1. Introduction

1.1 Definition

Asthma is a syndrome that includes different clinical phenotypes that share similar clinical manifestations, but probably of different etiologies. Classically, it is defined as a chronic inflammatory disease of the airways, in which different inflammatory cells and mediators are involved, conditioned in part by genetic factors and associated with bronchial hyperresponsiveness (BHR) and variable degree of airflow obstruction that is totally or partially reversible by either the action of drugs or spontaneously[1]. Being a chronic disease and included in the different current chronicity strategies, the objective of its approach is to achieve and maintain control of the disease and the prevention of future risk, especially exacerbations, which can be life-threatening for the patient and generate a burden for the society[2].

1.2 Prevalence

The prevalence of asthma is highly variable worldwide, ranging from 2% in Tartu (Estonia) to 11.9% in Melbourne (Australia). In addition, the prevalence of wheezing over the last 12 months varies from 4.1% in Mumbai (India) to 32% in Dublin (Ireland)[3,4].

According to the 2015 Global Burden of Disease study, the prevalence of asthma has increased worldwide by 12.6% from 1990 to 2015. On the contrary, the age-standardized mortality rate has decreased almost 59% during the same period[5]. This increase in prevalence affects mainly middle-aged people and women, and can be explained by an increase in allergic asthma, with stabilization of the non-allergic[6].

In our country, The European Respiratory Health Study reported prevalence rates of 4.7% in Albacete, 3.5% in Barcelona, 1.1% in Galdakao, 1% in Huelva and 1.7 % in Oviedo[7].

Other recent studies show very different prevalences based on different variables, such as: age (adolescents), between 10.6%[8] and 13.4%[9]; the method used (self-reported by the patient), 13.5%[10]; or the study setting (work environment), 2.5%[11].

In Spain, a study carried out in Navarra showed a prevalence of 10.6% in adolescents[8]. In another study also conducted in Navarra, but designed and carried out in rural areas, a prevalence of asthma of 13.4% was found in adolescents, the latter being slightly higher in females (13.7% vs. 10.9%), with rhinitis, wheezing (especially associated with physical activity) and dry cough as related symptoms[9].

A study carried out in Argentina showed a prevalence of asthma in adults (20 to 44 years old) of 6.4%[12] (Table 1.1).

1.3 Risk factors

Factors associated with the appearance of asthma syndrome should be distinguished from triggering factors of symptoms or asthma exacerbation episodes.

The most widely studied risk factors for asthma development, or those with a higher degree of association, are shown in Table 1.2. Many host-related factors are perinatal, while environmental factors vary greatly and can impact on patients of different age groups.

Table 1.1. Prevalence of asthma in adults and adolescents

Author	Area	Year	Prevalence	Comments
Álvarez[8]	Navarra	2014	10.6%	Adolescents
Elizalde[9]	Navarra (rural)	2018	13.4%	Adolescents
Vila-Rigat[11]	Barcelona	2014	2.5%	Working population 16-64 years
López[10]	Madrid	2017	6.3%/13.5%	Current asthma/accumulated asthma
Arias[12]	Argentina	2018	6.4%	Adults 20-44 years

Table 1.2. Factors associated with developing of asthma

Risk factors	Evidence	Association	Type of study	Reference
HOST-RELATED FACTORS				
Atopy	C	OR 3.5 (2.3-5.3)	b	Arbes 2007[13]
Early menarche	C	OR 1.08 (1.04-1.12)	b	Minelli 2018[14]
Obesity	B	RR 1.50 (1.22-1.83)	a	Egan 2013[15]
Bronchial hyperresponse	C	OR 4.2 (1.92-9.23)	b	Carey 1996[16]
Rhinitis	C	OR 3.21 (2.21-4.71)	b	Guerra 2002[17]
	C	OR 4.16 (3.57-4.86)	b	Burgess 2007[18]
	C	RR 3.53 (2.11-5.91)	b	Shaaban 2008[19]
PERINATAL FACTORS				
Maternal age	C	OR 0.85 (0.79-0.92) **1,4**	b	Gómez 2018[20]
Preeclampsia	C	OR 4.01 (1.11-14.43)	b	Stokholm 2017[21]
Prematurity	B	OR 2.81 (2.52-3.12) **2**	a	Been 2014[22]
	B	OR 1.37 (1.17-1.62) **3**	a	Been 2014[22]
	C	OR 4.30 (2.33-7.91)	b	Leps 2018[23]
Cesarean section	C	HR 1.52 (1.42-1.62)	b	Tollånes 2008[24]
Neonatal jaundice	C	OR 1.64 (1.36-1.98)	b	Ku 2012[25]
Lactation	C	OR 0.88 (0.82-0.95) **4**	b	Silvers 2012[26]
	B	OR 0.70 (0.60-0.81) **4**	a	Gdalevich 2001[27]
Tobacco consumption during pregnancy	C	OR 1.72 (1.11-2.67)	b	Strachan 1996[28]
	A	OR 1.85 (1.35-2.53)	a	Burke 2012[29]
	C	OR 2.70 (1.13-6.45)	b	Cunningham 1996[30]
	C	OR 1.65 (1.18-2.31)	b	Neuman 2012[31]
Maternal diet	C	OR 0.49 (0.27-0.90) **2,4**	b	Litonjua 2006[32]
	A	OR 0.54 (0.33-0.88) **5,4**	a	Wolks 2017[33]
	C	OR 0.33 (0.11-0.98) **4**	b	Devereux 2007[34]
	A	OR 0.86 (0.78-0.95) **6,4**	a	García-Marcos 2013[35]
Infant diet	A	RR 0.66 (0.47-0.94) **7,4**	d	Hibbs 2018[36]
Pulmonary function of the neonate	C	OR 2.10 (1.12-3.93)	b	Håland 2006[37]
ENVIRONMENTAL FACTORS				
Aeroallergens	C	OR 0.49 (0.29-0.83) **8,4**	b	Kerkhof 2009[38]
	C	OR 0.68 (0.49-0.95) **9,4**	b	Kerkhof 2009[38]
Allergens in the workplace	C	RR 2.2 (1.3-4.0)	b	Kogevinas 2007[39]
	C	OR 0.55 (0.43-0.70) **10,4**	b	Hoppin 2008[40]
Respiratory infections	C	OR 0.52 (0.29-0.92) **11,4**	b	Illi 2001[41]
Tobacco	C	RR 3.9 (1.7-8.5)	b	Gilliland 2006[42]
	C	HR 1.43 (1.15-1.77)	b	Coogan 2015[43]
	C	HR 1.21 (1.00-1.45) **12**	b	Coogan 2015[43]
Environmental pollution	A	OR 1.34 (1.17-1.54)	a	Orellano 2018[44]
DRUGS				
Paracetamol	C	OR 1.26 (1.02-1.58)	b	Sordillo 2015[45]
Antacids	A	RR 1.45 (1.35-1.56)	a	Lai 2018[46]
Antibiotics	B	OR 1.12 (0.88-1.42) **13**	a	Marra 2006[47]
	C	OR 0.6 (0.4-0.96) **4**	b	Goksör 2013[48]
	C	HR 1.23 (1.20-1.27) **14**	b	Loewen 2018[49]
	C	OR 1.75 (1.40-2.17) **15**	b	Hoskin-Parr 2013[50]
Hormone replacement therapy	C	HR (1.54 (1.13-2.09) **16**	b	Romieu 2010[51]

