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WHEEZING PHENOTYPES AND RISK FACTORS IN EARLY LIFE

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Phénotypes sifflants et facteurs de risque à un âge précoce

Résumé : Objectifs: L'objectif de l'étude française était de décrire les phénotypes respiratoires de sifflement chez l'enfant à l'âge d'un an, et d'évaluer les facteurs de risque associés à ces phénotypes de sifflement dans une grande cohorte de naissance. Dans l'étude libanaise, les objectifs étaient d'évaluer les associations entre l'utilisation de médicaments, d'alcool, tabac et l'exposition aux pesticides/détergents pendant la grossesse avec l'asthme infantile au Liban et de valider la version Arabe du test de contrôle de l'asthme (ACT) chez ces enfants et d'identifier les facteurs de risque qui pourraient affecter le contrôle de l'asthme.

Méthodes: Nous avons étudié 18 041 nourrissons de la cohorte de naissance ELFE (Étude Longitudinale Française depuis l'Enfance). Les parents ont signalé une respiration sifflante et des symptômes respiratoires à deux et 12 mois, et ont répondu à un questionnaire complet (exposition pendant la grossesse, allergie parentale). Le plan d'étude du projet libanais consistait en une étude cas-témoins, menée entre Décembre 2015 et Avril 2016, recrutant 1503 enfants, âgés de 3 à 17 ans. Le questionnaire administré évaluait les caractéristiques sociodémographiques et d'autres facteurs de risque connus de l'asthme.

Résultats: En comparant les sifflements persistants aux contrôles, on a observé qu'avoir un frère ou une sœur (ORa=2,19) ou deux frères et sœurs (ORa=2,23) contre aucun, une toux nocturne (OR=5,2), une détresse respiratoire (OR=4,1) et un excès de sécrétions bronchiques (OR=3,47) à deux mois, un reflux chez l'enfant à 2 mois (OR=1,55), des antécédents d'asthme maternel (OR=1,46) et le tabagisme maternel pendant la grossesse (OR=1,57) étaient associés à une respiration sifflante persistante. Avoir un frère (ORa=1,9) en comparaison à ne pas en avoir, une toux nocturne à 2 mois (OR=1,76) et un excès de sécrétions bronchiques à 2 mois (OR=1,65) étaient associés à une respiration sifflante persistante par rapport à une respiration sifflante intermittente.

Dans l'étude libanaise, le fait de fumer le narguileh pendant la grossesse et la cigarette pendant l'allaitement augmenterait le risque d'asthme chez les enfants (ORa=6,11; ORa=3,44). Pour l'échelle de contrôle de l'asthme (ACT), un alpha de Cronbach élevé a été trouvé pour l'échelle (0,959). Le faible niveau d'éducation de la mère ainsi que les antécédents d'asthme parentaux augmenteraient significativement le risque d'asthme incontrôlé. La consommation de cigarettes pendant l'allaitement et le fait que la mère ait fumé le narguileh pendant la grossesse étaient associés à l'asthme non contrôlé (Beta=2,105; Beta=2,325). Le niveau d'éducation élevé de la mère était associé à plus de contrôle de l'asthme (Bêta=-0,715).

Conclusion: Les symptômes respiratoires (toux, détresse respiratoire et sécrétions bronchiques excessive) étaient significativement associés à un risque élevé de respiration sifflante persistante à un an. L'exposition au tabac durant la grossesse était également un facteur de risque de respiration sifflante persistante et incidente.

De plus, l'asthme peut provenir de l'exposition environnementale à des substances toxiques telles que les pesticides et le tabac (cigarettes et narguileh) ou à l'alcool et aux médicaments prescrits pendant la grossesse et l'allaitement. Le narguileh

pendant la grossesse et le tabagisme pendant l'allaitement, ainsi qu'un faible niveau d'éducation sont des facteurs de risque d'asthme non contrôlé. La sensibilisation des professionnels de la santé à ces causes évitables peut aider à éduquer les parents et les enfants à prévenir l'asthme et son exacerbation. Finalement, la version arabe du questionnaire de contrôle de l'asthme est un outil valide chez les patients pédiatriques de la population libanaise pour évaluer le contrôle de l'asthme.

Mots clés : respiration sifflante; des phénotypes; les enfants l'asthme; conduite d'eau ; contrôle de l'asthme

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Wheezing phenotypes and risk factors at early age

Abstract : Objectives: In the French study, we aimed at describing wheezing phenotypes between the ages of two months and one year, and assess risk factors associated with these wheezing phenotypes in a large birth cohort. In the Lebanese study, the aims were to evaluate the associations between caregiver-reported use of medications, alcohol, cigarette and/or waterpipe (WP), and exposure to pesticides/detergents during pregnancy with childhood-onset asthma in Lebanon and to validate the Arabic version of the Asthma Control Test (ACT) among these children and identify risk factors that might affect asthma control.

Methods: We studied 18,041 infants from the ELFE (French Longitudinal Study of Children) birth cohort. Parents reported wheezing and respiratory symptoms at two and 12 months, and answered a complete questionnaire (exposure during pregnancy, parental allergy).

The study design of the Lebanese project consisted of a case-control study, conducted between December 2015 and April 2016, recruited 1503 children, aged between 3-16 years old. A questionnaire assessed the sociodemographic characteristics and other known risk factors of asthma.

Results: Children with no symptoms (controls) accounted for 77.2%, 2.1% had had wheezing at two months but no wheezing at one year (intermittent wheezing), 2.4% had persistent wheezing, while 18.3% had incident wheezing at one year. Comparing persistent wheezing to controls showed that having one sibling (ORa=2.19) or 2 siblings (ORa=2.23) compared to none, nocturnal cough (OR=5.2), respiratory distress (OR=4.1) and excess bronchial secretions (OR=3.47) at two months, reflux in the child at 2 months (OR=1.55), maternal history of asthma (OR=1.46) and maternal smoking during pregnancy (OR=1.57) were significantly associated with persistent wheezing. These same factors, along with cutaneous rash in the child at 2 months (OR=1.13) and paternal history of asthma (OR=1.32) were significantly associated with increased odds of incident wheezing. Having one sibling (ORa=1.9) compared to none, nocturnal cough at 2 months (OR=1.76) and excess bronchial secretions at 2 months (OR=1.65) were significantly associated with persistent compared to intermittent wheezing.

In the Lebanese study, smoking WP during pregnancy and cigarette during lactation would increase the risk of asthma in children (ORa=6.11; ORa=3.44 respectively). A high Cronbach's alpha was found for the full scale (0.959). Mother's low educational level as well as the history of asthma in the mother and the father would significantly increase the risk of uncontrolled asthma (Beta= 1.862; Beta= 3.534; and Beta= 1.885 respectively). Cigarette smoking during breastfeeding and waterpipe smoking by the mother during pregnancy were both significantly associated with uncontrolled asthma (Beta= 2.105; Beta=2.325 respectively). Mother's high educational level was significantly associated with more asthma control (Beta= -0.715).

Conclusion: Respiratory symptoms (cough, respiratory distress, and excessive bronchial secretion) were significantly associated with a high risk of persistent wheezing at one year. Smoking exposure during pregnancy was also a risk factor for persistent and incident wheezing.

In addition, asthma may originate from the environmental exposure to toxics such as pesticides and tobacco (cigarettes and WP) or to alcohol and prescribed medications during pregnancy and lactation. Waterpipe smoking during pregnancy and cigarette smoking during breastfeeding, as well as the lower education level are risk factors for uncontrolled asthma. Spreading awareness by health professionals about these preventable causes can help educate the parents and children to prevent asthma and its exacerbation. Finally, the Arabic version of the asthma control questionnaire is a valid tool to use in pediatric patients in the Lebanese population to assess asthma control.

Keywords: wheezing; phenotypes; children; asthma; waterpipe; asthma control.

Unité de recherche

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The PhD chapter is closed now. It is time to open a new page, with new objectives and new challenges.

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Publications

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3. Souheil Hallit, Chantal Raherison, Mirna Waked and Pascale Salameh. Exposure to toxics during pregnancy and asthma in childhood: a case-control study. Iran J Allergy Asthma Immunol December 2017; 16(6):488-500.
4. Hallit S, Raherison C, Waked M, Salameh P. Validation of asthma control questionnaire and risk factors affecting uncontrolled asthma among the Lebanese children's population. Respiratory Medicine (2016), doi: 10.1016/j.rmed.2016.11.018.

Communications

1. Respiratory and allergic symptoms in early life: The ELFE cohort. ELFE team reunion, Paris, France, February 2017.
2. Microbial exposure at birth and respiratory symptoms at one year: The ELFE cohort. ELFE team reunion, Paris, France, February 2017.
3. Validation of the asthma control and quality of life questionnaires among the Lebanese children's population. 24th Lebanese Order of Pharmacists Congress, Beirut, Lebanon, November 2016.
4. Exposure to toxics during pregnancy and asthma in childhood: a case-control study. CHEST conference, Dubai, UAE, November 2016.

Posters

1. S. Hallit, J. De Blic, C. Marguet, E. Scherer, G. Reboux, MC Delmas, B. Leynaert, S. Rocchi, L. Million, MN Dufourg, C. Bois, MA Charles, C. Raherison. Respiratory and allergic symptoms in early life: The ELFE cohort. European Respiratory Society International Congress, Milan, Italy. September 2017.
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1. INTRODUCTION

Asthma is a chronic disease that is characterized by episodes of wheezing respiratory disorders, resulting from inflammation of the airways[1]. It is highly prevalent worldwide, affecting approximately 300 million individuals of all ages and accounts for 250,000 deaths annually worldwide[2]. Asthma is also the most common chronic disease in children.

In clinical practice, asthma causes symptoms such as wheezing, shortness of breath, chest tightness, and coughing that vary over time in their occurrence, frequency, and intensity[3]. Symptoms may occur several times a day or week and become worse in some individuals during physical exertion or at night[4]. However, a proper asthma diagnosis cannot be based on a single common feature[5,6]. Currently, the intermittent symptoms of asthma are known to occur on a background of persistent airway inflammation and remodeling[7]. Asthma is no longer considered as just one disease but rather a multifaceted one, with multiple associated syndromes expressing different phenotypes[8]. Therefore, increasing knowledge of these phenotypes would provide better understanding of the disease in order to better assist and manage patients[8].

1.1. Prevalence of asthma and associated complications

Asthma is prevalent in all countries, but its prevalence is higher in high-resource countries than in countries with medium or limited resources. In 2001, asthma ranked 25th in the world in years of life lost in good health (disability adjusted life-years) (DALYs)[9]. In 2010, asthma was ranked 28th in the world[10]. Asthma is a serious disease that killed 255,000 people in 2005[11].

In Europe, approximately 30 million children and adults under the age of 45 suffer from asthma. In the latter part of the 20th century, the prevalence of asthma increased in Western Europe, and appears now to stabilize in many countries. The United Kingdom and Ireland are the countries with the highest prevalence of asthma in the world[12]. In Western Europe, this disease is ranked 23rd worldwide in years of life lost in good health. The countries most affected by the common symptoms of asthma are mostly of Anglo-Saxon origin. Indeed, among children aged 13-14 years, we have a prevalence of 20% or more in Oceania, New Zealand, North America, Ireland and the United Kingdom.

In France, the prevalence of asthma is 4.15 million, or 6.7% of the adult population[13]. As of January 1, 2015, the French population is estimated at 64.5 million[14]. Children under the age of 15 represent 18.6% of the population[14] according to data from the National Institute of Statistics and Economic Studies (INSEE). The prevalence of wheezing in these children varies from 8.3 to 10.7% depending on their age. The prevalence of asthma increases with the age of the child and varies between 12.3 and 13.4%[15]. France is therefore in an intermediate position compared to other countries[16], with an asthma prevalence of less than 20% but greater than or equal to 10%.

Asthma is a rare cause of mortality, contributing to less than 1% of all deaths in most countries worldwide[17]. In European countries, among all age groups, asthma contributes 0.6% of hospital admissions and 0.4% of all inpatient bed-days, with lacking data for most low- and middle-income countries[17]. In 2012, asthma surveillance data from the French Institute for Public Health Surveillance (InVS) indicated that there were 56,944 hospital stays because of asthma. Almost 63% of these hospitalizations were for children under the age of 15 years[18]. In addition, asthma remains a serious disease that causes approximately 1,000 deaths a year following a severe crisis, while effective treatments exist. Death may result from lack of management of the disease, inadequate treatment of the person or poor patient compliance. Deaths due to asthma can therefore be avoided with better care of patients.

In Lebanon, a study conducted in 1998 among school children in Beirut aged 13 to 14 years reported a prevalence of 11.9% for severe asthma[19]. Previous studies conducted on school children in Lebanon reported a rate of 5.6% for diagnosed asthma in children aged 13-14 years (2005)[20] and 8.2% in children aged 3-17 years (2017)[21].

1.2. Wheezing and asthma in infants

Wheezing is common throughout infancy and childhood except in the neonatal period when it is relatively rare. About 19% of 10-year-old children experience wheezing with an average age of onset of 3 years[22]. In addition, several population-based birth cohort studies documented that 30% of children suffer from wheezing during respiratory infections before their third birthday. Recurrent wheezing is

common, but most patients outgrow their symptoms by school age[23]. Infants are prone to wheezes because of anatomic factors related to the lung and chest wall in addition to immunologic and molecular influences in comparison to older children[24]. The obstruction to flow is affected by the airway caliber and compliance of the infant's lung. Resistance to airflow through a tube is inversely related to the radius of the tube to the 4th power. In children < 5 years old, small caliber peripheral airways can contribute up to 50% of the total airway resistance. Marginal additional narrowing can cause further flow limitation and a subsequent wheeze[25]. With the very compliant newborn chest wall, the inward pressure produced in expiration subjects the intrathoracic airways to collapse. Flow limitation is further affected in infants by the differences in tracheal cartilage composition and airway smooth muscle tone causing further increase in airway compliance compared with older children. All of these mechanisms combine to make the infant more susceptible to airway collapse, increased resistance, and subsequent wheezing. Many of these conditions are outgrown by the 1st year of life[26].

Immunologic and molecular influences can contribute to the infant's propensity to wheeze. In comparison to older children and adults, infants tend to have higher levels of lymphocytes and neutrophils, rather than mast cells and eosinophils in broncho-alveolar lavage fluid. A variety of inflammatory mediators have also been implicated in the wheezing infant such as histamine and leukotrienes. Fetal and/or early postnatal "programming" in which the structure and function of the lung are affected by factors including fetal nutrition and fetal and neonatal exposure to maternal smoking may also occur[27].

In the infant, there is no consensual definition of asthma due to the clinical variability of asthma. This leads to an under-diagnosis and therefore a sub-treatment of this disease. No definition exists but consensus has been reached. It concludes that there is asthma when there are three or more wheezing episodes. For some pediatricians, infants with three episodes of bronchiolitis, within three to six months, would become severe cases of asthma. For others, chronic coughs and repeat infections before the age of 36 months would presage asthma cases later. Patients will have an under-medication and others will have a medication based on the doctor's diagnosis. Indeed, some children with episodes of bronchiolitis will be

punctually treated for this problem but will, in the meantime, have other seizures which will lead to a decrease in their respiratory capacity later. Uncertainties in the diagnosis of asthma persist until the age of six years when the respiratory function test can be passed. This examination assesses the degree of airway obstruction and therefore confirms the diagnosis of asthma.

1.3. Wheezing phenotypes heterogeneity

The severity of symptoms has been correlated with a high frequency of wheezing episodes (usually more than three per year), resulting in the identification of frequent wheezing as a distinct phenotype[28-30]. Better understanding of these phenotypes is therefore of fundamental importance in addressing the risk factors for asthma and wheezing illnesses in children[31-33].

Four wheezing phenotypes (no wheezing, transient-early, late-onset, and persistent wheezing) were previously defined according to whether the child had reported wheezing during the first three years of life and whether they were still wheezing at age six[34]. Two British cohort studies used latent class analysis to identify distinct phenotypes underlying the observed heterogeneity in asthma symptoms during childhood[35,36]. The Avon Longitudinal Study of Parents and Children (ALSPAC) identified six wheezing phenotypes in childhood from birth to seven years old[35]. However, it is unclear whether phenotypes identified by latent class analysis are comparable between birth cohorts observed in different areas or countries, particularly because the number and timing of measurements, definitions of wheezing, and population characteristics may differ between studies[37-39].

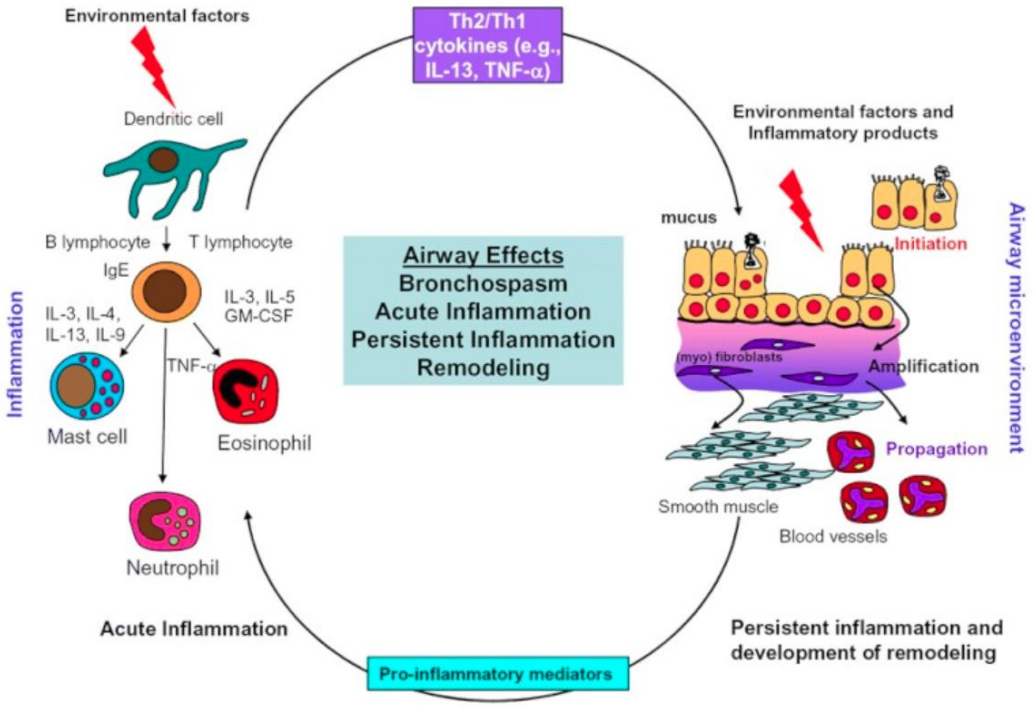
1.4. Pathophysiology of asthma

Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway. These include:

Bronchoconstriction. In asthma, the dominant physiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators

from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins that directly contract airway smooth muscle[40]. Aspirin and other nonsteroidal anti-inflammatory drugs (see section 3, component 3) can also cause acute airflow obstruction in some patients, and evidence indicates that this non-IgE-dependent response also involves mediator release from airway cells[41]. In addition, other stimuli (including exercise, cold air, and irritants) can cause acute airflow obstruction. The mechanisms regulating the airway response to these factors are less well defined, but the intensity of the response appears related to underlying airway inflammation. Stress may also play a role in precipitating asthma exacerbations. The mechanisms involved have yet to be established and may include enhanced generation of pro-inflammatory cytokines.

Airway edema. As the disease becomes more persistent and inflammation more progressive, other factors further limit airflow (figure 1). These include edema, inflammation, mucus hypersecretion and the formation of mucus plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle. These latter changes may not respond to usual treatment.



Key: GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL-3, interleukin 3 (and similar); TNF-α, tumor necrosis factor-alpha

Figure 1: *Factors that might further limit the workflow. Adapted and reprinted from The Lancet, 368, Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults, 780–93. Copyright (2006).*

Airway hyperresponsiveness. Airway hyperresponsiveness—an exaggerated bronchoconstrictor response to a wide variety of stimuli—is a major, but not necessarily unique, feature of asthma. The degree to which airway hyperresponsiveness can be defined by contractile responses to challenges with methacholine correlates with the clinical severity of asthma. The mechanisms influencing airway hyperresponsiveness are multiple and include inflammation, dysfunctional neuroregulation, and structural changes; inflammation appears to be a major factor in determining the degree of airway hyperresponsiveness. Treatment directed toward reducing inflammation can reduce airway hyperresponsiveness and improve asthma control[42].

