

Early Life Origins of Asthma: A Review of Potential Effectors

Short title: Early life origins of asthma

Bobolea I^{1-4*}, Arismendi E^{3-4*}, Valero A¹⁻⁴, Agustí A¹⁻⁴

*co-primary authors

¹Respiratory Institute, Hospital Clínic, Barcelona, Spain

²University of Barcelona, Spain

³Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS)

⁴Centro Investigación Biomédica en Red Enfermedades Respiratorias (CIBERES),
Spain

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Corresponding author:

Dr. Alvar Agustí.

Respiratory Institute, Hospital Clinic,
Villarroel 170, 08036 Barcelona, Spain.

e-mail: aagusti@clinic.cat

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Abstract:

There is currently growing evidence that events occurring early in life, both before and after birth, are significantly associated with the risk of asthma, COPD and low lung function later in life. In fact, from conception to death there are continuous, dynamic numbers of gene-environment interactions that determine two fundamental biologic processes, lung development and lung ageing. Over 130 birth cohorts have been initiated in the last 30 years. These birth cohorts have improved our understanding of asthma inception, progression and persistency. In this review, we summarize the main data upon those early life events proven to determine later development and persistence of asthma, such as maternal atopy or smoking, preterm birth/ bronchopulmonary dysplasia, or infections, nutrition and obesity, smoking and other environmental exposures in childhood and adolescence.

Some of these factors are obviously impossible to prevent or eliminate; others, in exchange, have been proven to have a protective role, and current research is aimed to optimally enhance them. The available prophylactic measures are also revised here. In case of environmental pollution for instance, large scale political interventions successfully managed to decrease contamination levels, leading to improved lung function and lower asthma prevalence in the respective geographical areas.

Future research should focus on better understanding these complex interactions, in order to develop and enhance effective preventive therapeutic measures.

Key words: Atopy. Asthma. Lung Function. Pregnancy. Prematurity. Obstructive Airway Disease. Airway Hyperreactivity.

1. Introduction

Almost 30 years ago, David Barker proposed that many adult diseases may have their roots very early in life, during pregnancy, childhood and/or adolescence [1]. Since then, the now known as “Barker hypothesis”, has been extensively confirmed for several human conditions, and respiratory diseases are not an exception [2]. Exposures in fetal and early postnatal life might influence lung growth and development, which can then lead to “asthma” and “chronic obstructive pulmonary disease” (COPD) later in life [3-7], as shown now by a number of birth cohorts [8-14] and other epidemiological studies [15-17]. The goal of this review is to summarize currently available knowledge on a number of potential environmental and genetic factors that, acting at different time points, may facilitate the early origins of asthma (Table 1).

However, two important caveat here are, first, that the diagnosis of “asthma” is quite non-specific, particularly in children, so many of them with respiratory symptoms may be diagnosed of asthma rightly or wrongly. For instance, a child with lung developmental problems is likely to have some degree of shortness of breath, wheezing and/or cough, which can be easily misdiagnosed of asthma [18]. And, second, the label of “asthma” should be the beginning (not the end) of the diagnostic process [19], which should try to really answer the question: what type of asthma does this patient has [20]. We believe that, in the context of this discussion, these two caveats should always be kept in mind.

2. Genetics factors

Asthma is a complex and heterogeneous disease caused by still poorly understood genetic and environmental interactions [21]. The heritability of asthma has been estimated to be around 60% [22,23] and large-scale genome wide association studies (GWAS) have identified multiple susceptibility loci [24], albeit the latter account for only a modest proportion of the total phenotypic variance. The interleukin (IL)-1 receptor-like 1 (IL1RL1), which encodes a member of the Toll-like/IL-1 receptor superfamily expressed in inflammatory and resident cells in the lungs [25] and a single nucleotide polymorphisms (SNPs) in IL1R1 have been associated with time to onset of asthma [25], although this has not been confirmed in other studies [26]. SNPs on chromosome 17q21 that regulate the expression of at least one nearby gene orosomucoid like 3 (ORMDL3) are also associated with the risk of asthma [21]. Cookson et al.[27] showed that ORMDL3 knock-out cells decreased the transcript and protein expression of intercellular adhesion molecule 1 (ICAM1), the major Human Rhinovirus (HRV) receptor, suggesting a mechanism for the association between ORMDL3, HRV infections and asthma. Additionally, ICAM1 is a receptor for the bacterial airway pathogen *Haemophilus influenzae* [28], which has an increased abundance in asthmatic airways in between exacerbations [29]. Demenais et al. [4] investigated the potential role in asthma of 36 SNPs in the 17q21 region in 1,511 subjects from 372 families. They showed that these variants were associated with early onset asthma and interact with exposure to environmental tobacco smoke. Epigenetic changes (DNA methylation) have also been identified in relation to early onset asthma [15]. Postma et al. [30] identified in 200 Dutch families that included 1,259 individuals that protocadherin-1 (PCDH1) was a novel gene (chromosome 5q31-q33) for bronchial

hyperresponsiveness (BHR) in adult and children. Specifically, they showed that PCDH1 mRNA and protein were expressed in airway epithelium, the first line of defense against inhaled allergens and toxic substances known to contribute to asthma development. Other genes that have been implicated in the development of childhood asthma are IL-17 and IL-23; their genetic variation has been associated with childhood asthma and total levels of serum IgE, the latter of which may be affected by mutations in IL21 and IL1R1 [31]. IL-17, IL-21 and IL-22 are secreted by TH17 cells and are potent inducers of inflammation. Likewise, interactions of maternal oxidative stress response genes (*GSTM1*, *GSTP1*, *CAT*, and *MPO*) with maternal prenatal exposure to air pollutants or tobacco smoke can contribute to asthma or allergic airway responsiveness [32].