HR: *hazard ratio*; OR: *odds ratio*. RR: risk ratio.Type of study: a meta-analysis-systematic review, b epidemiological prospective study, c epidemiological retrospective study, d clinical trial.
Comment: **1** female sex, **2** very preterm, **3** moderate preterm, **4** protective factor, **5** vitamin D level at initiation of pregnancy, **6** Mediterranean diet, **7** vitamin D supplement, **8** dog exposure, **9** cat exposure, **10** living in a farm, **11** non-respiratory viral infection, **12** passive tobacco consumption, **13** no association, **14** prenatal exposure, **15** postnatal exposure, **16** with estrogens only.

On the other hand, the most common triggers of asthma symptoms or exacerbations are shown in Table 1.3. It is important to be aware of them because they can lead to serious conditions and, therefore, should be avoided.

Genetic factors are becoming increasingly relevant with the progress of research. Current studies show their protagonism in the appearance of asthma, phenotypic expression of the disease, individual response to precipitating factors of asthma

Table 1.3. Precipitating factors of asthma symptoms and exacerbations

Environmental factors	Atmospheric	Pollution	- SO_2 - NO_2 - Ozone - CO - Particles in suspension
		Plants	- Grass pollen - Tree pollen - Weed pollen
	Domestic	Dust mites	- Animal epithelium - Cockroach
	Fungus and virus	- *Alternaria alternata* - *Cladosporium herbarum*	- *Penicillium* - *Aspergillus fumigatus*
		Rhinoviruses and other respiratory viruses	
Systemic factors	Drugs	- Antibiotics	Topical and systemic non-selective ß-blockers
		- *Ácido acetilsalicílico*	- NSAID
	Food	- Cow milk	- Cereals
		- Egg	- Fish
		- Nuts	- Seafood
		- Sulfite-containing foods	Nuts, wine, lemon, lime and grape juices, dried potatoes, vinegar, seafood, beer, etc.
		Plant panallergens such as profillins or lipid transfer protein (LTP)	
	Other	- Hymenoptera venom	- *Apis melifera* (bee) - *Vespula* spp, *Polistes dominulus* (wasp)
Occupational-related factors	**Low molecular weight substances**	**Industry involved**	
	Drugs	Pharmaceutical industry	
	Anhydrides	Plastic industry	
	Diisocyanates	Polyurethane, plastic, varnish and enamel manufacturing industries	
	Woods	Sawmills, carpentry, joinery	
	Metals	Foundries, nickel plating, silver industries, leather tanning, boiler cleaning	
	Other	Cosmetics industries, hairdressing salons, photography development, refrigeration, dyes	
	High molecular weight substances	**Industry involved**	
	Substances of plant origin, powder and flours	Farmers, dock workers, mills, bakeries, beer industry, soybean processing, cacao, coffee, tee industries, textile industry	
	Food	Food industry	
	Plant enzymes	Food industry, pharmaceutical industry	
	Plant gums	Food industry, printing, latex industry, sanitary	
	Fungi and spores	Bakeries, farms, farmers	
	Animal enzymes	Mills, carmine manufacturing	

symptoms or exacerbations and, very especially, in the response to new therapies in cases of severe asthma[52].

Finally, it should be emphasized the growing evidence of the importance of environmental pollution, both inside buildings from burning biomass and outdoors from burning fossil fuels[53,54]. Environmental pollution is an associated factor to the development of asthma and a precipitating factor of asthma symptoms and exacerbations. Also, it contributes to an increase of asthma-related morbimortality as well as the incidence of other chronic respiratory diseases, cardiovascular diseases, and different types of cancer[55].