Airway remodeling. In some persons who have asthma, airflow limitation may be only partially reversible. Permanent structural changes can occur in the airway (figure 1); these are associated with a progressive loss of lung function that is not prevented by or fully reversible by current therapy. Airway remodeling involves an activation of many of the structural cells, with consequent permanent changes in the airway that increase airflow obstruction and airway responsiveness and render the patient less responsive to therapy[43]. These structural changes can include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hypersecretion. Regulation of the repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response.

1.5. Asthma: a disease induced by multiple factors

Asthma is a multifactorial disease that results from the interaction between a genetic predisposition (family history of asthma), especially with atopy, and the occurrence of environmental factors. Atopy is a genetic predisposition "to develop manifestations of immediate hypersensitivity such as asthma, hay fever, urticaria, so-called atopic eczema, susceptibility to pollen grains, as well as various allergic digestive manifestations[44]. These manifestations of hypersensitivity are related to "a complex immunological disorder, where an imbalance between the various regulatory lymphocyte populations of immune responses results in

hyperproduction of IgE"[45]. There is a prognostic variability of asthma over time and clinical variability among individuals. Knowledge of the phenotypes of asthma would lead to a better understanding of the disease in order to allow better management of patients[46]. Crisis-triggering factors may be different between individuals and may cumulate for a given individual. These include dust, mold, animal hair allergies, pollen, pollutants, and nutritional habits. Indeed, overweight and obesity are risk factors for the onset of asthma. Obesity would lead to a change in the mechanisms of asthma and its phenotype[47]. Some studies have shown that, in adolescents and adults, overweight or obesity is the cause of more severe asthma. Obesity in childhood can lead to asthma at a later age[47]. In addition, there are different levels of asthma severity.

1.5.1. Genetics

It is well recognized that asthma has an inheritable component to its expression, but the genetics involved in the eventual development of asthma remain a complex and incomplete picture[48,49]. To date, many genes have been found that either are involved in or linked to the presence of asthma and certain of its features. The complexity of their involvement in clinical asthma is noted by linkages to certain phenotypic characteristics, but not necessarily the pathophysiologic disease process or clinical picture itself. The role of genetics in IgE production, airway hyperresponsiveness, and dysfunctional regulation of the generation of inflammatory mediators (such as cytokines, chemokines, and growth factors) has appropriately captured much attention. In addition, studies are investigating genetic variations that may determine the response to therapy. The relevance of polymorphisms in the beta-adrenergic and corticosteroid receptors in determining responsiveness to therapies is of increasing interest, but the widespread application of these genetic factors remains to be fully established[42].

1.5.2. Smoking (Cigarettes and waterpipe)

In utero exposure to environmental tobacco smoke increases the likelihood for wheezing in the infant. In adults who have asthma, cigarette smoking has been associated with an increase in asthma severity and decreased responsiveness to inhaled corticosteroids (ICSs)[50]. In the study of Asher et al.

(ISAAC), there was generally a positive relationship between women smoking and the three conditions (wheeze, rhinoconjunctivitis, eczema), yet an inverse association between men smoking and the three conditions[51]. This analysis indicates that the well-established individual level association between parental cigarette smoking and asthma does not account for the international differences in asthma prevalence[51]. The effect of parents' smoking, either in early life (pregnancy)[52-54] or active smoking[55], on children is a well-established trigger to express childhood-onset asthma. There is convincing evidence that maternal smoking during pregnancy and breastfeeding, leading to in utero and perinatal exposures to environmental tobacco smoke (cigarette and waterpipe), are associated with increased risk of asthma[56]. In Lebanon, similar results were shown in a post-hoc analysis, where passive exposure to mother's smoke from cigarettes and from waterpipe was associated with asthma and allergic diseases in children[57].

1.5.3. Waterpipe smoking

Additionally, in Lebanon, the prevalence of waterpipe smoking is dramatically increasing, reaching 36.9%, the highest among countries in the region[58]. On the basis of smoking machine data, the amount of water pipe tobacco used in a single smoking session was reported to produce 100-fold more tar, 4-fold more nicotine, 11-fold more CO, and 2- to 5-fold more polycyclic aromatic hydrocarbons than did a single cigarette[59]. Furthermore, a recent study conducted in Lebanon evaluated the acute and chronic effect of 45 min session of waterpipe on the respiratory functions (% Forced Expiratory Volume (FEV)1, %FEV6 and %FEV1/FEV6). The results showed that there was no statistically significant difference for all the respiratory functions between cigarette and waterpipe tobacco smoking[60]. In addition, Shafagoj and colleagues found that the waterpipe smokers had about 2-fold higher expired CO levels and about 3-fold higher plasma nicotine levels than cigarette smokers[61].

Although composition details may differ by culture, tobacco waterpipes most often seen in Lebanon have a fired-clay head, metal body, glass or acrylic water bowl, and leather or plastic hose (Figure 2). The bowl is partially filled

with water and the head is filled with moistened tobacco upon which a lit piece of charcoal is placed (tobacco and charcoal are often separated by perforated aluminum foil). The smoker inhales through the hose, thus drawing air over the burning charcoal, heating the tobacco, and producing smoke that travels through the body of the waterpipe, the water, and the hose to the user[62]. The most popular type of waterpipe tobacco is called moassal (also known as shisha tobacco), a wet mixture of tobacco, sweetener, and flavorings. Moassal comes in many flavors, including fruit and candy, and it produces an aromatic smoke that may be particularly appealing to youth[63]. Waterpipe charcoal products range from traditional earthen kiln charcoal to quick-lighting products that are particularly common in Lebanon[64]. Relative to a single cigarette, completed in about 5 minutes[65], a single waterpipe use episode typically lasts for about 1 hour[62]. Recent technical innovations[61,66,67] confirm this duration and also provide a more detailed analysis of waterpipe tobacco smoking episodes. Data collected from actual waterpipe tobacco smokers in natural settings show that a waterpipe use episode typically involves almost 200 puffs, with an average puff volume exceeding 500 ml[66,67]. Thus, compared to a cigarette, which involves inhalation of approximately 500–600 ml of smoke (ie, 10–13 puffs of about 50 ml, on average[68,69]), a single waterpipe use episode involves inhalation of approximately 90,000 ml of smoke[66,67].

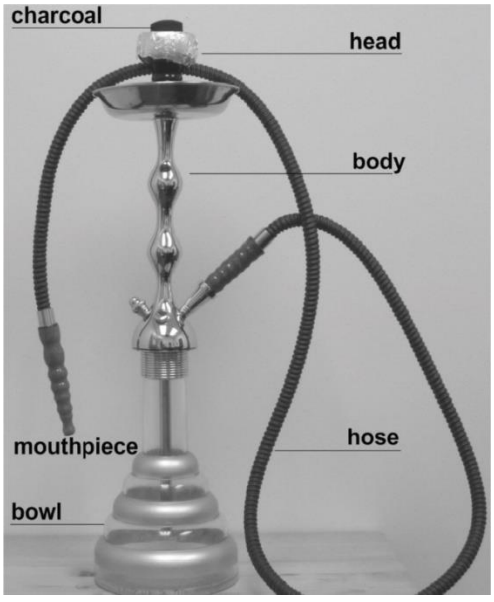


Figure 2: *A Waterpipe Prepared for Tobacco Smoking, Including Perforated Foil Separating the Charcoal from the Tobacco That Has Been Placed in the Head*

1.5.4. Environmental Factors

Two major environmental factors have emerged as the most important in the development, persistence, and possibly severity of asthma: airborne allergens and viral respiratory infections. In the susceptible host, and at a critical time of development (e.g., immunological and physiological), both respiratory infections and allergens have a major influence on asthma development and its likely persistence. It is also apparent that allergen exposure, allergic sensitization, and respiratory infections are not separate entities but function interactively in the eventual development of asthma.

Allergens

The role of allergens in the development of asthma has yet to be fully defined or resolved, but it is obviously important. Sensitization and exposure to house-dust mite and *Alternaria* are important factors in the development of asthma in children. Early studies showed that animal danders, particularly dog and cat, were associated with the development of asthma. Recent data suggest that under some circumstances, dog and cat exposure in early life may actually protect against the development of asthma[70]. The determinant of these diverse outcomes has not been established. Studies to evaluate house-dust mite and cockroach exposure have shown that the prevalence of sensitization and subsequent development of asthma are linked[71-73]. Exposure to cockroach allergen, for example, a major allergen in inner-city dwellings, is an important cause of allergen sensitization, a risk factor for the development of asthma[74]. In addition, allergen exposure can promote the persistence of airway inflammation and likelihood of an exacerbation.

Respiratory infections

During infancy, a number of respiratory viruses have been associated with the inception or development of the asthma. In early life, respiratory syncytial virus (RSV) and parainfluenza virus in particular, cause bronchiolitis that parallels many features of childhood asthma[75,76]. A number of long-term prospective studies of children admitted to hospital with documented RSV have shown that approximately 40 percent of these infants will continue to wheeze or have asthma in later childhood[76]. Symptomatic rhinovirus infections in early life also are emerging as risk factors for recurrent wheezing.

On the other hand, evidence also indicates that certain respiratory infections early in life—including measles and even RSV[77] or repeated viral infections (other than lower respiratory tract infections)[78,79] - can protect against the development of asthma. The "hygiene hypothesis" of asthma suggests that exposure to infections early in life influences the development of a child's immune system along a "non-allergic" pathway, leading to a reduced risk of asthma and other allergic diseases. Although the hygiene hypothesis continues to be investigated, this association may explain observed associations between large family size, later birth order, daycare attendance, and a reduced risk of asthma[6,78].

The influence of viral respiratory infections on the development of asthma may depend on an interaction with atopy. The atopic state can influence the lower airway response to viral infections, and viral infections may then influence the development of allergic sensitization. The airway interactions that may occur when individuals are exposed simultaneously to both allergens and viruses are of interest but are not defined at present.

In the past decade, novel culture-independent techniques of microbial identification have expanded upon our understanding of the abundance and diversity of microbial cells on and within the human body, collectively referred to as *the microbiome*. Infant microbiota is initially uniform across various body sites, differentiating in subsequent days and weeks into site-specific communities[80]. The constitution of the lung microbiome is determined by three factors: microbial immigration, microbial elimination and the relative reproduction rates of its members[81] (Figure 3). Any alteration of the lung microbiome detected in disease states must be attributable to some combination of these three factors. Active cigarette smoking appears to alter the microbial constitution of the upper airways[82]. Two important studies have studied the composition of the lung microbiome in patients with asthma as compared to healthy controls[83,84]. Hilty et al. compared the microbiome of oral, nasal and BAL specimens of patients with asthma to that of patients with Chronic Obstructive Pulmonary Disease and healthy controls[83]. Among asthmatics, the authors found increased frequency of *Proteobacteriae* and decreased frequency of *Bacteroidetes* when compared to controls. This relative

increase in *Proteobacteriae* was driven by *Haemophilus*, *Moraxella* and *Neisseria* species.

Subsequently, Huang et al. compared the lung microbiota (obtained bronchscopically using protected specimen brushes) of 65 poorly-controlled asthmatics with that of 10 control subjects and found both increased bacterial burden and bacterial diversity among the asthmatic subjects[84]. They confirmed the increased relative abundance of *Proteobacteriae* among asthmatics, and found a positive correlation between the presence of numerous species and the severity of bronchial hyperresponsiveness. Greater diversity was seen among patients who derived benefit in bronchial hyperresponsiveness when administered clarithromycin, one of the rare observations reported between lung microbiome constitution and a functional response to a clinical intervention.

In addition to the potential role that the lung microbiome may play in allergic disease of the airways (Figure 3), a complementary hypothesis is that perturbations in gastrointestinal microbiota composition due to antibiotic use and poor diet (low fiber, high sugar) in westernized areas have disrupted gastrointestinal microbiome-mediated mechanisms of mucosal tolerance.

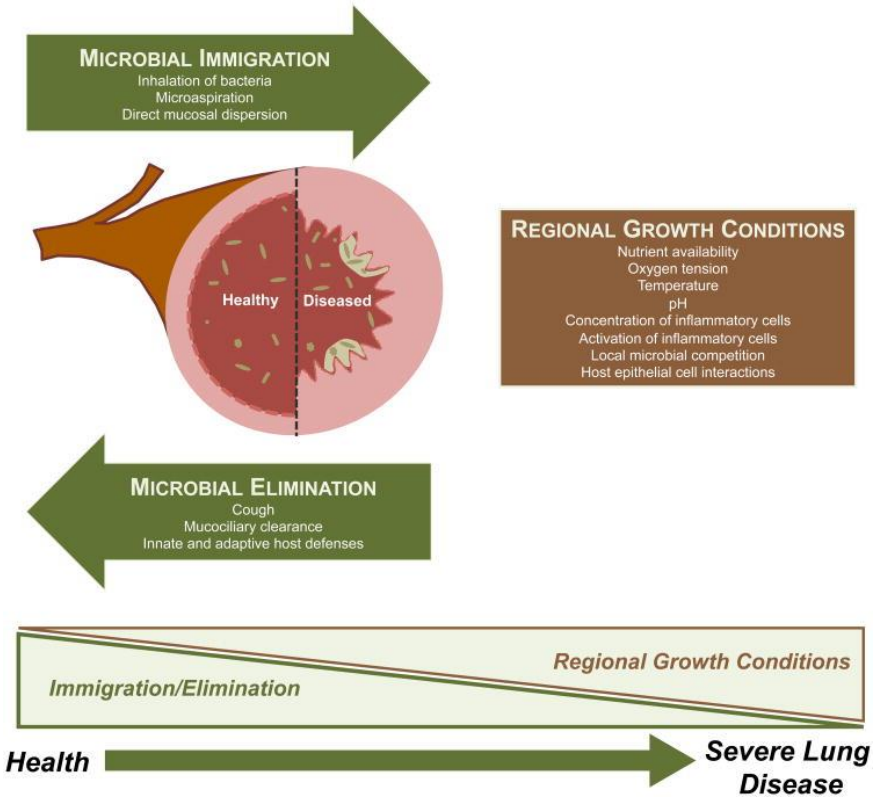


Figure 3: *Determinants of the respiratory microbiome*

1.5.5. Nutrition

The Mediterranean diet is considered a healthy diet and has been proven to be a protective factor against allergic diseases in most of the studies performed in children[85]. Numerous studies were done to study the effect of the adherence to this diet on asthma. Antonogeorgos et al. found that adherence to the Mediterranean diet was negatively related to asthma symptoms[86].

Although there have been several nutritional studies assessing single nutrients instead of assessing dietary patterns, the single food approach may fail to account for interactions between nutrients. Indeed, people eat meals consisting of a variety of foods with combined nutrients, not just isolated foods. Furthermore, Nagel *et al*. studied food categories in relation with asthma and wheezing in a multicenter study (ISAAC phase 2) of more than 50,000 school children aged between 8 and 12 years old. Fruit intake was associated with a low prevalence of current wheezing in both affluent and non-affluent countries while the consumption of fish in affluent countries and of cooked green vegetables in non-affluent countries was associated with a lower prevalence of current wheezing and asthma[87]. Eating fast food three or more times per week was associated with a 39% increased risk of severe asthma in adolescents and 27% increased risk among children, as well as an increased risk of severe rhinoconjunctivitis and severe eczema[88]. The results of that study suggest that fast food consumption may be contributing to the increasing prevalence of asthma, rhinoconjunctivitis, and eczema in adolescents and children. The authors postulated some possible mechanisms to explain the relationship between fast food consumption and asthma and allergic disease, which may involve higher concentrations of saturated fatty acids, trans fatty acids, sodium, carbohydrates, and sugar in fast foods, as well as preservatives that may modulate immune reactions[88].

Similar results were found with Barror R et al.[89] who concluded that “high fat, sugar and salt” dietary patterns (positively correlated with pastry, chocolate and sweet desserts, candies, salty snacks, chips, fruit juices, soft drinks and alcoholic beverages consumption at snacks) was associated with asthma prevalence and current severe asthma, while "fish, fruit and vegetables" dietary patterns (positively correlated with fish, vegetables and fruit intake at

meals) was negatively associated with current medicated asthma, after adjustment for confounders[89].

1.5.6. Toxics

Some toxics (alcohol, pesticides, medication intake and detergents) have been associated with increased asthma in children; the role of alcohol consumption during pregnancy in triggering asthmatic responses in the child at birth has not been well described. One study showed that approximately one third of asthmatic outpatients reported a worsening of asthma symptoms after alcohol consumption[90]. Another study showed that alcoholic drinks, and particularly wines, appear to be important triggers for asthmatic responses, possibly attributable to the sensitivity to the sulfite additives[91] and yeast in wines[92]. Children of parents working with pesticides may be exposed from occupational sources (storing working equipment in the house, contamination of clothes)[93-96]. Residing near pesticide treated areas or in agricultural regions, or having home and yard treated with pesticides also contribute to children exposure[95-99]. Direct indoor application of pesticides contaminates the house and exposes its occupants to volatile ingredients and residues. Salameh et al. also found that exposure to pesticides was associated with chronic respiratory symptoms and asthma in children[100]. Domestic use of cleaning products, in particular, those in spray form, has been also suggested as a risk factor for asthma[101,102]. Moreover, an association has been found between in utero exposures to several xenobiotics and increased risk of asthma. The literature is replete with evidence of a relationship between prescribed medications' intake by the mother during pregnancy and asthma in children[103-105]. While we know that exposures to toxics are common during pregnancy among Lebanese women[106], in utero and young childhood exposures to these toxics have not been fully assessed in Lebanon. A previous pilot study revealed that waterpipe smoking and alcohol intake during pregnancy, recurrent otitis and humidity at home seem to be significantly correlated with asthma in children[21].

In summary, our understanding of asthma pathogenesis and underlying mechanisms now includes the concept that gene-by-environmental

interactions are critical factors in the development of airway inflammation and eventual alteration in the pulmonary physiology that is characteristic of clinical asthma.

A summary of the risk factors and the direction of the association can be found in Table 1 below:

Table 1: *Summary of the risk factors associated with asthma, with the direction of the association.*

Factor	Direction of the association
Dust	Increase
Mold	Increase
Animal hair allergies	Increase
Pollen	Increase
Pollutants	Increase
Parental history of asthma	Increase
Smoking (cigarette, waterpipe)	Increase
Pesticides	Increase
Detergents	Increase
Alcohol	Increase
Respiratory infections	Increase
Mediterranean diet	Decrease

1.6. Asthma control

According to international guidelines, the primary goal of asthma management is to achieve and maintain asthma control defined as 'no daytime symptoms, no limitations of daily activities, no nocturnal symptoms or awakening, no need for reliever treatment, normal or near-normal lung function results[107] and thus reduce the risk of life-threatening exacerbations and long-term morbidity[108-111]. Nonetheless, in everyday practice, asthma remains poorly controlled in a large proportion of patients[112-115]. Previous findings have recognized the profits and advantages of good asthma control on a variety of consequences such as reduced loss of work/school days, a normal and even better quality of life, and reduced risk of exacerbations[116]. Furthermore, several other impacts on children may also be associated with uncontrolled asthma such as a reduced daily activity and a negative impact on cognitive and intellectual functions[116]. In an attempt to facilitate this assessment, several simple and easy to use tests have been developed such as the Asthma Control Test (ACT)[117], the Test for Respiratory and Asthma Control in Kids (TRACK)[118] and the Childhood ACT (C-ACT)[119]. The ACT is intended

to be used for patients 12 years and above[120], while the C-ACT should be used for patients 4-11 years of age[119]. The C-ACT and ACT are 7- and 5-item questionnaires, which assess asthma control (e.g., symptom frequency) over the prior week[119,120]. Since the various tests use the same symptoms of asthma (day and night symptoms, limitation of activities and use of rescue medication), the results of these tests are assumed to correlate to some extent with each other and with the GINA definition of asthma control[121]. A study comparing the C-ACT and the ACT tests showed a good agreement between them when detecting poor asthma controlled, as compared to the GINA criteria[122].

Asthma symptoms are influenced by the children's level of perception and the children's daily activities, including sports and social life events and activities. Hence, physical activity is one of the most important causes of symptoms and reliever use in children[123,124]. Furthermore, the risk of future disease- and treatment-related complications, including exacerbations, accelerated decline in pulmonary function, and adverse effects of drugs, should also be considered[107].

