	3,853	180	33,79	4,167	0,175
Arroz	68	34,00	4,200	837	33,99	3,623	121	32,81	5,034	0,007
Mantequilla	774	33,93	3,723	158	33,35	4,269	77	33,95	4,746	0,226
Margarina	795	33,90	3,797	129	33,13	4,247	77	34,40	4,133	0,048
Frutos secos	637	33,58	3,847	291	34,34	3,971	87	34,11	3,916	0,019
Patatas	230	34,13	3,506	619	33,79	3,845	172	33,49	4,526	0,250
Snacks	709	33,89	3,855	245	33,87	3,758	51	33,10	3,946	0,364
Leche	44	33,27	4,712	52	33,69	3,928	939	33,83	3,875	0,641
Yogur	74	33,70	4,312	187	33,53	3,965	783	33,89	3,863	0,528
Huevos	12	34,83	4,130	670	33,84	3,817	348	33,76	4,073	0,635
Bollería industrial	290	33,93	4,049	437	33,66	3,824	302	33,91	3,903	0,564
Bebidas alcohólicas	1012	33,80	3,894	14	35,14	3,416	8	33,75	5,285	0,441
Bebidas gaseosas	647	34,15	3,819	269	33,29	3,966	115	33,48	3,881	0,005

Tabla IV
Puntuaciones de la dieta mediterránea según los factores

	N	*Media*	*Desv. típica*	*Mínimo*	*Máximo*	*p*
Nivel de educación						<0,001
Educación universitaria	537	24,24	3,049	7	33	
Educación secundaria completa	416	23,61	3,291	14	32	
Educación secundaria incompleta	57	24,14	3,335	15	32	
Educación básica	30	21,93	3,648	12	29	
Ocupación						0,015
Directivos, administrativos	160	24,66	2,668	17	31	
Otros directivos, técnicos medios	144	24,26	2,938	15	31	
Cuadros intermedios, administrativos	219	23,78	3,146	14	33	
Trabajadores manuales cualificados	126	23,83	3,505	14	32	
Trabajadores manuales semicualificados	32	23,47	3,121	14	30	
Trabajadores manuales no cualificados	28	23,68	3,255	17	29	
Otros casos, mal especificado	36	24,39	2,930	16	29	
Actualmente no trabaja	278	23,47	3,548	7	32	
Lugar de nacimiento						0,204
España	954	23,97	3,200	7	33	
Europa	31	23,13	3,149	16	28	
América	48	23,19	3,606	14	30	
Resto del mundo	8	23,88	3,563	17	27	
Edad de la madre						<0,001
≥40	77	24,57	3,105	14	30	
35-39	375	24,27	3,006	14	33	
30-34	471	23,87	3,013	14	32	
25-29	108	22,66	3,824	7	29	
≤25	16	22,63	5,536	12	30	
Número previo de hijos						0,861
0	533	23,90	3,338	7	33	
1	434	23,90	3,098	12	32	
2	63	23,78	3,195	15	30	
3	10	23,30	2,312	20	27	
4 o más	10	25,40	1,897	23	28	

Referencias

1. Khoury J, Henriksen T, Christophersen B, Tonstad S. Effect of cholesterol-lowering diet on maternal cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. *Am J Obstet Gynecol* 2005; 193(4):1292-1301.
2. Oken E, Ning Y, Rifas-Shiman SL, Rich-Edwards JW, Olsen SF, Gillman MW. Diet during pregnancy and risk of preeclampsia or gestational hypertension. *Ann Epidemiol* 2007; 17(9):663-668.
3. Sausenthaler S, Koletzko S, Schaaf B, Lehmann I, Borte M, Herbarth O, et al. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. *Am J Clin Nutr* 2007; 85(2):530-537.
4. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, et al. Mediterranean diet pyramid: a cultural model for healthy eating. *Am J Clin Nutr* 1995; 61(suppl.):1402S-1406S.
5. Silva-Del Valle MA, Sánchez-Villegas A, Serra-Majem L. Association between the adherence to the Mediterranean diet and overweight and obesity in pregnant women in Gran Canaria. *Nutr Hosp* 2013; 28(3):654-659.
6. 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(6):507-513.
7. Knudsen VK, Orozova-Bekkevold IM, Mikkelsen TB, Wolff S, Olsen SF. Major dietary patterns in pregnancy and fetal growth. *Eur J Clin Nutr* 2008; 62(4):463-470.
8. Rodríguez-Bernal CL, Rebagliato M, Iñiguez C, Vioque J, Navarrete-Muñoz EM, Murcia M, et al. Diet quality in early pregnancy and its effects on fetal growth outcomes: the Infancia y Medio Ambiente (Childhood and Environment) Mother and Childhood Cohort Study in Spain. *Am J Clin Nutr* 2010; 91(6):1659-1666.
9. Timmermans S, Steegers-Theunissen RP, Vujkovic M, den Breeijen H, Russcher H, Lindemans J, et al. The Mediterranean diet and fetal size parameters: the Generation R study. *Br J Nutr* 2012; 108(8):1399-1409.
10. Vujkovic M, Steegers EA, Looman CW, Ocké MC, van der Spek PJ, Steegers-Theunissen RP. The maternal Mediterranean dietary pattern is associated with a reduced risk of spina bifida in the offspring. *BJOG* 2009; 116(3):408-415.
11. Cánovas-Conesa A, Gomariz-Peñalver V, Sánchez-Sauco MF, Jaimes Vega DC, Ortega-García JA, Aranda García MJ, et al. Asociación de la adherencia a la dieta mediterránea al inicio del embarazo y riesgo de gastrosquisis en la descendencia: un estudio de casos-controles. *Cir Pediatr* 2013; 26(1):37-43.
12. Mallol J, Garcia-Marcos L. Estudio internacional de Sibilancias en Lactantes (EISL) *http://www.respirar.org/pdf/eisl/eisl_visiondeconjunto.pdf* 2006 (Consultada el día 23/9/2014)
13. Chong Neto HJ, Rosario N, Dela Bianca AC, Solé D, Mallol J. Validation of a questionnaire for epidemiologic studies of wheezing in infants. *Pediatr Allergy Immunol* 2007; 18(1):86-87.
14. García-Marcos L, Miner Canflaca I, Batlles Garrido J, López-Silvarrey Varela A, García-Hernández G, Guillén Grima F, et al. Relationship of asthma and rhinoconjunctivitis with obesity, exercice and Mediterranean diet in Spanish schoolchildren. *Thorax* 2007; 62(6):503-508.
15. Hu EA, Toledo E, Diez-Espino J, Estruch R, Corella D, Salas-Salvado J, et al. Lifestyles and risk factors associated with the adherence to the Mediterranean diet: a baseline assessment of the PREDIMED trial. *PLoS One*, 8(4):e60166.
16. Olmedo-Requena R, Gómez Fernández J, Amezcua Prieto C, Mozas Moreno J, Bueno-Cavanillas A, Jiménez-Moleón JJ. Factors associated with a low adherence to a Mediterranean diet pattern in healthy Spanish women before pregnancy. *Public Health Nutr* 2014; 17(3):648-656.
17. Bonaccio M, Di Castelnuovo A, Costanzo S, De Lucia F, Olivieri M, Donati MB, et al. Nutrition knowledge is associated with higher adherence to Mediterranean diet and lower prevalence of obesity. Results from the Moli-sani study. *Appetite* 2013; 68:139-146.
18. Bonaccio M, Bonnani AM, Di Castelnuovo A, De Lucia F, Donati MB, de Gaetano, G, et al. Low income is associated with poor adherence to a Mediterranean diet and a higher prevalence of obesity: cross-sectional results from the Moli-sani study. *BMJ Open* 2012; 2(6):e001685.
19. León-Muñoz LM, Guallar-Castillón P, Graciani A, López-García E, Mesas AE, Aguilera MA, et al. Adherence to the Mediterranean diet pattern has declined in Spanish adults. *J Nutr* 2012; 142(10):1843-1850.
20. El Rhazi K, Nejjari C, Romaguera D, Feart C, Obtel M, Zidouh A, et al. Adherence to a Mediterranean diet in Morocco and its correlates: cross-sectional analysis of a sample of the adult Moroccan population. *BMC Public Health* 2012; 12(1):345-352.
21. Rodrigues SSP, Caraher M, Trichopoulou A, De Almeida MDV. Portuguese households' diet quality (adherence to Mediterranean food pattern and compliance with WHO population dietary goals): trends, regional disparities and socioeconomic determinants. *Eur J Clin Nutr* 2008; 62(11):1263-1272.

Allergol Immunopathol (Madr). 2016;44(5):415–421

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

Prevalence and risk factors for wheezing in infants in the region of Pamplona, Spain

I. Alvarez-Alvarez[a,*], H. Niu[a], I. Aguinaga-Ontoso[a], F. Guillen-Grima[a,b,c]

[a] *Department of Health Sciences, Public University of Navarre, Pamplona, Spain*
[b] *IDISNA, Navarra's Institute for Health Research, Pamplona, Spain*
[c] *Preventive Medicine, University of Navarra Clinic, Pamplona, Spain*

Received 11 May 2015; accepted 11 August 2015
Available online 8 January 2016

KEYWORDS
Asthma;
Epidemiology;
Infant;
Prevalence;
Risk factors;
Wheezing

Abstract
Background: Wheezing in the first year of life affects the baby's and family's quality of life. Risk factors such as male gender, nursery attending or a family history of asthma, and protective factors such as breastfeeding more than six months have been previously described. The aim of this study is to study the prevalence and risk factors for wheezing ever and recurrent wheezing in the first year of life in infants in the region of Pamplona, Spain.
Material and methods: This cross-sectional study was part of the International Study of Wheezing in Infants (Estudio Internacional de Sibilancias en Lactantes, EISL). Between 2006 and 2008, participating families answered a standardised validated questionnaire on respiratory symptoms, environmental factors or family issues. An analysis with the chi square test (statistical significance $p < 0.05$) identified the risk factors for wheezing ever and recurrent wheezing, which were assessed using logistic regression.
Results: 1065 questionnaires were answered. The prevalence of wheezing ever and recurrent wheezing were 31.2% and 12.3%, respectively. Male gender ($p = < 0.001$), a history of pneumonia ($p = < 0.001$) or nursery attendance ($p = < 0.001$) were some of the risk factors found for wheezing ever. Infant eczema ($p = < 0.001$), nursery attendance ($p = < 0.001$) or prematurity ($p = < 0.001$) were risk factors for recurrent wheezing. No associations with duration of breastfeeding ($p = 0.116$ and $p = 0.851$) or mould stains at home ($p = 0.153$ and $p = 0.992$) were found.
Conclusion: The study of prevalence and risk factors for wheezing shows the importance of this public health problem, and allows the development of control and treatment strategies against preventable factors.

* Corresponding author.
E-mail address: alvarez.80114@e.unavarra.es (I. Alvarez-Alvarez).

http://dx.doi.org/10.1016/j.aller.2015.08.002

Introduction

Wheezing in infants is an important problem, affecting children's health-related quality of life,[1] and can lead to asthma in childhood.[2,3]

Prevalence of wheezing ever in infants varies across different regions, from 29% in countries in Northern Europe, to 48% in countries in Southern Europe, and 27% in the United States of America (USA).[4] Previous studies have found associations between rainy weather and severe current wheeze in schoolchildren,[5] and stronger associations of some risk and protective factors of recurrent wheezing when latitude increases.[6]

Several risk factors have been described, with the most important being male sex, familiar history of asthma, nursery attendance, history of pneumonia, smoking during pregnancy, mould stains in the house and breastfeeding fewer than six months.[7–9] Protective factors such as breastfeeding more than eight months[10] and adherence to the Mediterranean diet[11] have been found.

Although previous studies about wheezing in infants have been conducted, none of them have studied the epidemiology of the disease in the North of Spain. The aim of this cross-sectional study is to examine the prevalence and risk factors of wheezing ever and recurrent wheezing in the first year of life in infants from the region of Pamplona.

Materials and methods

Study population

This study was part of the International Study of Wheezing in Infants (in Spanish, Estudio Internacional de Sibilancias en Lactantes, EISL), an observational cross-sectional multicentre study conducted in countries of Europe and Latin America.[12]

In the region of Pamplona, this study was conducted between 2006 and 2008, where 20 primary care centres participated. The population of the study were the infants of the metropolitan area of Pamplona (an urban area consisting of Pamplona and adjacent cities) who went to a health check-up at 15 months of age. The sample size was 3284 infants (from urban localities), all the children in the age range (12–15 months of age). Random sampling was not carried out, the questionnaire was given to all families, who were asked to complete it and return after completion. The study was approved by the Management of Primary Care of Navarre's Health Service and the Scientific Ethic Committee of University of Murcia.