1.4 Pathogenesis

C

Inflammation affects the whole airways including the nasal mucosa, and is present even when symptoms are episodic. However, the relationship between severity of asthma and intensity of inflammation has not been consistently established[56]. The epithelium initiates the response to inhaletd substances secreting cytokines, such as thymic such as *Thymic Stromal Lymphopoietin* (TSLP), IL-33 and IL-25, which are crucial for the activation of type 2 innate immune system (Table 1.4)[59,60].Once type 2 innate lymphoid cells have been activated, type 2 proinflammatory cytokines are released, such as IL-4, IL-5 and IL-13, which assume the role of starting and maintaining T2 response (Table 1.5). On the other hand, dendritic cells promote the development of T-helper lymphocytes (Th2) with secretion of type cytokines. Recent studies show that not all patients develop Th2 inflammation, since other molecules such as IL-17 and IF-γ are involded in the so-called, Th2-low asthma. Molecules that participate in this inflammatory cascade are summarized in Table 1.6.

C

C

Patients with asthma often exhibit characteristic structural changes, known as airway remodeling, which include thickening of the reticular layer of the basal membrane, subepithelial fibrosis, hypertrophy and hyperplasia of the bronchial smooth muscle, vascular proliferation and dilatation, mucosal gland hyperplasia and mucus

Table 1.4. Airway cells and structural elements involved in asthma

Bronchial epithelium: it is damaged, with loss of ciliated and secretory cells. Epithelial cells are sensitive to changes in their microenvironment, express multiple inflammatory proteins, and release cytokines, chemokines, and lipid mediators in response to physical modifications. Pollutants and viral infections can also stimulate its production. The repair process that follows epithelial damage can be abnormal, increasing the obstructive lesions that occur in asthma[57].
Aiway smooth muscle: their cells show an increase in proliferation (hyperplasia) and growth (hypertrophy) expressing proinflammatory mediators, similar to those of epithelial cells[58].
Endothelial cells: participate in the recruitment of inflammatory cells from the vessels to the airway, through the expression of adhesion molecules.
Fibroblasts and myofibroblasts: stimulated by inflammatory and growth mediators, they produce components of the connective tissue, such as collagen and proteoglycans, which are involved in the remodeling of the airway.
Airway cholinergic system: it can be activated by nerve reflexes and cause bronchoconstriction and mucus secretion. Sensory nerves can cause symptoms such as cough and chest tightness, and can release inflammatory neuropeptides.

Table 1.5. Inflammatory cells involved in asthma

T lymphocytes (TL): are increased in number in the airways, with an imbalance in the Th1/Th2 ratio and predominance of Th2 that release specific cytokines, including IL-4, 5, 9 and 13. The cytokines orchestrate the eosinophilic inflammation and IgE production by B lymphocytes. Levels of TL regulators are decreased and TL NK increased[61].
Mastocytes: are increased in the bronchial epithelium and infiltrate the bronchial wall smooth muscle. Their activation releases mediators with bronchoconstrictor and proinflammatory activity, such as histamine, leukotrienes and prostaglandin D2[62]. They are activated by allergens, osmotic stimuli (such as exercise-induced bronchoconstriction) and neuronal connections.
Eosinophils: are increased in the airways and its number correlates with severity. They are activated and their apoptosis is inhibited. They release inflammatory enzymes that harm epithelial cells and generate mediators that amplify the inflammatory response[63].
Neutrophils: are increased in the airways of some patients with severe asthma during exacerbations and in smokers with asthma. Their pathophysiological role is not well defined and their increase may be due to treatment with glucocorticoids[64].
Dendritic cells: are antigen-presenting cells that interact with lymph node regulating cells and stimulate the production of Th2 lymphocytes[65].
Macrophages: these cells may be activated by allergens through the low affinity IgE receptors and release mediators that boost the inflammatory response, particularly in severe asthma[66].
Pulmonary neuroendocrine cells: contribute to Th2 response and stimulate mucus producing cells[67].

Table 1.6. Relevant molecules involved in the asthma inflammatory process

Chemokines. These are mainly expressed by epithelial cells and are important in the recruitment of inflammatory cells in the airways.
Cysteinyl leukotrienes. Potent bronchoconstrictors released by mastocytes and eosinophils.
Cytokines. They drive and modify the inflammatory response in asthma, and determine its severity[68]: • IL-1β and TNFα: amplify the inflammatory response. • GM-GSF: prolong survival or eosinophils in the airway. • Epithelium-derived cytokines: - IL-33: promotes proallergic inflammatory properties of CD4 cells and acts as chemoattractant for Th2 cells. - IL-25: involved in eosinophilic inflammation, remodelling and bronchial hyperresponsiveness (this last most controversal). - TSLP: induces eosinophilia, increases IgE level, and airway hyperresponsiveness and remodelling. • Th2-derived cytokines: - IL-4: important to the differentiation of Th2 lymphocytes, increased mucus secretion and IgE synthesis. - IL-5: necessary for the differentiation and survival of eosinophils. - IL-13: importante for IgE synthesis and metaplasia of mucus cells.
Histamine. Released by mastocytes contributes to bronchoconstriction and inflammatory response.
Nitric oxide: A potent vasodilator predominantly produced in the epithelial cells by the inducible nitric oxide synthase enzyme.
Prostaglandin D2: A bronchoconstrictor mostly derived from mastocytes; it is involved in the recruitment of Th2 lymphocytes in the airways.

GM-CSF: granulocyte-mactrophage colony-stimulating factor; TNF: tumor necrosis factor.