3. Maternal/ pregnancy related factors

3.1 Atopy

In a Swiss adult cohort maternal atopy was associated with higher prevalence of asthma and allergic rhinitis in the offspring [33]. Maternal atopy significantly affected antenatal IgE production, as reflected by cord blood serum IgE elevation [32]. Traherne et al. [34] showed that a polymorphism of the *high-affinity IgE receptor beta-chain (FceRI-beta)* was strongly associated with positive allergy skin-prick tests and greater allergen-specific IgE levels when inherited from mothers. The severity of maternal allergic rhinitis, asthma co-morbidity, elevated serum IgE levels and nasal eosinophilia were all associated with an increased risk of offspring developing allergic conditions [35]. On the other hand, Sunyer et al. [36] evaluated mothers and their children from the Asthma

Multi-centre Infants Cohort Study (AMICS), with the aim of examining the effects of pre- and post-natal environmental exposures in the inception of atopy and asthma. They showed that mothers with allergic sensitizations, determined by skin prick-test, have a lower number of offspring, using three European cohorts of pregnant women (Ashford, Kent [UK]; Menorca island [Spain] and Barcelona city [Spain]) [36]. Karmaus W et al. [37] studied the association between maternal atopy and the number of offspring, and suggested that a higher number of siblings is protective against the development of atopic manifestation in the offspring [37]. They proposed that bi-directional maternal-fetal cell trafficking resulting in micro-chimerism occurring during pregnancy and delivery may set up a pocket of non-host cells that remains in the maternal circulation years after delivery, inducing a range of immune reactions including a reduction in the maternal Th2 response in successive pregnancies.

3.2. Maternal asthma

Maternal asthma is the main risk factor associated with the development of early-life asthma [38]. A meta-analysis of 33 studies showed that children with maternal asthma (defined as self-reported physician diagnosed asthma or as self-reported asthma) had approximately threefold greater risk of asthma than those without maternal asthma [39]. Compared with paternal asthma, maternal asthma was associated with significantly greater odds of childhood asthma ($p=0.04$).

Maternal asthma control during pregnancy is another potential risk factor for asthma in offspring. A higher prevalence of early-onset persistent asthma was observed among children of asthmatic mothers [40] with mild uncontrolled (PR, 1.19; 95% CI, 1.05-1.35), moderate-to-severe controlled (PR, 1.33; 95% CI, 1.09-1.63), and moderate-to-

severe uncontrolled asthma (PR, 1.37; 95% CI, 1.17-1.61), compared with mothers with mild controlled asthma. Hence, maintaining asthma control in pregnancy may be a potential preventive strategy for some specific phenotypes of offspring asthma [40].

3.3 Nutrition

Several studies suggest that the development of asthma is influenced by maternal nutritional status [41]. Turner et al. [42] suggested that maternal vitamin E (α-tocopherol) levels may influence lung fetal growth in early pregnancy in a birth cohort of 1,924 subjects because reduced fetal size in the first trimester was associated with reduced childhood lung function and increased asthma symptoms and maternal vitamin E status appears relevant to this association. Likewise, Wolsk et al. [43] combined two randomized controlled trials that used prenatal vitamin D (25(OH)D) supplementation during pregnancy [44,45] and showed that it reduced the risk of asthma/recurrent wheeze in the offspring, particularly among women with vitamin D level ≥ 30 ng/ml at randomization, where risk was almost halved. On the other hand, a prospective pre-birth cohort study of participants unselected for atopic propensity, found that higher maternal intake of allergenic foods (peanuts) during the first trimester of pregnancy was associated with a 47% reduction in the odds of childhood peanut allergic reaction [46], maternal milk intake during the first trimester was associated with reduced odds of childhood asthma and allergic rhinitis, and maternal intake of wheat during the second trimester was associated with reduced childhood atopic dermatitis [46].

3.4. Infections

Maternal infections during pregnancy, including respiratory tract infections, febrile infectious diseases, urinary tract infections or vaginitis, are associated with a higher risk of childhood asthma [41]. Chorioamnionitis is a common cause of *in utero* inflammation (i.e., presence of inflammation within fetal membranes) and neonates born from mothers with chorioamnionitis are at increased risk of mortality and of developing significant lung morbidity, including acute respiratory distress syndrome, bronchopulmonary dysplasia (BPD), reactive airway disorders and an increase in risk of preterm infants for developing asthma, even after correction for confounding factors [47].