On the other hand, multiple socioeconomic and environmental factors contribute to the exacerbation of asthma symptoms. Among these factors, we have the sustainable exposure to triggers and lower educational status[125,126]. One of the most important triggers that the child might be exposed to is tobacco smoking. In particular, household cigarette smoke exposure was the single most significant factor in predicting poor control according to McGhan et al[127]. In fact, each hour per week of smoke exposure increased the likelihood of poor control by 33%[127].

2. OBJECTIVES

The first study was conducted in France based on a large French cohort, which objective was to characterize wheezing phenotypes found in infants between two months and one year of age, and identify risk factors associated with these phenotypes in a large French birth cohort at the age of 1 year, and identify risk factors associated with these phenotypes in a large French birth cohort.

The second study's objective was to evaluate the associations between caregiver-reported use of medications, alcohol, cigarette and/or waterpipe, and exposure to pesticides/detergents during pregnancy and childhood-onset asthma in Lebanon and to

validate the Arabic version of the Asthma Control Test in Lebanese asthmatic children in Lebanon and identify risk factors that might affect the asthma control in these children (4 accepted publications)[128-131].

3. METHODS

3.1. Study 1

3.1.1. Study design and population

A representative random sample of mothers from maternity hospitals throughout France was established. The target population consisted of every one in 50 children born in 2011 in French maternity units [132]. After a written informed consent was obtained, medical records of the mother were consulted. The mother then answered a general questionnaire about the health of the baby and mental, social, family, and environmental exposures at age one. Follow-up is planned until age 18. The children were selected to represent all seasons of the year, having been born between April 1-4, June 27 - July 4, September 27 - October 4, and November 28 - December 5, 2011. The exclusion criteria were: prematurity, childbirth under 18 years old, and no response to the questionnaire after two months. Mothers with multiple pregnancies with more than two children and those unable to give informed consent in one of the languages in which the information and consent forms were translated were also excluded.

Before the study began in 2011, a pilot study started in 2006-2007 in a small cohort (n=470) to test the different parts of the study, and the questionnaires. Questions showing poor completion rates or that were not well understood by the participants were removed or corrected. Before the study, a training course was organized for the investigators (questionnaire, filters inside the questionnaire). Investigators traveled to maternity units and undertook the study in person with the parents. Initially, 18 322 children including 289 pairs of twins were enrolled in the study at birth. Among the 18,322 selected families who gave their consent, 281 eventually refused to participate, leaving 18,041 families in the study. The children were followed up at two months of age and then again at one year. At two months, trained investigators

interviewed the parents in a face to face interview at home. When the child reached one year old, parents answered a standardized questionnaire through a telephone conversation conducted by specially trained professionals (phone-platforms currently involved in health studies in France, by the French institute of statistics (INSEE)). By the time of the phone interview, 4270 participants had been lost during the follow-up, leaving a total of 14059 children included in the present analysis (figure 4).

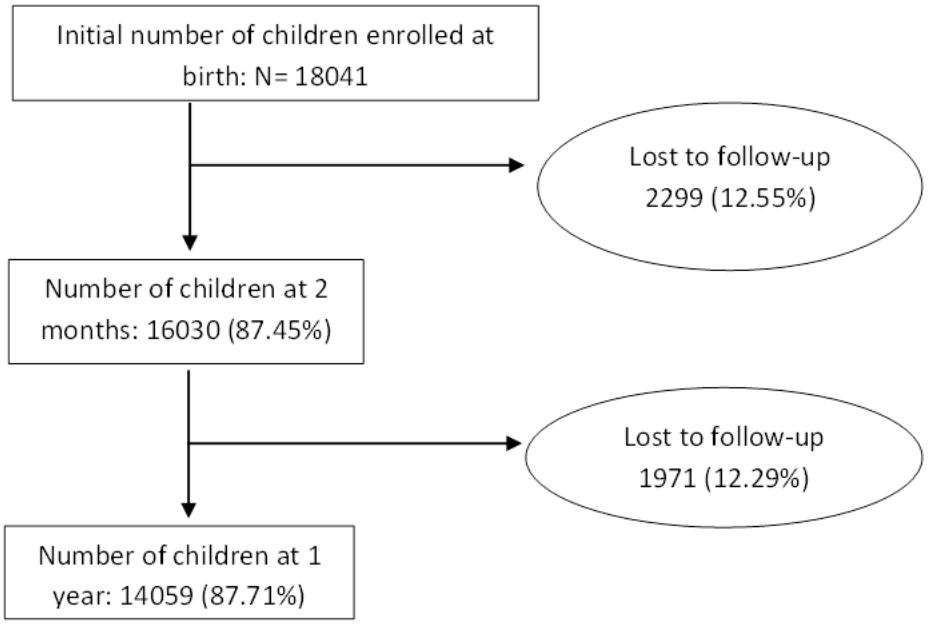


Figure 4: *Flow chart*

3.1.2. Wheezing phenotypes

Four groups were defined: non-wheezers (no current wheezing symptoms at both two months and one year old), intermittent (current wheezing symptoms at two months but no wheezing at one year), persistent (current wheezing at two months and at one year) and incident (no current wheezing at two months but wheezing at one year). Wheezing at two months was defined by a positive answer yes to the question "Does your child currently have wheezing or whistling in the chest?"[133]. Wheezing at one year was defined by a positive answer to the question "Does your child ever have wheezing or whistling in the chest?"

3.1.3. Risk factors

The questionnaire assessed the sociodemographic characteristics (age, gender, region, number of rooms and number of persons living in the house, level of education for both parents), type of delivery, Apgar scores at one and five minutes respectively, mother's previous pregnancies, and family history of asthma in parents and siblings of the child and other potential risk factors of asthma (heating system used inside the house, dampness inside the house, work done during pregnancy in the house, presence of pets in the house, child's history of recurrent otitis, rash history of the child, bronchiolitis, bronchitis episodes, and breastfeeding). Information concerning parental allergies was recorded by questions about family history of eczema, asthma, eczema, and rhinitis (hay fever) for both parents and siblings. Finally, environmental exposure to toxic substances was considered: smoking during pregnancy, passive smoking, occupational and domestic pesticide exposure, and the use of cleaning products. Respiratory symptoms at two months were taken into account. The presence of coughing was ascertained by an affirmative answer to the question: "Has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?" To know whether the child had respiratory problems, the following questions were used: "Has your child had any sign of respiratory distress?" and "At present does your child have any sign of respiratory distress?". To investigate the presence of excess bronchial secretions, the following questions were used: "Has your child had an excess of bronchial secretion or phlegm?" and "At present are you noticing that your child has an excess of bronchial secretion or phlegm?". A question was further asked if the child had ever been diagnosed with a bronchitis, and whether a doctor had prescribed medications, and a list of medications by class was proposed, to the parents.

3.1.4. Ethical approval

Each parent gave written informed consent at the maternity unit. Every level of the project and each procedure was monitored by the National Council for Statistical Information (CNIS) and approved by the French Data Protection Authority (CNIL), in conjunction with the Consultative Committee for Data

Processing in Health Research (CCTIRS), which assesses the scientific relevance of health projects, properly conducted from start to finish. Each parent retains the right to withdraw his/her child at any point during the study.

3.1.5. Statistical analysis

Data analysis was performed by SPSS software, version 23. Two-sided statistical tests were used to test the association of each respiratory symptom at two months across all four wheezing groups; the Chi-2 test for dichotomous or multinomial qualitative variables, with Fisher's exact test whenever appropriate. Regarding multivariate analysis, backward logistic regressions were performed by taking into account the variables in the bivariate analysis that showed a p-value <0.10[134,135], which included recommended covariates (such as maternal asthma, smoking, and educational level of the mother used as a proxy for socio-economical status). Educational level of the mother was categorized into 3 categories (low, intermediate and high level). Number of siblings was categorized into 0 (reference), 1, 2 and "3 or more" siblings. Several logistic regressions were conducted taking the dependent variables as follows: (1) intermittent vs persistent wheezing, (2) non-wheezers vs persistent wheezers and (3) non-wheezers vs incident wheezers.

3.2. Study 2

After conducting the study to assess risk factors associated with the different wheezing phenotypes in French infants, we conducted the second study in Lebanon in order to assess the association of these risk factors and asthma in Lebanese children. In addition, we aimed at validating the Asthma Control Test in Arabic in order to help clinicians use it in their practice.

3.2.1. Study design

This case-control study was conducted between December 2015 and April 2016. In addition to cases (asthmatic) and controls (healthy), a third group of participants (undiagnosed / probable asthma) was defined as the presence of respiratory symptoms (wheezing, cough, excess bronchial secretions, respiratory distress), but without a physician diagnosis of asthma.

3.2.2. Participants' characteristics

Controls were chosen using a sample of healthy Lebanese students, from schools in all districts of Lebanon, including children from different socioeconomic levels. Directors of the schools were contacted to take the permission to enter classrooms to distribute the questionnaires. Children were then given the questionnaire to be filled at home by their parents after a parental written informed consent. Classification into a control (healthy child) requires a double absence of a diagnosis of a respiratory disease by a physician and absence of respiratory symptoms (wheezing, cough, dyspnea).

As for cases, they were taken mainly (85%) from a specialized center for the treatment of asthma in children, which provides free services to children with respiratory diseases from all areas of the country. Children came to the center either as new patients or for follow-up visits on their asthma symptoms, and not for any other reason. After the administration's approval, the questionnaire was distributed in the Asthma Center to asthmatic children's parents after a written informed consent was obtained. Classification into the diagnosed asthma group was defined as the child having asthma-related symptoms (chronic wheezing, cough, and dyspnea), as well as an affirmative answer to the question "Have your doctor ever told you that your child has asthma?". We note that some asthmatic children encountered in schools and fullfilling the case criteria were also enrolled in the study as cases (15%); this allowed an increase in the sample size and the power of the study.

A third group of participants that had a state of "probable asthma" was suggested for children in schools, having chornic respiratory symptoms but no physician confirmation of asthma diagnosis. They were neither cases nor controls. "Probable asthma" was thus defined as the presence of one of the following symptoms: a recurrent wheezing during the day, the evening, the night, the whole day or at exercise, a recurrent cough during the day, the evening, the night, the whole day or at exercise, a history of more than one dyspnea plus wheezing episode treated by a doctor.

Children with diagnosed asthma and those with probable asthma constituted the mixed group of children with "respiratory problem". Finally, no matching was done for cases and controls regarding any variable.

3.2.3. Questionnaire and variables

A self-administered questionnaire adapted to local Arabic language (the native language of the country) from the standardized and validated American Thoracic Society chronic respiratory disease questionnaire, was used[136]. The same conditions were applied for questionnaires for all participants, to evaluate the diagnosis of asthma and respiratory symptoms. The standardized International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was translated into Arabic and back translated into English to ensure the accuracy of questions[137]. Questions regarding wheezing and night cough without having a cold were also taken from the ISAAC questionnaire[137].

This questionnaire assessed the socio-demographic characteristics, including age, gender, region, the number of rooms and the number of persons living in the house, the level of education for both parents, the family history of asthma, and other known risk factors of asthma (i.e. the heating system used at home, child history of recurrent otitis, humidity inside the house defined as molds seen on the house's walls, the presence of pets at home, if the child went to a daycare, breastfeeding).

Questions about smoking or alcohol intake during pregnancy and during breastfeeding, the kind of smoking or alcohol along with the quantity were included, in addition to the use of any prescribed medication during pregnancy or lactation, occupational, regional, local, and domestic pesticides exposures and cleaning products use. For pesticide exposure, information was recorded using the following questions: i.e. ''Have you ever used pesticides in your work?'' ''Have you ever used pesticides out of your work (for house or garden treatment…)?'' ''Do you live in a region heavily treated by pesticides?'' ''Do you live in the proximity of a heavily treated field by pesticides?'' along with the duration of exposure during work and the number of times the house or the garden get sprayed by pesticides per week or per year. Active smoking was determined by several questions (i.e. number of daily cigarettes, weekly waterpipes smoked, other nictotine/tobacco use), categorizing subjects in non-smokers or current smokers. Passive smoking will be characterized by the number of smokers at home.

Detergents use was determined by questions about who uses these products at home, the type of detergents and if there is any mixture of these products or not (the use of 2 or more detergents simultaneously). Education level was quantified according to the number of years of studying. Information about the heating system used at home, the presence of an air conditioner and a dehumidifier, the presence of humidity or mold at home as seen on walls, the child's history of recurrent otitis, tonsillectomy, cardiac problems, premature birth, and kindergarten were also recorded.

The validated ACT questionnaire in Arabic was sent to us by Professor Elizabeth Juniper (Department of Clinical Epidemiology and Biostatistics, McMaster University) to be used in our study. We decided to choose to use the ACT in our study since the purpose of the study is to check asthma control in all school children from all ages; we could not use the childhood version of this test for children aged more than 11 years. Furthermore, children's parents would be answering the test questions for younger children (4-11 years).

The asthma control questionnaire was composed of 6 questions, asking about the frequency of awakening at night because of the disease (0 for never and 7 unable to sleep because of asthma), the severity of the symptoms upon waking up the next morning (0 for no symptoms and 7 for very severe symptoms), the limitations of the activity due to asthma during the last month (0 for no limitation of activity and 7 for severe limitation), the frequency of shortness of breath (0 for never and 7 for very high frequency) and wheezing (0 for never and 7 for all the time), as well as the number of puffs of a short-acting bronchodilator the patient had to use in the last week because of the disease (0 for never and 7 for more than 16 puffs most of the days)[138]. The answers varied between 0 and 7, with 0 being the answer to no bothering or no symptoms at all and 7 being the answer to very severe symptoms. In addition, the percentage of Forced Expiratory Volume (%FEV) was recorded by a staff member from the Asthma Center, which was categorized into 6 categories according to the original ACT[138]: category 0 refers to an FEV>95%, category 1 between 90-95%, category 2 between 80-89%, category 3 between 70-79%, category 4 between 60-69%, category 5 between 50-59% and category 6 for less than 50%.

3.2.4. Ethical aspect

The Institutional Review Board of the Lebanese University Faculty of Pharmacy waived the need for an approval based on the facts that it was an observational study that respected participants' autonomy and confidentiality and induced minimal harm to them.

3.2.5. Sample size calculation

Using the Gpower 3.1.9.2 software for the calculation of the minimal sample size needed for our study, with a 1-β = 0.8, a proportion p2= 0.05 (5% reflects the percentage of the mothers that smoked during pregnancy in the healthy children group) according to the pilot study that was done last year[139] and considering a ratio of 4 controls for every case and an odds ratio OR=2, the results showed that we need 296 cases versus 1184 controls[140].

3.2.6. Statistical analysis

Data analysis was performed using SPSS software, version 23. Percentages were shown for qualitative variables, while means and standard deviation were given for quantitative variables.

Two sided statistical tests were used to compare between group percentages and Student's t test for quantitative variables of normal distribution and homogeneous variances. Moreover, two multivariable backward logistic regressions were applied taking healthy children versus asthmatics and healthy children versus those with respiratory symptoms (probable asthma) as the dependent variables respectively; the independent variables taken into the multivariable analysis were those that showed a p-value < 0.2 in the bivariate analysis. To confirm the asthma control questionnaire construct validity in the Lebanese population, a factor analysis was launched for the 6 items of the questionnaire, using the principal component analysis technique, with a promax rotation since the extracted factors were found to be significantly correlated. The Kaiser-Meyer-Olkin measure of sampling adequacy and Bartlett's test of sphericity were ensured to be adequate. The retained number of factors corresponded to Eigen values higher than one. Moreover,

Cronbach's alpha was recorded for reliability analysis for the total score and for subscale factors. A p-value <0.05 was considered significant.

4. RESULTS

4.1. Study 1

During the two-month old survey, 146 families quit the study and 29 children were born outside the dates of inclusion, reducing the total to 17,866 families. There were also 1295 non-responders, as well as 541 referent parents who did not answer the questions on the respiratory health of their children, leaving a final total of 16,030 children.

4.1.1. Prevalence of wheezing and other respiratory symptoms at two months and one year

Prevalence of wheezing was higher at one year (6.5 percent to 27.5 percent). The prevalence of nocturnal coughing increased between two months and one year (25.5 percent to 67.5 percent), and the same trend was also observed for those with signs of respiratory distress (from 29.1 percent to 38.8 percent) and excess bronchial secretions from (34.7 percent to 65.1 percent) respectively (p<0.0001 for all variables) (Table 2).

Table 2: *Prevalence of wheezing and other respiratory symptoms at two months and one year in ELFE cohort.*

	Two months N= 15896	One year N= 14059	p-value
Wheezing			<0.0001
No	14870 (93.5%)	10188 (72.5%)	
Yes	1026 (6.5%)	3871 (27.5%)	
Nocturnal cough			<0.0001
No	11845 (74.5%)	4565 (32.5%)	
Yes	4050 (25.5%)	9494 (67.5%)	
Respiratory distress sign			<0.0001
No	11275 (70.9%)	8599 (61.2%)	
Yes	4620 (29.1%)	5460 (38.8%)	
Excess bronchial secretion			<0.0001
No	10375 (65.3%)	4904 (34.9%)	
Yes	5519 (34.7%)	9155 (65.1%)	

A significantly higher proportion of children with wheezing at two months and nocturnal coughing at two months were lost to follow-up, whereas a

significantly higher proportion of children with maternal eczema and paternal hay fever were still participating at the one-year mark. There was no significant difference in patients lost to follow-up in terms of gender, signs of respiratory distress or excess bronchial secretion in the child at two months, maternal history of asthma or hay, and paternal history of asthma and eczema (Table 3).

Table 3: *Comparison between children at one year and children lost to follow-up in ELFE cohort.*

	Included (N=14059)	Lost to follow-up Yes (N=4270)	Total (N=18329)	p-value
Gender				
Male	7112 (51%)	2169 (52.4%)	9281 (51.3%)	0.227
Female	6813 (48.9%)	1966 (47.5%)	8779 (48.5%)	
Wheezing in child at two months	830 (6.1%)	196 (8.7%)	1026 (6.5%)	<0.001
Nocturnal cough in child at two months	3437 (25.2%)	613 (27.3%)	613 (27.3%)	0.037
Respiratory distress sign in child at two months	3954 (29%)	666 (29.6%)	4620 (29.1%)	0.537
Excess bronchial secretion in child at two months	4729 (34.7%)	790 (35.1%)	5519 (34.7%)	0.653
Maternal asthma	1629 (12%)	239 (11%)	1868 (11.8%)	0.43
Maternal eczema	2063 (15.1%)	280 (12.9%)	2343 (14.8%)	0.01
Maternal hay fever	2758 (20.2%)	400 (18.5%)	3158 (20%)	0.156
Paternal asthma	1477 (12.8%)	129 (11.6%)	1606 (12.6%)	0.414
Paternal eczema	1049 (9.1%)	93 (8.3%)	1142 (9%)	0.717
Paternal hay fever	2256 (19.5%)	159 (14.2%)	2415 (19%)	<0.001

4.1.2. Wheezing phenotypes at one year

Children with no symptoms (controls) accounted for 77.2 percent, 2.1 percent had had wheezing at two months but no wheezing at one year (remission), 2.4 percent had persistent wheezing, while 18.3 percent had incident wheezing at one year.

4.1.3. Maternal and infant factors associated with wheezing phenotypes

A significantly higher proportion of boys (59.5 percent) had incident wheezing than girls (40.5 percent) ($p<0.0001$). A significantly higher proportion of children who were delivered by spontaneous labor (69.9 percent) had higher incident wheezing than those delivered by triggering childbirth (11 percent)

or caesarean section (19.2 percent) (p=0.016). A significantly higher proportion of children from mothers with previous pregnancies (71 percent) had incident wheezing than those from mothers without previous pregnancies (29 percent) (p<0.0001). Having a nocturnal cough, signs of respiratory distress, and excess bronchial secretions at two months was associated with wheezing at one year (persistent wheezing) (p<0.0001 for all three variables). A significantly higher proportion of children who had their own room were persistent wheezers or incident wheezers than those who did not have their own room (p<0.0001). Children with maternal atopy (i.e. asthma, eczema, or hay fever) were at a higher risk of persistent or incident wheezing. Smoking during pregnancy was significantly associated with persistent wheezing (p=0.001 and p<0.0001) respectively (Tables 4 and 5). No significant difference was found between the different wheezing phenotypes and respiratory infections during the first year of life, i.e. bronchitis, anti-asthmatics medication, and antibiotics taken by the child during the first year (data not shown).