Table 1.7. Mechanisms of airway obstruction in asthma

Bronchial smooth muscle contraction: it occurs in response to multiple mediators and neurotransmitters with bronchoconstrictor effects and is the main mechanism of airway narrowing. Monomeric G proteins (RhoA and Rac1) are involved contributing to contraction and proliferation of muscle cells. It is largely reversible with bronchodilators.
Edema of the airways: it is due to microvascular exudate in response to inflammatory mediators. It is particularly important during acute exacerbations.
Mucus hypersecretion: it is due to an increased number of epithelial goblet cells and an increased size of submucosal glands. It can cause a mucus plug, which is associated with severity of asthma[71].
Structural changes of the airways: subepithelial fibrosis due to deposition of collagen fibers and proteoglycans under the basal membrane; smooth muscle hypertrophy and hyperplasia and increased circulation within the blood vessels of the bronchial wall, with enhanced permeability.

hypersecretion, all of which are associated with a progressive deterioration of pulmonary function[69]. Some of these phenomena are related to the severity of asthma and may lead to a bronchial obstruction, which is occasionally irreversible[69]. These changes may result from a repairing response to chronic inflammation or may occur independently of the inflammatory process[70].

Narrowing of the airways is the final event of all pathophysiological changes and the cause of most symptoms. However, airflow limitation and symptoms may resolve either spontaneously or in response to medication (reversibility) or even remain absent during some periods of time in a given patient. The different mechanisms contributing to bronchial obstruction are shown in Table 1.7.

Different triggering factors may cause severe narrowing of the airways leading to asthma exacerbation. The most severe episodes occur in relation to viral infections of the upper respiratory tract (rhinovirus and respiratory syncytial virus) o by allergenic exposure[72]. Other precipitationg factors include non-steroidal anti-inflammatory drugs (NSAID) in patients with hypersensitivity to these agents, exercise, exposute to cold air or certain non-specific irritants[73-75]. The intensity of the response to these stimuli is related to the underlying inflammation.

Bronchial hyperresponsiveness (HRB) is a characteristic component of asthma, which leads to airway narrowing in response to stimuli that are harmless to people without asthma. It is linked to airway inflammation and repair, and is partially or totally reversible with treatment. Mechanisms involved in BHR are shown in Table 1.8. The degree of BHR is partially correlated with clinical severity of asthma and inflammatorty biomarkers[77]. Anti-inflammatory treatment improves asthma control and reduces BHR but does not completely suppress it[78].

Variability is another imortant feature of asthma, and is defined as the variation or fluctuation of both symptoms and pulmonary function over time, even during the same day, beyond physiological circadian changes.

Table 1.8. Mechanisms of bronchial hyperresponsiveness

Excessive contraction of airway smooth muscle. It may result from increased volume and/or contractility of bronchial smooth muscle cells.
Uncoupling of airway contraction. It is a result of inflammatory changes in the airway wall that may lead to its narrowing and to loss of the maximum level of contraction, which can be found in healthy airways when a bronchoconstrictor substance is inhaled.
Thickening of the airway wall. Edema and structural changes amplify the bronchial wall narrowing due to airway muscle contraction[69].
Sensitized sensory nerves. Their sensitivity may be enhanced by inflammation, which results in excessive bronchoconstriction in response to sensorial stimuli[76].

1.5 Childhood asthma

C Asthma is one of the most prevalent chronic diseases in childhood. According to the International Study of Asthma and Allergies in Childhood (ISAAC) the prevalence in Spain is 10%; similar to that of the European Union, being more prevalent in the coastal areas and in males, in the age group of 6-7 years[79-82].

D It is estimated that more than half of adults with asthma had already asthma in childhood[83].

D During the first three years of life, the definition, diagnostic criteria, and even classification of asthma are complicated and are a matter of controversy[84], making it difficult to establish its prevalence at these ages. D

This is because the usual asthma symptoms (cough, wheezing and respiratory difficulty) are frequent in children younger than 3 years of age without asthma and also due to the impossibility of routinely evaluating pulmonary function. D

The definitive diagnosis requires the exclusión of other diseases that can present with similar signs and symptoms (Table 1.9)[87-90]. In fact, some of these disorders may be associated with asthma[91]. C

The presence of personal and family history of atopy is the most important risk factor for the subsequent development of D

Table 1.9. Differential diagnosis of childhood asthma

Cystic fibrosis	Airway anomalies. Tracheomalacia. Vascular ring
Bronchiectasis	Respiratory dysfunction. Induced laryngeal obstruction
Ciliary dyskinesia	Psychogenic cough
Chronic lung disease of prematurity	Pulmonary tuberculosis
Chronic aspiration. Dysphagia	Chronic interstitial disease
Foreing body aspiration	Congenital heart diseases
Gastoesophageal reflux	Primary or secondary tumors

Table 1.10. Phenotypes of children with wheezing in the Tucson study based on the long-term outcome

1. Transient early wheezing

- Wheezing started before the first year of age and disappeared around the age of 5.
- Negative IgE and/or patch tests, without features or atopy history.
- Decreased lung function at birth, with low values at 16 years of age.
- Bronchial hyperresponsiveness and variability of peak expitarory flow (PEF) negative at 11 years of age.
- Risk factors: maternal smoking during pregnency, male sex, prematurity, exposure to siblings and/or children at daycare centers.

2. Persistent wheezing (non-atopic)

- Usually beging before the first year of age and persist at 6 years of age.
- Males and females are equally affected.
- Negative IgE and/or cutaneous tests, without features or history of atopy.
- Normal lung function at birth and reduced at 6 and 11 years of age.
- Bronchial hyperresponsiveness decreases with age.
- Usually dissappears at adolescence.