Data collection

Paediatric nurses of the primary health centres explained the study to the families, and if they agreed to participate, after signing a full-informed written consent, a questionnaire and the instructions to complete it were given. Families filled out the questionnaire and could hand it in at the same primary health centre on the following visit, or send it to the Public University of Navarre by mail.

The questionnaire consisted of 74 questions about the infant (respiratory symptoms, feeding), his/her family (habits, diseases), environmental factors and pregnancy. No personal data were collected. This questionnaire has been previously validated.[13] A Spanish version of the questionnaire was back translated to Basque (an official regional language) by the Department of Euskera of the Public University of Navarre, and both models were available.

Wheeze ever was defined as a positive answer to the question ''Has your child wheeze in the first 12 months of his/her life?'' Recurrent wheeze was defined as three or more episodes of wheezing in the first year of life.

Statistical analysis

A descriptive analysis was carried out. Chi Square and Student's-t test (as appropriate), with a statistical significance set at $\alpha < 0.05$, were performed in a univariate analysis to study the associations between the presence of wheezing ever and recurrent wheezing and factors, and the odds ratios (OR) with a confidence interval of 95% (95% CI) were calculated.

Non-conditional logistic regression analysis to calculate adjusted odds ratios (aOR) by sex and age was used in those factors with $p < 0.1$. Analyses were performed with IBM SPSS version 20 (Armonk, NY, USA).

Results

A total of 1065 questionnaires were answered, which meant a participation rate of 32.4%. Results from the descriptive analysis are shown in Table 1. Prevalence of wheezing in the first year was 31.2% (327), and 12.3% (106) were recurrent wheezers. Most of the questionnaires were completed by the mothers (79.9%) or both parents (15.8%), and almost all the infants were Caucasian and had been born in Spain (96.8% and 99.5%, respectively). 121 (13.1%) infants had attended the Emergency Department due to the severity of wheezing, and 27 (2.7%) had been hospitalised once and three (0.3%) twice for this cause.

Risk factors for wheezing ever are shown in Table 2. A history of pneumonia, paternal allergic dermatitis and nursery attendance presented the largest OR. There were also associations between wheezing ever and a higher number of colds ($p = < 0.001$; aOR 1.164, 95% CI 1.102–1.230) and number of persons at home ($p = 0.037$; aOR 1.155, 95% CI 1.008–1.323).

No associations were found with low weight at birth ($p = 0.268$), pets, nor at birth or when the questionnaire was answered ($p = 0.810$ and $p = 0.372$, respectively), mould stains in the house ($p = 0.153$), or breastfeeding fewer than six months ($p = 0.116$).

In Table 3, risk factors for recurrent wheezing are presented. A history or pneumonia, infant eczema, nursery attendance and prematurity at birth were the most important risk factors. Higher number of colds ($p = < 0.001$; aOR 1.381, 95% CI 1.266–1.505) and higher number of smokers at home ($p = 0.029$; aOR 1.328; 95% CI 1.017–1.735) were also risk factors for recurrent wheezing. There were no associations with low weight at birth ($p = 0.158$), mould stains

Table 1 Results from the descriptive analysis.

Variables	*N*	%
Study participation	1065	32.4
Male gender	519	50.3
Age (in months)	12.08 ± 0.94	
Low weight at birth (<2500 g)	82	7.7
Wheezing		
Ever	327	31.2
Recurrent	106	12.3
Age of first episode (in months)	6.88 ± 5.66	
Colds		
Number of colds	3.78 ± 3.60	
Age of the first cold (in months)	5.84 ± 4.25	
Pneumonia	42	4.2
Eczema	134	13.2
Smoking mother	216	20.6
Smoking father	306	29.8
Smoking in pregnancy	170	16.2
Asthma		
Father	44	4.2
Mother	53	5.3
Siblings	28	2.8
Allergic rhinitis		
Father	135	13.1
Mother	138	13.2
Siblings	22	2.2
Allergic dermatitis		
Father	38	3.7
Mother	61	5.9
Siblings	55	5.9
Number of siblings		
0	542	50.9
1	438	41.1
2	64	6.0
3 or more	20	1.9
Number of persons at home	3.45 ± 0.99	
Nursery attendance	349	33.2
Breastfeeding (in months)	5.50 ± 4.99	
Pets (at birth)		
No pets	853	81.9
Dog	63	6.0
Cat	33	3.2
Pets (when questionnaire was completed)		
No pets	840	81.0
Dog	55	5.3
Cat	33	3.2
Mould stains at home	45	4.3
Atmospheric contamination	263	25.1

($p = 0.992$), atmospheric contamination ($p = 0.708$) or breastfeeding fewer than six months ($p = 0.851$).

Discussion

Wheezing in infants is a major problem, affecting not only the quality of life of infants, but also of their families. Our study has found several risk factors related to wheezing ever and recurrent wheezing in infants from the region of Pamplona.

Prevalence of wheezing ever in infants in our study was 31.2%, a similar prevalence compared to other EISL studies conducted in Spain, in the city of Salamanca, which found 32.3%[14] and in Netherlands, 28.5%,[7] but less prevalence than in Latin America countries, where mean prevalence was 47.3%.[15] Prevalence of recurrent wheezing was 12.3%, similar to the other Spanish EISL study,[14] but lower than other European and Latin American studies.[7,9]

Male gender was a risk factor for wheezing ever and recurrent wheezing in our study. This finding is in accordance with what has been found in other studies,[16,17] suggesting a genetic role in the appearance of wheezing.

In our study, low birth weight did not show any association with wheezing ever or recurrent wheezing. Our results contrast with findings from another Brazilian study in which low birth was an independent risk factor for occasional wheezing.[18]

Both a history of pneumonia and a higher number of colds were risk factors for wheezing ever and recurrent wheezing. Several studies agree with these findings,[19,20] with pneumonia being a strong risk factor for recurrent wheezing in European and Latin American countries.[21] The relevance of infections of the respiratory tract has been previously studied, describing the relation between viral infections[22] and the development of wheezing.

In our study, infant eczema presented a higher risk for both wheezing ever and recurrent wheezing. This relation was also found in another EISL study,[14] although it is not a general finding, suggesting it affects some populations. Garcia-Marcos et al.[21] found that infant eczema was a risk factor for pneumonia in infants, which suggests a role between eczema and the development of other risk factors which lead to wheezing.

We found that smoking mother, as well as smoking during pregnancy, were risk factors for wheezing ever and recurrent wheezing, findings which have been previously described in many studies.[23–25] Although a Spanish study found that paternal smoking was not associated with wheezing,[26] we found it as risk factor for recurrent wheezing. Our results also show that number of smokers at home was a risk factor for recurrent wheezing, according to the finding that household smoking increases the risk of wheeze.[24] Exposure to smoke, especially during pregnancy, is related to decreased lung function in children,[27] suggesting an important influence in the apparition of the disease.

As in our study, a parental history of asthma has been found as risk factors in many studies.[9,15] These results may suggest the existence of a hereditary mechanism for asthma and wheezing.[28] Maternal allergic rhinitis was found as a risk factor for recurrent wheezing, and paternal allergic dermatitis for wheezing ever. These results agree with results from others EISL studies,[7,9] where allergic diseases were risk factors for wheezing ever and recurrent wheezing.

Attending nursery school was found as a risk factor for both wheezing ever and recurrent wheezing. Previous results are conflictive, with several studies which either not found any association,[29] or described a protective effect,[30] while others agree with our results.[31] An explanation for our results may be that children who attended a nursery school were in contact with other children and a different environment, increasing the exposure to possible risk factors.

Table 2 Risk factors for wheezing ever in the first year of life.

Variables	*N* (%)	*p*-Value	OR (95% CI)	Adjusted OR (95% CI)
Male gender	193 (60.7%)	<0.001	1.825 (1.393–2.390)	1.836 (1.398–2.413)
Pneumonia	33 (10.5%)	<0.001	11.173 (4.885–25.558)	10.745 (4.638–24.896)
Eczema	57 (18.0%)	0.003	1.764 (1.215–2.561)	1.886 (1.278–2.783)
Smoking mother	79 (24.6%)	0.027	1.429 (1.042–1.962)	1.462 (1.054–2.029)
Smoking father	98 (31.2%)	0.444	1.120 (0.838–1.496)	–
Smoking in pregnancy	65 (20.1%)	0.022	1.491 (1.058–2.102)	1.617 (1.133–2.308)
Asthma				
Father	20 (6.2%)	0.036	1.900 (1.034–3.492)	1.926 (1.027–3.611)
Mother	25 (8.0%)	0.015	1.978 (1.133–3.452)	1.749 (0.978–3.126)
Siblings	7 (2.2%)	0.428	0.706 (0.297–1.678)	–
Allergic rhinitis				
Father	38 (12.0%)	0.546	0.883 (0.590–1.322)	–
Mother	53 (16.5%)	0.050	1.447 (0.998–2.099)	1.391 (0.946–2.045)
Siblings	6 (2.0%)	0.674	0.816 (0.316–2.106)	–
Allergic dermatitis				
Father	19 (6.0%)	0.012	2.258 (1.178–4.326)	2.492 (1.268–4.896)
Mother	19 (5.9%)	0.956	0.984 (0.563–1.721)	–
Siblings	20 (6.5%)	0.454	1.241 (0.704–2.188)	–
Nursery attendance	138 (42.7%)	<0.001	1.867 (1.419–2.455)	2.003 (1.507–2.663)
Mould stains at home	18 (5.6%)	0.153	1.561 (0.843–2.891)	–
Gestational diabetes	29 (9.6%)	0.075	1.572 (0.952–2.596)	1.501 (0.882–2.553)
Prematurity	32 (11.0%)	0.077	1.526 (0.953–2.442)	1.461 (0.892–2.393)

We did not find any relation between mould stains in the house and wheezing ever or recurrent wheezing, contrary to the Dutch EISL study,[7] which found damp housing as a strong risk factor in both cases. In our study, only a few families reported mould stains or damp at home, which may have affected our findings, causing an underestimation of its influence.

Complications during pregnancy, specifically prematurity and malposition of the foetus, were risk factors for recurrent wheezing. Both, prematurity[32] and malpresentation of the foetus[33] were previously found associated with recurrent wheezing and asthma. Premature infants are born with abnormalities in their airways, which probably provoke the apparition of wheezing.[34] In the same way, malposition is supposed to affect the lung function of the foetus, which can cause respiratory problems at an early age.

Breastfeeding showed no association in our study. Findings from previous studies are conflictive. Breastfeeding was found as a protective factor in some of them.[10] However, other studies did not reach any relationship,[35] or even described breastfeeding as a risk factor for asthma in childhood.[36]

Although previous studies have described a protective effect in those children with pets in the house,[37] probably due to the exposition at early age to certain microorganisms that confer protection against asthma, findings

Table 3 Risk factors for recurrent wheezing in the first year of life.

Variables	*N* (%)	*p*-Value	OR (95% CI)	Adjusted OR (95% CI)
Male gender	64 (61.0%)	0.004	1.852 (1.208–2.842)	1.838 (1.198–2.821)
Pneumonia	15 (14.6%)	<0.001	14.574 (5.506–38.575)	15.758 (5.852–42.430)
Eczema	25 (24.0%)	<0.001	2.941 (1.723–5.019)	3.134 (1.811–5.425)
Smoking mother	27 (25.7%)	0.028	1.731 (1.057–2.833)	1.665 (1.008–2.748)
Smoking father	42 (40.0%)	0.022	1.654 (1.072–2.551)	1.605 (1.033–2.493)
Smoking in pregnancy	25 (24.0%)	0.006	2.033 (1.217–3.396)	2.034 (1.208–3.426)
Asthma				
Father	7 (6.7%)	0.195	1.780 (0.737–4.302)	–
Mother	11 (10.9%)	0.005	2.858 (1.332–6.131)	2.806 (1.290–6.102)
Siblings	2 (2.1%)	0.662	0.718 (0.161–3.190)	–
Allergic rhinitis				
Father	14 (13.6%)	0.822	1.073 (0.578–1.992)	–
Mother	24 (22.9%)	0.002	2.275 (1.343–3.852)	2.234 (1.298–3.845)
Siblings	3 (3.1%)	0.566	1.458 (0.399–5.326)	–
Allergic dermatitis				
Father	6 (5.9%)	0.266	1.699 (0.661–4.364)	–
Mother	6 (5.8%)	0.987	1.008 (0.409–2.480)	–
Siblings	6 (6.1%)	0.539	1.334 (0.531–3.354)	–
Nursery attendance	55 (53.4%)	<0.001	2.906 (1.890–4.467)	3.045 (1.960–4.731)
Mould stains at home	4 (3.9%)	0.992	0.995 (0.334–2.960)	–
Malposition of the foetus	6 (6.2%)	0.036	2.853 (1.029–7.910)	2.933 (1.039–8.277)
Placental problems	8 (8.3%)	0.055	2.268 (0.963–5.342)	2.285 (0.956–5.460)
Prematurity	18 (18.8%)	<0.001	3.115 (1.676–5.789)	3.112 (1.653–5.856)

are conflictive.[38] Our results did not show any association between the presence of pets at home and wheezing ever or recurrent wheezing.