Table 4: *Parental risk factors associated with wheezing phenotypes in ELFE cohort*

Variable	Controls (N=14151)	Remission (N=393)	Persistent (N=437)	Incident (N=3348)	p-value
Maternal history of asthma (yes)	1006 (10.6%)	52 (13.3%)	80 (18.3%)	491 (14.7%)	<0.0001
Maternal history of eczema (yes)	1369 (14.5%)	60 (15.3%)	69 (15.8%)	565 (16.9%)	0.01
Maternal history of hay fever (yes)	1827 (19.3%)	76 (19.4%)	112 (25.7%)	743 (22.3%)	<0.0001
Paternal history of asthma (yes)	956 (11.9%)	39 (12.7%)	47 (13.7%)	435 (15.1%)	<0.0001
Maternal smoking before pregnancy (yes)	4049 (41.4%)	175 (44.8%)	216 (49.8%)	1437 (43.3%)	0.001
Maternal smoking during pregnancy (yes)	1698 (17.4%)	85 (22%)	110 (25.5%)	657 (19.8%)	<0.0001
Type of delivery					0.016
Spontaneous labor	6577 (68.5%)	262 (68.2%)	306 (72.2%)	2283 (69.9%)	
Triggered childbirth	1269 (13.2%)	45 (11.7%)	42 (9.9%)	358 (11%)	
Caesarean	1753 (18.3%)	77 (20.1%)	76 (17.9%)	626 (19.2%)	
Breastfeeding (yes)	2322 (49.1%)	93 (44.9%)	127 (52.7%)	818 (48.7%)	0.426
Previous pregnancies (yes)	6271 (63.8%)	276 (70.6%)	347 (79.8%)	2365 (71%)	<0.0001

Mother's professional and social category					0.002
Employed	351 (3.6%)	14 (3.6%)	13 (3%)	106 (3.2%)	
Unemployed	1817 (18.6%)	55 (14.1%)	69 (15.9%)	642 (19.3%)	
Housewife	2229 (22.8%)	79 (20.2%)	91 (21%)	816 (24.6%)	
Retired	3988 (40.7%)	165 (42.2%)	196 (45.3%)	1332 (40.1%)	
Father's professional and social category					0.113
Employed by temporary agency	2349 (23.8%)	81 (20.6%)	85 (19.5%)	861 (25.7%)	
Part-time / temporary	1423 (14.4%)	53 (13.5%)	61 (14%)	453 (13.5%)	
Paid internship	3527 (35.7%)	147 (37.4%)	167 (38.2%)	1202 (35.9%)	
Subsidized employment	1255 (12.7%)	59 (15%)	66 (15.1%)	401 (12%)	
All others**	1327 (13.4%)	53 (13.5%)	58 (13.3%)	431 (12.9%)	
Detergent use in house					0.126
Yes	2793 (28.3%)	99 (25.2%)	127 (29.1%)	1002 (29.9%)	
Use of toiletry products of animal origin					0.146
Yes	2223 (22.5%)	93 (23.7%)	90 (20.6%)	696 (20.8%)	

* Results are expressed as frequency (percentage) or mean ± Standard deviation.
** includes contract without time limit, contract with time limit, apprenticeship contract, seasonal contract, other type of fixed-term employment.

Table 5: *Infant risk factors and previous symptoms associated with wheezing phenotypes in ELFE cohort*

Variable	Controls (N=14151)	Remission (N=393)	Persistent (N=437)	Incident (N=3348)	p-value
Apgar score at one minute	9.42 ± 1.34	9.37 ± 1.34	9.32 ± 1.65	9.42 ± 1.34	0.407
Apgar score at five minutes	9.89 ± 0.55	9.87 ± 0.54	9.81 ± 0.77	9.88 ± 0.53	0.068
Nocturnal cough at two months (yes)	1954 (20.6%)	242 (61.6%)	338 (77.3%)	903 (27%)	<0.0001
Respiratory distress signs at two months (yes)	2343 (24.7%)	279 (71%)	360 (82.4%)	972 (29%)	<0.0001
Excess bronchial secretions at 2two months (yes)	2863 (30.2%)	294 (74.8%)	377 (86.3%)	1195 (35.7%)	<0.0001
Gender					<0.0001
Male	4661 (47.7%)	208 (53.6%)	266 (61.1%)	1977 (59.5%)	
Female	5119 (52.3%)	180 (46.4%)	169 (38.9%)	1345 (40.5%)	
Presence of bronchiolitis in child at two months (yes)	120 (5.5%)	43 (37.4%)	71 (43%)	41 (4.9%)	<0.0001

Rash on child's skin at two months (yes)	1375 (14.5%)	74 (18.8%)	95 (21.7%)	559 (16.7%)	<0.0001
Child receiving treatment for reflux (yes)	1854 (19.6%)	96 (24.4%)	131 (30%)	768 (22.9%)	<0.0001
Child has own room (yes)	6496 (68.7%)	235 (60.4%)	253 (58.3%)	2155 (64.9%)	<0.0001

* Results are expressed as frequency (percentage) or mean ± Standard deviation.
** includes contract without time limit, contract with time limit, apprenticeship contract, seasonal contract, other type of fixed-term employment.

4.1.4. Risk factors and wheezing phenotypes: multivariable analysis

A first logistic regression taking remission and persistent wheezing as dependent variables showed that previous pregnancies (OR=1.683) and a nocturnal cough at two months (OR=1.795) were associated with an increased risk of persistent wheezing. Having a respiratory distress (OR=1.548) and excess bronchial secretions (OR=1.441) at two months was associated with persistent wheezing respectively (trend not significant) (Table 6).

A second logistic regression taking persistent and incident wheezing as dependent variables showed that Apgar score at birth was associated with incident wheezing (OR=1.233). Having a nocturnal cough (OR=1.766), respiratory distress (OR=1.725), and excess bronchial secretions (OR=1.695) at two months was significantly associated with persistent wheezing respectively. Furthermore, maternal eczema was associated with incident wheezing (OR=1.539), and maternal smoking before pregnancy was associated with persistent wheezing (OR=1.274) (Table 6; Figure 5).

Comparing persistent wheezing to controls showed that nocturnal cough (OR=5.318), respiratory distress (OR=3.933), and bronchial secretions (OR=3.601) at two months, as well as maternal smoking during pregnancy (OR=1.536), were significantly associated with persistent wheezing.

Lastly, the use of detergents in the child's house (OR=1.121), smoking during pregnancy (OR=1.152), and a child's eczema/rash on the skin (OR=1.145) at two months, were significantly associated with incident wheezing compared to controls (Table 7).

Table 6 : *Risk factors and wheezing phenotypes using multivariable analysis in ELFE cohort*

Logistic regression 1 taking remission* and persistent wheezing patients as dependent variable.				
Variables	**p-value**	**ORa**	**Confidence interval**	
Mother's previous pregnancies	.008	1.683	1.148	2.467
Nocturnal cough at two months	.003	1.795	1.212	2.657
Respiratory distress sign at two months	.060	1.548	.982	2.442
Excess bronchial secretion at two months	.067	1.441	.975	2.130
Logistic regression 2 taking persistent* and incident wheezing patients as dependent variable.				
Variables	**p-value**	**ORa**	**Confidence interval**	
Apgar score at five minutes (>7)	.049	1.233	1.001	1.519
Rash on child's skin at two months	.094	.758	.548	1.048
Nocturnal cough at two months	<0.0001	.234	.173	.316
Respiratory distress sign at two months	<0.0001	.275	.195	.387
Excess bronchial secretion at two months	<0.0001	.305	.208	.449
Maternal history of eczema	.020	1.539	1.071	2.212
Maternal smoking before pregnancy	.016	.726	.561	.941

* Reference group

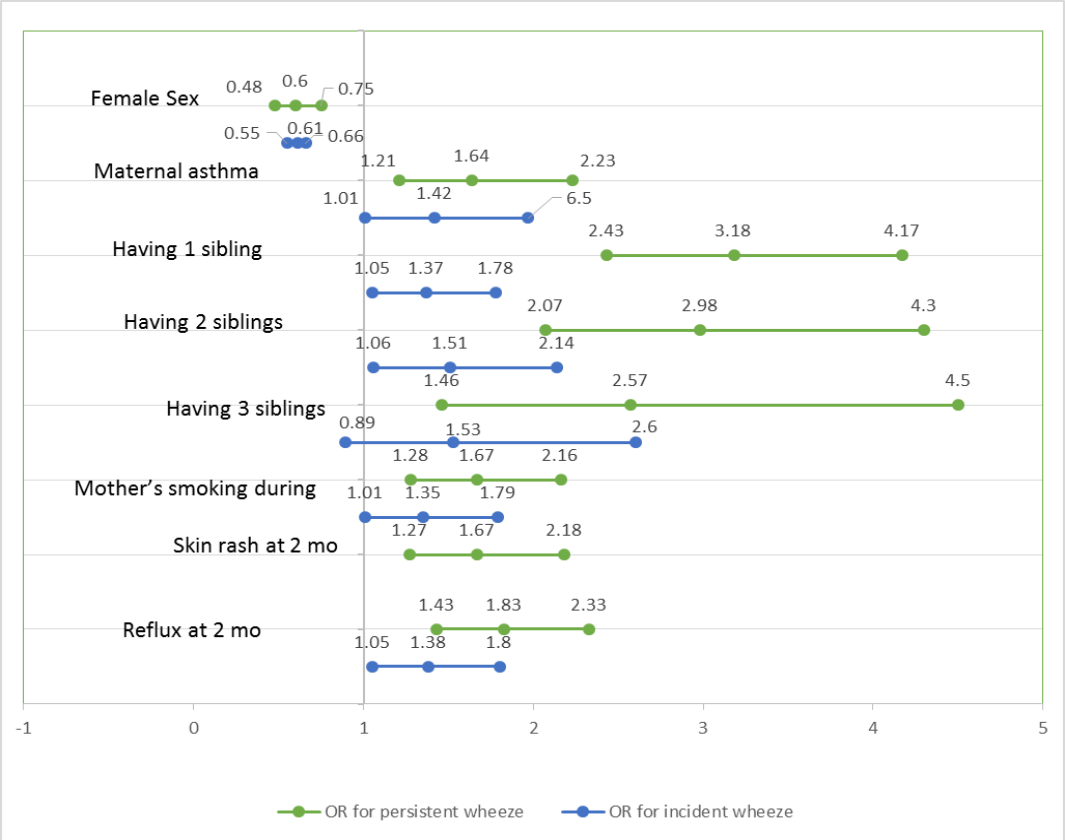
Table 7 : *Risk factors and wheezing phenotypes using multivariable analysis in ELFE cohort*

Logistic regression 3 taking controls* and persistent wheezing patients as dependent variable.				
Variables	**p-value**	**ORa**	**Confidence interval**	
Gender (boys* vs girls)	.001	.653	.511	.835
Previous pregnancies	<0.0001	1.949	1.441	2.635
Nocturnal cough at two months	<0.0001	5.318	3.990	7.087
Respiratory distress sign at two months	<0.0001	3.933	2.843	5.442
Excess bronchial secretion at two months	<0.0001	3.601	2.501	5.183
Child receiving reflux treatment	.003	1.500	1.146	1.963
Child having a cold at first medical consult	.015	1.414	1.069	1.871
Child has own room	.042	.769	.597	.990
Maternal smoking during pregnancy	.003	1.536	1.152	2.048
Logistic regression 4 taking controls* and incident wheezing patients as dependent variable.				
Variables	**p-value**	**ORa**	**Confidence interval**	
Gender (boys* vs girls)	<0.0001	.616	.564	.674
Previous pregnancies	<0.0001	1.400	1.269	1.544
Use of detergents in child's house	.023	1.121	1.016	1.237
Rash on child's skin at two months	.029	1.145	1.014	1.292
Nocturnal cough at two months	<0.0001	1.278	1.152	1.418
Child receiving reflux treatment	.002	1.183	1.063	1.318
Maternal history of asthma	.000	1.420	1.244	1.621
Maternal history of eczema	.057	1.126	.996	1.272
Paternal history of asthma	<0.0001	1.311	1.154	1.489
Child has own room	.013	.883	.800	.974
Maternal smoking during pregnancy	.018	1.152	1.024	1.295

* Reference group

** compared to working mothers

***Variables entered in the models: maternal history of asthma, eczema and hay fever, paternal history of asthma, maternal smoking before pregnancy, maternal smoking during pregnancy, type of delivery, Apgar score at 5 minutes, nocturnal cough at 2 months, respiratory distress signs at 2 months, excess bronchial secretions at 2 months, gender, previous pregnancies, presence of bronchiolitis in the child at 2 months, rash on the child's skin at 2 months, reflux treatment in the child, child has his own room, mother and father's professional and social categories, detergent use in the child's house, use of toiletry products of animal origin.



*P-value for having 3 siblings for incident wheeze=0.119; all other p-values are significant (p<0.05).

Figure 5: *Different factors associated with persistent and incident wheezing at one year compared to non-wheezers.*

4.2. Study 2

4.2.1. Sociodemographic and socio economic characteristics

Out of 1680 questionnaires distributed in schools, 1503 (89.46%) were collected back from parents of the children aged between 3-16 years old. There were missing values in our results since not all questions were answered by all parents. The sample included 527 children having respiratory problems (35.1%; 95% CI 32.65-37.48), with 300 having diagnosed asthma (20%; 95% CI 17.937-21.983) and 227 having probable asthma (15.1%; 95% CI 13.29-16.92) respectively.

Table 8 summarizes the sociodemographic and socioeconomic factors. The results showed that our sample included 1,503 children aged 3-16 years (51.6% boys and 48.4% girls). 55.9% of these children had 1 or 2 person(s)

living with them. Parents' university education was 35.8% for fathers and 55.1% of the mothers.

Table 8: *Sociodemographic and socioeconomic factors associated with the health status (asthma and probable asthma)*

Disease status/ Factors	Total number of subjects N=1503 (100%)	Healthy Subjects N=976 (64.9%)	Probable Asthma N=227 (15.1%)	Diagnosed Asthma N=300 (20%)	P-value
Age (in years)	9.92 ± 3.34	9.12 ± 3.43	8.83 ± 3.60	8.83 ± 3.60	<0.0001
Age category					<0.0001
3-6 years	331 (22%)	163 (16.8%)	68 (30.2%)	100 (33.8%)	
7-10 years	337 (22.4%)	208 (21.5%)	56 (24.9%)	73 (24.7%)	
11-13 years	640 (42.6%)	459 (47.4%)	80 (35.6%)	101 (34.1%)	
> 14 years	181 (12%)	138 (14.3%)	21 (9.3%)	22 (7.4%)	
Gender					<0.0001
Male	775 (51.6%)	476 (48.8%)	113 (49.8%)	186 (62.4%)	
Female	726 (48.3%)	500 (51.2%)	114 (50.2%)	112 (37.6%)	
District					<0.0001
Beirut	348 (23.3%)	241 (24.7%)	46 (20.3%)	61 (20.4%)	
Mount Lebanon	637 (42.4%)	416 (42.6%)	100 (44.1%)	121 (40.5%)	
North	189 (12.6%)	98 (10%)	33 (14.5%)	58 (19.4%)	
South	25 (1.7%)	4 (0.4%)	0 (0%)	21 (7%)	
Bekaa	303 (20.2%)	217 (22.2%)	48 (21.1%)	38 (12.7%)	
Education father					0.027
Low *	133 (8.8%)	70 (7.2%)	27 (12.1%)	36 (12%)	
Intermediate **	820 (54.6%)	545 (56.3%)	112 (50%)	163 (54.5%)	
High ***	538 (35.8%)	353 (36.5%)	85 (37.9%)	100 (33.4%)	
Education mother					0.012
Low *	89 (5.9%)	49 (5%)	10 (4.4%)	30 (10.1%)	
Intermediate **	577 (38.4%)	383 (39.4%)	81 (35.8%)	113 (38%)	
High ***	828 (55.1%)	539 (55.5%)	135 (59.7%)	154 (51.9%)	
Number of persons per room					0.844
[0-1]	542 (36.3%)	354 (36.5%)	80 (35.6%)	108 (36.4%)	
[1-2]	849 (56.9%)	550 (56.7%)	133 (59.1%)	166 (55.9%)	
More than 2	101 (6.8%)	66 (6.8%)	12 (5.3%)	23 (7.7%)	

* Low level of education: Education for 8 years or less
** Intermediate level of education: Education for more than 8 years but no university degree
*** High level of education: university degree

4.2.2. Bivariable analysis

The bivariate analysis results for the factors that might be associated with the respiratory problem are summarized in table 9. A significantly greater proportion of asthmatic children (37%) as compared to healthy ones (4.2%) had more respiratory infections (p<0001), a higher number of smokers at

home (46% vs 44.7%, p=0.019), played in the dust (26% vs 8.1%, p<0.001), had respiratory problems or eczema before the age of 2 years (p<0.001 for both variables), had recurrent otitis (35.2% vs 16.7%, p<0.001) and heart problems (2.7% vs 0.6%, p=0.01), had humidity in the house as seen on the walls (26% vs 11%, p<0.001), parental history of eczema (p=0.001), asthma (p<0.001) or rhinitis (p<0.001). A higher proportion of children with respiratory disease (14.5%) as compared to the healthy ones (8.5%) had pets at home (p=0.021).

Table 9: *Bivariable analysis for the factors associated with the health status*

Disease status/ Factors	Total number of subjects N=1503 (100%)	Healthy Subjects N=976 (64.9%)	Probable Asthma N=227 (15.1%)	Diagnosed Asthma N=300 (20%)	P-value
Respiratory infections					<0.0001
No	1324 (88.1%)	935 (95.8%)	200 (88.1%)	189 (63%)	
Yes	179 (11.9%)	41 (4.2%)	27 (11.9%)	111 (37%)	
Number of smokers at home					0.913
0	828 (55.1%)	540 (55.3%)	126 (55.5%)	162 (54%)	
1 or more	675 (44.9%)	436 (44.7%)	101 (44.5%)	138 (46%)	
Pets in the house					0.021
No	1358 (90.4%)	893 (91.5%)	194 (85.5%)	271 (90.3%)	
Yes	145 (9.6%)	83 (8.5%)	33 (14.5%)	29 (9.7%)	
Play in dust					<0.0001
No	1318 (87.7%)	897 (91.9%)	199 (87.7%)	222 (74%)	
Yes	185 (12.3%)	79 (8.1%)	28 (12.3%)	78 (26%)	
Play outside					0.032
No	786 (52.3%)	530 (54.3%)	119 (52.4%)	137 (45.7%)	
Yes	717 (47.7%)	446 (45.7%)	108 (47.6%)	163 (54.3%)	
Play on carpet					<0.0001
No	425 (28.3%)	314 (32.2%)	45 (19.8%)	66 (22%)	
Yes	1078 (71.7%)	662 (67.8%)	182 (80.2%)	234 (78%)	
Pulmonary problems forbidding daily activities					<0.0001
No	1351 (89.9%)	962 (98.6%)	197 (86.8%)	192 (64.2%)	
Yes	151 (10.1%)	14 (1.4%)	30 (13.2%)	107 (35.8%)	
Humidifier at home					<0.0001
No	1190 (79.2%)	781 (80%)	158 (69.6%)	251 (83.7%)	
Yes	313 (20.8%)	195 (20%)	69 (30.4%)	49 (16.3%)	
Respiratory problems before 2 years of age					<0.0001
No	1334 (88.8%)	947 (97%)	212 (93.4%)	175 (58.3%)	
Yes	169 (11.2%)	29 (3%)	15 (6.6%)	125 (41.7%)	
Eczema before the age of 2 years ago					<0.0001
No	1404 (93.4%)	933 (95.6%)	210 (92.5%)	261 (87%)	

Yes	99 (6.6%)	43 (4.4%)	17 (7.5%)	39 (13%)	
Recurrent otitis					<0.001
No	1186 (79%)	813 (83.3%)	180 (79.3%)	193 (64.8%)	
Yes	315 (21%)	163 (16.7%)	47 (20%)	105 (35.2%)	
Heart problems					0.01
No	1487 (98.9%)	970 (99.4%)	225 (99.1%)	292 (97.3%)	
Yes	16 (1.1%)	6 (0.6%)	2 (0.9%)	8 (2.7%)	
Premature birth					0.005
No	1400 (93.1%)	922 (94.5%)	211 (93%)	267 (89%)	
Yes	103 (6.9%)	54 (5.5%)	16 (7%)	33 (11%)	
Humidity at home seen on walls					<0.0001
No	1273 (84.7%)	869 (89%)	182 (80.2%)	222 (73%)	
Yes	230 (15.3%)	107 (11%)	45 (19.8%)	78 (26%)	
Child sent to the kindergarten					0.066
No	863 (57.4%)	581 (59.5%)	118 (52%)	164 (57.4%)	
Yes	640 (42.6%)	395 (40.5%)	109 (48%)	136 (45.3%)	
Smoking father					0.099
No	828 (55.5%)	561 (58%)	113 (50.4%)	154 (51.5%)	
Yes	661 (44.3%)	406 (41.9%)	111 (49.6%)	144 (48.2%)	
Parents respiratory problems					<0.0001
No	1327 (88.3%)	892 (91.4%)	208 (91.6%)	227 (75.9%)	
Father	92 (6.1%)	43 (4.4%)	12 (5.3%)	37 (12.4%)	
Mother	67 (4.5%)	33 (3.4%)	7 (3.1%)	27 (9%)	
Parents with rhinitis problems					<0.0001
No	1290 (85.9%)	887 (90.9%)	185 (81.5%)	218 (72.9%)	
Father	94 (6.3%)	49 (5%)	17 (7.5%)	28 (9.4%)	
Mother	87 (5.8%)	24 (2.5%)	18 (7.9%)	45 (15.1%)	
Both	31 (2.1%)	16 (1.6%)	7 (3.1%)	8 (2.7%)	
Parents history of eczema					0.001
No	1268 (84.4%)	852 (87.3%)	179 (78.9%)	237 (79.3%)	
Father	113 (7.5%)	61 (6.3%)	27 (11.9%)	25 (8.4%)	
Mother	84 (5.6%)	42 (4.3%)	16 (7%)	26 (8.7%)	
Both	37 (2.5%)	21 (2.2%)	5 (2.2%)	1 (3.7%)	
Parental asthma history					<0.0001
No	1270 (84.6%)	859 (88%)	201 (88.5%)	210 (70.2%)	
Father	124 (8.3%)	69 (7.1%)	15 (6.6%)	40 (13.4%)	
Mother	70 (4.7%)	28 (2.9%)	7 (3.1%)	35 (11.7%)	
Both	38 (2.5%)	20 (2%)	4 (1.8%)	14 (4.7%)	
Maid at home					0.051
No	1095 (72.9%)	722 (74%)	171 (75.3%)	202 (67.3%)	
Yes	408 (27.1%)	254 (26%)	56 (24.7%)	98 (32.7%)	
Reflux					<0.0001
No	1379 (91.7%)	940 (96.3%)	197 (86.8%)	242 (80.7%)	
Yes	124 (8.3%)	36 (3.7%)	30 (13.2%)	58 (19.3%)	

Table 10 summarizes the bivariate analysis performed concerning the exposure of pregnant mothers and infancy to active smoking, alcohol, prescribed medication intake and detergent mixing. Taking any medication during pregnancy (p<0.001) or breastfeeding (p=0.001), alcohol during lactation (p=0.028), presence of a person at home working with pesticides (p<0.001), the child living in an area with pesticide use (p<0.001), pesticide use in the interior of the house (p<0.001) were all significantly associated positively with the asthma status.