3. Late-onset wheezing (atopic)

- The first eppisode appears after the first year of age and predominates in males.
- Increased IgE and/or positive cutaneous tests, features and family history of atopy.
- Normal lung function at birth with decrease up to 6 years of age and subsequent stabilization below normal values.
- Bronchial hyperresponsiveness is present.
- It usually persists during adolescence.

D

asthma. Other factors are: age at presentation, severity and frequency of episodes, male sex, and severe bronchiolitis (RSV, rhinovirus)[91-93].

C

After the first description of phenotypes of childhood asthma based on the Tucson study (Table 1.10)[94], a number of prospective studies (cohorts followed from birth)[95-97] or complex biostatistics analyses (grouping of populations without prior hypotheses)[98] have been conducted trying to identify different phenotypes of childhood asthma. Its clinical usefulness is controversial[96].

D

Base on findings of these studies, tools or prediction models of future risk of asthma have been developed, but a few have been validated. The best known is the Asthma Predictive Index (Table 1.11) developed from the Tucson cohort study[99].

D

C

Although other indexes or modifications have subsequently appeared, it continues to be the most useful, as it is simple to perform, has been more validated than other tools and has a better positive likelihood ratio[100].

D

The diagnosis of asthma in children under 3 years of age should be probabilistic, a probability that increases in the presence of atopy. The term asthma should not be avoided when there are more than 3 episodes per year, or severe episodes of cough, wheezing and difficult breathing, with a good response to maintenance treatment with inhaled corticosteroids and if a worsening occurs after its withdrawal.

Table 1.11. Asthma Predictive Index

Previous condition
• Infants with 3 episodes of wheezing per year during the first 3 years of life and 1 major or 2 minor criteria.
Major criteria
• Asthma in a parent, documented by a physician. • Atopic eczema in the child (at 2-3 years of age), documented by a physician.
Minor criteria
• Allergic rinitis in the child (at 2-3 years of age), documented by a physician. • Wheezing apart from colds, reported by the parents. • Peripheral eosinophilia greater than or equal to 4%.
Predictive values for asthma diagnosis at any time between 6 and 13 years of age
• Positive predictive value 77%. • Negative predictive value 68%.

References

1. Guía Española para el Manejo del Asma (GEMA4.4). Madrid: Luzán 5; 2019.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention (GINA 2019). Disponible en: www.ginasthma.org
3. ECRHHS 1996. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey. Eur Respir. 1996; 9: 687-95.
4. ECRHHS 2002. The European Community Respiratory Health Survey II. EurRespir J. 2002; 20: 1071-9.
5. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015 Lancet Respir Med. 2017; 5(9): 691-706.
6. Lundbäck B, Backman H, Lötvall J, Rönmark E. Is asthma prevalence still increasing? Expert Rev Respir Med. 2016; 10(1): 39-51.
7. Grupo Español del Estudio Europeo en Asma. Estudio europeo del asma Prevalencia de hiperreactividad bronquial y asma en jóvenes en 5 regiones de España. Med Clin (Barc). 1996; 106: 761-7.
8. Álvarez N, Guillén F, Aguinaga I, Hermoso de Mendoza J, Marín B, Serrano I, et al. Estudio de prevalencia y asociación entre síntomas de asma y obesidad en la población pediátrica de Pamplona. Nutr Hosp. 2014; 30: 519-25.
9. Elizalde I, Guillén F, Aguinaga I. Factores asociados al asma en los niños y adolescentes de la zona rural de Navarra (España). Aten Primaria. 2018; 50: 332-9
10. López P, Gandarilla AM, Díez L, Ordobás M. Evolución de la prevalencia de asma y factores demográficos y de salud asociados en población de 18-64 años de la Comunidad de Madrid (1996-2013) Rev Esp Salud Pública. 2017; 91: e1-e14.
11. Vila-Rigat R, Panadès R, Hernandez E, Sivecas J, Blanché X, Muñoz-Ortiz L, et al. Prevalence of Work-Related Asthma and its Impact in Primary Health Care. Arch Bronconeumol. 2015; 51(9): 449-55.
12. Arias SJ, Neffen H, Bossio JC, Calabrese CA, Videla AJ, Armando GA, et al. Prevalencia y características clínicas del asma en adultos jóvenes en zonas urbanas de Argentina. Arch Bronconeumol. 2018; 54: 134-9.
13. Arbes SJ Jr, Gergen PJ, Vaughn B, Zeldin DC. Asthma cases attributable to atopy: results from the Third National Health and Nutrition Examination Survey. J Allergy Clin Immunol. 2007; 120:1139-45.
14. Minelli C, van der Plaat DA, Leynaert B, Granell R, Amaral AFS, Pereira M, et al. Age at puberty and risk of asthma: A Mendelian randomisation study. PLoS Med. 2018; 15: e1002634.
15. Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physiciandiagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. BMC Pediatr. 2013; 13: 121.
16. Carey VJ, Weiss ST, Tager IB, Leeder SR, Speizer FE. Airways responsiveness, wheeze onset, and recurrent asthma episodes in Young adolescents. The East Boston Childhood Respiratory Disease Cohort. Am J Respir Crit Care Med. 1996; 153: 356-61.
17. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. J Allergy Clin Immunol. 2002; 109: 419-25.
18. Burgess JA, Walters EH, Byrnes GB, Matheson MC, Jenkins MA, Wharton CL, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. J Allergy Clin Immunol. 2007; 120: 863-9.
19. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet. 2008; 372: 1049-57.
20. Gómez F, Burgess JA, Villani S, Dratva J, Heinrich J, Janson C, et al. Maternal age at delivery, lung function and asthma in offspring: a population-based survey. Eur Respir J. 2018; 51(6). pii: 1601611. doi: 10.1183/13993003.01611-2016. Print 2018 Jun.
21. Stokholm J, Sevelsted A, Anderson UD, Bisgaard H. Preeclampsia Associates with Asthma, Allergy, and Eczema in Childhood. Am J Respir Crit Care Med. 2017; 195: 614-21.
22. Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, et al. Preterm birth and childhood wheezing disorders: a systematic review and metaanalysis. PLoS Med. 2014; 11: e1001596.
23. Leps C, Carson C, Quigley MA. Gestational age at birth and wheezing trajectories at 3-11 years. Arch Dis Child. 2018; 103: 1138-44.
24. Tollånes MC, Moster D, Daltveit AK, Irgens LM. Cesarean section and risk of severe childhood asthma: a populationbased cohort study. J Pediatr. 2008; 153: 112-6.