Other infections have also been associated with an increased risk of asthma in children, but the overarching mechanisms by which maternal infections result in increased risk of childhood asthma are still unclear. The so-called “hygiene hypothesis” proposes that allergic sensitization starts *in utero* so the asthma phenotype is programmed before birth and that exposure to endotoxin and other microbial products after birth influence the innate immune system [41] and changes the lung microbiome thus contributing to asthma [48]. Stockholm *et al.* [49] showed in 910,301 children born in Denmark between 1997 and 2010 that maternal use of antibiotics in pregnancy was associated with an increased risk of childhood asthma.

3.5 Tobacco smoking

Tobacco smoking continues to be a major prenatal problem in the USA, with 10-12% of women admitting smoking tobacco during pregnancy [50]. Despite widely available

evidence of the deleterious impact of *in utero* tobacco exposure on fetal development, approximately half of women smokers continue to do so during early pregnancy [50]. Many studies have now clearly demonstrated that maternal smoking during pregnancy results in abnormal lung function in the offspring, and that it tracks into childhood and adult life [51]. Burke *et al.* [52] performed a meta-analysis of 71 studies of environmental tobacco smoke, wheeze and asthma. Pre- or postnatal passive smoke exposure was associated with a 30% to 70% increased risk of incident wheezing. Exposure to prenatal maternal smoking was associated with 40% increase in risk of wheeze in children aged ≤ 2 years (OR = 1.41, 95% CI = 1.20–1.67, $I^2 = 82.5\%$, 14 studies). A similar effect size was observed for the relation between prenatal maternal smoking and incidence of wheeze between the ages of 3 and 4 (OR = 1.28, 95% CI = 1.14–1.44, $I^2 = 65.5\%$, 8 studies). Prenatal passive smoke exposure was associated with a 52% increased risk of wheeze in children aged 5 to 18 years (OR = 1.52, 95% CI = 1.23–1.87, $I^2 = 21.1\%$, 5 studies). In summary, exposure to passive smoking increases the incidence of wheeze and asthma in children and young people by at least 20% [52]. More recently, Dehmel *et al.* used an animal model to highlight a potential novel link between smoke exposure, aberrant lung development and impaired lung function. These authors showed that prenatally exposed mice had intrauterine and postnatal growth retardation, and impaired lung function, that 1,340 genes and 133 miRNAs were significantly dysregulated, and that Insulin-like growth factor 1 (Igf1) was a top hierarchical node in their network analysis [53]. Moreover, Igf1 mRNA was increased in female murine offspring and in prenatally exposed children, suggesting that prenatal smoking is associated with dysregulation of several genes, including Igf1 in a sex-specific manner [53].

Another upraising, hot-topic relates to nicotine replacement therapy. Molero *et al.* [54] observed that parental varenicline treatment was associated with a lower rate of visits for bronchitis/bronchiolitis in their children (incidence rate ratio [IRR]=0.67; 95% CI=0.50–0.91), but no association was found for asthma (IRR=1.08; 95% CI=0.97–1.19). Rate reduction of bronchitis/bronchiolitis was similar when data was restricted to children aged 0–3 years (IRR=0.71; 95% CI=0.52–0.97) and to maternal varenicline treatment (IRR=0.64; 95% CI=0.43–0.96). When restricting the outcomes to unplanned visits only (i.e., excluding booked appointments, follow-ups, and referrals), no associations were found (IRR=0.72, 95% CI=0.51–1.02).

Finally, exposure to tobacco smoking increases the incidence of wheeze and asthma in children and young people, and maternal nicotine replacement therapy is associated with a reduction of visits for bronchitis/bronchiolitis in their offspring.

3.6. Drugs

Antibiotic use [55,56] has been associated with an increased risk of childhood asthma. The Copenhagen Prospective Study on Asthma in Childhood data showed increased risk of asthma exacerbation (hazard ratio 1.98 [95% CI 1.08-3.63]) in mothers who used antibiotics during third trimester [55]. The Danish National Birth Cohort confirmed the increased risk of asthma hospitalization (HR 1.17 [1.00-1.36]), and inhaled corticosteroids use (HR1.18 [1.10-1.27]) in children below the age of 5, if mothers used antibiotics any time during pregnancy. In the subgroup of mothers who used antibiotics for non-respiratory infection, children also had an increased risk of asthma, which supports a role for bacterial ecology in pre- or peri-natal life for the development of

asthma. Finally, a meta-analysis of ten studies [56] investigating the potential role of antibiotic exposure showed an OR of 1.20 (95% CI, 1.13–1.27) for wheeze/asthma. After excluding case-control studies and prospective studies without achieving high scores on the Newcastle–Ottawa Quality Assessment Scale (NOS), the pooled OR was 1.18 (95% CI, 1.11–1.26) and that the risk of antibiotic use varied according to the time of exposure being the pooled ORs for wheeze/asthma 1.09 (95% CI, 0.92–1.29) for the first trimester, 1.14 (95% CI, 1.01–1.29) for the second trimester, and 1.33 (95% CI, 1.11–1.60) for the third trimester. All in all, these observations indicate that antibiotic exposure during pregnancy increases the risk of wheeze/asthma in childhood, particularly during the last two trimesters of pregnancy [56].