We did not find any relation with air pollution in our study. However, several studies have found associations between this factor and wheezing.[39,40] The questionnaire asked for a personal perception of air pollution level, which means a subjective measure that may have led to underestimation.

One of the strengths of this study was the use of a validated questionnaire, a well-recognised tool which has been used in other studies. Moreover, this study is part of the multicentre EISL project, which enables the comparison of the results obtained with other centres from Spain or other countries. One of the limitations of the study is its cross-sectional design, although the main weakness is its low participation, probably due to the low participation of the immigrant population, and to data protection issues and authorisations of the Health System, which made it not possible to send reminder letters or telephone calls to participants, which would have increased the participation, reducing the confusion of some results, or allows finding others.

In conclusion, wheezing in infants is a common disease, with several identified risk factors, like pneumonia, family history of asthma and nursery attendance. Further studies are needed to test if these findings are consistent, and intervention against the preventable factors should be addressed.

Ethical disclosures

Protection of human and animals subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Sources of support

Research grant from Carlos III Institute, Spanish Ministry of Health and Consumer Affairs Ref, PI 050918; research grant from the Department of Health, Government of Navarra, Spain, Ref 6106.

Conflict of interest

No author has any conflict of interest to declare.

Acknowledgments

This study has been funded by two Research Grants from Carlos III Institute, Spanish Ministry of Health and Consumer Affairs Ref, PI 050918, and from the Department of Health, Government of Navarra, Spain, Ref 6106.

References

1. Hafkamp-de Groen E, Mohangoo AD, Landgraf JM, de Jongste JC, Duijts L, Moll HA, et al. The impact of preschool wheezing patterns on health-related quality of life at age 4 years. Eur Respir J. 2013;41:952–9.
2. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med. 2008;178:667–72.
3. Kappelle L, Brand PLP. Severe episodic viral wheeze in preschool children: high risk of asthma at age 5-10 years. Eur J Pediatr. 2012;171:947–54.
4. Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. Pediatr Pulmonol. 2007;42:723–8.
5. Arnedo-Pena A, Garcia-Marcos L, Bercedo-Sanz A, Aguinaga-Ontoso I, Gonzalez-Diaz C, Garcia-Merino A, et al. Prevalence of asthma symptoms in schoolchildren, and climate in west European countries: an ecologic study. Int J Biometeorol. 2013;57:775–84.
6. Garcia-Marcos L, Mallol J, Sole D, Brand PLP, Sanchez-Bahillo M, Sanchez-Solis M, et al. Latitude modifies the effect size of factors related to recurrent wheeze in the first year of life. Respir Med. 2013;107:665–72.
7. Visser CAN, Garcia-Marcos L, Eggink J, Brand PLP. Prevalence and risk factors of wheeze in Dutch infants in their first year of life. Pediatr Pulmonol. 2010;45:149–56.
8. Bianca AD, Wandalsen G, Mallol J, Sole D. Risk factors for wheezing disorders in infants in the first year of life living in São Paulo. Brazil J Trop Pediatr. 2012;58:501–4.
9. Costa Bessa OAA, Madeiro Leite AJ, Sole D, Mallol J. Prevalence and risk factors associated with wheezing in the first year of life. J Pediatria. 2014;90:190–6.
10. Oddy WH, Sly PD, de Klerk NH, Landau LI, Kendall GE, Holt PG, et al. Breast feeding and respiratory morbidity in infancy: a birth cohort study. Arch Dis Child. 2003;88:224–8.
11. Castro-Rodriguez JA, Garcia-Marcos L, Alfonseda JD, Valverde-Molina J, Sanchez-Solis M. Mediterranean diet as a protective factor for wheezing in preschool children. J Pediatr. 2008;152:823–8.
12. Observatorio del Estudio Internacional de Sibilancias en Lactantes (EISL) [Internet] 2015 April 10 Available from: http://www.respirar.org/respirar/epidemiologia/observatorio-del-estudio-internacional-de-sibilancias-en-lactantes-eisl.
13. Mallol J, Garcia-Marcos L, Aguirre V, Martinez-Torres A, Perez-Fernández V, Gallardo A, et al. The International Study of wheezing in infants: questionnaire validation. Int Arch Allergy Immunol. 2007;144:44–50.
14. Pellegrini-Belinchon J, Miguel-Miguel G, De Dios-Martín B, Vicente-Galindo E, Lorente-Toledano F, Garcia-Marcos L. Study of wheezing and its risk factors in the first year of life in the Province of Salamanca, Spain. The EISL Study. Allergol Immunopathol. 2012;40:164–71.
15. Mallol J, Garcia-Marcos L, Sole D, Brand P, the EISL Study Group. International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources. Thorax. 2010;65:1004–9.
16. Garcia-Marcos L, Mallol J, Sole D, Brand PLP, the EISL Study Group. International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life. Pediatr Allergy Immunol. 2010;21:878–88.
17. Caudri D, Savenije OEM, Smit HA, Postma DS, Koppelman GH, Wijga AH, et al. Perinatal risk factors for wheezing phenotypes in the first 8 years of life. Clin Exp Allergy. 2013;43:1395–405.
18. Reis GG, Miranda VM, Cardoso M-RA, Sole D, Barral A, Nascimento-Carvalho CM. Prevalence and risk factors for wheezing in Salvador, Brazil: a population-based study. Quart J Med. 2015;108:213–8.
19. Medeiros D, Silva AR, Rizzo JA, Sarinho E, Mallol J, Sole D. Prevalence of wheezing and associated risk factors among infants in Recife, Pernambuco State, Brazil. Cad Saude Publica. 2011;27:1551–9.
20. Moraes LSL, Takano OA, Mallol J, Sole D. Risk factors associated with wheezing in infants. J Pediatria. 2013;89:559–66.
21. Garcia-Marcos L, Mallol J, Sole D, Brand PLP, Martinez-Torres A, Sanchez-Solis M, et al. Pneumonia and wheezing in the first year: an international perspective. Pediatr Pulmonol. 2015;50:1277–85.
22. Takeyama A, Hashimoto K, Sato M, Sato T, Tomita Y, Maeda R, et al. Clinical and epidemiological factors related to subsequent wheezing after virus-induced lower respiratory tract infections in hospitalized pediatric patients younger than 3 years. Eur J Pediatr. 2014;173:959–66.
23. Duijts L, Jaddoe VWV, van der Valk RJP, Henderson JA, Hofman A, Raat H, et al. Fetal exposure to maternal and paternal

smoking and the risk of wheezing in preschool children: The Generation R Study. Chest. 2012;141:876–85.
24. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics. 2012;129:735–44.
25. Schvartsman C, Lima Farhat SC, Schvartsman S, Nascimento Saldiva PH. Parental smoking patterns and their association with wheezing in children. Clinics. 2013;68:934–9.
26. Jurado D, Muñoz C, de Dios Luna J, Muñoz-Hoyos A. Is maternal smoking more determinant than paternal smoking on the respiratory symptoms of young children? Respir Med. 2005;99:1138–44.
27. Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. Thorax. 2000;55:271–6.
28. Paaso EMS, Jaakkola MS, Rantala AK, Hugg TT, Jaakkola JJK. Allergic diseases and asthma in the family predict the persistence and onset-age of asthma: a prospective cohort study. Resp Res. 2014;15:152.
29. Celedon JC, Litonjua AA, Ryan L, Weiss ST, Gold DR. Day care attendance, respiratory tract illnesses, wheezing, asthma, and total serum IgE level in early childhood. Arch Pediatr Adolesc Med. 2002;156:241–5.
30. Nicolaou NC, Simpson A, Lowe LA, Murray CS, Woodcock A, Custovic A. Day-care attendance, position in sibship, and early childhood wheezing: a population-based cohort study. J Allergy Clin Immunol. 2008;122:500–6.
31. Hagerhed-Engman L, Bornehag C-G, Sundell J, Aberg N. Day-care attendance and increased risk for respiratory and allergic symptoms in preschool age. Allergy. 2006;61:447–53.
32. Kumar R, Yu Y, Story RE, Pongracic JA, Gupta R, Pearson C, et al. Prematurity, chorioamnionitis, and the development of recurrent wheezing: a prospective birth cohort study. J Allergy Clin Immunol. 2008;121:878–84.
33. Annesi-Maesano I, Moreau D, Strachan D. *In utero* and perinatal complications preceding asthma. Allergy. 2001;56:491–7.
34. Broughton S, Thomas MR, Marston L, Calvert SA, Marlow N, Peacock JL, et al. Very prematurely born infants wheezing at follow-up: lung function and risk factors. Arch Dis Child. 2007;92:776–80.
35. Miyake Y, Tanaka K, Sasaki S, Kiyohara C, Ohya Y, Fukushima W, et al. Breastfeeding and the risk of wheeze and asthma in Japanese infants: the Osaka Maternal and Child Health Study. Pediatr Allergy Immunol. 2008;19:490–6.
36. Sears MR, Greene JM, Willian AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. Lancet. 2002;360:901–7.
37. Litonjua AA, Milton DK, Celedon JC, Ryan L, Weiss ST, Gold DR. A longitudinal analysis of wheezing in young children: the independent effects of early life exposure to house dust endotoxin, allergens, and pets. J Allergy Clin Immunol. 2002;110:736–42.
38. Apelberg BJ, Aoki Y, Jaakkola JJK. Systematic review: exposure to pets and risk of asthma and asthma-like symptoms. J Allergy Clin Immunol. 2001;107:455–60.
39. Ryan PH, LeMasters G, Biagini J, Bernstein D, Grinshpun SA, Shukla R, et al. Is it traffic type, volume, or distance? Wheezing in infants living near truck and bus traffic. J Allergy Clin Immunol. 2005;116:279–84.
40. Andersen ZJ, Loft S, Ketzel M, Stage M, Scheike T, Hermansen MN, et al. Ambient air pollution triggers wheezing symptoms in infants. Thorax. 2008;63:710–6.

Allergol Immunopathol (Madr). 2016;xxx(xx):xxx-xxx

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

Meta-analysis of prevalence of wheezing and recurrent wheezing in infants

I. Alvarez-Alvarez[a,*], H. Niu[a], F. Guillen-Grima[a,b,c], I. Aguinaga-Ontoso[a]

[a] *Department of Health Sciences, Public University of Navarre, Pamplona, Spain*
[b] *IDISNA, Navarre's Institute for Health Research, Pamplona, Spain*
[c] *Preventive medicine, University of Navarre Clinic, Pamplona, Spain*

Received 4 July 2016; accepted 19 August 2016

KEYWORDS
Epidemiology;
Infants;
Meta-analysis;
Prevalence;
Recurrent wheezing;
Wheezing

Abstract
Background: Wheezing affects children's quality of life, and is related with asthma in childhood. Although prevalence of wheezing has been previously studied in several countries, there is no reference of worldwide prevalence in infants. The aim of this meta-analysis is to estimate the prevalence of wheezing and recurrent wheezing in infants aged up to two years, and compare the prevalence across world regions.
Methods: Literature search was conducted in MEDLINE and SCOPUS databases, looking for observational studies published up to June 2016, including as keywords ''prevalence'' or ''epidemiology'' combined with ''wheeze'', ''wheezing'' or ''asthma symptoms'' and ''infant'' or ''preschool''. Fast*Pro software and random effects Bayesian model were used. Heterogeneity was estimated using I^2 statistic, and sensitivity analyses were performed.
Results: We identified 109 studies after duplicates were removed. After exclusions, 14 studies were included in the meta-analysis. Prevalence of wheezing and recurrent wheezing were 36.06% (95% CI 35.17–36.96), and 17.41% (95% CI 16.74–18.09), respectively. In European countries, prevalence of wheezing was 30.68% (95% CI 28.97–32.45), and 12.35% (95% CI 11.27–13.47) for recurrent wheezing. Prevalence of wheezing and recurrent wheezing in Latin America were higher, 40.55% (95% CI 39.40–41.71), and 19.27% (95% CI 18.44–20.11), respectively. In Africa, prevalence of wheezing was 15.97% (95% CI 14.05–18.00). Low or no heterogeneity was found in all cases.
Conclusions: More than one third of infants suffer from wheezing and almost one fifth from recurrent wheezing, being these illnesses especially prevalent in Latin American countries, pointing out an important public health problem.