25. Ku MS, Sun HL, Sheu JN, Lee HS, Yang SF, Lue KH. Neonatal jaundice is a risk factor for childhood asthma: a retrospective cohort study. Pediatr Allergy Immunol. 2012; 23: 623-8
26. Silvers KM, Frampton CM, Wickens K, Pattemore PK, Ingham T, Fishwick D, et al.; New Zealand Asthma and Allergy Cohort Study Group. Breastfeeding protects against current asthma up to 6 years of age. J Pediatr. 2012; 160: 991-6.
27. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. J Pediatr. 2001;139: 261-6.
28. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ. 1996; 312: 1195-9.
29. 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
30. Cunningham J, O'Connor GT, Dockery DW, Speizer FE. Environmental tobacco smoke, wheezing, and asthma in children in 24 communities. Am J Respir Crit Care Med. 1996; 153: 218-24
31. Neuman Å, Hohmann C, Orsini N, Pershagen G, Eller E, Kjaer HF, et al. ENRIECO Consortium. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. Am J Respir Crit Care Med. 2012; 186: 1037-43.
32. Litonjua AA, Rifas-Shiman SL, Ly NP, Tantisira KG, Rich-Edwards JW, Camargo CA Jr, et al. Maternal antioxidant intake in pregnancy and wheezing illnesses in children at 2 y of age. Am J Clin Nutr. 2006; 84: 903-11.
33. Wolsk HM, Chawes BL, Litonjua AA, Hollis BW, Waage J, Stokholm J, et al. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood: A combined analysis of two randomized controlled trials. PLoS One. 2017 Oct 27;12(10):e0186657.
34. Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, Martindale S, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. Am J Clin Nutr. 2007; 85: 853-9
35. García-Marcos L, Castro-Rodriguez JA, Weinmayr G, et al. Influence of Mediterranean diet on asthma in children: a systematic review and meta-analysis. Pediatr Allergy Immunol. 2013; 24: 330-38.
36. Hibbs AM, Ross K, Kerns LA, Wagner C, Fuloria M, Groh-Wargo S, et al. Effect of Vitamin D Supplementation on Recurrent Wheezing in Black Infants Who Were Born Preterm: The D-Wheeze Randomized Clinical Trial. JAMA. 2018; 319: 2086-94.
37. Håland G, Carlsen KC, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M, et al. Reduced lung function at birth and the risk of asthma at 10 years of age. N Engl J Med. 2006; 355: 1682-9.
38. Kerkhof M, Wijga AH, Brunekreef B, Smit HA, de Jongste JC, Aalberse RC, et al. Effects of pets on asthma development up to 8 years of age: the PIAMA study. Allergy. 2009; 64: 1202-8.
39. Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). Lancet. 2007; 370: 336-41.
40. Hoppin JA, Umbach DM, London SJ, Henneberger PK, Kullman GJ, Alavanja MC, et al. Pesticides and atopic and nonatopic asthma among farm women in the Agricultural Health Study. Am J Respir Crit Care Med. 2008; 177: 11-8.
41. Illi S, von Mutius E, Lau S, Bergmann R, Niggemann B, Sommerfeld C, et al.; MAS Group. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. BMJ. 2001; 322: 390-5.
42. Gilliland FD, Islam T, Berhane K, Gauderman WJ, McConnell R, Avol E, et al. Regular smoking and asthma incidence in adolescents. Am J Respir Crit Care Med. 2006; 174: 1094-100.
43. Coogan PF, Castro-Webb N, Yu J, O'Connor GT, Palmer JR, Rosenberg L. Active and passive smoking and the incidence of asthma in the Black Women's Health Study. Am J Respir Crit Care Med. 2015; 191: 168-76.
44. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Association of outdoor air pollution with the prevalence of asthma in children of Latin America and the Caribbean: A systematic review and meta-analysis. J Asthma. 2018; 55(11): 1174-86. doi: 10.1080/02770903.2017.1402342. Epub 2017 Dec 6.
45. Sordillo JE, Scirica CV, Rifas-Shiman SL, Gillman MW, Bunyavanich S, Camargo CA Jr, et al. Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. J Allergy Clin Immunol. 2015; 135: 441.
46. Lai T, Wu M, Liu J, Luo M, He L, Wang X, et al. Acid-Suppressive Drug Use During Pregnancy and the Risk of Childhood Asthma: A Meta-analysis. Pediatrics. 2018; 141(2): e20170889.
47. Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM, et al. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. Chest. 2006; 129: 608-10.
48. Goksör E, Alm B, Pettersson R, Möllborg P, Erdes L, Aberg N, et al. Early fish introduction and neonatal antibiotics affect the risk of asthma into school age. Pediatr Allergy Immunol. 2013; 24: 339-44.
49. Loewen K, Monchka B, Mahmud SM, 't Jong G, Azad MB. Prenatal antibiotic exposure and childhood asthma: a population-based study. Eur Respir J. 2018; 52. pii: 1702070. doi: 10.1183/13993003.02070-2017. Print 2018 Jul.
50. Hoskin-Parr L, Teyhan A, Blocker A, Henderson AJ. Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: a dose-dependent relationship. Pediatr Allergy Immunol. 2013; 24: 762-71.
51. Romieu I, Fabre A, Fournier A, Kauffmann F, Varraso R, Mesrine S, et al. Postmenopausal hormone therapy and asthma onset in the E3N cohort. Thorax. 2010; 65: 292-7.
52. Thomsen SF. Genetics of asthma: an introduction for the clinician. Eur Clin Respir J. 2015 Jan 16;2. doi: 10.3402/ecrj.v2.24643. eCollection 2015.
53. World Health Organization. (2016). Ambient air pollution: a global assessment of exposure and burden of disease. World Health Organization. Disponible en https://apps.who.int/iris/handle/10665/250141.
54. Health Effects Institute. 2019. State of Global Air 2019: Special Report on global exposure to air pollution and