By contrast, the potential effects of maternal paracetamol use during pregnancy on the risk of asthma of the off-spring are controversial. On the one hand, Cheelo et al. [57] evaluated 11 observational cohort studies and concluded that there was insufficient evidence to warrant changing guidelines on early life paracetamol exposure. On the other, another meta-analysis of six studies by Eysers *et al.* [58] concluded that the use of paracetamol during all trimesters of pregnancy was indeed associated with an increased risk of childhood asthma (OR 1.21 (95% CI 1.02–1.44)

4. Perinatal factors: the “birth lung”

4.1. Preterm birth. Bronchopulmonary dysplasia.

Bronchopulmonary dysplasia (BPD) is a chronic respiratory disease associated with premature birth that primarily affects infants born at less than 28 weeks’ gestational age. BPD also develops in approximately 10 to 40% of very low birth weight (VLBW) and

extremely low birth weight infants, respectively, with 5,000 to 10,000 new cases in the USA each year [59]. BPD is associated with later risk of asthma [60] and airflow limitation in adults [61,62]. For instance, in the European Community Respiratory Health Survey, adults with a history of BPD were twice more likely to report wheeze and three times more likely to use asthma medications than full-term controls [63]. Indeed, the severity of BPD is also an important predictor of health care utilization during childhood, between 8 and 15 years of age [62]. A recent meta-analysis quantified the FEV₁ deficit in later life in a number of different groups of subjects born preterm and confirmed that, even in subjects without BPD, FEV₁ percentage is lower than in the population born at term [5].

4.2. Low birth-weight

Early life growth patterns have been associated with increased risk of respiratory morbidity later in life [6,64]. Recently, den Dekker *et al.* [6] have shown that both, restricted and accelerated fetal growth predispose children for lower lung function and respiratory diseases later in life. Specifically, this study showed that between birth and age 3 months, restricted weight growth was associated with an increased risk of childhood asthma (OR (95% CI): 1.57 (1.01, 2.45)), likewise accelerated weight growth was associated with lower FEV₁, FEV₁/FVC and FEF₇₅, compared to normal weight growth.

Very low birth weight (VLBW; <1500 g) has been associated with low lung function at 6-12 months of corrected age [65]. Birth weight is associated with lung function in term-born children at 8-9 years, but less at 14-17 years, suggesting that birth weight influences lung function in early childhood but has a lesser effect later in life. A meta-

analysis of 147,000 European children [64] assessed the association of preterm birth (gestational age <37 weeks) and low birth weight (<2,500 g) with childhood asthma outcomes and concluded that younger gestational age at birth and higher infant weight gain were independently associated with higher risks of preschool wheezing and school-age asthma ($p < 0.05$). Compared with term-born children with normal infant weight gain, they [64] observed the highest risks of school-age asthma in children born preterm with high infant weight gain ([OR], 4.47; 95% CI, 2.58-7.76). Preterm birth was positively associated with an increased risk of preschool wheezing (pooled odds ratio [pOR], 1.34; 95% CI, 1.25-1.43) and school-age asthma (pOR, 1.40; 95% CI, 1.18-1.67) independent of birth weight.

Finally, fetal size also has been related with increased risk of childhood asthma [48]. Turner *et al.* [66] showed that each reduction of the z-score for first trimester size was associated with increased odds for dispensed asthma medication at 15 years of age (OR 1.26, 95% CI 1.03–1.54) and self-reported use of asthma medications (OR 1.55, 95% CI 1.16–2.08). In that study, investigators also measured the crown–rump length in the first trimester, biparietal diameter and femur length in the second trimester, and performed spirometry at 5, 10 and 15 years of age, and collected data about asthma medication. Results showed that, first and second trimester size and FEV₁ at ages 5, 10 and 15 years were reduced for those dispensed asthma medications compared with those not dispensed asthma medications ($p=0.003$) [66].

5. Childhood- preschool and scholar infant

At this point, it is important to differentiate between risk factors for asthma development vs. those that may aggravate early onset asthma, although some factors

(e.g. allergens, respiratory infections and environmental pollution) can influence both. For instance, birth cohorts identified early allergic sensitization [64] and wheezing rhinovirus infections in infancy [65] as major triggers of asthma exacerbations later in life [66] and strong predictors of the subsequent development of asthma. Based on all these findings, the current concern focuses on prevention, as a potential approach for the primary prophylaxis of childhood asthma and/or low lung function in adult life [67].

5.1. Environmental factors: protective and enhancing effects for the risk for asthma

Air pollution increases the risk for asthma attacks [68] and for asthma hospitalizations [69]. Reductions in peak expiratory flow, increases in respiratory symptoms and asthma medication use were reported in patients with asthma exposed to elevated fine particulate pollution levels [70]. These results, added to a large number of similar studies worldwide, have contributed to environmental policy changes that, in turn, have resulted in significant improvements in lung function growth in children [71]. In Southern California, Gauderman *et al.* measured lung function annually in 2,120 children from three separate cohorts corresponding to three separate calendar periods: 1994–1998, 1997–2001, and 2007–2011. Mean ages of the children within each cohort were 11 years at the beginning of the period and 15 years at the end. Over the 13 years spanned by the three cohorts, declining atmospheric levels of nitrogen dioxide, particulate matter with an aerodynamic diameter of less than 2.5 μm and less than 10 μm were significantly associated with improvements in both FEV₁ and FVC [71]. These associations persisted after adjustment for several potential confounders and were observed both in boys and girls as well as in children with and without asthma.