* Corresponding author.
E-mail address: alvarez.80114@e.unavarra.es (I. Alvarez-Alvarez).

http://dx.doi.org/10.1016/j.aller.2016.08.011
0301-0546/

Appendix 3

Internship at the Institut de Santé Publique, d'Epidémiologie et de Développement (ISPED)

1. Background

The Institut de Santé Publique, d'Epidémiologie et de Développement

In 1989, the Victor Segalen Bordeaux II University created a Training and Research Unit of Public Health, transformed in 1997 into the Institut de Santé Publique, d'Epidémiologie et de Développement (ISPED), nowadays known as the Bordeaux School of Public Health.

It provides both teaching and research activities, and promotes a multidisciplinary approach around epidemiology, biostatistics, health management and social sciences. Their main areas of research are related to brain aging, HIV, clinical research, nutrition, trauma, occupational health, environmental health, cancer, hospital management, public health policy evaluation, etcetera.

The ISPED provides teaching and research activities at national and international level, with relations with many developing countries, allowing the reception of foreign students or realization of cooperative research (ISPED webpage).

Figure 1. Institut de Santé Publique, d'Epidémiologie et de Développement logo.

My internship took place in the ISPED during three months in the year 2014, under the academic supervision of Dr. Chantal Raherison, from the "Equipe Santé travail environnement".

I worked in the Etude Longitudinale Française depuis l'Enfance (Elfe, in English French Longitudinal Study in Children). The Elfe study is divided in twenty thematic groups, divided in social sciences, health, environmental heath, and cross-cutting groups, where Dr. Raherison, is responsible of the "Respiratory disease, asthma & allergies" group.

2. Methods

Etude Longitudinale Française depuis l'Enfance

The Elfe study is a multidisciplinary national longitudinal study conducted in France. Longitudinal studies in the first years of life are essential to identify health risk factors which can affect children's development.

The Elfe study is the result of the coalescence of several projects which were promoted by different research and government institutions. In 2005, these projects converged in this unique study.

The purpose of the study was to build a national representative cohort of twenty thousand children, who will be followed from birth to adulthood, using a multidisciplinary approach, to characterise the relationship between environmental exposures and the socio-economic context on health and behaviours.

The cohort was based on the INSEE Permanent Demographic Sample (in French, EDP), which include all French citizens born on specific days of the year. The base panel included all children born in hospital maternity units on sixteen days, four days in each of the four quarters, to enable a representative sample of births. The official starting date for enrolments in the cohort started in the beginning of 2011.

Two pilot studies were carried out in 2007 in two different regions to validate data collection methods used in the first year of the study. They also allowed to estimate the participation acceptance rate, the field feasibility, and to test procedures of collection and bio-banking of biological samples.

The project objectives cover fields as the epidemiology, public health and social sciences. In the field of health, the study gives a central place to children growth, examining all the relationships between growth, social, environmental exposures and health events.

One of the research topics address asthma and allergies. During the study, prevalence and incidence data of asthma and its different degrees of severity at different ages and socioeconomic groups are collected to evaluate early determinants of asthma and allergies in childhood.

The design of the cohort was based on an initial enrolment interview of mothers at child's birth to obtain retrospective data about exposures during pregnancy, and then a prospective follow-up of the child along the childhood and adolescence.

The follow-up is based on data retrieval and record linkage from existing databases, as the INSEE demographic data, health insurance records, school follow-up, etcetera, and several waves of cross-sectional surveys at different ages: six weeks, and one, two, three, five, six, eight, ten, eleven and fourteen years old.

Surveys are based on face-to-face interview surveys or telephone interviews, biological samples collection, clinical examinations and psychomotor development tests, self-administered questionnaires, environmental measurements, etcetera.

The strengths of the study are the large size of the cohort and its statistical power, which allows to test a wide variety of hypothesis, and the multiple fields involved, which lead to a better understanding of the factors involved in child growth and their interaction.

The main weaknesses are the absence of data collection before birth, and the difficulties of maintaining the representativeness of the sample throughout the follow-up (Léridon, 2007; Vandentorren et al., 2009).

Nowadays, the Elfe study continues, and new results are highlighted. For more information about the study and main findings, the official webpage could be visited (Elfe study webpage).

Statistical analysis

The following analyses were conducted using data from participating one-year-old infants. First, a descriptive analysis was performed, computing frequencies for the categorical variables included. Furthermore, a descriptive analysis by gender was also conducted.

Bivariate analyses were performed, using the chi-squared test, to study the relationships between potential risk factors (maternal asthma, bronchiolitis and smoking during pregnancy) and outcomes of interest. A p value lower than 0.05 was regarded as statistically significant.

Finally, a cluster analysis, to classify participants in homogenous groups, and then explore similarities and divergences among different groups, was performed. The cluster analysis was repeated classifying infants into three, four and nine groups.

All analyses were performed using IBM SPSS version 20 software (Armonk, NY, USA).

3. Results

Descriptive analysis

Almost half of infants in the study (48.6%) had at least one symptom in the first year of life. 6.5% of the children had wheezing in the chest, and 25.5% suffered night cough. Besides, 4.5% of the children suffered from both wheezing and cough. 4,624 infants (29.1%) had difficulties when they breathed, and more frequently, had their airways congested (34.7%). 2,475 children (15.6%) suffered from atopic dermatitis.

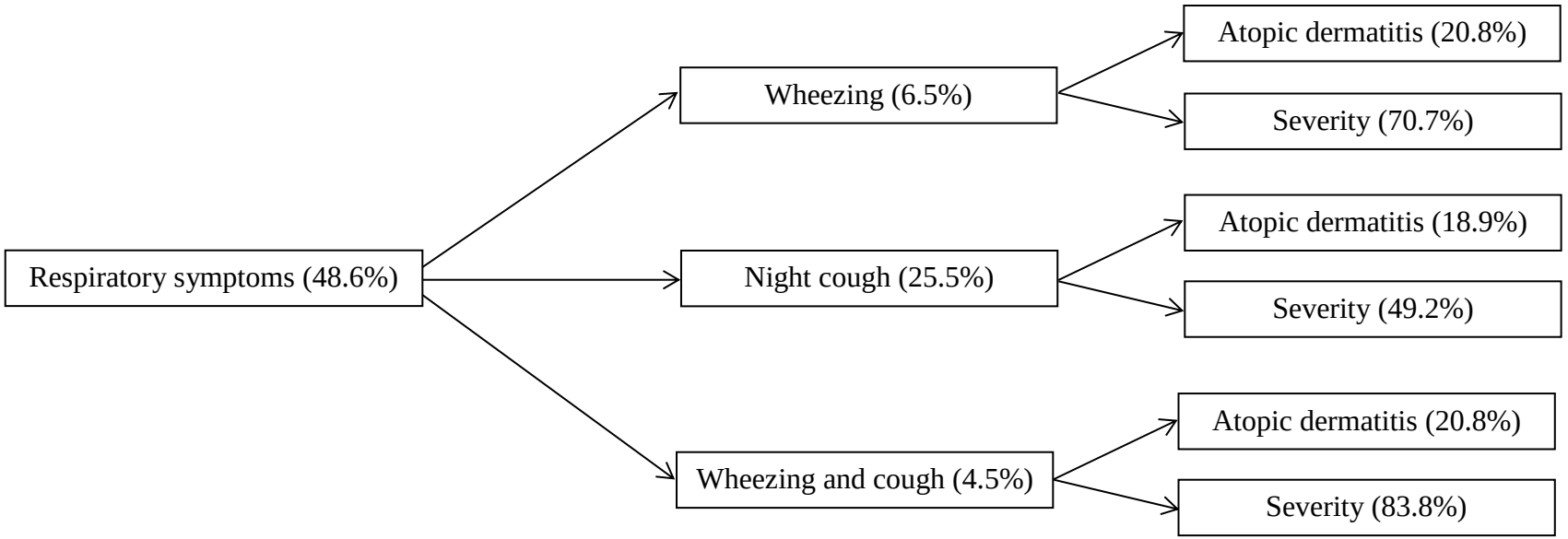
On the other hand, the 7.9% of children had colds or rhinitis in the first year of life, and 5.7% went to see a doctor for these causes. Frequencies of the illnesses are presented in Table 1.

Table 1. Baseline characteristics of the sample.

	N (%)
Symptoms	7,733 (48.6)
Wheezing in the chest	
Yes	1,027 (6.5)
No	14,884 (93.5)
Night cough	
Yes	4,051 (25.5)
No	11,862 (74.5)
Difficulty breathing	
Yes	4,624 (29.1)
No	11,289 (70.9)
Congested airways	
Yes	5,523 (34.7)
No	10,389 (65.3)
Atopic dermatitis	
Yes	2,475 (15.6)
No	13,432 (84.4)
Colds, rhinitis	
Yes	1,450 (43.9)
No	1,854 (56.1)
First medical consult (colds, rhinitis)	
Yes	1,052 (24.5)
No	3,220 (75.1)
Do not know	14 (0.3)

In Figure 2, frequencies of symptoms in the first year of life are shown. Severity was defined as infants with difficulties to breathe and congested airways.

Figure 2. Frequencies of symptoms in the first year of life.



After the analysis, we searched for different phenotypes described in the literature to classify the children. 20.8% of infants who had wheezing in the chest also suffered from atopic dermatitis. Therefore, they can be considered atopic wheezers (Taussig et al., 2003). They can also be classified as late onset wheezers according to the phenotypes proposed in the ALSPAC study (Henderson et al., 2008).

A 4.5% of children were atopic persistent wheezers (or had persistent cough), because they suffered from wheezing and cough. Also, the 18.9% of children who had cough and atopic dermatitis were classified in the atopic persistent phenotype.

Analysis by gender

The 7.4% of boys, and 5.5% of girls, had wheezing in the chest. More frequently, 26.7% of boys, and 24.2% of girls, had night cough. Nearly 30% of the boys had difficulties to breathe, compared to 27.9% of girls. Both 35.8% of boys, and 33.5% of girls had congested airways.

Atopic dermatitis was reported by 15.7% of boys and 15.5% of girls. The 43.6% of boys suffered from colds or rhinitis, against 44.2% of girls. Further, 23.8% of boys, and 25.4% of girls, went to a medical consult for colds or rhinitis. (Table 2)

Table 2. Frequencies of the illnesses by gender.

	Boys	Girls	Do not know
	N (%)	N (%)	N (%)
Wheezing in the chest			
Yes	596 (7.4)	424 (5.5)	0 (0)
No	7,490 (92.6)	7,258 (94.5)	20 (100)
Night cough			
Yes	2,159 (26.7)	1,857 (24.2)	4 (20.0)
No	5,926 (73.3)	5,825 (75.8)	16 (80.0)
Difficulty breathing			
Yes	2,443 (30.2)	2,140 (27.9)	5 (25.0)
No	5,642 (69.8)	5,542 (72.1)	15 (75.0)
Congested airways			
Yes	2,893 (35.8)	2,575 (33.5)	6 (30.0)
No	5,191 (64.2)	5,107 (66.5)	14 (70.0)
Atopic dermatitis			
Yes	1,265 (15.7)	1,191 (15.5)	2 (10.0)
No	6,815 (84.3)	6,490 (84.5)	18 (90.0)
Colds, rhinitis			
Yes	755 (43.6)	677 (44.2)	0 (0)
No	976 (56.4)	854 (55.8)	5 (100)
First medical consult (colds, rhinitis)			
Yes	526 (23.8)	517 (25.4)	0 (0)
No	1,683 (76.1)	1,506 (74.1)	4 (100)
Do not know	4 (0.2)	9 (0.4)	0 (0)

Bivariate analysis

Among asthmatic mothers, 8.5% had children who wheezed, compared to 6.1% of non-asthmatic mothers, finding significant differences (p<0.001). Almost half of children with bronchiolitis (48.4%) suffered from wheezing, against 6.2% who did not report the condition, also detecting statistical differences (p<0.001). Furthermore, 8.5% of mothers who smoked during pregnancy had a child who wheezed, against 5.9% of non-smoking mothers, also showing evidence of a statistical association (p<0.001). (Table 3)

Table 3. Associations between maternal asthma, bronchiolitis and smoking during pregnancy and wheezing in the chest.