its disease burden. Boston, MA: Health Effects Institute. Disponible en https://www.stateofglobalair.org/sites/default/files/soga_2019_report.pdf
55. WMO-No. 1233. World Meteorological Organization, 2019.
56. Levine SJ, Wenzel SE. Narrative review: the role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes. Ann Intern Med. 2010; 152: 232-7.
57. Lambrecht BN, Hammad H. The airway epithelium in asthma. Nat Med. 2012; 18: 684-92
58. Koziol-White CJ, Panettieri RA Jr. Airway smooth muscle and mmunomodulation in acute exacerbationsof air way disease. Immunol Rev. 2011; 242: 178-85.
59. Komai-Koma M, Xu D, Li Y, McKenzie AN, McInnes IB, Liew FY. IL-33 is a chemoattractant for human Th2 cells. Eur J Immunol. 2007; 37: 2779-86.
60. Zhou B, Comeau MR, De Smedt T, Liggitt HD, Dahl ME, Lewis DB, et al. Thymic stromal lymphopoietin as a key initiator of allergic airway inflammation in mice. Nat Immunol. 2005; 6: 1047-53.
61. Lloyd CM, Hessel EM. Functions of T cells in asthma: more than just T(H)2 cells. Nat Rev Immunol. 2010; 10: 838-48.
62. Galli SJ, Tsai M. IgE and mast cells in allergic disease. Nat Med. 2012; 18: 693-704.
63. Rosenberg HF, Dyer KD, Foster PS. Eosinophils: changing perspectives in health and disease. Nat Rev Immunol. 2013; 13: 9-22.
64. Macdowell AL, Peters SP. Neutrophils in asthma. Curr Allergy Asthma Rep. 2007; 7: 464-8.
65. Lambrecht BN, Hammad H. The role of dendritic and epithelial cells as master regulators of allergic airway inflammation. Lancet. 2010; 376: 835-43.
66. Yang M, Kumar RK, Hansbro PM, Foster PS. Emerging roles of pulmonary macrophages in driving the development of severe asthma. J Leukoc Biol. 2012; 91: 557-69.
67. Sui P, Wiesner DL, Xu J, Zhang Y, Lee J, van Dyken S, et al. Pulmonary neuroendocrine cells amplify allergic asthma responses. Science. 2018; 360(6393). pii: eaan8546. doi: 10.1126/science.aan8546. Epub 2018 Mar 29.
68. Veldhoen M. Interleukin 17 is a chief orchestrator of immunity. Nat Immunol. 2017; 18(6): 612-21.
69. Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. J Allergy Clin Immunol. 2011; 128: 451-62.
70. Grainge CL, Lau LC, Ward JA, Dulay V, Lahiff G, Wilson S, et al. Effect of bronchoconstriction on airway remodeling in asthma. N Engl J Med. 2011; 364: 2006-15.
71. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. J Clin Invest. 2018; 128: 997-1009.
72. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. J Allergy Clin Immunol. 2010; 125: 1178-87.
73. Weiler JM, Brannan JD, Randolph CC, Hallstrand TS, Parsons J, Silvers W, et al. Exercise-induced bronchoconstriction up to date. J Allergy Clin Immunol. 2016; 138: 1292-5.
74. Aguiar KB, Anzolin M, Zhang L. Global prevalence of exercise-induced bronchoconstriction in childhood: A meta-analysis. Pediatr Pulmonol. 2018; 53: 412-25
75. Izquierdo A, Bobolea I, Doña I, Campo P, Segura C, Ortega N, et al. Position Statement of the Spanish Society of Allergology and Clinical Immunology on Provocation Tests with Aspirin/Nonsteroidal anti-inflammatory drugs. J Investig Allergol Clin Immunol. 2020; 30(1): 1-13.
76. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ. 2000; 320: 1368-73.
77. O'Byrne PM, Inman MD. Airway hyperresponsiveness. Chest. 2003; 123: 411S-6S.
78. West AR, Syyong HT, Siddiqui S, Pascoe CD, Murphy TM, Maarsingh H, et al. Airway contractility and remodeling: links to asthma symptoms. Pulm Pharmacol Ther. 2013; 26: 3-12.
79. Carvajal-Urueña I, García-Marcos L, Busquets-Monge R, Morales M, García de Andoin N, Batlles-Garrido J, et al. Variaciones geográficas en la prevalencia de síntomas de asma en los niños y adolescentes españoles. International Study of Asthma and Allergies in Childhood (ISAAC) fase III España. Arch Bronconeumol. 2005; 41: 659-66.
80. García-Marcos L, Quirós AB, Hernández GG, Guillén-Grima F, Díaz CG, Ureña IC, et al. Stabilization of asthma prevalence among adolescents and increase among schoolchildren (ISAAC phases I and III) in Spain. Allergy. 2004; 59: 1301-7.
81. López-Silvarrey-Varela A, Pértega-Díaz S, Rueda-Esteban S, Sánchez-Lastres JM, San-José-González MA, Sampedro-Campos M, et al. Prevalence and geographic variations in asthma symptoms in children and adolescents in Galicia (Spain). Arch Bronconeumol. 2011; 47: 274-82.
82. Bercedo A, Redondo C, Lastra L, Gómez M, Mora E, Pacheco M, et al. Prevalencia de asma bronquial, rinitis alérgica y dermatitis atópica en adolescentes de 13-14 años de Cantabria. Bol. Pediatr. 2004; 44 (187): 9-19.
83. Tai A, Tran H, Roberts M, Clarke N, Gibson A-M, Vidmar S, et al. Outcomes of childhood asthma to the age of 50 years. J Allergy Clin Immunol. 2014; 133: 1572-78.
84. Moral L, Vizmanos G, Torres-Borrego J, Praena-Crespo M, Tortajada-Girbés M, Pellegrini FJ, et al. Asthma diagnosis in infants and preschool children: a systematic review of clinical guidelines. Allergol Immunopathol (Madr). 2019; 47: 107-21.
85. Dharmage SC, Perret JL, Custovic A. Epidemiology of Asthma in Children and Adults. Front Pediatr. 2019; 7: 246.
86. Pennington AF, Strickland MJ, Freedle KA, Klein M, Drews-Botsch C, Hansen C, et al. Evaluating early-life asthma definitions as a marker for subsequent asthma in an electronic medical record setting. Pediatr Allergy Immunol. 2016; 27: 591-6.
87. Hines D, Modi N, Lee SK, Isayama T, Sjörs G, Gagliardi L, et al. Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus. Acta Paediatr. 2017; 106: 366-74.
88. Isayama T, Lee SK, Yang J, Lee D, Daspal S, Dunn M, et al. Revisiting the Definition of Bronchopulmonary Dysplasia: Effect of Changing Panoply of Respiratory Support for Preterm Neonates. JAMA Pediatr. 2017; 171: 271-9.
89. Hancock DG, Charles-Britton B, Dixon DL, Forsyth KD. The heterogeneity of viral bronchiolitis: A lack of universal consensus definitions. Pediatr Pulmonol. 2017; 52: 1234-40.
90. Dumas O, Mansbach JM, Jartti T, Hasegawa K, Sullivan AF, Piedra P, et al. A clustering approach to identify severe bronchiolitis profiles in children. Thorax. 2016; 71: 712-8.
91. Kuzik BA. Maybe this is just asthma. Pediatr Pulmonol. 2017; 52: 1531.