The proportions of children with low FEV₁ (defined as <80% of the predicted value) at 15 years of age declined significantly, from 7.9% to 6.3% to 3.6% across the three periods, as the air quality improved (p= 0.001) [71].

Shortly after the reunification of Germany in 1989, von Mutius and coworkers [72] reported that the prevalence of current asthma and bronchial hyperresponsiveness was significantly higher in West than in East Germany. Higher exposure to endotoxins at home was found to be protective against the development of allergic sensitization in children. These results opened a new field, namely, the search for protective environmental exposures in early life that could prevent subsequent asthma. In this context, living on a farm during infancy has been found to be associated with lower risk of asthma in adulthood. A prospective longitudinal association between farming environment during infancy and lung function in adulthood was studied in a Finnish birth cohort study [73]. 5.666 participants born in 1966 were followed up at the age of 31 years. Being born in a farmer's family was associated with higher FEV₁ and FVC at the age of 31 years, and contact with farm animals during infancy was associated with higher FEV₁. There was a suggestive dose-dependent association with the number of animal species during childhood and higher FEV₁ and FVC at adulthood, especially among women. The study concluded that farming environment in early life may have a positive impact on lung function in adulthood. In summary, environmental measures aimed at reducing air pollution and a more rural, less industrialized environment in childhood, improve lung function in adults.

5.2. Atopy, allergy, eczema: the atopic march

The classical Tucson birth cohort proposed three categories of wheezing phenotypes at early age: transient wheezers (wheezing symptoms before 3 years, no wheezing at age 6), late onset wheezers (no wheeze until 3 years, wheezing at age 6), and persistent wheeze (wheezing in the first 3 years, wheezing at 6 years)[76]. This latter group of persistent wheezers can be further sub-divided into atopic and non-atopic. One third of all children aged 3 or younger had lower respiratory tract illnesses with wheezing; however, by the age of 6 close to 60 percent of these children no longer had wheezing symptoms. Transient early wheezers were found to have lower levels of lung function compared to other groups of wheezers, possibly reflecting congenitally smaller airways.

These observations allowed the development of an asthma predictive index [74], which has been further used in major clinical trials [75, 76] to identify young children at high risk for the disease. A stringent index included: frequent wheezing during the first 3 years of life and either one major risk factor (parental history of asthma or eczema) or two of three minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis). A loose index required any wheezing during the first 3 years of life plus the same combination of risk factors described previously. Children with a positive loose index were 2.6 to 5.5 times more likely to have active asthma between ages 6 and 13 than children with a negative loose index [74]. Risk of having subsequent asthma increased to 4.3 to 9.8 times when a stringent index was used.

In the Tucson Children's Respiratory Study (CRS), a non-selected birth cohort, early sensitisation to *Alternaria* was associated with increased airway hyper-responsiveness (AHR) in adult life among non-asthmatics. The increase in AHR was of a similar magnitude to that seen for *Alternaria* sensitised asthmatics and was primarily evident

among those who were overweight or obese. In contrast, there was no significant association between early sensitisation to aeroallergens other than *Alternaria* and AHR among non-asthmatics [77]. These observations indicate that, in clinical practice, physicians should always ask about the “atopic march”- atopic dermatitis, food allergy, allergic rhinitis in childhood. Independently of other factors, this will give us valuable information about a potential T2 signature of the individual. Yet, the relationship between the level of exposure and sensitization varies widely among studies, from no significant association to a simple linear dose–response relationship or a ‘bell-shaped’ dose–response model with a protective effect of high allergen exposure. A Cochrane review found in 2009 that multifaceted interventions (reducing exposure to both inhalant and food allergens) resulted in a significant decrease in asthma compared to usual care (<5 years: OR 0.72, 95% CI 0.54 to 0.96; >5 years: OR 0.52, 95% CI 0.32 to 0.85) [78]. There is also growing evidence on the potential of immunotherapy to alter the natural course of allergic march from allergic sensitization to asthma. A recent study included 812 children (5–12 years), with grass pollen allergic rhino-conjunctivitis and no medical history or signs of asthma. Children were double blinded and randomly allocated to receive immunotherapy or placebo for three years and were followed for two additional years [79]. The study showed reduced risk of experiencing asthma symptoms and using asthma medication, but did not show an effect on the time to onset of asthma. Hence, the relationship of allergic desensitization and asthma is complex, and seem to depend as well on other environmental factors and individual genetic predispositions. Thus, the role and the measures of prevention of sensitization in the development of IgE-mediated sensitization asthma are yet to be determined.