Wheezing in the chest	Yes	No	
	N (%)	N (%)	p value
Maternal asthma			<0.001
Yes	159 (8.5)	1,707 (91.5)	
No	856 (6.1)	13,075 (93.9)	
Do not know	0 (0)	5 (100)	
Bronchiolitis			<0.001
Yes	133 (48.4)	142 (51.6)	
No	189 (6.2)	2,837 (93.8)	
Smoking during pregnancy			<0.001
Yes	263 (8.5)	2,825 (91.5)	
No	750 (5.9)	11,896 (94.1)	

A 30.1% of asthmatics mothers had children who had night cough, compared to 24.8% who were not asthmatics, detecting a significant relation (p<0.001). Furthermore, statistical differences were observed between the 86.9% of children who had bronchiolitis and coughed at night, against 36.2% who did not suffer from bronchiolitis (p<0.001). Conversely, no significant association was found between prenatal exposure to tobacco smoke and night cough in the offspring (p=0.126). (Table 4)

Table 4. Associations between maternal asthma, bronchiolitis and smoking during pregnancy and night cough.

Night cough	Yes	No	
	N (%)	N (%)	p value
Maternal asthma			<0.001
Yes	562 (30.1)	1,304 (69.9)	
No	3,460 (24.8)	10,471 (75.2)	
Do not know	2 (40.0)	3 (60.0)	
Bronchiolitis			<0.001
Yes	239 (86.9)	36 (13.1)	
No	1,096 (36.2)	1,930 (63.8)	
Smoking during pregnancy			0.126
Yes	817 (26.5)	2,270 (73.5)	
No	3,178 (25.1)	9,468 (74.9)	

A statistically significant association was observed between history of maternal asthma and difficulties to breathe (p<0.001). Among asthmatic mothers, 32.6% had a child with difficulty breathing, in contrast to 28.6% of non-asthmatics mothers. Most of the children with bronchiolitis (84.7%) had difficulties to breath, compared to 40.9% of children who did not have bronchiolitis, also showing statistical differences (p<0.001). A significant relation was also observed when prenatal exposure to smoke was studied (p<0.001). Among smoking mothers, 31.3% had offspring with difficulties to breathe, compared to 28.4% of non-smoking mothers. (Table 5)

Table 5. Associations between maternal asthma, bronchiolitis and smoking during pregnancy and difficulties to breathe.

Difficulties to breathe	**Yes**	**No**	
	N (%)	**N (%)**	**p value**
Maternal asthma			<0.001
Yes	609 (32.6)	1,257 (67.4)	
No	3,984 (28.6)	9,947 (71.4)	
Do not know	4 (80.0)	1 (20.0)	
Bronchiolitis			<0.001
Yes	233 (84.7)	42 (15.3)	
No	1,237 (40.9)	1,789 (59.1)	
Smoking during pregnancy			0.001
Yes	967 (31.3)	2,120 (68.7)	
No	3,591 (28.4)	9,055 (71.6)	

The 38.1% of asthmatics mothers had a child with congested airways, compared to 34.3% of non-asthmatic mothers, detecting statistical differences (p=0.002). Similarly, 93.8% of children who suffered from bronchiolitis also had congested airways, against 47.5% who did not suffer from bronchiolitis, also finding a significant relation (p<0.001). In addition, the 38.9% of mothers who smoked during pregnancy, and 33.6% who did not, had a child with congested airways, showing statistical differences (p<0.001). (Table 6)

Table 6. Associations between maternal asthma, bronchiolitis and smoking during pregnancy and congested airways.

Congested airways	**Yes**	**No**	
	N (%)	**N (%)**	**p value**
Maternal asthma			0.002
Yes	711 (38.1)	1,155 (61.9)	
No	4,773 (34.3)	9,158 (65.7)	
Do not know	3 (60.0)	2 (40.0)	
Bronchiolitis			<0.001
Yes	258 (93.8)	17 (6.2)	
No	1,436 (47.5)	1,590 (52.5)	
Smoking during pregnancy			<0.001
Yes	1,200 (38.9)	1,887 (61.1)	
No	4,249 (33.6)	8,396 (66.4)	

Among asthmatic mothers, 19.5% had a child with atopic dermatitis, against 15.1% of non-asthmatic mothers, finding a significant relation (p<0.001). On the contrary, no statistical differences were found between bronchiolitis and atopic dermatitis (p=0.062). The 14.5% of children who had bronchiolitis, and 19.1% who did not, reported atopic dermatitis. Moreover, 15.0% of mothers who smoked during pregnancy, and 15.7% who were non-smokers, had children with atopic dermatitis, not finding statistical differences (p=0.321). (Table 7)

Table 7. Associations between maternal asthma, bronchiolitis and smoking during pregnancy and atopic dermatitis.

Atopic dermatitis	**Yes**	**No**	
	N (%)	**N (%)**	**p value**
Maternal asthma			<0.001
Yes	357 (19.1)	1,509 (80.9)	
No	2,099 (15.1)	11,832 (84.9)	
Do not know	3 (60.0)	2 (40.0)	
Bronchiolitis			0.062
Yes	40 (14.5)	235 (85.5)	
No	579 (19.1)	2,447 (80.9)	
Smoking during pregnancy			0.321
Yes	462 (15.0)	2,625 (85.0)	
No	1,983 (15.7)	10,657 (84.3)	

No significant association was found between maternal history of asthma and colds/rhinitis in the offspring (p=0.456). A 43.7% of asthmatic mothers, and 43.9% of non-asthmatic, had a child with colds or rhinitis. On the other hand, 61.1% of children with bronchiolitis also had colds or rhinitis, against 42.3% of children who did not report bronchiolitis, finding statistical differences (p<0.001). The 44.6% of mothers who smoked during pregnancy, and 43.6% who did not, had children with colds/rhinitis, not detecting any statistically significant relation (p=0.651). (Table 8)

Table 8. Associations between maternal asthma, bronchiolitis and smoking during pregnancy and colds and rhinitis.

Colds, rhinitis	**Yes**	**No**	
	N (%)	**N (%)**	**p value**
Maternal asthma			0.456
Yes	202 (43.7)	260 (56.3)	
No	1,241 (43.9)	1,584 (56.1)	
Do not know	0 (0)	2 (100)	
Bronchiolitis			<0.001
Yes	168 (61.1)	107 (38.9)	
No	1,282 (42.3)	1,747 (57.7)	
Smoking during pregnancy			0.651
Yes	275 (44.6)	342 (55.4)	
No	1,158 (43.6)	1,500 (56.4)	

Among asthmatic mothers, 27.7% had children who went to see a doctor for colds or rhinitis, compared to 24.1% of non-asthmatic mothers, not finding any significant association (p=0.383). On the contrary, statistical differences were observed between bronchiolitis and the first medical consult for colds or rhinitis (p=0.001). The 34.0% of children with bronchiolitis went to the doctor for these causes, compared to 18.6% of children who did not report bronchiolitis. Among smoking mothers during pregnancy, 25.9% went with their child to a medical consult for colds/rhinitis, compared to 23.8% who did not smoke, not finding a statistical relation (p=0.378). (Table 9)

Table 9. Associations between maternal asthma, bronchiolitis and smoking during pregnancy and first medical consult.

First medical consult (colds, rhinitis)	Yes	No	Do not know	
	N (%)	N (%)	N (%)	p value
Maternal asthma				0.383
Yes	159 (27.7)	412 (71.9)	2 (0.3)	
No	883 (24.1)	2,774 (75.7)	9 (0.2)	
Do not know	0 (0)	1 (100)	0 (0)	
Bronchiolitis				0.001
Yes	33 (34.0)	64 (66.0)	0 (0)	
No	161 (18.6)	703 (81.2)	2 (0.2)	
Smoking during pregnancy				0.378
Yes	250 (25.9)	713 (73.7)	4 (0.4)	
No	780 (23.8)	2,481 (75.8)	10 (0.3)	

Cluster analysis

In the following sections, three, four and nine cluster analyses' results are presented.

- **Three cluster analysis**

Wheezing, cough and atopic dermatitis

Table 10. Final cluster centres (wheezing, cough and atopic dermatitis) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	1 (Yes)	2 (No)

Distances	1	2	3
1		1.218	1.011
2	1.218		1.049
3	1.011	1.049	

Children who only cough (Cluster 1) were more related to children without symptoms (Cluster 3) than children with atopic dermatitis (Cluster 2). Children with cough (Cluster 1) and those who suffered from atopic dermatitis (Cluster 2) were farther. (Table 10)

Wheezing, cough and severity

Table 11. Final cluster centres (wheezing, cough and severity) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	1 (Yes)	2 (No)
Cough	1 (Yes)	2 (No)	2 (No)
Severity	0.64	0.30	0.00

Distances	1	2	3
1		1.058	0.980
2	1.058		1.078
3	0.980	1.078	

Children with cough and medium severity (Cluster 1) were more related to children with no symptoms or severity (Cluster 3), than to children with wheezing and low severity (Cluster 2). Children from Cluster 2 and Cluster 3 were farther between them. (Table 11)

Wheezing, cough, atopic dermatitis and severity

Table 12. Final cluster centres (wheezing, cough, atopic dermatitis and severity) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	1 (Yes)	2 (No)
Severity	0.50	0.22	0.13

Distances	1	2	3
1		1.250	1.085
2	1.250		1.041
3	1.085	1.041	

Children with no wheezing or cough, but with atopic dermatitis and low severity (Cluster 2) were more related to children with no symptoms and low severity (Cluster 3) than to children with cough and medium severity (Cluster 1). This latter group was also more related to children classified in Cluster 3, than to children in Cluster 2. (Table 12)

Wheezing, cough, atopic dermatitis, severity and rhinitis

Table 13. Final cluster centres (wheezing, cough, atopic dermatitis, severity and rhinitis) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	2 (No)	2 (No)	1 (Yes)
Atopic dermatitis	2 (No)	2 (No)	2 (No)
Severity	0.11	0.26	0.98
Rhinitis	2 (No)	2 (No)	1 (Yes)

Distances	1	2	3
1		1.022	1.440
2	1.022		1.070
3	1.440	1.070	

Children with no symptoms, low severity and no rhinitis (Cluster 1) were related to children who also did not have symptoms, low severity and no rhinitis (Cluster 2). This latter group was farther from children with cough, very high severity and rhinitis (Cluster 3). Moreover, Clusters 1 and 3 were the farthest. (Table 13)

Wheezing, cough, atopic dermatitis, severity and gender

Table 14. Final cluster centres (wheezing, cough, atopic dermatitis, severity and gender) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	2 (No)	1 (Yes)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)
Severity	0.20	0.84	0.09
Gender	3 (Unknown)	1 (Male)	1 (Male)

Distances	1	2	3
1		7.616	7.506
2	7.616		1.129
3	7.506	1.129	

Boys who had cough and high severity (Cluster 2) were related to boys without symptoms and very low severity (Cluster 3). Cluster 1 (children without symptoms, low severity and unknown gender) were not related neither to Cluster 3 nor Cluster 2. (Table 14)

Wheezing, cough, atopic dermatitis, severity and maternal asthma

Table 15. Final cluster centres (wheezing, cough, atopic dermatitis, severity and maternal asthma) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	1 (Yes)	2 (No)
Severity	0.49	0.60	0.13
Maternal asthma	2 (No)	3 (Unknown)	2 (No)

Distances	1	2	3
1		7.180	1.076
2	7.180		7.152
3	1.076	7.152	

Children with cough, medium severity and non-asthmatic mother (Cluster 1) were related to children with no symptoms, low severity and non-asthmatic mother (Cluster 3). Children with atopic dermatitis, medium severity and mothers with unknown asthmatic status (Cluster 2) were also more related to Cluster 3 subjects than with Cluster 1 children. (Table 15)

Wheezing, cough, atopic dermatitis, severity and paternal asthma

Table 16. Final cluster centres (wheezing, cough, atopic dermatitis, severity and paternal asthma) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	2 (No)	1 (Yes)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)
Severity	0.09	0.83	0.00
Paternal asthma	2 (No)	2 (No)	3 (Unknown)

Distances	1	2	3
1		1.121	7.140
2	1.121		7.208
3	7.140	7.208	

Children with no symptoms and very low severity, whose fathers were not asthmatics (Cluster 1), were related to those with cough, high severity, and non-asthmatic fathers (Cluster 2). These groups were not related to children with no symptoms or severity, and unknown paternal asthmatic status (Cluster 3). (Table 16)

Wheezing, cough, atopic dermatitis, severity and smoking mother

Table 17. Final cluster centres (wheezing, cough, atopic dermatitis, severity and smoking mother) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	2 (No)	1 (Yes)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)
Severity	0.10	0.84	0.13
Smoking mother	2 (No)	2 (No)	1 (Yes)

Distances	1	2	3
1		1.206	0.799
2	1.206		1.268
3	0.799	1.268	

Children with no symptoms, very low severity and non-smoking mothers (Cluster 1) were related to children with no symptoms and low severity, but exposed to tobacco smoke (Cluster 3). These groups were not related to children with cough, high severity and non-smoking mothers (Cluster 2). (Table 17)