92. Balekian DS, Linnemann RW, Hasegawa K, Thadhani R, Camargo CA Jr. Cohort Study of Severe Bronchiolitis during Infancy and Risk of Asthma by Age 5 Years. J Allergy Clin Immunol Pract. 2017; 5: 92-6.
93. Ruotsalainen M, Hyvärinen MK, Piippo-Savolainen E, Korppi M. Adolescent asthma after rhinovirus and respiratory syncytial virus bronchiolitis. Pediatr Pulmonol. 2013; 48: 633-9.
94. Stein RT, Martinez FD. Asthma phenotypes in childhood: lessons from an epidemiological approach. Paediatr Respir Rev. 2004; 5: 155-61.
95. Oksel C, Granell R, Haider S, Fontanella S, Simpson A, Turner S. et al.; STELAR investigators, breathing Together investigators. Distinguishing Wheezing Phenotypes from Infancy to Adolescence. A Pooled Analysis of Five Birth Cohorts. Ann Am Thorac Soc. 2019; 16: 868-76.
96. Bousquet J, Gern JE, Martinez FD, Anto JM, Johnson CC, Holt PG, et al. Birth cohorts in asthma and allergic diseases: Report of a NIAID/NHLBI/MeDALL joint workshop. J Allergy Clin Immunol. 2014; 133: 1535-46.
97. Howrylak JA, Fuhlbrigge AL, Strunk RC, Zeiger RS, Weiss ST, Raby BA; for the Childhood Asthma Management. Program Research Group. Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. J Allergy Clin Immunol. 2014; 133: 1289-300.
98. Depner M, Fuchs O, Genuneit J, Karvonen AM, Hyvärinen A, Kaulek V, et al.; The PASTURE Study Group. Clinical and epidemiologic phenotypes of childhood asthma. Am J Respir Crit Care Med. 2014; 189: 129-38.
99. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care. Med. 2000; 162: 1403-6.
100. Castro-Rodriguez JA, Cifuentes L, Martinez FD. Predicting Asthma Using Clinical Indexes. Front Pediatr. 2019; 7: 320.