More recently, the role of non-allergic rhinitis in early life in relation to subsequent asthma has also been explored in the Tucson CRS [80]. Allergy skin prick testing was performed at age 6, atopy being defined as ≥ 1 positive tests. Physician diagnosed active asthma from ages 6-32 and physician diagnosed rhinitis at age 6 were determined by questionnaire. Participants with asthma or active wheezing at age 6 were excluded from analyses. 521 participants met the inclusion criteria. Results showed that the hazard ratio for subsequently acquiring a diagnosis of asthma between the ages of 8 and 32 for those with non-atopic rhinitis was 2.1 (95% CI: 1.2, 3.4, $p=0.005$), compared with the non-atopic no rhinitis group, after adjusting for sex, ethnicity, maternal asthma, maternal education and smoking, and history of 4+ colds per year at age 6. Among the atopic participants, both the active and no rhinitis groups were more likely to develop and have asthma through age 32. The relation between non-atopic rhinitis and asthma was independent of total serum IgE levels at age 6. In conclusion, early rhinitis, either allergic or non-allergic, confers significant risk for asthma development through adulthood. These findings underscore the importance of non-allergic mechanisms in the development of asthma, an issue that will be further discussed.

5.3. Infections: RSV, Rhinovirus and “the viral march”

A better understanding of the "viral march" could yield new therapeutic approaches for the prevention and treatment of acute severe airway obstruction during childhood. The majority of infants aged <1 year who wheeze remit by the age of 3 (the so-called transient wheezers), and their episodes are associated with viral infections. Young children who will develop asthma later in life usually have recurrent episodes of wheezing, cough, and difficulty to breathe ("persistent wheezers"), and these episodes

are associated with molecular evidence of viral respiratory infection in up to 90% of cases [67]. Currently, it is widely recognized that early life respiratory syncytial virus (RSV) and human rhinovirus (HRV) lower respiratory tract infections (LRTIs) are strongly associated with increased asthma risk. During early infancy, RSV is a more common cause of severe LRTI. Severe RSV bronchiolitis requiring hospitalization is considered a risk factor for future asthma. With advancing age, the situation is reversed, with HRV (human rhinovirus) becoming more common.

In a recent Finnish study, 127 steroid-naive children with the first severe wheezing episode (90% hospitalized/10% emergency department treated) were followed for 7 years. The primary outcome was current asthma at age 8 years. At study entry, median age was 11 months; 17% were sensitized, and 98% were virus positive. Current asthma (n = 37) at 8 years was divided into atopic (n = 19) and nonatopic (n = 18) asthma. The risk factors for current atopic asthma at study entry were sensitization (adjusted odds ratio [OR], 12; $p < .001$), eczema (adjusted OR, 4.8; $P = .014$), and wheezing with rhinovirus (adjusted OR, 5.0; $p = 0.035$). The risk factors for nonatopic asthma were the first severe respiratory syncytial virus/ rhinovirus-negative wheezing episode (adjusted OR, 8.0; $p = 0.001$), first wheezing episode at age less than 12 months (adjusted OR, 7.3; $p = 0.007$), and parental smoking (adjusted OR, 3.8; $p = 0.028$) [81].

Even more so, the CRS Tucson cohort aimed to determine if there were individuals with a distinct, persistently low lung function trajectory [82]. 1,246 participants included between 1980 and 1984 were followed prospectively; distinct lung function trajectories among participants with two or more spirometry measurements between ages 11 and 32 years were determined. Among 599 participants, a model with two distinct trajectories

(a low trajectory [$n = 56$; 9.3%] and a normal trajectory) fit the data significantly better than a model with only one trajectory ($P = 0.0007$). As compared with those with a normal trajectory, participants with a persistently low trajectory were more likely to have a history of maternal asthma (20.0% vs. 9.9%; $P = 0.02$); early life lower respiratory illness caused by RSV (41.2% vs. 21.4%; $P = 0.001$); and physician-diagnosed active asthma at age 32 years (43.9% vs. 16.2%; $P < 0.001$). From all these factors, early RSV is obviously the only preventable one.

Hence, these findings are important for designing early intervention strategies for prevention of asthma. Currently, the role of strategies to prevent RSV (palivizumab, azithromycin, specific vaccine) has yet to be confirmed. In a study performed in 937 young children with histories of recurrent severe LRTIs, for instance, the use of azithromycin early during an apparent RTI compared with placebo reduced the likelihood of severe LRTI, without significant adverse events. More information is needed on the development of antibiotic-resistant pathogens with this strategy [83]. As for HRV, strategies for developing an effective vaccine or for preventing viral contact and invasion by forming a barrier on the host mucosa are being developed; however, currently there is no approved strategy against HRV. Limiting viral spread is the main available protective measure.

5.4. Nutrition and obesity

Dietary interventions in childhood are attractive and not very expensive, so they are being intensively investigated. More than 2 decades ago, Hodge *et al.* examined the relation between certain food consumption and asthma. They found a significantly reduced risk of current asthma in children who ate fresh, oily fish (OR 0.26; 95% CI

0.09-0.72; $p < 0.01$) [84]. Vitamin D is associated with asthma, but evidence for its role in primary prevention is still lacking. Other vitamins studied (such as C and E) failed to show a beneficial effect.