Table 10: *Association between exposure to toxics during pregnancy and infancy and the health status*

Disease status/ Factors	Total number of subjects N=1503 (100%)	Healthy Subjects N=976 (64.9%)	Probable Asthma N=227 (15.1%)	Diagnosed Asthma N=300 (20%)	P-value
Any drug used by the mother during pregnancy					<0.0001
No	1317 (87.7%)	890 (91.2%)	186 (82.7%)	241 (80.3%)	
Yes	184 (12.3%)	86 (8.8%)	39 (17.3%)	59 (19.7%)	
Any drug used by the mother during breastfeeding					0.001
No	1461 (97.2%)	957 (98.1%)	222 (97.8%)	282 (94%)	
Yes	42 (2.8%)	19 (1.9%)	5 (2.2%)	18 (6%)	
Active smoking mother during pregnancy					0.122
No	1433 (95.3%)	938 (96.1%)	215 (94.7%)	280 (93.3%)	
Yes	70 (4.7%)	38 (3.9%)	12 (5.3%)	20 (6.7%)	
Kind of smoking during pregnancy					0.172
Non smoker	1433 (95.3%)	938 (96.1%)	215 (94.7%)	280 (93.3%)	
Cigarette	47 (3.1%)	26 (2.7%)	7 (3.1%)	14 (4.7%)	
Waterpipe	19 (1.3%)	10 (1%)	3 (1.3%)	6 (2%)	
Active smoking mother during breastfeeding					0.289
No	1436 (95.5%)	938 (96.1%)	216 (95.2%)	282 (94%)	
Yes	67 (4.5%)	38 (3.9%)	11 (4.8%)	18 (6%)	
Kind of smoking during breastfeeding					0.212
Non smoker	1436 (95.5%)	938 (96.1%)	216 (95.2%)	282 (94%)	
Cigarette	45 (3%)	25 (2.6%)	5 (2.2%)	15 (5%)	
Waterpipe	19 (1.3%)	11 (1.1%)	5 (2.2%)	3 (1%)	
Alcohol during pregnancy					0.515
No	1469 (97.7%)	957 (98.1%)	221 (97.4%)	291 (97%)	
Yes	34 (2.3%)	19 (1.9%)	6 (2.6%)	9 (3%)	
Alcohol drinking during breastfeeding					0.028
No	1476 (98.2%)	962 (98.6%)	218 (96%)	296 (98.7%)	
Yes	27 (1.8%)	14 (1.4%)	9 (4%)	4 (1.3%)	
Person at home using pesticides					<0.0001
No	1187 (79%)	770 (78.9%)	154 (67.8%)	263 (87.7%)	

Yes	316 (21%)	206 (21.1%)	73 (32.2%)	37 (12.3%)	
Child living in a region with pesticide use					<0.0001
No	1428 (95%)	947 (97%)	215 (94.7%)	266 (88.7%)	
Yes	75 (5%)	29 (3%)	12 (5.3%)	34 (11.3%)	
Child living near a prairie/field treated with pesticides					0.065
No	1247 (83%)	826 (84.6%)	182 (80.2%)	239 (79.7%)	
Yes	256 (17%)	150 (15.4%)	45 (19.8%)	61 (20.3%)	
Pesticides use at home					<0.0001
No	854 (56.8%)	586 (60%)	105 (46.3%)	163 (54.3%)	
Yes	649 (43.2%)	390 (40%)	122 (53.7%)	137 (45.7%)	
Active smoking father					0.099
No	828 (55.5)	561 (58%)	113 (50.4%)	154 (51.5%)	
Yes	661 (44.3%)	406 (41.9%)	111 (49.6%)	144 (48.2%)	
Father smoking kind					0.054
Non smoker	836 (55.6%)	566 (58%)	114 (50.2%)	156 (52%)	
Cigarette	439 (29.2%)	285 (29.2%)	68 (30%)	86 (28.7%)	
Waterpipe	199 (13.2%)	110 (11.3%)	38 (16.7%)	51 (17%)	
Cigarette & waterpipe	27 (1.8%)	14 (1.4%)	6 (2.6%)	7 (2.3%)	
Detergent mixing					0.004
No	1277 (85%)	849 (87%)	190 (83.7%)	238 (79.3%)	
Yes	226 (15%)	127 (13%)	37 (16.3%)	62 (20.7%)	

4.2.3. Multivariable analysis

At first, a multivariable analysis was performed taking children with diagnosed asthma as the dependent variable as compared to all other children. This analysis showed that the boys had a significantly higher risk of having asthma by 36.4% (ORa = 0.646, CI 0.489-0.854, p = 0.002); increasing the age of one year significantly increased the risk of asthma in 62.5% (ORa = 1.625, CI 1.034-2.554, p = 0.035); children living in North and South Lebanon had an increased risk of asthma in 62.5% and 13.6 times respectively (ORa = 1.625, CI 1.034-2.554, p = 0.035 and ORa = 13.65, CI 3.698-50.385; p <0.001 respectively). The fact that the child lives in an area that has frequent use of pesticides increased the risk of asthma significantly by more than 3 times (ORa = 3.307, CI 1.848-5.918, p <0.001 respectively). Smoking waterpipe by the mother during pregnancy increased the risk of asthma in children 6 times (ORa = 6.11; CI 1.244-30.008; p = 0.026), while cigarette smoking by the

mother during lactation increased that risk by more than 3 times (ORa = 3.44; CI 1.024-11.554; p = 0.046) (table 11).

A second multivariable analysis performed on children with a respiratory problem (probable asthma or diagnosed asthma) as dependent variable and compared to totally healthy children showed that boys have a significantly higher risk of respiratory disease 23.1% as compared to girls (ORa = 0.769, CI 0.613-0.965, p = 0.023); children living in North and South Lebanon have a significant risk of respiratory disease 61.4% and 6 times respectively (ORa = 1.614, CI 1.087-2.396, p = 0.018 and ORa = 6.335, CI 1.778-22.574; p = 0.004 respectively). Living in an area with a frequent use of pesticides or pesticide in the house significantly increased the risk of respiratory diseases in children 2.5 times and 29.3% respectively (ORa = 2.48; CI 1.459-4.217; p = 0.001 and ORa = 1.293, CI 1.029-1.626, p = 0.028 respectively). Taking any medicine during pregnancy and the paternal positive smoking status significantly increased the risk of respiratory diseases in children by 69.7% and 26.5% (ORa = 1.697, CI 1.206-2.387, p = 0.002 and ORa = 1.265, CI 1.01-1.584; p = 0.04) respectively (table 11).

Table 11: *Multivariable analysis*

Regression 1: Diagnosed asthma versus healthy children as dependent variable				
Factors	**P-value**	**ORa**	**Confidence Interval**	
Gender	0.002	0.646	0.489	0.854
Age	0.035	1.625	1.034	2.554
District*				
Mount Lebanon	0.723	1.067	0.747	1.523
North	0.035	1.625	1.034	2.554
South	<0.0001	13.65	3.698	50.385
Bekaa	0.215	0.743	0.466	1.188
Person using pesticides who lives with the child at home	0.001	0.5	0.337	0.744
Child living in a region sprayed with pesticides	<0.0001	3.307	1.848	5.918
Any drug during pregnancy	0.058	1.462	0.988	2.164
Smoking kind during pregnancy**				
Cigarettes	0.785	0.841	0.243	2.911
Waterpipe	0.026	6.11	1.244	30.008

Smoking kind during breastfeeding**				
Cigarettes	0.046	3.44	1.024	11.554
Waterpipe	0.086	0.154	0.018	1.303
* District as compared to Beirut taken as a reference				
** Smoking during pregnancy or breastfeeding as compared to non-smoking mothers				

Regression 2: Respiratory disease versus healthy children as dependent variable				
Factors	**P-value**	**ORa*****	**Confidence Interval**	
Gender*	0.023	0.769	0.613	0.965
Age	<0.0001	0.892	0.86	0.924
District **				
Mount Lebanon	0.326	1.159	0.864	1.556
North	0.018	1.614	1.087	2.396
South	0.004	6.335	1.778	22.574
Bekaa	0.851	1.035	0.722	1.485
Child living in a region sprayed with pesticides	0.014	2.709	1.219	6.020
Pesticides use at home	0.016	1.668	1.100	2.527
Any drug use during pregnancy	0.002	2.242	1.355	3.711
Smoking father (cigarette versus non-smoker)	0.012	1.618	1.114	2.351
Alcohol during breastfeeding	0.007	9.961	1.894	52.384
* Male gender as a reference ** District as compared to Beirut taken as a reference *** ORa= Adjusted Odds Ratio				

4.2.4. Asthma control questionnaire validity checking

Out of all the items asked in the questionnaire, all variables could be extracted from the list, with no items that over-correlated to each other (r>0.9), having a low loading on factors (< 0.3) or because of a low communality (< 0.3).

The factor analysis for the asthma control questionnaire was run over the sample of healthy individuals and asthmatic patients (Total n = 1503). The asthma control items converged over a solution of one factor that had an Eigenvalue over 1, explaining a total of 66.34% of the variance. A Kaiser-Meyer-Olkin measure of sampling adequacy of 0.900 was found, with a significant Bartlett's test of sphericity (P <0.001). Moreover, a high Cronbach's alpha was found for the full scale (0.959) (Table 12).

Table 12: *Factor analysis of the asthma control questionnaire in the Lebanese population**

Factor	Loading on factor
Waking up due to asthma during the night	.906
Bad asthma symptoms when waking up in the morning	.855
Limited activities because of asthma	.816
Experiencing shortness of breath due to asthma	.795
Number of times of wheeze due to asthma	.732
Average number of puffs of a SABA*	.628
FEV category**	.930

**SABA= Short Acting Beta Agonist*
*** FEV= Forced Expiratory Volume*
**** Cronbach's alpha= 0.959*

The mean FEV percentage was 85.96% ± 8.79% while the mean ACT score was 10.84 ± 7.13 among asthmatic children. The correlation between the full scale and FEV1 revealed a significant correlation between both items ($p<0.001$ and $r= -0.682$).

Table 13 displays the correlation factors between each item of the ACT scale and the whole scale. The correlation factors ranged between 0.710 for the limited activities item to 0.775 for the average number of puffs of SABA. To note that all factors were highly significantly correlated with the whole scale with a $p<0.001$ for all items.

Table 13: *Correlation factor of each item of the scale with the whole scale.*

Factor	Correlation factor	p-value
Wake up due to asthma	0.708	<0.001
Bad asthma symptoms when waking up	0.721	<0.001
Limited activities	0.710	<0.001
Shortness of breath from asthma	0.755	<0.001
Wheezing	0.759	<0.001
Average number of puffs of SABA*	0.775	<0.001

**SABA= Short Acting Beta Agonist*

4.2.5. Relationship between asthma control and FEV

We calculated the regression equation between the FEV1 and the whole scale. We obtained the equation:

ACT score= 50.49 – [(0.5*FEV)] with $r= -0.682$ and $p<0.001$ (figure 6). The better the FEV1 (higher scores), the better the asthma control (lower scores).

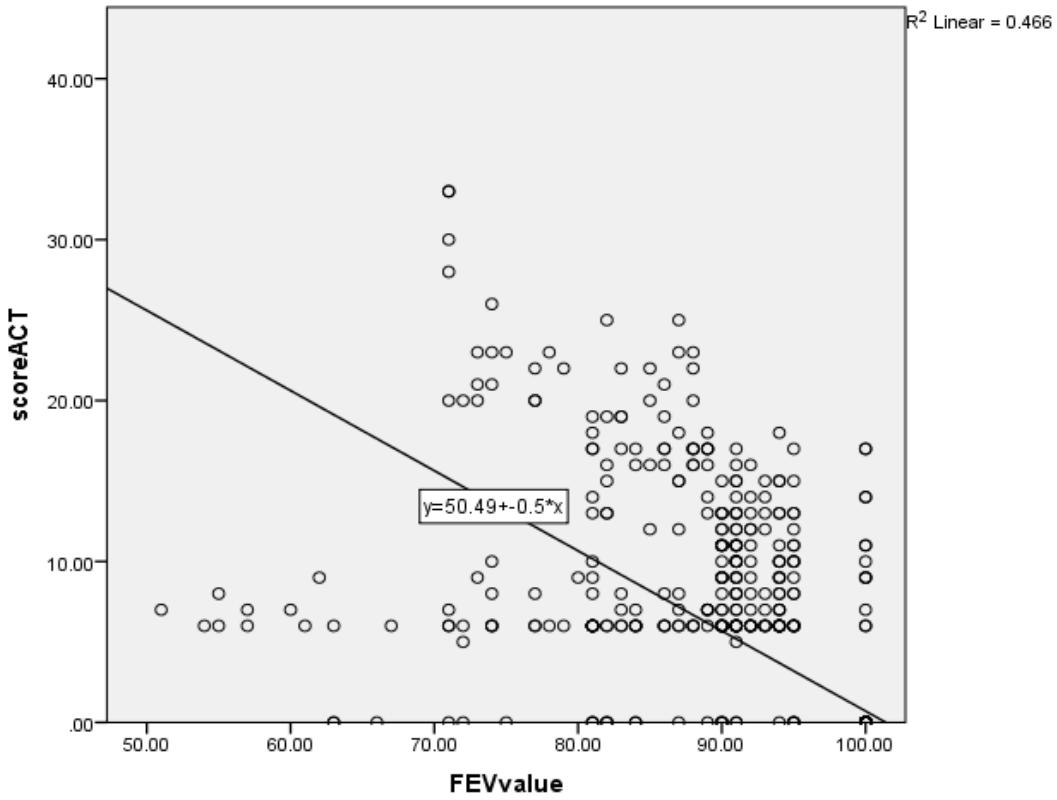


Figure 6: *Scatter plot of FEV value versus ACT score. R= -0.682 (R^2=0.466); p<0.001; ACT score= 50.49 – [(0.5*FEV)]*

Figure 7 shows the mean ACT score in the presence and absence of asthma symptoms (wheezing, allergy, cough or expectoration without flu). The results showed there was a significant difference in the mean ACT score in the absence or presence of all 4 symptoms (p<0.001 for all variables), with a lower ACT score (better control) in the absence of any of these symptoms.

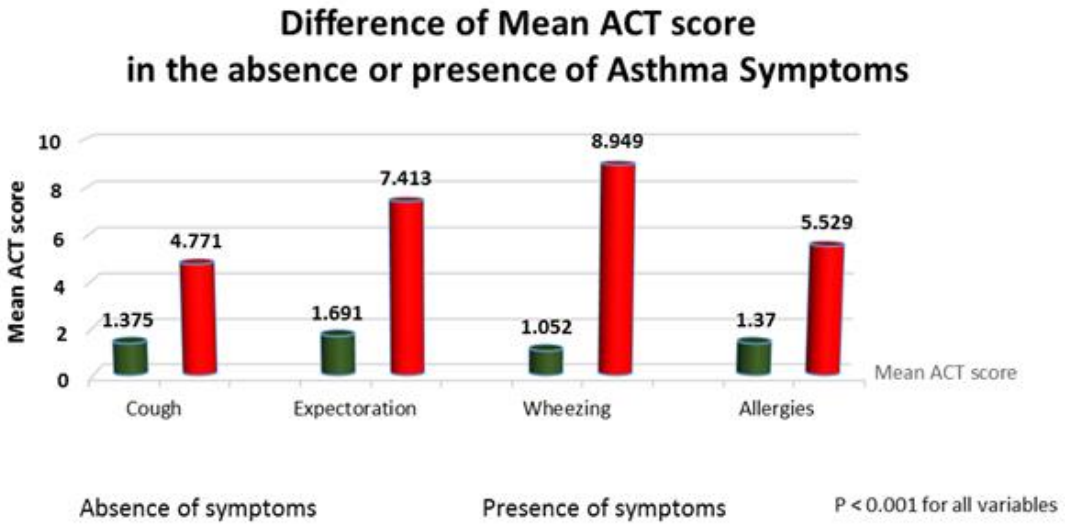


Figure 7: *Difference of mean ACT score in the absence or presence of asthma symptoms*

4.2.6. Multivariable analysis for asthma control as the dependent variable

Table 14 summarizes the results of the 2 stepwise linear regressions conducted on asthma control as dependent variable. The results of the first regression conducted on these asthmatic children, with the risk factors as independent variables showed that the low mother's educational level as well as the history of asthma in the mother and the father would significantly increase the risk of uncontrolled asthma by 1.862, 3.534 and 1.885 points respectively (p=0.001; Beta= 1.862; CI 0.766-2.958; p<0.001; Beta= 3.534; CI 2.324-4.744 and p<0.001; Beta= 1.885; CI 0.978-2.793 respectively). Cigarette smoking by the mother during breastfeeding, as well as waterpipe smoking by the mother during pregnancy, were both significantly associated with a lower asthma control by 2.105 and 2.325 points respectively (p=0.005; Beta= 2.105; CI 0.646-3.565 and p=0.041; Beta=2.325; CI 0.093-4.558 respectively). On the other hand, the high mother's level of education was significantly associated with more asthma control by 0.715 points (p=0.008; Beta= -0.715; CI -1.241- -0.189).