Wheezing, cough, atopic dermatitis, severity and smoking father

Table 18. Final cluster centres (wheezing, cough, atopic dermatitis, severity and smoking father) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	2 (No)	2 (No)	1 (Yes)
Atopic dermatitis	2 (No)	2 (No)	2 (No)
Severity	0.11	0.11	0.96
Smoking father	1 (Yes)	2 (No)	2 (No)

Distances	1	2	3
1		1.000	1.379
2	1.000		1.280
3	1.379	1.280	

Children with no symptoms and low severity, whose fathers smoked (Cluster 1), were related to children with no symptoms, low severity, and non-smoking fathers (Cluster 2). Children from Cluster 1 were farther from those with cough, very high severity, and non-smoking fathers (Cluster 3). (Table 18)

Wheezing, cough, atopic dermatitis, severity and smoking during pregnancy

Table 19. Final cluster centres (wheezing, cough, atopic dermatitis, severity and smoking during pregnancy) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	2 (No)	1 (Yes)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)
Severity	0.10	0.84	0.13
Smoking during pregnancy	2 (No)	2 (No)	1 (Yes)

Distances	1	2	3
1		1.204	0.797
2	1.204		1.266
3	0.797	1.266	

Children with no symptoms, very low severity, and non-smoking mothers during pregnancy (Cluster 1), were related to children who also had no symptoms and very low severity, but prenatally exposed to tobacco smoke (Cluster 3). Both groups were farther from children with cough and high severity, but non-smoking mothers during pregnancy (Cluster 2). (Table 19)

Wheezing, cough, atopic dermatitis, severity and exposure to smoke at home

Table 20. Final cluster centres (wheezing, cough, atopic dermatitis, severity and exposure to smoke at home) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	2 (No)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)
Severity	0.25	0.22	0.24
Exposure to smoke	3 (2-5 hours/day)	0 (Never)	1 (<1 hour/day)

Distances	1	2	3
1		3.042	2.088
2	3.042		1.314
3	2.088	1.314	

Children with no symptoms and low severity, and not exposed to tobacco smoke (Cluster 2), were related to children with no symptoms, low severity and low exposition to tobacco smoke (Cluster 3). Cluster 2 was farther from children with no symptoms and low severity, but high exposition to tobacco smoke (Cluster 1). (Table 20)

Wheezing, cough, atopic dermatitis, severity and bronchiolitis

Table 21. Final cluster centres (wheezing, cough, atopic dermatitis, severity and bronchiolitis) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	2 (No)	1 (Yes)	1 (Yes)
Atopic dermatitis	2 (No)	2 (No)	2 (No)
Severity	0.18	0.00	1.00
Bronchiolitis	2 (No)	2 (No)	2 (No)

Distances	1	2	3
1		1.019	1.310
2	1.019		1.056
3	1.310	1.056	

Children with no symptoms and low severity (Cluster 1) were related to children with cough, but no severity nor bronchiolitis (Cluster 2). Moreover, children from Cluster 1 were farther from children with cough and severity, but who did not report bronchiolitis (Cluster 3). (Table 21)

Wheezing, cough, atopic dermatitis, severity and reflux

Table 22. Final cluster centres (wheezing, cough, atopic dermatitis, severity and reflux) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	2 (No)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	1 (Yes)	2 (No)
Severity	0.20	0.26	0.25
Reflux	2 (No)	2 (No)	1 (Yes)

Distances	1	2	3
1		1.030	1.003
2	1.030		1.266
3	1.003	1.266	

Children with no symptoms, low severity and no reflux (Cluster 1), were related to children with no symptoms, low severity and reflux (Cluster 3). Children in this latter group were farther from children with atopic dermatitis and low severity, but with no other symptoms or reflux (Cluster 2). (Table 22)

Wheezing, cough, atopic dermatitis, severity and breastfeeding

Table 23. Final cluster centres (wheezing, cough, atopic dermatitis, severity and breastfeeding) and distances between centres.

Clusters	1	2	3
Wheezing	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)
Severity	0.95	0.10	0.11
Breastfeeding	1 (Yes)	2 (No)	1 (Yes)

Distances	1	2	3
1		1.343	1.305
2	1.343		1.000
3	1.305	1.000	

Children with no symptoms, low severity, who did not breastfeed (Cluster 2), were related to children without symptoms, low severity, and who breastfed (Cluster 3). On the contrary, children from Cluster 2 were farther from children with cough and very high severity who breastfed (Cluster 1). (Table 23)

- **Four cluster analysis**

Wheezing, cough and atopic dermatitis

Table 24. Final cluster centres (wheezing, cough and atopic dermatitis) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	1 (Yes)	2 (No)
Cough	1 (Yes)	2 (No)	1 (Yes)	2 (No)
Atopic dermatitis	2 (No)	1 (Yes)	2 (No)	2 (No)

Distances	1	2	3	4
1		1.241	1.044	1.000
2	1.241		1.374	1.035
3	1.044	1.374		1.256
4	1.000	1.035	1.256	

Children with cough, but who did not wheeze or suffer from atopic dermatitis (Cluster 1) were related to children with no symptoms (Cluster 4). Children in Cluster 2 (children with atopic dermatitis but who did not wheeze or cough) were also related to those in Cluster 4. On the other hand, children who wheezed and coughed but did not suffer from atopic dermatitis (Cluster 3) and children classified in Cluster 2 were the farthest. (Table 24)

Wheezing, cough and severity

Table 25. Final cluster centres (wheezing, cough and severity) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	2 (No)	2 (No)	1 (Yes)
Severity	0.00	1.00	0.00	1.00

Distances	1	2	3	4
1		1.414	1.001	1.029
2	1.414		1.002	1.023
3	1.001	1.002		1.442
4	1.029	1.023	1.442	

Children with cough who did not wheeze or reported severity (Cluster 1) were related to children with no symptoms (Cluster 3). Children classified in Cluster 2 (no cough or wheeze, but very high severity) were also related to those in Cluster 3. The farthest clusters were children in Cluster 3 and children with cough and very high severity (Cluster 4). (Table 25)

Wheezing, cough, atopic dermatitis and severity

Table 26. Final cluster centres (wheezing, cough, atopic dermatitis and severity) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	1 (Yes)
Cough	1 (Yes)	2 (No)	2 (No)	1 (Yes)
Atopic dermatitis	2 (No)	2 (No)	2 (No)	2 (No)
Severity	0.00	1.00	0.00	0.97

Distances	1	2	3	4
1		1.120	1.001	1.373
2	1.120		1.117	1.057
3	1.001	1.117		1.615
4	1.373	1.057	1.615	

Children with cough but who did not wheeze, or have atopic dermatitis or severity (Cluster 1) were related to children with no symptoms (Cluster 3). On the other hand, children who did not wheeze, cough or suffer from atopic dermatitis, but showed very high severity (Cluster 2) were related to those who wheezed, coughed and reported very high severity, but did not have atopic dermatitis (Cluster 4). Children from this latter cluster and those in Cluster 3 were the farthest. (Table 26)

Wheezing, cough, atopic dermatitis, severity and rhinitis

Table 27. Final cluster centres (wheezing, cough, atopic dermatitis, severity and rhinitis) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	2 (No)	1 (Yes)	2 (No)	1 (Yes)
Atopic dermatitis	2 (No)	2 (No)	1 (Yes)	2 (No)
Severity	0.10	0.77	0.05	0.97
Rhinitis	2 (No)	1 (Yes)	1 (Yes)	2 (No)

Distances	1	2	3	4
1		1.379	0.844	1.284
2	1.379		1.169	1.004
3	0.844	1.169		1.358
4	1.284	1.004	1.358	

Children with no symptoms and low severity (Cluster 1) were related to children with atopic dermatitis, rhinitis and very low severity (Cluster 3). Children with cough, rhinitis and high severity (Cluster 2) were related to children with cough and very high severity (Cluster 4). Children classified in Clusters 1 and 2 were the farthest. (Table 27)

Wheezing, cough, atopic dermatitis, severity and gender

Table 28. Final cluster centres (wheezing, cough, atopic dermatitis, severity and gender) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	2 (No)	2 (No)	1 (Yes)
Atopic dermatitis	2 (No)	2 (No)	2 (No)	2 (No)
Severity	0.00	0.20	0.10	1.00
Rhinitis	1 (Male)	3 (Unknown)	1 (Male)	1 (Male)

Distances	1	2	3	4
1		7.570	1.008	1.048
2	7.570		7.505	7.633
3	1.008	7.505		1.282
4	1.048	7.633	1.282	

Boys with cough, but without any other symptoms (Cluster 1) were related to boys who did not wheeze, cough or suffer from atopic dermatitis and reported low severity (Cluster 3). Children from Cluster 1 were also related to boys with cough and very high severity (Cluster 4). Children in this latter cluster, and children from Cluster 2 (unknown gender, no symptoms and low severity) were the less related groups. (Table 28)

Wheezing, cough, atopic dermatitis, severity and maternal asthma

Table 29. Final cluster centres (wheezing, cough, atopic dermatitis, severity and maternal asthma) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	2 (No)	1 (Yes)	2 (No)
Atopic dermatitis	2 (No)	1 (Yes)	2 (No)	2 (No)
Severity	0.00	0.60	1.00	0.10
Maternal asthma	2 (No)	3 (Unknown)	2 (No)	2 (No)

Distances	1	2	3	4
1		7.476	1.072	0.790
2	7.476		7.236	7.045
3	1.072	7.236		1.260
4	0.790	7.045	1.260	

Children with cough, but without any other symptoms and non-asthmatics mothers (Cluster 1) were related to children with no symptoms, very low severity and asthmatic mothers (Cluster 4). Children classified in Cluster 1 were also related to children with cough and very high severity, but with no other symptoms, and non-asthmatic mothers (Cluster 3). Children who suffered from atopic dermatitis, showed medium severity, and unknown maternal asthmatic status (Cluster 2), were the farthest from children from Cluster 1. (Table 29)

Wheezing, cough, atopic dermatitis, severity and paternal asthma

Table 30. Final cluster centres (wheezing, cough, atopic dermatitis, severity and paternal asthma) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	1 (Yes)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)	2 (No)
Severity	0.84	0.07	0.12	0.00
Paternal asthma	2 (No)	1 (Yes)	2 (No)	3 (Unknown)

Distances	1	2	3	4
1		1.061	1.248	7.188
2	1.061		0.771	7.576
3	1.248	0.771		7.018
4	7.188	7.576	7.018	

Children with cough, very low severity and asthmatic fathers (Cluster 2) were related to children with no symptoms, low severity, and non-asthmatic fathers (Cluster 3).

Children in Cluster 2 were farther from those with no symptoms or severity, and unknown paternal asthmatic status (Cluster 4). Children from this latter group were less related to children with cough, high severity and non-asthmatic fathers (Cluster 1) and children in Cluster 3. (Table 30)

Wheezing, cough, atopic dermatitis, severity and smoking mother

Table 31. Final cluster centres (wheezing, cough, atopic dermatitis, severity and smoking mother) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	1 (Yes)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)	2 (No)
Severity	0.00	1.00	0.09	0.12
Smoking mother	2 (No)	2 (No)	1 (Yes)	2 (No)

Distances	1	2	3	4
1		1.045	1.142	1.034
2	1.045		1.377	1.322
3	1.142	1.377		0.805
4	1.034	1.322	0.805	

Children with no symptoms, very low severity, and smoking mothers (Cluster 3) were related to children with no symptoms, low severity, and non-smoking mothers (Cluster 4). Children in these two groups were farther from children with cough and severity, whose mothers were not smokers (Cluster 2). (Table 31)

Wheezing, cough, atopic dermatitis, severity and smoking father

Table 32. Final cluster centres (wheezing, cough, atopic dermatitis, severity and smoking father) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	2 (No)	1 (Yes)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)	2 (No)
Severity	0.26	0.12	0.97	0.13
Smoking father	2 (No)	2 (No)	1 (Yes)	1 (Yes)

Distances	1	2	3	4
1		1.041	0.934	1.257
2	1.041		1.475	1.000
3	0.934	1.475		1.414
4	1.257	1.000	1.414	

Children with cough, low severity and non-smoking father (Cluster 1) were related to children with cough, very high severity, and smoking father (Cluster 3).