On the other hand, overweight/ obesity (OW) is linked to worse asthma and poorer inhaled corticosteroid (ICS) response in older children and adults. A post hoc study of 3 large NIH/NHL multicenter trials involving 2- to 5-year-old children compared annualized asthma symptom days and exacerbations among normal weight (NW) (body mass index: 10th-84th percentiles) versus OW (body mass index: ≥ 85 th percentile) participants. Within the group not treated with a daily controller, OW children had more asthma symptom days (90.7 vs 53.2, $p = 0.020$) and exacerbations (1.4 vs 0.8, $p = 0.009$) than NW children did. Within the ICS-treated groups, OW and NW children had similar asthma symptom days and similar exacerbations [85]. So, unlike older asthmatic patients, OW preschool children do not demonstrate reduced responsiveness to ICS therapy. Nonetheless, early primary and secondary prevention of obesity, a real epidemic as we are all aware nowadays, is of utmost importance from numerous points of view related to health outcomes and quality of life at any age.

6. Teenage/ Young adult

After reaching puberty, a series of other factors come into play and complicate the puzzle of the early life origins of asthma. Among them, tobacco smoking, hormonal changes and exposure to occupational agents are the most relevant ones.

6.1. Smoking

Several reports have suggested that, among active tobacco smokers, previous exposure to parental smoking may increase susceptibility to development of chronic obstructive pulmonary disease. This was assessed prospectively using data from the Tucson Children's Respiratory Study [88]. Maternal and paternal smoking was assessed via questionnaires completed by the parents at the time of the participant's birth. Active smoking in study participants was assessed via personal questionnaires completed at ages 16 (YR16), 22 and 26 years. Participants were stratified in four groups based on the combination of parental and active smoking. Lung function parameters, including FEV₁/FVC, were assessed by spirometry before and after inhalation of 180 µg of albuterol at YR11, YR16, YR22 and YR26. Complete data were available for 519 participants. Pre-bronchodilator FEV₁/FVC values did not differ at YR11, YR16 or YR22 by parental or active smoking. However, at YR26 participants with exposure to parental and active smoking had pre-bronchodilator FEV₁/FVC levels that were, on average, 2.8% (0.9% to 4.8%; p=0.003) lower than participants who were not exposed to parental or active smoking. In contrast, subjects who were only exposed to active smoking or only exposed to parental smoking did not differ from those who were not exposed to either. Between YR11 and YR26, participants with exposure to parental and active smoking had the steepest decline in sex, age and height adjusted residuals of FEV₁/FVC, FEV₁, forced expiratory flow between 25% and 75% of the FVC (FEF₂₅₋₇₅) and FEF₂₅₋₇₅/FVC (all p values between 0.03 and <0.001). In conclusion, parental and active smokings act synergistically to affect early lung function deficits in young adulthood [86].

The role of viral infections in the development of early asthma has been previously discussed. In addition, it seems that smoking is particularly dangerous in patients with RSV illnesses in early life [87]. A total of 1,246 non-selected infants from the Tucson cohort were enrolled at birth and prospectively followed. Virologically confirmed RSV previous infections were assessed during the first 3 years of life. At age 22, 24, 26, and 29 years, current asthma and smoking behavior were evaluated by questionnaire. Peak flow variability was assessed at age 26 and expressed as amplitude % mean. A longitudinal analysis was used to investigate the relation of RSV-LRI and active smoking to adult outcomes. Neither RSV nor active smoking were directly associated with increased current adult asthma or peak flow variability. However, there was a significant interaction between RSV-LRI and active smoking in relation to current asthma (p for interaction = 0.004) and peak flow variability (p for interaction = 0.04). Among subjects with early RSV-LRI, those who actively smoked were 1.7 times more likely to have current asthma (95% confidence interval, 1.2-2.3; p = 0.003) and had greater amplitude % mean (10.0% vs. 6.4%; p = 0.02) than nonsmokers. So smoking is associated with increased risk of having asthma in young adults who had RSV-LRI in early life, but not among subjects without these illnesses. There is no question that smoking is a preventable and modifiable risk factor in asthma. There is definitely a need for robust measures to reduce prenatal and postnatal smoking, as a strategy for primary prevention of asthma.

6.2. Hormonal factors

Little is known about predictors of remission of childhood asthma after the onset of puberty. To investigate this question, data was collected in 781 children of the Tucson

Children's Respiratory Study at ages 6, 8, 11, 13, and 16 years [88]. Of these 781 children, 166 had asthma in at least one survey before puberty. In this group, 58% of the children reported the presence of wheezing after the onset of puberty (unremitting asthma). In contrast, only 30% of the children with infrequent wheezing before puberty experienced wheezing episodes after the onset of puberty (unremitting wheezing). In addition to frequent wheezing before puberty, obesity, early onset of puberty, active sinusitis, and positive skin tests were significant and independent predictors of unremitting asthma after the onset of puberty [88].