The second regression conducted, considering the risk factors and the treatment classes as independent variables, showed that treatment with a long-acting beta agonist combined with an inhaled corticosteroid (ICS), treatment with an ICS alone, treatment with a short-acting beta agonist, an inhaled anticholinergic or with a leukotriene inhibitor would significantly increase the asthma control by 11.20, 5.04, 3.02, 2.24 and 1.73 points respectively (p<0.001 for all variables) (table 3). In addition to that, the moderate and high mother's educational level would significantly increase the asthma control by 0.737 and 1.12 points respectively (p=0.024; Beta= -0.737; CI -1.375- -0.099 and p<0.001; Beta= -1.12; CI -1.747- -0.493 respectively). On the contrary, cigarette and waterpipe smoking by the mother during pregnancy would significantly increase the risk of uncontrolled asthma by 1.457 and 1.714 points respectively (p=0.001; Beta=1.457; CI 0.599-2.315 and p=0.013; Beta= 1.714; CI 0.363-3.065 respectively).

Table 14: *Linear regression with uncontrolled asthma as dependent variable*

Regression 1: Regression for risk factors alone on asthmatic children					
Factor	Unstandardized Beta	Standardized Beta	P-value	Confidence interval	
History of asthma in the mother	3.534	0.147	<0.001	2.324	4.744
Low mother's educational level	1.862	0.090	0.001	0.766	2.958
History of asthma in the father	1.885	0.105	<0.001	0.978	2.793
High mother's educational level	-0.715	-0.072	0.008	-1.241	-0.189
Cigarette smoking during breastfeeding	2.105	0.074	0.005	0.646	3.565
Waterpipe smoking during pregnancy	2.325	0.053	0.041	0.093	4.558
Regression 2: risk factors and treatment classes on asthmatic children					
Factor	Unstandardized Beta	Standardized Beta	P-value	Confidence interval	
Treatment with inhaled corticosteroids (ICS)	-5.041	.562	<0.001	4.762	5.321
Treatment with short-acting beta agonists	-3.027	.507	<0.001	2.843	3.210
Treatment with long acting beta agonists associated to ICS	-11.201	.309	<0.001	10.096	12.307
Treatment with inhaled anticholinergics	-2.247	.216	<0.001	1.930	2.564
Treatment with leukotriene inhibitors	-1.732	.160	<0.001	1.403	2.061
Cigarette smoking during pregnancy	1.457	.053	.001	.599	2.315
High mother's level of education	-1.120	-.112	<0.001	-1.747	-.493
Waterpipe smoking during pregnancy	1.714	.039	.013	.363	3.065
Moderate mother's level of education	-.737	-.072	.024	-1.375	-.099

*Variables entered in the model for regression 1: person working with pesticides that lives at home, low educational level of the mother, moderate educational level of the mother, high educational level of the mother, body mass index of the child, heart problems in the child, cigarette smoking during breastfeeding, waterpipe smoking during breastfeeding, cigarette smoking during pregnancy, waterpipe smoking during pregnancy, alcohol drinking during pregnancy, breastfeeding of the child, father history of asthma, mother history of asthma, both parents history of asthma.

**Variables entered in the model for regression 2: person working with pesticides that lives at home, low educational level of the mother, moderate educational level of the mother, high educational level of the mother, body mass index of the child, heart problems in the child, cigarette smoking during breastfeeding, waterpipe smoking during breastfeeding, cigarette smoking during pregnancy, waterpipe smoking during pregnancy, alcohol drinking during pregnancy, breastfeeding of the child, father history of asthma, mother history of asthma, both parents history of asthma, treatment with LABA + ICS, treatment with ICS alone, treatment with SABA, treatment with anti-leukotrienes, treatment with inhaled anti-cholinergics

5. DISCUSSION

5.1. Study 1

In this large ELFE cohort, we found a high prevalence of respiratory symptoms in early life. We also assessed different risk factors and respiratory symptoms associated with persistent wheezing at one year.

The percentage of children with respiratory symptoms at age two months and at one year old was higher compared to the Columbia Center for Children's Environmental Health (CCCEH) (20.4 percent at age one)[141] and the ALSPAC[142] cohorts (26 percent at 18 months old). Overall, only wheezing was considered as the main respiratory symptom, although coughing could also play a role[142]. A nocturnal cough, signs of respiratory distress, and excess bronchial secretion symptoms continued to increase from two months old to one year. To our knowledge, no other cohort has evaluated these three symptoms with the development of respiratory symptoms at age one. Time will reveal the association between each of these symptoms and asthma; at a later stage of these children's lives. However, other respiratory symptoms seem to be associated with all wheezing phenotypes compared to controls, confirming that these symptoms could be related to asthma or viral/bacterial infection. These other respiratory symptoms occurred before the age of two months, and it is very likely they occurred alongside the wheeze reported before two months. This would explain why these other respiratory symptoms strongly increase the likelihood of persistent wheezing, but also strongly increase the likelihood of remission. Both these outcomes, by definition, exist only in the presence of wheeze before two months, which was probably accompanied by other respiratory symptoms.

Maternal smoking was associated with persistent wheezing (from two months to one year) and incident wheezing at one year, in agreement with what was found in previous cohorts[143]. The association between maternal smoking and transient early wheezing may be mediated, at least in part, by narrower airways in the children of women who smoke[143]. Parental asthma is thought to influence the risk of asthma in children[144]. However, hereditary patterns are multifaceted with many important questions remaining unanswered, such as heredity effects at different ages[143,145], and the potential additional effect of having relatives with asthma. Our

results indicate that a mother's history of hay fever and paternal history of asthma were associated with an increased risk of persistent wheezing in children, corroborating previous findings146.

An Apgar score above seven was associated with incident compared to persistent wheezing. In fact, lower Apgar scores were reported to be associated with childhood asthma[147]. To our knowledge, papers that studied the association between the Apgar score and wheeze/asthma were done on preterm children. More research are needed to address this correlation in children born on term.

Furthermore, children with their own room had protection from both persistent wheezing and incident wheezing[148], suggesting that being in rooms with siblings increase the risk of viral infection or contamination.

The domestic use of cleaning products, in particular, those in spray form, has been suggested to be a risk factor for asthma [149]. Our results suggest an association between asthma symptoms and detergent use at home by the mother, in keeping with a cohort study conducted in adults [150] and another which suggested that cleaning personnel with asthma or asthma symptoms may be affected by non-reversible airway obstruction and non-eosinophilic inflammation [151]. This might be explained by the likelihood that mothers clean when their children are present at home with them, so the latter may be exposed to detergents for a considerable period of time during their life.

The relationship between gastroesophageal reflux disease (GERD) and asthma in children has been investigated, although the nature of the association (if any) between them is unclear[152]. A clinical study showed that GERD is highly predominant in children with asthma, with estimations reaching as high as 80 percent, but nearly half of the children were asymptomatic; a finding in agreement with ours[153].

Our findings are similar to those of Spycher et al who compared two birth cohorts and found three wheezing phenotypes[154], but different from those of the ALSPAC and PIAMA cohorts, in which six and five phenotypes were identified, respectively[155]. A recent latent class analysis including respiratory symptoms (wheeze, night cough, and rhinitis) and atopy in children aged 18 months from the Pollution and Asthma Risk Infant Study identified a mild, a non-atopic severe and an atopic severe phenotype, respectively[156]. At age one, we also identified a

transient wheezing phenotype consistent with the findings of Tucson[143], possibly viral or infection wheezing.

Wheezing in early life was usually associated with viral infections[157], however in this case the proportion of children still wheezing at age one suggested a chronic disease like asthma.

5.2. Study 2

This is a case-control study carried out on schoolchildren in all districts of the country to assess potential risk factors for asthma, respiratory diseases, and allergy, specifically evaluating the effect of exposure to toxic substances during pregnancy and infancy. This type of study has been done before showing similar results[137,158], however, the originality of the current study was the findings that WP smoking during pregnancy and cigarette smoking during lactation were both significantly associated with the asthma diagnosis in children.

A child living in an area where pesticides are used was significantly associated with both asthma diagnosis and respiratory diseases. A child living with a person that works with pesticides and/or living in a home where pesticides are used was significantly associated with asthma diagnosis and respiratory diseases respectively. Finally, age and gender were both significantly correlated with asthma diagnosis and respiratory diseases while the use of any prescribed medication during pregnancy and the father smoking cigarettes were both positively correlated with respiratory diseases.

We found that age was significantly associated with asthma or allergy but in significant correlation with probable asthma, in line with the observation made by Porsbjerg et al[159]. Living in South Lebanon was significantly associated with a higher risk of asthma and respiratory diseases as compared to all other districts, probably as a consequence of the bombardments during the war in 2006. This finding is opposite to the observation of Salameh et al. who found that living in the capital would predispose the child to more respiratory diseases[160]. However, we cannot exclude the fact that healthy families are more likely to leave conflicted zones than families with diseased members and thus the causal relationship be inverse. Diagnosis of asthma was more frequently done in males compared to females, similar to the results of Waked and Salameh[160] and as shown previously in

the literature that male sex is predominant in asthma population in the first decade[161,162].

5.2.1. Smoking

Our study did show a correlation between waterpipe smoking during pregnancy, cigarette smoking during breastfeeding and asthma on one hand and cigarette smoking in the father and respiratory diseases in children on another hand. This is the first study conducted in Lebanon that shows a positive correlation between waterpipe smoking during pregnancy and asthma in infancy. This could be explained by the fact that a low number of mothers consumed cigarettes during pregnancy maybe due to its known toxicity, while waterpipe's false conception[163] of safety in the Lebanese population induced a higher consumption, the effect of which was easily detected in our study. Our results showed, however, prominent effects for waterpipe but no significant results for cigarette smoking: These alarming results are to be confirmed by further larger scale studies. Our results were strengthened by other studies done by Neuman et al.[164] and Simons et al.[165], showing an increased risk for preschool wheeze and asthma among children exposed to cigarette smoke by their mothers during pregnancy and breastfeeding as well.

5.2.2. Alcohol

Alcohol consumption during lactation, but not during pregnancy, was significantly correlated with respiratory diseases in children. Our results were not in concordance with the results found by Magnus et al[166] that the low levels of alcohol exposure during pregnancy or lactation observed in the cohort study they conducted were not associated with increased risk of asthma[166]. Few studies assess the exposure to alcohol during pregnancy and breastfeeding and the risk of asthma in children, thus more specific studies would be needed for this purpose.

5.2.3. Pesticides, Detergents, Medication Intake

Occupational exposure to pesticides has been associated with respiratory symptoms and chronic respiratory diseases such as asthma[167]. The general

population is also exposed to pesticides by domestic use or accidental exposure. Non-occupational chronic respiratory indoor exposure can result in high annual cumulative doses and thus may aggravate or enhance asthmatic symptoms[168]. Child exposure to pesticides (either at home, or in an area surrounding his house, or by living with a person who works with pesticides) was significantly associated with both asthma and respiratory diseases in our study, similarly to the results of Salameh et al. that showed that chronic exposure to pesticides in children was associated with chronic respiratory symptoms and diseases, especially asthma[158].

On the other hand, domestic use of cleaning products, in particular, those in spray form, has been also suggested as a risk factor for asthma[149,169]. Our results did not show any correlation between asthma and detergent use at home by the mother or the maid in the multivariate analysis in opposite to what Vizcaya et al. suggested that cleaning workers with asthma or asthma symptoms are characterized by non-reversible airway obstruction and non-eosinophilic inflammation[151]. We hypothesize that mothers clean their home probably when the child is outside the house to avoid exposure; in this way, children may not be exposed to detergents for a long period of time during their life.

Furthermore, the results of this study did show a significant correlation between the use of prescribed medications during pregnancy with respiratory diseases and tended to significance with diagnosed asthma. This goes in line with many studies showing a positive relationship between prescribed medications intake by the mother during pregnancy and asthma in children[149,170,171]. Further researches might be needed to know the classes of medications that might be implicated in this disease.

5.2.4. Validation of the ACT scale

In the current study, we were able to validate the asthma control questionnaire, intended specifically for use among the Lebanese population. Results provided initial evidence supporting the reliability and validity of the scale as a screening instrument for asthma control in the Lebanese children. The one factor identified in the asthma control scale demonstrated good

psychometric properties, with excellent internal consistency for the scale. Thus, it can be used in the Lebanese population.

Another way to verify the reproducibility of the questionnaire was to use correlation coefficients, as the one proposed by Kirshner and Guyatt[172]. The correlation coefficients showed high correlation between each item of the ACT questionnaire and the disease.

The association between ACT score and asthma symptoms is pretty tight. In fact, Juniper et al. originally generated a list of ten symptoms that might be used by clinicians to assess the adequacy of asthma control, including 3 out of 4 symptoms (wheezing, cough, expectoration) assessed in our study[138]. However, the ACT includes the five highest scoring symptoms that most commonly reveal lack of control in the majority of patients, in addition to one question about beta 2 agonist use and another about FEV[138]. Our results showed that the presence of allergies was even related to a worse control of asthma, a factor that was not taken into consideration in Juniper's study. Furthermore, our results showed a strong correlation between the ACT and the severity of the disease as described by FEV1 value, similar to the results of Perez-Yarza et al. that also showed that patients with more severe symptoms and exacerbations had a worse ACT score, indicating a clear relationship between the ACT score and patients' clinical status[173]. These results are similar to those observed in an earlier study to develop and test an asthma control test for use in adult populations. In that study, the authors also found that the questionnaire discriminated well between patients with different degrees of symptom intensity and frequency[174].

Poor asthma control can result in distressing symptoms including chronic cough, persistent wheezing, annoying nighttime awakenings and difficulty in performing daily activities[175]. This will result in a higher emergency department visits and a higher number of hospitalizations and consequently a lower quality of life[52]. Moreover, patients with inadequately controlled asthma remain at a high risk of serious morbidity and mortality[176]. Despite adequate treatment, continuous exposure to risk factors would still jeopardize asthma control.

5.2.5. Modifiable risk factors associated with asthma control

Smoking

Constituents of tobacco smoke can cause loss of cilia along with a hypertrophy in the mucus gland in the upper airways. Thus, inflammation, epithelial changes, fibrosis and secretory congestion can occur in the peripheral airways, and alveoli are destroyed with loss of gas exchange surface area and airways flexibility. Indeed, vascular changes to the small arteries and capillaries of the bronchioles and the alveoli also occur[177]. Hence, the nicotine passes through the breast milk of the mother to the baby in an amount of nicotine more than double that transferred to maternal serum[178], and consequently inducing airway inflammation in non-asthmatic smokers without airflow obstruction compared with nonsmokers[179-182].

In our study, mother's waterpipe smoking during pregnancy and cigarette smoking during breastfeeding were associated with more uncontrolled asthma. Results were not significant for cigarette smoking during pregnancy though. Our new finding about waterpipe could be explained by the fact that a low number of mothers consumed cigarettes during pregnancy maybe due to its known toxicity[183], however restarted smoking after delivery. Waterpipe false conception of safety in the Lebanese population induced a higher consumption during pregnancy[163], the effect of which was easily detected in our study. To our knowledge, our study is the first to assess the effect of waterpipe smoking during pregnancy on asthma control in asthmatic children. These alarming results are to be confirmed by further larger scale studies.

Level of education

Low mother's level of education was significantly associated with a poor asthma control, in opposite to the higher educational level significantly associated with a better asthma control. Our results confirm the solid findings of multiple previous studies: it is plausible that parents with high literacy levels were likely to take an active role and intensively engage in the shared decision process, leading to an increase in their satisfaction with shared-decision making[184]. This implies that if physicians improve the interactions with their patient and assure a better patient's understanding for the asthma treatment plan, the likelihood of achieving good asthma control is high.

From another point of view, it is also credible that parents with a lower level of education are of lower socio-economic status, thus the poor asthma control could also be a result of poor housing, lack of access to good quality healthcare and/or lack of access to medication. In fact, Peters et al. identified low education and household income, as predictive factors of uncontrolled asthma[185]; these 2 factors were consistent and associated with asthma in other populations[186-189].

5.2.6. Non modifiable risk factors

On the other hand, some other non-modifiable factors such as the history of asthma in the mother and the father, would significantly increase the risk of uncontrolled asthma.

Parental history of respiratory disease

A history of asthma in either parent was significantly associated with more uncontrolled asthma in the child similar to the findings of Konradsen et al. [190]. There could be a genetic association with asthma related outcomes based on Kondarsen's study; this relationship needs however to be better defined. Another explanation for these findings is the "hygiene hypothesis". This hypothesis suggests that the young child's environment can be "too clean" to effectively challenge and promote the development of a mature immune system [21]. Parents with a history of asthma may exaggerate in their children's hygiene, which may give an inverse effect and lead to an increase asthma severity.

6. GENERAL DISCUSSION

These two studies were able to define, for the first time, 3 wheezing phenotypes at 1 year of age only, to demonstrate that waterpipe smoking during pregnancy, one of the environmental risk factors associated with an increased odds of asthma in childhood, and to validate the Arabic version of the Asthma Control Test to be used by clinicians in their daily practice for the assessment of asthma control in Lebanon. Early identification of pregnant women who smoke, and appropriate counselling and referral to smoking cessation services need to be intensified for women living in more disadvantaged

conditions. Health care professionals should spread awareness to parents in order to minimize these risk factors in children as much as possible.

Environmental factors seem to play a major role in the development of asthma symptoms in children. If simple environmental factors could be identified, this would allow for better prevention of the asthma. A number of factors have already been identified as triggering factors for asthma symptoms; there is convincing evidence that maternal smoking during pregnancy and breastfeeding, leading to in utero and perinatal exposures to environmental tobacco smoke, are associated with increased risk of asthma[191]. Furthermore, exposure to passive smoke significantly increased the risks of asthma, wheeze, lower respiratory infections, and reduced lung function in children[192]. Alcohol drinking and drug intake during pregnancy, along with the detergent use are also factors incriminated in childhood asthma.

Both French and Lebanese studies showed that smoking during pregnancy was associated with an increased risk of wheezing and diagnosed asthma respectively. The new findings in the Lebanese findings is that waterpipe smoking during pregnancy would significantly increase the odds of asthma diagnosis as well.

Many air toxics have been linked to asthma, lung irritation, and other adverse respiratory effects but the evidence largely comes from animal or occupational studies at substantively higher concentrations than occurs from environmental exposures[193]. Environmental tobacco smoke (ETS) is independently associated with asthma prevalence among children[193-195], and of the 49 main components of ETS, twenty-nine are air toxics[194]. The evidence shows that exposure to tobacco smoke during pregnancy or infancy increases the risk for asthma and rhinitis mainly in early childhood and the risk for eczema at later ages[196]. The reason behind the relation between smoking and allergic diseases is that Th2 cytokines in the human blood samples which are responsible for allergy predisposition were elevated in the neonates whose mothers were smokers during pregnancy. In addition, bronchial airway hyperresponsiveness and positive results on skin prick tests were also more common in children who were exposed to smoking either during pregnancy or in early childhood[197]. This implies that if physicians improve the interactions with their patient and assure a better patient's and parents' understanding for the asthma treatment plan, the likelihood of avoiding the exposure to toxics is high.

Chronic exposure to various types of pesticides may aggravate or enhance asthmatic symptoms (wheeze, phlegm, flu-like symptoms), through interaction with functional irritant receptors in the airway and promoting neurogenic inflammation or can cause airway hyper-reactivity via a common mechanism of disrupting negative feedback control of cholinergic regulation in the lungs, thus making pesticides an overlooked contributor to asthma risk[198]. Child exposure to pesticides (in an area surrounding his house) was significantly associated to asthma in our study, in agreement with a previous study that showed chronic exposure to pesticides in children was moderately associated with chronic respiratory symptoms and diseases, especially asthma[158].

The most commonly used methods for chemical mixtures risk assessment include basic concepts of additivity and rely on determining toxicological similarity or dissimilarity among the components of a mixture that lack supporting data[199]. The toxicity of complex mixtures remains a concern for risk assessment. To be able to validate quantitative risk assessment models and to support model assumptions, testing for similar shapes of component dose–response curves are needed to determine whether additivity assumptions are applicable or not for describing mixture risk[199].

Cumulative risk, as defined in the Environment Protective Agency (EPA) Framework for Cumulative Risk Assessment as "the combined risks from aggregate exposures to multiple agents or stressors", is growing and evolving for asthmatic patients in general. It has existed in some form for many years, such as in the consideration of multiple chemical exposures and sensitive sub-populations[200]. Cumulative risk assessment has been proposed as an approach to evaluate the health risks associated with simultaneous exposure to multiple chemical and non-chemical stressors[201]. Cumulative risk assessment has the potential to expand our understanding of the public health impacts of environmental exposures and will consequently reduce risks to the extent that it can be integrated into prevention strategies to track and protect the public's health[202]. It is necessary to define and study groups of multiple stressors as in US Environmental Protection Agency's (EPA) Framework for Cumulative Risk Assessment. Increased knowledge of the greater sensitivity of the unborn baby, the infant and the child, has led to general recognition that a higher degree of precaution is now needed in regulating for multiple stressors on the young[203]. Consequently, the need to conduct studies with the objective of assessing the odds of cumulative risk factors on the increase of asthma prevalence in children, is warranted.