On the other hand, both children in Cluster 2 (no symptoms, low severity and non-smoking father) and children in Cluster 4 (no symptoms, low severity and smoking father) were farther from children classified in Cluster 3. (Table 32)

Wheezing, cough, atopic dermatitis, severity and smoking during pregnancy

Table 33. Final cluster centres (wheezing, cough, atopic dermatitis, severity and smoking during pregnancy) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	1 (Yes)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)	2 (No)
Severity	0.00	1.00	0.09	0.11
Smoking during pregnancy	0 (No)	0 (No)	1 (Yes)	0 (No)

Distances	1	2	3	4
1		1.045	1.142	1.034
2	1.045		1.379	1.319
3	1.142	1.379		0.803
4	1.034	1.319	0.803	

Children with no symptoms, very low severity, and smoking mothers during pregnancy (Cluster 3) were related to children with no symptoms, low severity and non-smoking mothers (Cluster 4). Children in these groups were farther from children with cough, severity, who were not prenatally exposed to tobacco smoke (Cluster 2). (Table 33)

Wheezing, cough, atopic dermatitis, severity and exposure to smoke at home

Table 34. Final cluster centres (wheezing, cough, atopic dermatitis, severity and exposure to smoke at home) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	2 (No)	2 (No)	2 (No)	1 (Yes)
Atopic dermatitis	2 (No)	2 (No)	2 (No)	2 (No)
Severity	0.25	0.00	0.16	1.00
Exposure to smoke	3 (2-5 hours/day)	0 (Never)	1 (<1 hour/day)	0 (Never)

Distances	1	2	3	4
1		3.414	2.063	3.444
2	3.414		1.354	1.106
3	2.063	1.354		1.592
4	3.444	1.106	1.592	

Children with no symptoms, no severity, and not exposed to tobacco smoke (Cluster 2) were related to children with cough and severity, but not exposed to smoke (Cluster 4). On the other hand, children in this latter group were farther from children with no symptoms, low severity, but highly exposed to tobacco smoke (Cluster 1). (Table 34)

Wheezing, cough, atopic dermatitis, severity and bronchiolitis

Table 35. Final cluster centres (wheezing, cough, atopic dermatitis, severity and bronchiolitis) and distances between centres.

Clusters	1	2	3	4
Wheezing	1 (Yes)	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	1 (Yes)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	2 (No)	2 (No)	2 (No)
Severity	0.96	0.43	0.00	1.00
Bronchiolitis	1 (Yes)	2 (No)	2 (No)	2 (No)

Distances	1	2	3	4
1		0.952	1.577	1.219
2	0.952		1.090	1.156
3	1.577	1.090		1.002
4	1.219	1.156	1.002	

Children who wheezed, coughed, reported very high severity and bronchiolitis (Cluster 1) were related to children with cough, medium severity, but who did not suffer from bronchiolitis (Cluster 2). Children in Cluster 1 were far from children with no symptoms or bronchiolitis, but high severity (Cluster 4), and even farther from children with no symptoms, severity or bronchiolitis (Cluster 3). (Table 35)

Wheezing, cough, atopic dermatitis, severity and reflux

Table 36. Final cluster centres (wheezing, cough, atopic dermatitis, severity and reflux) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	1 (Yes)	2 (No)	2 (No)
Atopic dermatitis	2 (No)	1 (Yes)	2 (No)	2 (No)
Severity	0.38	0.91	0.00	0.40
Reflux	2 (No)	1 (Yes)	2 (No)	1 (Yes)

Distances	1	2	3	4
1		0.941	1.085	1.153
2	0.941		1.454	1.120
3	1.085	1.454		0.801
4	1.153	1.120	0.801	

Children with no symptoms, no severity or reflux (Cluster 3) were related to children with no symptoms, medium severity, and reflux (Cluster 4). Children classified in Cluster 3 were far from those with cough, atopic dermatitis, very high severity and reflux (Cluster 2), while children in Cluster 4 were far from those with cough, medium severity and no reflux (Cluster 1). (Table 36)

Wheezing, cough, atopic dermatitis, severity and breastfeeding

Table 37. Final cluster centres (wheezing, cough, atopic dermatitis, severity and breastfeeding) and distances between centres.

Clusters	1	2	3	4
Wheezing	2 (No)	2 (No)	2 (No)	2 (No)
Cough	1 (Yes)	2 (No)	2 (No)	1 (Yes)
Atopic dermatitis	2 (No)	2 (No)	2 (No)	2 (No)
Severity	0.83	0.10	0.00	1.00
Breastfeeding	1 (Yes)	1 (Yes)	2 (No)	2 (No)

Distances	1	2	3	4
1		1.129	1.539	1.089
2	1.129		1.006	1.429
3	1.539	1.006		1.094
4	1.089	1.429	1.094	

Children with no symptoms, low severity, and who breastfed (Cluster 2) were related to children with no symptoms, no severity, who were not breastfed (Cluster 3). Children classified in Cluster 2 were far from those who had cough, severity, and were not breastfed (Cluster 4), whilst children in Cluster 3 were far from those with cough, high severity, who breastfed (Cluster 1). (Table 37)

- **Nine cluster analysis**

Wheezing, cough, atopic dermatitis, severity and maternal asthma

Children with atopic dermatitis, low severity, and non-asthmatic mother (Cluster 3) were related to those with no symptoms, low severity, and non-asthmatic mother (Cluster 4). On the other hand, children who had atopic dermatitis, low severity and an unknown maternal asthmatic status (Cluster 2) were the farthest from those with cough, atopic dermatitis, medium severity, and asthmatic mother (Cluster 9). (Table 38)

Table 38. Final cluster centres (wheezing, cough, atopic dermatitis, severity and maternal asthma) and distances between centres.

Clusters	1	2	3	4	5	6	7	8	9
Wheezing	No	No	No	No	Yes	No	No	Yes	No
Cough	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Atopic dermatitis	No	Yes	Yes	No	Yes	No	No	No	Yes
Severity	1.00	0.33	0.11	0.10	0.74	0.21	1.00	1.00	0.65
Maternal asthma	UNK	UNK	No	No	No	Yes	No	No	Yes

UNK: Unknown

Distances	1	2	3	4	5	6	7	8	9
1		1.213	7.530	7.128	7.101	7.849	7.096	7.315	8.029
2	1.213		7.425	7.037	7.123	7.882	7.208	7.290	8.052
3	7.530	7.425		0.769	1.428	1.239	1.425	1.510	1.112
4	7.128	7.037	0.769		1.637	1.236	1.275	1.351	1.653
5	7.101	7.123	1.428	1.637		1.490	1.238	1.248	1.282
6	7.849	7.882	1.239	1.236	1.490		1.094	1.477	1.169
7	7.096	7.208	1.425	1.275	1.238	1.094		1.276	1.331
8	7.315	7.290	1.510	1.351	1.248	1.477	1.276		1.742
9	8.029	8.052	1.112	1.653	1.282	1.169	1.331	1.742	

Wheezing, cough, atopic dermatitis, severity and paternal asthma

Table 39. Final cluster centres (wheezing, cough, atopic dermatitis, severity and paternal asthma) and distances between centres.

Clusters	1	2	3	4	5	6	7	8	9
Wheezing	No	No	No	Yes	No	No	Yes	Yes	Yes
Cough	No	No	No	Yes	Yes	Yes	Yes	No	Yes
Atopic dermatitis	Yes	No	No	Yes	No	No	No	No	No
Severity	0.10	0.10	0.00	0.72	0.61	1.00	0.00	0.30	1.00
Paternal asthma	No	No	UNK	No	Yes	No	No	No	Yes

UNK: Unknown

Distances	1	2	3	4	5	6	7	8	9
1		1.000	7.117	1.301	1.416	1.516	1.653	1.436	1.907
2	1.000		7.119	1.655	1.190	1.293	1.334	1.029	1.750
3	7.114	7.119		7.149	8.036	7.115	7.255	7.194	8.141
4	1.301	1.655	7.149		1.625	1.215	1.270	1.297	1.306
5	1.416	1.190	8.036	1.625		1.146	1.501	1.552	1.077
6	1.516	1.293	7.115	1.215	1.146		1.279	1.454	1.288
7	1.653	1.334	7.255	1.270	1.501	1.279		1.046	1.358
8	1.436	1.029	7.194	1.297	1.552	1.454	1.046		1.382
9	1.907	1.750	8.141	1.306	1.077	1.288	1.358	1.382	

Children with atopic dermatitis, very low severity and non-asthmatic father (Cluster 1) were related to children who did not report any symptoms, had very low severity and non-asthmatic fathers (Cluster 2).

Children classified in Cluster 3, who did not report any symptoms nor severity, and the paternal asthmatic status was unknown, were the farthest from children who wheezed, coughed, presented very high severity, and had asthmatic fathers (Cluster 9). (Table 39)

Wheezing, cough, atopic dermatitis, severity and smoking mother

Table 40. Final cluster centres (wheezing, cough, atopic dermatitis, severity and smoking mother) and distances between centres.

Clusters	1	2	3	4	5	6	7	8	9
Wheezing	No	No	No	No	No	No	No	Yes	Yes
Cough	Yes	No	No	No	No	Yes	Yes	No	Yes
Atopic dermatitis	Yes	No	No	No	No	No	No	No	Yes
Severity	0.00	1.00	0.00	1.00	0.00	0.22	1.00	1.00	0.81
Smoking mother	No	Yes	Yes	No	No	Yes	No	No	No

Distances	1	2	3	4	5	6	7	8	9
1		1.470	1.218	1.212	0.781	1.148	1.171	1.625	1.392
2	1.470		1.101	1.101	1.494	1.031	1.159	1.264	1.603
3	1.218	1.101		1.415	1.009	1.090	1.744	1.528	1.909
4	1.212	1.101	1.415		1.012	1.591	1.026	1.070	1.536
5	0.781	1.494	1.009	1.012		1.401	1.439	1.459	1.799
6	1.148	1.031	1.090	1.591	1.401		1.187	1.499	1.448
7	1.171	1.159	1.744	1.026	1.439	1.187		1.319	1.188
8	1.625	1.264	1.528	1.070	1.459	1.499	1.319		1.203
9	1.392	1.603	1.909	1.536	1.799	1.448	1.188	1.203	

Children with cough, atopic dermatitis, and no severity or smoking mother (Cluster 1) were related to children with no symptoms or severity, and non-smoking mothers (Cluster 5). On the other hand, children with no symptoms or severity, but whose mothers smoked (Cluster 3), were the farthest to children who suffered from wheeze, cough, atopic dermatitis and high severity, but had non-smoking mothers (Cluster 9). (Table 40)

Wheezing, cough, atopic dermatitis, severity and smoking father

Children who wheezed, had medium severity and smoking fathers (Cluster 2) were related to children who also wheezed, but did not report any other symptoms or severity, and whose fathers did not smoke (Cluster 5). Children in this latter group were the farthest from children with cough, atopic dermatitis, medium severity, and who also had smoking fathers (Cluster 9). (Table 41)

Table 41. Final cluster centres (wheezing, cough, atopic dermatitis, severity and smoking father) and distances between centres.

Clusters	1	2	3	4	5	6	7	8	9
Wheezing	No	Yes	No	No	Yes	No	No	Yes	No
Cough	Yes	No	No	No	No	No	Yes	Yes	Yes
Atopic dermatitis	No	No	No	No	No	No	Yes	No	Yes
Severity	0.73	0.61	0.00	0.00	0.00	1.00	0.52	0.82	0.63
Smoking father	Yes	Yes	No	Yes	No	No	No	No	Yes

Distances	1	2	3	4	5	6	7	8	9
1		1.298	1.195	1.135	1.621	1.081	1.253	1.060	1.067
2	1.298		1.344	1.231	0.885	1.247	1.638	1.070	1.457
3	1.195	1.344		1.009	1.009	1.010	1.352	1.612	1.618
4	1.135	1.231	1.009		1.414	1.415	1.747	1.746	1.336
5	1.621	0.885	1.009	1.414		1.414	1.624	1.362	1.867
6	1.081	1.247	1.010	1.415	1.414		1.396	1.491	1.568
7	1.253	1.638	1.352	1.747	1.624	1.396		1.382	1.030
8	1.060	1.070	1.612	1.746	1.362	1.491	1.382		1.482
9	1.067	1.457	1.618	1.336	1.867	1.568	1.030	1.482	

Wheezing, cough, atopic dermatitis, severity and smoking during pregnancy

Table 42. Final cluster centres (wheezing, cough, atopic dermatitis, severity and smoking during pregnancy) and distances between centres.