In addition, accumulating evidence indicates that hormonal factors play a role in new-onset allergic rhinitis and asthma after puberty. A large prospective community-based cohort study performed in Germany followed 1,191 girls 9 to 11 years old to early adulthood (19-24 years old) [91]. Data on age at menarche, use of hormonal contraceptives, and status and age at onset of physician-diagnosed allergic rhinitis and asthma were collected at 16 to 18 and 19 to 24 years of age. 11% of girls developed allergic rhinitis after menarche and 3% reported new-onset asthma. Late menarche (>13 years of age) was statistically significantly inversely related to allergic rhinitis (adjusted odds ratio [OR] 0.32, 95% confidence interval [CI] 0.14-0.74) but did not reach the level of statistical significance for asthma (OR 0.32, 95% CI 0.07-1.42). Use of hormonal contraceptives was inversely associated with new-onset allergic rhinitis (OR 0.14, 95% CI 0.08-0.23) and asthma (OR 0.27, 95% CI 0.12-0.58) after puberty. These results show that girls with late onset of menarche are less likely to develop allergic rhinitis after puberty compared with those who have menarche at an average age. These findings also suggest that hormonal contraceptives might play a protective role in young

women from allergies and asthma [89], but further evidence is required before a prevention recommendation could be made in this direction.

6.3. Occupational agents

In genetically predisposed individuals, certain occupations, like baker, hairdresser, cleaner, constructions or car workers- especially those exposed to isocyanates (paint, varnish), might induce occupational asthma, as is nowadays well recognized by both physicians and labor laws. Poor clinical outcomes and levels of lung function in these young individuals might be aggravated by other early life disadvantages, such as parental or active patient smoking at an early age, infections, low income conditioning poor medical attention and proper treatment in some countries, or a combination of all these factors; plus -a long-time exposure to the occupational agent- i.e. starting to work at a very young age and/ or impossibility to change the workplace when the symptoms start. For instance, a cross-sectional study performed in Northern Europe cleaners investigated if early life factors influenced susceptibility to occupational cleaning's unhealthy effects in 13,499 participants [90]. Associations with respiratory symptoms, asthma and self-reported COPD were analyzed with multiple logistic regression, adjusted for sex, age, smoking, educational level, parent's educational level, BMI and participating centre. Interaction of occupational cleaning with early life disadvantage (maternal smoking, severe respiratory infection <5 years, born during winter months, maternal age at birth >35 years) was investigated. Among 2,138 ever-cleaners the risks of wheeze (OR 1.4, 95% CI 1.3-1.6), adult-onset asthma (1.5 [1.2-1.8]) and self-reported COPD (1.7 [1.3-2.2]) were increased. The risk increased with years in occupational cleaning (adult-onset asthma: ≤ 1 year 0.9 [0.7-1.3]; 1-4 years 1.5

[1.1-2.0]; ≥ 4 years 1.6 [1.2-2.1]). The association of wheeze with cleaning activity ≥ 4 years was significantly stronger for those with early life disadvantage than in those without (1.8 [1.5-2.3] vs. 1.3 [0.96-1.8]; p interaction 0.035). These results indicate that occupational cleaners had increased risk of asthma and self-reported COPD, particularly those with early life disadvantage.

7. Conclusions

As reviewed above, there is now overwhelming evidence that events occurring early in life, both before and after birth, are significantly associated with the risk of asthma, and low lung function later in life. In fact, from conception to death there are continuous, dynamic numbers of gene-environment interactions (Table 2) that determine two fundamental biologic processes, lung development and lung ageing (Figure 1). It is the interaction of these two processes what determines the presence or absence of early or late respiratory (and other) diseases [94]. Future research should focus on better understanding these complex interactions, in order to develop more effective preventive and precise therapeutic measures [9].

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Accepted Article

Table 1. Early life events in childhood and adult asthma**Prenatal factors**

- Genetic

Maternal /pregnancy factors

- Atopy
- Nutrition
- Smoking
- Drugs

Perinatal factors

- Preterm birth/ Bronchopulmonary dysplasia
- Low birth-weight

Childhood-preschool and scholar infants

- Environmental factors
- The atopic march
- Infections
- Nutrition and obesity

Teneage-young adult

- Smoking
- Hormonal factors
- Occupational agents

Table 2. Factors that influence asthma development, in chronological order.

Perinatal factors	References	Childhood and Adolescent factors	References
Prenatal factors:		Preschool and scholar infants	
- Genetic factors	4,21-31	<i>Environmental factors during childhood</i>	
Maternal factors:		- Air pollution	70-73
- Atopy	32-37	- Urban versus Rural lifestyle	70, 74-75
- Asthma	9,40	<i>Early Events</i>	
- Nutrition	42-46	- Atopy/allergy	66, 76, 79-81
- Infections	47-49	- Infections	67, 84, 85
- Smoking	51-54	- Nutrition	86, 87
- Drugs	55-58	Teenage- young adulthood	
Perinatal factors:		- Smoking	88, 89
- Preterm birth/BPD	5,59-63	- Hormones	90, 91
- Low birth-weight	64-66	- Occupational exposure	92

FIGURE LEGENDS

Figure 1. Interplay between organ development, maintenance and repair (green triangle) and cumulative tissue injury and ageing (red triangle). Dashed arrows (green and red) indicate that the slope of these lines can vary (for better or worse) in different individuals. This interplay over a lifetime determines health and life expectancy (top triangle). For further explanations, see text. Reproduced with permission from reference [94].