6.1. The Bradford Hill causality criteria

In 1965, the English statistician Sir Austin Bradford Hill proposed a set of nine criteria to provide epidemiologic evidence of a causal relationship between a presumed cause and an observed effect[204]. These criteria can be resumed as follows: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy.

The **strength** of both studies rely in the fact that in enrolled a big sample size and can be generalized to the whole population through the methods followed. The questionnaire used are validated to be **specifically** used in the pediatric population and to detect asthma and its risk factors among this group (ISAAC, ACQ).

The strength of association between smoking and wheezing or asthma is most commonly measured via risk ratios, rate ratios, or odds ratios. In fact, the multivariate results showed that cigarette smoking during pregnancy would modestly increase the odds of wheezing in French children ($1<OR<1.5$), but would increase the odds of childhood asthma in older children from mothers who smoked waterpipe during pregnancy ($OR>6$). Despite these results, we cannot confirm a direct causality between these variables, due to the methodology used in both studies. The study design can only identify associations and whilst agree that evidence from other studies does implicate maternal smoking during pregnancy and pesticides in asthma causation, the authors cannot infer causation. However, the consistent findings observed by the authors in different countries with different samples strengthens the likelihood of that effect. In general, the greater the consistency, the more likely a causal association[204].

The plausibility of the causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship[204]. This rule cannot be applied on both samples since there were other factors incriminated in wheezing and asthma respectively.

Concerning **temporality**, the design of a cohort may allow us to identify the relationship between smoking and asthma. The follow-up of these children will allow us to confirm our suspicions. Moreover, evidence clearly demonstrates that smoking does not lead solely to asthma but to a myriad of other clinical disorders

ranging from emphysema to heart disease. In addition, there are multiple factors that were demonstrated to be associated with asthma in children other than smoking.

Our results could not detect any **dose-effect relationship** between waterpipe smoking during pregnancy and asthma in children. The presence of a dose-response relationship between an exposure and outcome provides good evidence for a causal relationship; however, its absence should not be taken as evidence against such a relationship. We hypothesize that maybe a threshold association where a given level of exposure to waterpipe is required for asthma initiation in the child, may be needed. Further studies are needed to evaluate this association through biological results.

In addition, **analogy** is speculative in nature and is dependent upon the subjective opinion of the researcher. While smoking may cause asthma, not all children with asthma are from mothers who smoked during pregnancy or who are exposed to passive smoking. Absence of analogies should not be taken as evidence against causation.

6.2. Limitations

The strengths of the French study include the earlier prospective documentation of respiratory symptoms and wheezing in a large nationally representative cohort with adjustment for key confounders including maternal asthma, smoking and education. The use of parental reporting to identify respiratory symptoms and wheezing is a limitation, although we used an internationally validated questionnaire. A selection bias is possible because of the refusal rate and the exclusion criteria. Indeed, a premature child or one from multiple pregnancies may exhibit respiratory or worse health at birth. In this case, the associations between phenotypes and severity criteria could be underestimated. In the French context, our inclusion criteria may have led to a selection bias with younger parents more often born abroad and having a lower occupational status being excluded from the study. Such women are more often single mothers and have a lower level of education than the parents in our sample. This may have led to an over-estimation of the number of less healthy children in our sample since children of such underprivileged mothers could have been under-represented in our sample.

Furthermore, we cannot rule out an information bias since we used parent reporting. Another limitation of our study, was the lack of viral measurement by PCR, which was not possible in this large population of newborn children, or even in a subsample of children because of the cost aspect.

However, the questionnaires were tested during pilot surveys, thus minimizing the information bias. Further, a follow-up of the ELFE cohort is underway, including respiratory symptoms, pulmonary function testing, and formal examination at age 10. These assessments will facilitate extended evaluation of the association between earlier wheezing phenotypes and subsequent respiratory health.

Concerning the Lebanese study, it was devoid of limitations as well as strength points. The total sample size is acceptable, withdrawn from all districts in Lebanon and might be representative of the whole population. A selection bias is still, however, possible because of the ten percent refusal rate. The questionnaire used in our methodology, including ISAAC one, is similar to that used in other case-control studies, which is necessary for international comparisons. This is a case-control study with retrospective reports, and consequently a low level of evidence, due to the possibility of recall bias; parents might have given us wrong information probably because they don't remember what really happened during the pregnancy period or during the childhood period. The use of a questionnaire in parents may not always be accurate: problems in question understanding, recall deficiency and over or under evaluating symptoms as well as a possible underestimation to toxics exposure may still be possible, which can lead to a possible information bias. The study design can only identify associations and whilst agree that evidence from other studies does implicate maternal smoking during pregnancy and pesticides in asthma causation, the authors cannot infer causation. In addition, smoking mothers may be more prone to take other risky behaviors, or that might have low access to healthier lifestyle (alcohol, medications, pregnancy health controls, diet, etc. The frequency of pesticides use in fields nearby living places couldn't be measured; the answers obtained are subjective by the parents. We did not differentiate between maternal and paternal pesticides use in pregnancy. We did not take into account the season of birth, as this could have an influence on exposure in pregnancy and thus differ between children. Furthermore, we did not assess if the pre- or the postnatal exposure or

both had an influence on asthmatic symptoms. Asthmatics were included from all Lebanon, but healthy controls only recruited in schools; this might cause a bias in the results, as there might be less smoking/pesticides in controls. The amounts of alcohol and smoking during pregnancy and breastfeeding are subjective and could not be measured due to the retrospective nature of this study.

6.3. Perspectives

The conclusions of this research program tend to associate the various circumstances of exposure to environmental toxics observed in France and Lebanon with the occurrence or aggravation of certain chronic respiratory diseases. This information is in addition to that already published on other acute and chronic effects in relation to asthma. The resulting perspectives for action and reflection are primarily at several levels:

Education and prevention programs:

International collaboration would be very useful for the development of such a project. In all developing countries, there are several important barriers to the safety of environmental toxics: insufficient or poorly enforced legislation, illiteracy, poverty, low health levels, and inadequate access to care result in higher health risks during occupational, accidental or chronic pesticide exposure. They can serve as bases for an application in Lebanon, provided they are adapted to the political, socio-economic and cultural particularities of the country. They must help educate parents to protect themselves and their children by handling these environmental factors with the appropriate precautions for each toxic. This should also apply to professionals and users of consumer products. In addition, it would be desirable to impose labeling standards and safety data sheets on marketed products and preparations, and to better guide the nature of the requirements.

The general Lebanese population could also benefit from pesticide education. This population is at risk because of long periods of time before the ban of products already banned in other countries. The education of the general population would help in their contribution to the processes of regulation of the poisons, and increase their adherence to the new laws. Informed individuals can even identify and solve local problems without always resorting to government intervention (Environmental Protection Agency, 1997). The development of action plans for

indoor air quality control, and education on the use of pesticides in the home is also essential (American Thoracic Society, 1998a; 1999).

The Lebanese population can also benefit from smoking cessation education. Quit rates (the proportion of ever smokers who have quit) are also low in many developing countries[205]. The inadequate organization of the public health system in many developing countries contributes to the general lack of information about the extent to which tobacco use causes harm. Political instability in some countries also works against public health action. Promoting smoking cessation, creating an environment supportive of non-smoking, and providing appropriate services has produced encouraging results in the UK[206], the US[207], and Hong Kong[208]. Tobacco control efforts in the developing world have mostly concentrated on increasing tobacco taxes, restricting or banning advertising, adding or expanding warning messages, and restricting smoking in certain venues, but implementation of these policies has been limited[209].

Obstacles to promoting smoking cessation in developing countries:

Important obstacles to the promotion of smoking cessation in developing countries include: (1) economic factors; (2) lack of awareness by policy makers of the health consequences and costs of tobacco; (3) low perception of risks among the public; (4) lack of policies that promote cessation; (5) smoking behavior of service providers and their own lack of knowledge or awareness; (6) poor healthcare systems; (7) lack of infrastructure; and (8) industry action[210]. Targeting some of these obstacles would be a major step towards increasing smoking cessation in Lebanon. Finland is on its way to becoming the first country in the world to eradicate smoking[97], with the updated legislation mentioning the year 2030 as the new goal. This country has followed several strategies to eradicate smoking; advertising of nicotine products has been banned since 1978, smoking at the workplace since 1995 and in bars and restaurants since 2007. Nowadays, stores are seeing fees multiply to the point that selling cigarettes is becoming unprofitable[97]. According to statistics gathered by the National Institute for Health and Welfare, the popularity of smoking cigarettes has been on a steady decline over the past 20 years – though 17% of Finns are still daily smokers as of 2015 (levels have historically been over 60%)[97].

6.4. Research Programs

Future research programs should be based upon "Scales validation and adaption to the Lebanese population". This includes (1) validating the children's asthma quality of life (QOL) questionnaire and assessing risk factors affecting the QOL, (2) the St George's Respiratory Questionnaire, an index designed to measure and quantify health-related health status in patients with chronic airflow limitation, (3) Inventing a scale that would screen for asthma risk factors in children under 6 years (who cannot do a spirometry test), (4) evaluating the influence of caregivers' knowledge and understanding of asthma etiology on domiciliary management of children with asthma, (5) validating the asthmatic children's caregivers questionnaire and assess risk factors associated with this burden.

7. CONCLUSION

We found a high prevalence of respiratory symptoms in early life with an increase in incident wheezing at age one. Others respiratory symptoms (cough, respiratory distress, and excessive bronchial secretion) were significantly associated with a higher risk of persistent wheezing and increase the likelihood of remission at the age one. Smoking exposure during pregnancy remains a known risk factor of persistent wheezing. However, using detergents at home could be associated with incident wheezing at age one and this putative association warrants further attention. Follow-up with these children at age five will l offer more information regarding the natural history of respiratory health.

Asthma seems to be linked to several risk factors in our population of school children across Lebanon. The origin of asthma may be due to the environmental exposure to pesticides, tobacco (cigarettes and waterpipe), alcohol or prescribed medications during pregnancy and lactation.

The Arabic version of the asthma control questionnaire is a valid tool that can be safely used in pediatric patients in the Lebanese population to assess asthma control. We were also able to address some factors related to a worse asthma control in asthmatic children. The most significant were waterpipe smoking during pregnancy and cigarette smoking during breastfeeding, as well as the lower education level. Spreading awareness by health professionals about these preventable causes can help educate the

parents and children to prevent asthma and its exacerbation. Additional larger scale studies are necessary to confirm our results, particularly for waterpipe and alcohol exposures.

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Conflict of interest

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RESEARCH ARTICLE

Wheezing phenotypes and risk factors in early life: The ELFE cohort

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Data Availability Statement: As regards the ELFE data, data requests are examined by the CADE (accessibility data committee). There are ethical restrictions on sharing a re-identified data set, (e.g., data contain potentially identifying or sensitive patient information) and both the ethics committee and the CADE (accessibility data committee) have imposed them. Data requests may be sent to the CADE: Unité mixte ELFE, secrétariat du CADE INED. 133 Bd Davout, Paris cedex 20, FRANCE (contact@elfe-france.fr).

Abstract

Objective

Different phenotypes of wheezing have been described to date but not in early life. We aim to describe wheezing phenotypes between the ages of two months and one year, and assess risk factors associated with these wheezing phenotypes in a large birth cohort.

Methods

We studied 18,041 infants from the ELFE (French Longitudinal Study of Children) birth cohort. Parents reported wheezing and respiratory symptoms at two and 12 months, and answered a complete questionnaire (exposure during pregnancy, parental allergy).

Results

Children with no symptoms (controls) accounted for 77.2%, 2.1% had had wheezing at two months but no wheezing at one year (intermittent), 2.4% had persistent wheezing, while 18.3% had incident wheezing at one year. Comparing persistent wheezing to controls showed that having one sibling (ORa = 2.19) or 2 siblings (ORa = 2.23) compared to none, nocturnal cough (OR = 5.2), respiratory distress (OR = 4.1) and excess bronchial secretions (OR = 3.47) at two months, reflux in the child at 2 months (OR = 1.55), maternal history of asthma (OR = 1.46) and maternal smoking during pregnancy (OR = 1.57) were significantly associated with persistent wheezing. These same factors, along with cutaneous rash in the child at 2 months (OR = 1.13) and paternal history of asthma (OR = 1.32) were significantly associated with increased odds of incident wheezing. Having one sibling (ORa = 1.9) compared to none, nocturnal cough at 2 months (OR = 1.76) and excess bronchial secretions at 2 months (OR = 1.65) were significantly associated with persistent compared to intermittent wheezing.

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Competing interests: The authors have declared that no competing interests exist.

Conclusion

Respiratory symptoms (cough, respiratory distress, and excessive bronchial secretion) were significantly associated with a high risk of persistent wheezing at one year. Smoking exposure during pregnancy was also a risk factor for persistent and incident wheezing.

Introduction

Asthma is one of the most common chronic diseases worldwide with an estimated 300 million individuals affected [1]. In clinical practice, asthma causes symptoms such as wheezing, shortness of breath, chest tightness, and coughing that vary over time in their occurrence, frequency, and intensity. However, a proper asthma diagnosis cannot be based on a single common feature [2, 3]. Currently, the intermittent symptoms of asthma are known to occur on a background of persistent airway inflammation and remodeling [4]. Asthma is no longer considered as just one disease but rather a multifaceted one, with multiple associated syndromes expressing different phenotypes [5]. Therefore, increasing knowledge of these phenotypes will provide better understanding of the disease in order to better assist and manage patients [5].

Approximately 25 to 30 percent of infants will have at least one episode of wheezing during their lifetime [6]. Children with persistent asthma may have reduced lung function, and some are at risk of accelerated decline in lung function in early adult life [7]. Irregularities in pulmonary function that are correlated with persistent wheezing become recognized during early childhood and continue into adult life, suggesting that early life exposures are critical in determining the onset and natural history of wheezing disorders [8–10]. The etiology of wheezing is usually difficult to ascertain, and wheezing is not specific for asthma and could be due to viral infection [11], or environmental exposure (such as smoking) [12]. The number of wheezing episodes in childhood seems to have an impact as outcomes are generally quite good in children with small number of wheezing episodes associated with viral illness [13].

The severity of symptoms has been correlated with a high frequency of wheezing episodes (usually more than three per year), resulting in the identification of frequent wheezing as a distinct phenotype [14–16]. Better understanding of the respiratory phenotypes in early childhood is of fundamental importance in addressing the risk factors for asthma and wheezing illnesses in children [8–10]. Four wheezing phenotypes (no wheezing, transient-early, late-onset, and persistent wheezing) were previously defined according to whether the child had reported wheezing during the first three years of life and whether they were still wheezing at age six [6]. Two British cohort studies used latent class analysis to identify distinct phenotypes underlying the observed heterogeneity in asthma symptoms during childhood [17, 18]. The Avon Longitudinal Study of Parents and Children (ALSPAC) identified six wheezing phenotypes in childhood from birth to seven years old [17]. However, it is unclear whether phenotypes identified by latent class analysis are comparable between birth cohorts observed in different areas or countries, particularly because the number and timing of measurements, definitions of wheezing, and population characteristics may differ between studies [19–21].

ELFE (French Longitudinal Study of Children) is the first large-scale French longitudinal birth cohort. The future follow-ups of the ELFE cohort will permit to derive phenotypes of wheezing throughout childhood and assess association with the development of asthma. However, to date, there is scarce available data on the distribution and change in respiratory symptoms at a very early age. Phenotypes of wheeze during the first year of life have not been studied before. The ELFE cohort comprises data on respiratory symptoms at two months and one year of age.

The aim of the present study was to characterize early wheezing phenotypes in infants, and identify risk factors associated with these phenotypes in a large French birth cohort.

Methods

A representative random sample of mothers from maternity hospitals throughout France was established. The target population consisted of every one in 50 children born in 2011 in French maternity units [22]. After a written informed consent was obtained, medical records of the mother were consulted. The mother then answered a general questionnaire about the health of the baby and mental, social, family, and environmental exposures at age one. Follow-up is planned until age 18. The children were selected to represent all seasons of the year, having been born between April 1–4, June 27—July 4, September 27—October 4, and November 28—December 5, 2011. The exclusion criteria were: prematurity, childbirth under 18 years old, and no response to the questionnaire after two months. Mothers with multiple pregnancies with more than two children and those unable to give informed consent in one of the languages in which the information and consent forms were translated were also excluded.

Before the study began in 2011, a pilot study started in 2006–2007 in a small cohort (n = 470) to test the different parts of the study, and the questionnaires. Questions showing poor completion rates or that were not well understood by the participants were removed or corrected. Before the study, a training course was organized for the investigators (questionnaire, filters inside the questionnaire). Investigators traveled to maternity units and undertook the study in person with the parents. Initially, 18 322 children including 289 pairs of twins were enrolled in the study at birth. Among the 18,322 selected families who gave their consent, 281 eventually refused to participate, leaving 18,041 families in the study. The children were followed up at two months of age and then again at one year. At two months, trained investigators interviewed the parents in a face to face interview at home. When the child reached one year old, parents answered a standardized questionnaire through a telephone conversation conducted by specially trained professionals (phone-platforms currently involved in health studies in France, by the French institute of statistics (INSEE)). By the time of the phone interview, 4270 participants had been lost during the follow-up, leaving a total of 14059 children included in the present analysis (Fig 1).

Wheezing phenotypes

Four groups were defined: non-wheezers (no current wheezing symptoms at both two months and one year old), intermittent (current wheezing symptoms at two months but no wheezing at one year), persistent (current wheezing at two months and at one year) and incident (no current wheezing at two months but wheezing at one year). Wheezing at two months was defined by a positive answer yes to the question "Does your child currently have wheezing or whistling in the chest? "[23]. Wheezing at one year was defined by a positive answer to the question "Does your child ever have wheezing or whistling in the chest? "

Risk factors

The questionnaire assessed the sociodemographic characteristics (age, gender, region, number of rooms and number of persons living in the house, level of education for both parents), type of delivery, Apgar scores at one and five minutes respectively, mother's previous pregnancies, and family history of asthma in parents and siblings of the child and other potential risk factors of asthma (heating system used inside the house, dampness inside the house, work done during pregnancy in the house, presence of pets in the house, child's history of recurrent otitis, rash history of the child, bronchiolitis, bronchitis episodes, and breastfeeding). Information

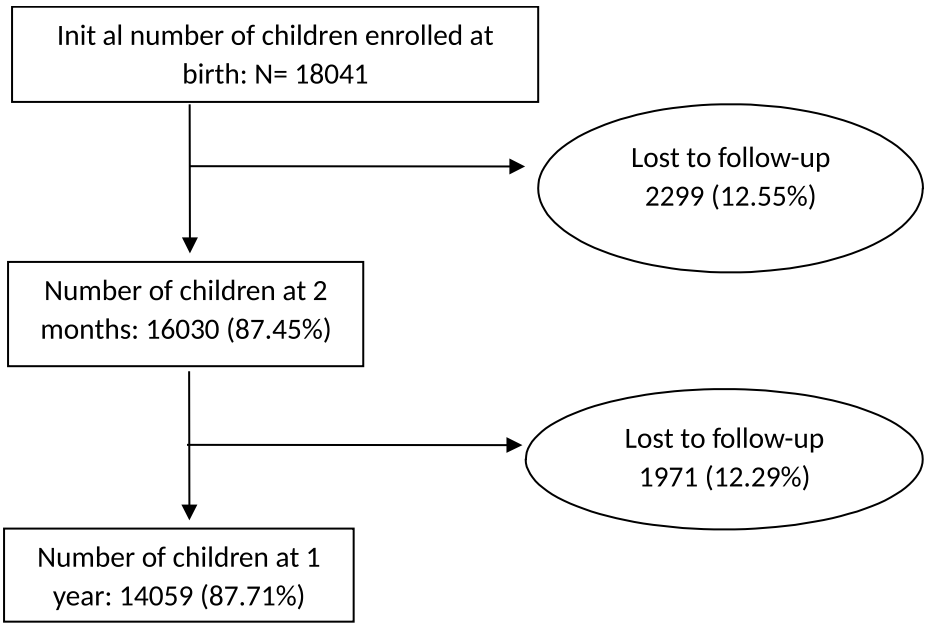


Fig 1. Flow chart.