Clusters	1	2	3	4	5	6	7	8	9
Wheezing	No	No	No	Yes	No	No	No	Yes	No
Cough	No	Yes	No	Yes	No	Yes	Yes	No	No
Atopic dermatitis	No	Yes	Yes	Yes	No	No	No	No	Yes
Severity	0.08	0.48	0.00	0.88	1.00	0.51	1.00	0.20	1.00
Smoking during pregnancy	No	No	Yes	No	Yes	Yes	No	No	No

Distances	1	2	3	4	5	6	7	8	9
1		1.337	1.256	1.722	1.276	1.339	1.326	1.017	1.298
2	1.337		1.336	1.105	1.770	1.379	1.163	1.597	1.132
3	1.256	1.336		1.653	1.426	1.412	1.939	1.628	1.299
4	1.722	1.105	1.653		1.753	1.547	1.273	1.298	1.289
5	1.276	1.770	1.426	1.753		1.119	1.426	1.512	1.292
6	1.339	1.379	1.412	1.547	1.119		1.115	1.441	1.716
7	1.326	1.163	1.939	1.273	1.426	1.115		1.327	1.454
8	1.017	1.597	1.628	1.298	1.512	1.441	1.327		1.608
9	1.298	1.132	1.299	1.289	1.292	1.716	1.454	1.608	

The nearest groups were children with no symptoms, very low severity, and not prenatally exposed to tobacco smoke (Cluster 1) and children who wheezed and had low severity, but did not suffer from any other symptoms, and whose mothers did not smoke during pregnancy (Cluster 8).

On the contrary, children with atopic dermatitis, but without any other symptoms or severity, whose mothers smoked during pregnancy (Cluster 3) were the farthest from children who had cough and very high severity, but did not report any other symptoms, and were not prenatally exposed to tobacco smoke (Cluster 7). (Table 42).

Wheezing, cough, atopic dermatitis, severity and exposure to smoke at home

Table 43. Final cluster centres (wheezing, cough, atopic dermatitis, severity and exposure to smoke at home) and distances between centres.

Clusters	1	2	3	4	5	6	7	8	9
Wheezing	No	No	No	Yes	No	No	No	Yes	No
Cough	No	No	No	Yes	Yes	Yes	Yes	No	No
Atopic dermatitis	No	No	Yes	Yes	No	No	No	No	No
Severity	0.12	0.00	0.16	0.61	1.00	0.64	0.78	0.28	0.00
Exposure to smoke	1	0	1	3	0	3	1	0	3

0: Never; 1: <1 hour/day; 2: 1-2 hours/day; 3: 2-5 hours/day; 4: >5 hours/day

Distances	1	2	3	4	5	6	7	8	9
1		1.301	1.008	1.860	1.649	2.334	1.164	1.605	2.138
2	1.301		1.554	2.974	1.103	3.580	1.866	1.048	3.416
3	1.008	1.554		1.794	1.784	2.471	1.345	1.763	2.301
4	1.860	2.974	1.794		2.861	1.069	1.506	2.761	1.364
5	1.649	1.103	1.784	2.861		3.496	1.522	1.142	3.608
6	2.334	3.580	2.471	1.069	3.496		2.065	3.572	0.977
7	1.164	1.866	1.345	1.506	1.522	2.065		1.780	2.362
8	1.605	1.048	1.763	2.761	1.142	3.572	1.780		3.519
9	2.138	3.416	2.301	1.364	3.608	0.977	2.362	3.519	

Children with cough, medium severity, who were exposed to tobacco smoke for 2-5 hours/day (Cluster 6) were related to children with no symptoms nor severity, but the same exposition to tobacco smoke (Cluster 9). On the other hand, children in this latter group were the farthest from those with cough, severity, but not exposed to tobacco smoke (Cluster 5). (Table 43)

Wheezing, cough, atopic dermatitis, severity and bronchiolitis

Children with cough, but no severity nor bronchiolitis (Cluster 1) were related to children with cough and atopic dermatitis, but who did not report severity nor bronchiolitis (Cluster 8). Children who suffered from wheeze, cough, very high severity and bronchiolitis (Cluster 2) were the farthest from children who had atopic dermatitis, low severity, and did not suffer from bronchiolitis (Cluster 9). (Table 44)

Table 44. Final cluster centres (wheezing, cough, atopic dermatitis, severity and bronchiolitis) and distances between centres.

Clusters	1	2	3	4	5	6	7	8	9
Wheezing	No	Yes	No	No	Yes	No	No	No	No
Cough	Yes	Yes	No	Yes	No	Yes	No	Yes	No
Atopic dermatitis	No	No	No	No	Yes	Yes	No	Yes	Yes
Severity	0.00	0.98	0.00	1.00	0.50	1.00	0.65	0.00	0.18
Bronchiolitis	No	Yes	No	No	No	No	Yes	No	No

Distances	1	2	3	4	5	6	7	8	9
1		1.366	1.001	1.099	1.783	1.430	1.542	1.000	1.426
2	1.366		1.721	1.091	1.609	1.220	1.188	1.644	1.882
3	1.001	1.721		1.140	1.493	1.750	1.218	1.416	1.016
4	1.099	1.091	1.140		1.581	1.123	1.217	1.486	1.406
5	1.783	1.609	1.493	1.581		1.350	1.538	1.462	1.053
6	1.430	1.220	1.750	1.123	1.350		1.700	1.018	1.320
7	1.542	1.188	1.218	1.217	1.538	1.700		1.814	1.492
8	1.000	1.644	1.416	1.486	1.462	1.018	1.814		1.019
9	1.426	1.882	1.016	1.406	1.053	1.320	1.492	1.019	

Wheezing, cough, atopic dermatitis, severity and reflux

Table 45. Final cluster centres (wheezing, cough, atopic dermatitis, severity and reflux) and distances between centres.

Clusters	1	2	3	4	5	6	7	8	9
Wheezing	No	No	No	No	Yes	No	No	Yes	No
Cough	No	No	No	No	Yes	Yes	No	No	Yes
Atopic dermatitis	No	Yes	Yes	No	No	No	No	No	Yes
Severity	0.00	0.14	0.12	1.00	0.89	0.00	0.21	0.27	1.00
Bronchiolitis	No	Yes	No	No	No	No	Yes	Yes	No

Distances	1	2	3	4	5	6	7	8	9
1		1.438	1.007	1.110	1.617	1.015	1.053	1.470	1.751
2	1.438		1.024	1.678	1.789	1.521	1.003	1.280	1.383
3	1.007	1.024		1.416	1.727	1.303	1.440	1.638	1.356
4	1.110	1.678	1.416		1.125	1.140	1.294	1.621	1.155
5	1.617	1.789	1.727	1.125		1.363	1.575	1.157	1.282
6	1.015	1.521	1.303	1.140	1.363		1.277	1.612	1.322
7	1.053	1.003	1.440	1.294	1.575	1.277		1.024	1.654
8	1.470	1.280	1.638	1.621	1.157	1.612	1.024		1.800
9	1.751	1.383	1.356	1.155	1.282	1.322	1.654	1.800	

Children with atopic dermatitis, low severity, and reflux (Cluster 2) were related to children with no symptoms, low severity, and reflux (Cluster 7). Children who wheezed, and had low severity and reflux (Cluster 8) were the farthest from children with cough, atopic dermatitis, very high severity, but no reflux (Cluster 9). (Table 45)

Wheezing, cough, atopic dermatitis, severity and breastfeeding

Table 46. Final cluster centres (wheezing, cough, atopic dermatitis, severity and breastfeeding) and distances between centres.

Clusters	1	2	3	4	5	6	7	8	9
Wheezing	No	Yes	Yes	No	No	No	No	Yes	Yes
Cough	Yes	No	Yes	Yes	No	No	No	Yes	No
Atopic dermatitis	Yes	No	No	No	No	Yes	No	No	No
Severity	0.07	0.43	0.85	1.00	0.00	0.57	0.00	1.00	0.00
Breastfeeding	Yes	Yes	Yes	Yes	No	No	Yes	No	No

Distances	1	2	3	4	5	6	7	8	9
1		1.299	1.357	1.113	1.206	1.166	0.898	1.701	1.451
2	1.299		1.088	1.384	1.508	1.424	1.119	1.448	1.143
3	1.357	1.088		1.131	1.869	1.727	1.663	1.020	1.469
4	1.113	1.384	1.131		1.319	1.153	1.232	1.248	1.616
5	1.206	1.508	1.869	1.319		0.865	1.011	1.596	1.034
6	1.166	1.424	1.727	1.153	0.865		1.276	1.422	1.263
7	0.898	1.119	1.663	1.232	1.011	1.276		1.945	1.466
8	1.701	1.448	1.020	1.248	1.596	1.422	1.945		1.131
9	1.451	1.143	1.469	1.616	1.034	1.263	1.466	1.131	

Children with no symptoms nor severity, and who were not breastfed (Cluster 5) were related to children with atopic dermatitis, medium severity, who also were not breastfeed (Cluster 6). On the contrary, children with no symptoms nor severity, and who breastfed (Cluster 7) were the less related to children who wheezed, had cough and very high severity, and who were not breastfeed (Cluster 8). (Table 46)

- **Twelve cluster analysis**

Children with no symptoms, no severity, and who did not suffer from bronchiolitis, whose mothers did not smoke during pregnancy and were not current smokers nor asthmatics, and whose fathers were neither smokers nor asthmatics (Cluster 1) were related to children with cough and atopic dermatitis, no severity nor bronchiolitis, whose mothers did not smoke during the pregnancy, and whose parents were non-smokers and non-asthmatics (Cluster 9).

On the contrary, children who reported suffering from cough and atopic dermatitis, but no severity nor bronchiolitis, whose mothers did not smoke during pregnancy, and were non-smokers and non-asthmatics, and whose fathers were non-smokers and showed an unknown paternal asthmatic status (Cluster 5) were the farthest from those children who did not report any symptoms, no severity nor bronchiolitis, but whose mothers smoked during pregnancy and were current smokers, and showed an unknown maternal asthmatic status, and whose fathers were smokers and asthmatics (Cluster 10). (Table 47)

Table 47. Final cluster centres (multiple risk factors) and distances between centres

Clusters	1	2	3	4	5	6	7	8	9	10	11	12
Wheezing	No	No	No	No	No	No	Yes	No	No	No	No	No
Cough	No	No	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Atopic dermatitis	No	Yes	No	No	Yes	No	No	No	Yes	No	No	No
Severity	0.00	1.00	1.00	0.18	0.00	0.15	0.95	0.94	0.00	0.00	0.71	0.98
Maternal asthma	No	DNK	No	No	No	No	No	No	No	DNK	Yes	No
Paternal asthma	No	No	No	No	DNK	No	No	No	No	Yes	No	No
Smoking mother	No	No	No	Yes	No	No	No	Yes	No	Yes	No	No
Smoking father	No	No	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Smoking during pregnancy	No	No	No	Yes	No	No	No	Yes	No	Yes	No	No
Bronchiolitis	No	No	No	No	No	No	Yes	No	No	No	No	No

DNK: Do not know

Distances	1	2	3	4	5	6	7	8	9	10	11	12
1		7.269	1.176	1.574	7.277	1.039	1.713	2.098	0.833	7.380	1.397	1.745
2	7.269		7.070	7.385	10.000	7.248	7.245	7.433	7.210	2.449	8.084	7.213
3	1.176	7.070		1.795	7.251	1.386	1.085	1.654	1.067	7.351	1.099	1.119
4	1.574	7.385	1.795		7.408	1.315	2.121	1.207	1.639	7.177	1.854	1.759
5	7.277	10.000	7.251	7.408		7.313	7.380	7.410	7.140	10.863	7.290	7.370
6	1.039	7.248	1.386	1.315	7.313		1.777	1.732	1.167	7.240	1.427	1.207
7	1.713	7.245	1.085	2.121	7.380	1.777		1.555	1.466	7.490	1.377	1.216
8	2.098	7.433	1.654	1.207	7.410	1.732	1.555		1.896	7.344	1.713	1.291
9	0.833	7.210	1.067	1.639	7.140	1.167	1.466	1.896		7.393	1.235	1.497
10	7.380	2.449	7.351	7.177	10.863	7.240	7.490	7.344	7.393		8.261	7.320
11	1.397	8.084	1.099	1.854	7.290	1.427	1.377	1.713	1.235	8.261		1.288
12	1.745	7.213	1.119	1.759	7.370	1.207	1.216	1.291	1.497	7.320	1.288	

4. References

Etude Longitudinale Française depuis l'Enfance. Accessed 17/12/2016. From: https://www.elfe-france.fr/index.php/en/

Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, et al. (2008). Associations of wheezing phenotypes in the first six years of life with atopy, lung function and airway responsiveness in mid childhood. *Thorax*, 63(11), 974-980.

Institut de Santé Publique, d'Epidémiologie et de Développement. Accessed 14/02/2016. From: http://www.isped.u-bordeaux.fr/

Léridon H. (2007). Le projet de cohorte nationale d'enfants : ELFE. *Arch Pediatr*, 14(6), 702-704.

Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. (2003). Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol*, 111(4), 661-675.

Vandentorren S, Bois C, Pirus C, Sarter H, Salines G, Leridon H, et al. (2009). Rationales, design and recruitment for the Elfe longitudinal study. *BMC Pediatr*, 9, 58.