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concerning parental allergies was recorded by questions about family history of eczema, asthma, eczema, and rhinitis (hay fever) for both parents and siblings. Finally, environmental exposure to toxic substances was considered: smoking during pregnancy, passive smoking, occupational and domestic pesticide exposure, and the use of cleaning products. Respiratory symptoms at two months were taken into account. The presence of coughing was ascertained by an affirmative answer to the question: "Has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?" To know whether the child had respiratory problems, the following questions were used: "Has your child had any sign of respiratory distress?" and "At present does your child have any sign of respiratory distress?". To investigate the presence of excess bronchial secretions, the following questions were used: "Has your child had an excess of bronchial secretion or phlegm?" and "At present are you noticing that your child has an excess of bronchial secretion or phlegm?". A question was further asking if the child had ever been diagnosed with a bronchitis, and whether a doctor had prescribed medications, and a list of medications by class was proposed, to the parents.

Ethical approval

Each parent gave written informed consent at the maternity unit. Every level of the project and each procedure was monitored by the National Council for Statistical Information (CNIS) and approved by the French Data Protection Authority (CNIL), in conjunction with the Consultative Committee for Data Processing in Health Research (CCTIRS), which assesses the scientific relevance of health projects, properly conducted from start to finish. Each parent retains the right to withdraw his/her child at any point during the study.

Statistical analysis

Data analysis was performed by SPSS software, version 23. Two-sided statistical tests were used to test the association of each respiratory symptom at two months across all four wheezing groups; the Chi-2 test for dichotomous or multinomial qualitative variables, with Fisher's

exact test whenever appropriate. Regarding multivariate analysis, backward logistic regressions were performed by taking into account the variables in the bivariate analysis that showed a p-value <0.10 [24, 25];which included recommended covariates (such as maternal asthma, smoking, and educational level of the mother used as a proxy for socio-economical status). Educational level of the mother was categorized into 3 categories (low, intermediate and high level). Number of siblings was categorized into 0 (reference), 1, 2 and "3 or more" siblings. Several logistic regressions were conducted taking the dependent variables as follows: (1) intermittent vs persistent wheezing, (2) non-wheezers vs persistent wheezers and (3) non-wheezers vs incident wheezers.

Results

During the two-month survey, 146 families quit the study and 29 children were born outside the dates of inclusion, reducing the total to 17,866 families. There were also 1295 non-responders, as well as 541 referent parents who did not answer the questions on the respiratory health of their children, leaving a final total of 16,030 children (Fig 1).

Prevalence of wheezing and other respiratory symptoms at two months and one year

Prevalence of wheezing was 6.5 percent at two months and reached 27.5 percent at one year. The prevalence of nocturnal coughing increased from 25.5 percent to 67.5 percent between two months and one year, signs of respiratory distress increased from 29.1 percent to 38.8 percent and excess bronchial secretions from 34.7 percent to 65.1 percent respectively (Table 1).

A significantly higher proportion of children with wheezing at two months and nocturnal coughing at two months were lost to follow-up, whereas a significantly higher proportion of children with maternal eczema and paternal hay fever were still participating at the one-year follow-up. There was no significant difference in patients lost to follow-up and those included in regards to gender, signs of respiratory distress or excess bronchial secretion in the child at two months, maternal history of asthma or hay-fever, and paternal history of asthma and eczema (Table 2).

Wheezing phenotypes at one year

Children with no symptoms (controls) accounted for 77.2 percent, 2.1 percent had had wheezing at two months but did not report wheezing at one year (intermittent), 2.4 percent had persistent wheezing, while 18.3 percent had incident wheezing at one year.

Parental and infant factors associated with wheezing phenotypes

A significantly higher proportion of boys (59.5 percent) was observed among incident wheezers than among non wheezers (47.7%) (Table 3). Incident wheezers also showed a significantly higher proportion of children who were delivered by caesarean (19.2 percent) (vs.

Table 1. Prevalence of wheezing and other respiratory symptoms at two months and one year in ELFE cohort.

	Two months N = 15,896	One year N = 14,059
Wheezing	1026 (6.5%)	3871 (27.5%)
Nocturnal cough	4050 (25.5%)	9494 (67.5%)
Respiratory distress sign	4620 (29.1%)	5460 (38.8%)
Excess bronchial secretion	5519 (34.7%)	9155 (65.1%)

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Table 2. Comparison between children at one year and children lost to follow-up in ELFE cohort.

	Included (N = 14059)	Lost to follow-up Yes (N = 4270)	Total (N = 18329)	p-value
Gender				
Male	7112 (51%)	2169 (52.4%)	9281 (51.3%)	0.227
Female	6813 (48.9%)	1966 (47.5%)	8779 (48.5%)	
Wheezing in child at two months	830 (6.1%)	196 (8.7%)	1026 (6.5%)	<0.001
Nocturnal cough in child at two months	3437 (25.2%)	613 (27.3%)	613 (27.3%)	0.037
Respiratory distress sign in child at two months	3954 (29%)	666 (29.6%)	4620 (29.1%)	0.537
Excess bronchial secretion in child at two months	4729 (34.7%)	790 (35.1%)	5519 (34.7%)	0.653
Maternal asthma	1629 (12%)	239 (11%)	1868 (11.8%)	0.43
Maternal eczema	2063 (15.1%)	280 (12.9%)	2343 (14.8%)	0.01
Maternal hay fever	2758 (20.2%)	400 (18.5%)	3158 (20%)	0.156
Paternal asthma	1477 (12.8%)	129 (11.6%)	1606 (12.6%)	0.414
Paternal eczema	1049 (9.1%)	93 (8.3%)	1142 (9%)	0.717
Paternal hay fever	2256 (19.5%)	159 (14.2%)	2415 (19%)	<0.001
Mother's educational level*				<0.001
Category 1	1997 (14.3%)	1379 (33.2%)	3376 (18.6%)	
Category 2	2632 (18.8%)	1164 (28%)	3796 (20.9%)	
Category 3	9361 (66.9%)	1608 (38.7%)	10969 (60.5%)	
Age of the mother	31.03 ± 4.81	29.41 ± 5.63		<0.001
Number of siblings categories				<0.001
None	6531 (46.5%)	2088 (48.9%)	8619 (47%)	
1	4971 (35.4%)	1276 (29.9%)	6247 (34.1%)	
2	1848 (13.1%)	540 (12.6%)	2388 (13%)	
3 or more	709 (5%)	366 (8.6%)	1075 (5.9%)	

* Category 1 includes illiteracy, primary and complementary levels of education; category 2 includes certificate of professional competence or professional qualifications, technological baccalaureate and secondary level of education; category 3 includes university and higher university degrees.

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18.3% in non-wheezers), and a higher proportion of children with at least one sibling (60 percent vs. 50% in non-wheezers). Having a nocturnal cough, signs of respiratory distress, and excess bronchial secretions at two months were associated with wheezing at one year (persistent wheezing). Persistent wheezers also comprise a significantly higher proportion of children with at least one sibling as compared to non wheezers. Maternal atopy (i.e. asthma, eczema, or

Table 3. Infant risk factors associated with wheezing phenotypes in ELFE cohort.

Variable	Controls (N = 14151)	Intermittent (N = 393)	Persistent (N = 437)	Incident (N = 3348)	p-value
Nocturnal cough at two months	1954 (20.6%)	242 (61.6%)	338 (77.3%)	903 (27%)	<0.0001
Respiratory distress signs at two months	2343 (24.7%)	279 (71%)	360 (82.4%)	972 (29%)	<0.0001
Excess bronchial secretions at two months	2863 (30.2%)	294 (74.8%)	377 (86.3%)	1195 (35.7%)	<0.0001
Gender					<0.0001
Male	4661 (47.7%)	208 (53.6%)	266 (61.1%)	1977 (59.5%)	
Female	5119 (52.3%)	180 (46.4%)	169 (38.9%)	1345 (40.5%)	
Presence of bronchiolitis in child at two months	120 (5.5%)	43 (37.4%)	71 (43%)	41 (4.9%)	<0.0001
Rash on the child's skin at two months	1375 (14.5%)	74 (18.8%)	95 (21.7%)	559 (16.7%)	<0.0001
Reflux in the child at 2 months	1854 (19.6%)	96 (24.4%)	131 (30%)	768 (22.9%)	<0.0001

Results are expressed as frequency (percentage).

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Table 4. Parental risk factors associated with wheezing phenotypes in ELFE cohort.

Variable	Controls (N = 14151)	Intermittent (N = 393)	Persistent (N = 437)	Incident (N = 3348)	p-value
Maternal history of asthma	1006 (10.6%)	52 (13.3%)	80 (18.3%)	491 (14.7%)	<0.0001
Maternal history of eczema	1369 (14.5%)	60 (15.3%)	69 (15.8%)	565 (16.9%)	0.01
Maternal history of hay fever	1827 (19.3%)	76 (19.4%)	112 (25.7%)	743 (22.3%)	<0.0001
Paternal history of asthma	956 (11.9%)	39 (12.7%)	47 (13.7%)	435 (15.1%)	<0.0001
Maternal smoking during pregnancy	1698 (17.4%)	85 (22%)	110 (25.5%)	657 (19.8%)	<0.0001
Age of the mother at the child's birth	30.99 ± 4.88	30.97 ± 4.93	30.71 ± 4.57	31.19 ± 4.58	0.062
Maternal educational level**					<0.0001
Category 1	1407 (14.3%)	73 (18.7%)	71 (16.3%)	446 (13.4%)	
Category 2	1871 (19%)	86 (22%)	93 (21.4%)	582 (17.5%)	
Category 3	6555 (66.7%)	232 (59.3%)	271 (62.3%)	2303 (69.1%)	
Number of siblings					<0.0001
None	4891 (49.5%)	165 (42%)	129 (29.5%)	1346 (40.2%)	
1	3263 (33%)	146 (37.2%)	213 (48.7%)	1349 (40.3%)	
2	1237 (12.5%)	57 (14.5%)	74 (16.9%)	480 (14.3%)	
3 or more	490 (5%)	25 (6.4%)	21 (4.8%)	173 (5.2%)	
Type of delivery					0.016
Spontaneous labor	6577 (68.5%)	262 (68.2%)	306 (72.2%)	2283 (69.9%)	
Triggered childbirth	1269 (13.2%)	45 (11.7%)	42 (9.9%)	358 (11%)	
Caesarean	1753 (18.3%)	77 (20.1%)	76 (17.9%)	626 (19.2%)	
Exposure to tobacco smoke inside the house (yes)	1705 (17.3%)	76 (19.3%)	82 (18.8%)	537 (16%)	0.167
Detergent use in house	2793 (28.3%)	99 (25.2%)	127 (29.1%)	1002 (29.9%)	0.126
Use of toiletry products of animal origin	2223 (22.5%)	93 (23.7%)	90 (20.6%)	696 (20.8%)	0.146

Results are expressed as frequency (percentage) or mean ± Standard deviation.

** Category 1 includes illiteracy, primary and complementary levels of education; category 2 includes certificate of professional competence or professional qualifications, technological baccalaureate and secondary level of education; category 3 includes university and higher university degrees.

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hay fever) was also more frequent in persistent and incident wheezers. Smoking before and during pregnancy were significantly associated with persistent wheezing respectively (Tables 3 and 4). No significant difference was found between the different wheezing phenotypes and bronchitis, anti-asthma medication, and antibiotics taken by the child during the first year (data not shown).

Risk factors and wheezing phenotypes: Multivariate analysis

The results of a first backward logistic regression taking the intermittent vs persistent wheezers as the dependent variable, without entering the respiratory symptoms at 2 months as independent variables (Table 5), showed that having 1 sibling (adjusted odds-ratio ORa = 2.15; 95%CI 1.50–3.09) or 2 siblings (ORa = 1.75; CI 1.08–2.82) compared to none were significantly associated with persistent wheezing.

Fig 2 shows the odds ratios from the logistic regression for persistent wheezing and incident wheezing, as compared to non-wheezers. Female gender was associated with a decreased odds of both persistent wheezing and incident wheezing with OR of similar magnitude (Fig 2). Conversely, the presence of reflux in the child at 2 months, a maternal history of asthma and maternal smoking during pregnancy were significantly associated with an increased risk of both persistent and incident wheezing. Having 1, 2 or 3 or more siblings was a strong risk factor for persistent wheezing (with all OR>2.5) and was also associated with incident wheeze,

Table 5. Multivariable analysis.

Logistic regression 1 taking intermittent vs persistent wheezers as the dependent variable (without the respiratory symptoms at 2 months as independent variables)				
Variable	**p-value**	**ORa**	**Confidence Interval**	
Number of siblings categories (compared to no siblings)	<0.001			
1 sibling	<0.001	2.15	1.50	3.09
2 siblings	0.022	1.75	1.08	2.82
3 or more siblings	0.289	1.48	.71	3.10
Logistic regression 2 taking non-wheezers vs persistent wheezers as the dependent variable (without the respiratory symptoms at 2 months as independent variables)				
Variable	**p-value**	**ORa**	**Confidence Interval**	
Gender (males* vs females)	<0.001	.60	.48	.75
Number of siblings categories (compared to no siblings)	<0.001			
1 sibling	<0.001	3.18	2.43	4.17
2 siblings	<0.001	2.98	2.07	4.30
3 or more siblings	0.001	2.57	1.46	4.50
Cutaneous rash in the child at 2 months	<0.001	1.67	1.27	2.18
Reflux in the child at 2 months	<0.001	1.83	1.43	2.33
Maternal history of asthma	<0.001	1.64	1.21	2.23
Maternal smoking during pregnancy	<0.001	1.67	1.28	2.16
Logistic regression 3 taking non-wheezers vs incident wheezers as the dependent variable (without the respiratory symptoms at 2 months as independent variables)				
Variable	**p-value**	**ORa**	**Confidence Interval**	
Gender (males* vs females)	0.018	.61	.55	.66
Number of siblings categories (compared to no siblings)	0.03			
1 sibling	0.018	1.37	1.05	1.78
2 siblings	0.021	1.51	1.06	2.14
3 or more siblings	0.119	1.53	0.89	2.60
Reflux in the child at 2 months	0.019	1.38	1.05	1.80
Maternal history of asthma	0.044	1.42	1.01	1.97
Maternal smoking during pregnancy	0.039	1.35	1.01	1.79

* Reference group

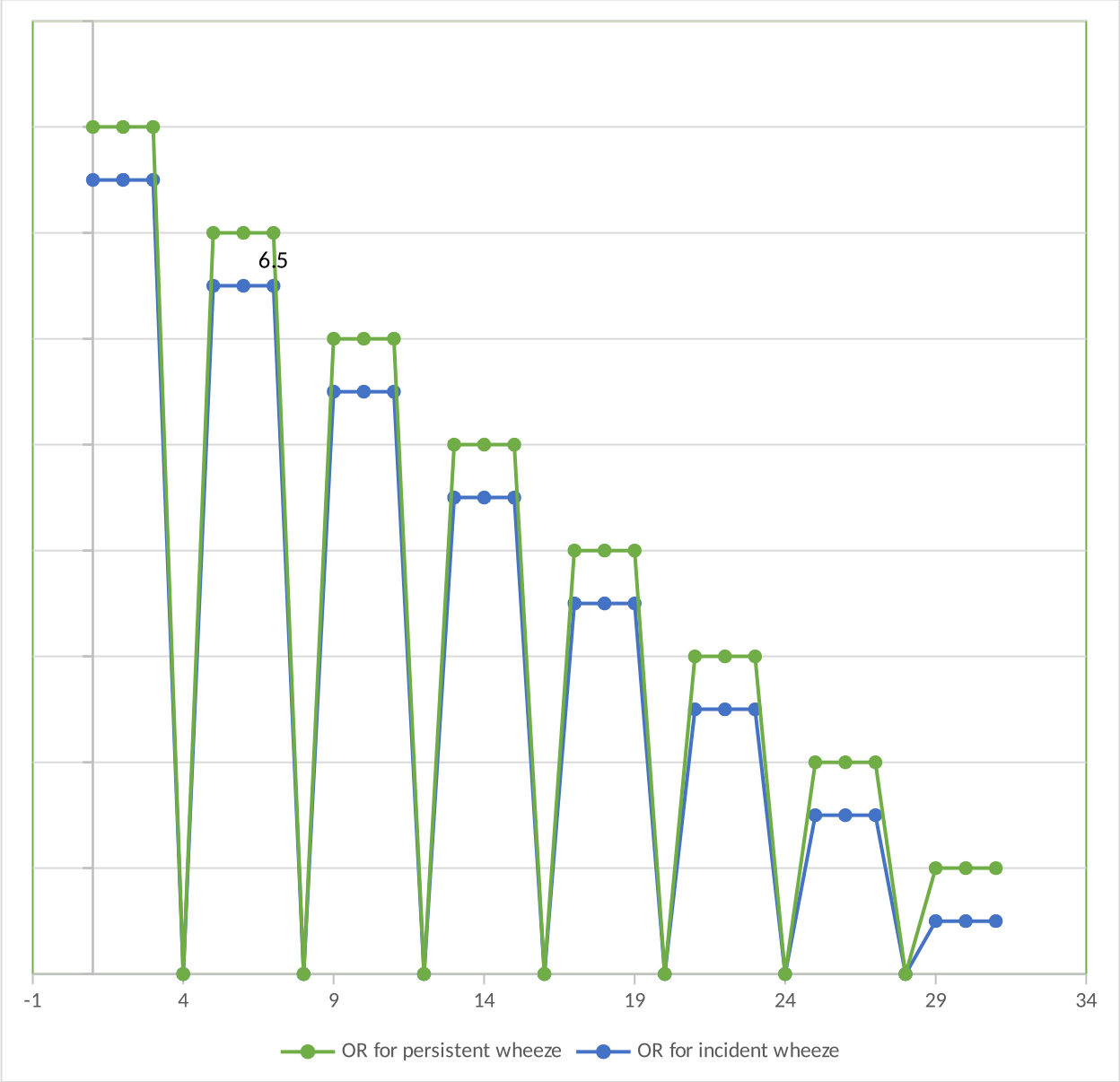
-Variables entered in the models: maternal history of asthma, maternal history of eczema or hay fever, paternal history of asthma, maternal smoking during pregnancy, type of delivery, gender, number of siblings categories, rash on the child's skin at 2 months, reflux in the child at 2 months, age of the mother at the child's birth, educational level of the mother.

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although the association somewhat less strong. The presence of cutaneous rash in the child at 2 months was significantly associated with an increase in persistent wheezing.

When the respiratory symptoms at 2 months were entered in the model as independent variables (Table 6), the first backward logistic regression taking the intermittent vs persistent wheezers as the dependent variable, showed that the presence of a nocturnal cough in the child at 2 months (ORa = 1.76; CI 1.19–2.60) and excess bronchial secretions in the child at 2 months (ORa = 1.65; CI 1.04–2.59) were associated with an increase in the odds of persistent wheezing.

A second backward logistic regression, taking non-wheezers vs persistent wheezers, with the respiratory symptoms at 2 months entered in the model as independent variables, showed



P-value for having 3 siblings for incident wheeze=0.119; all other p-values are signif cant (p<0.05).

Fig 2. Factors associated with persistent and incident wheezing at one year compared to non-wheezers (odds-ratios from backward logistic regressions).

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that the presence of nocturnal cough in the child at 2 months (ORa = 5.2; CI 3.91–6.92), respiratory distress in the child at 2 months (ORa = 4.1; CI 2.96–5.67) and the excess bronchial secretions in the child at 2 months (ORa = 3.47; CI 2.41–4.98) were associated with an increase in the odds of persistent wheezing.

A third backward logistic regression, taking non-wheezers vs incident wheezers, with the respiratory symptoms at 2 months entered in the model as independent variables, showed that the presence of nocturnal cough in the child at 2 months (ORa = 1.22; CI 1.09–1.36) was associated with an increased odds of incident wheezing (Table 6).

Table 6. Multivariable analysis.

Logistic regression 1 taking intermittent vs persistent wheezers as the dependent variable (with the respiratory symptoms at 2 months as independent variables).				
Variable	**p-value**	**ORa**	**Confidence Interval**	
Number of siblings categories (compared to no siblings)	.008			
1 sibling	0.001	1.90	1.31	2.76
2 siblings	0.121	1.47	0.90	2.41
3 or more siblings	0.69	1.16	0.55	2.45
Nocturnal cough in the child at 2 months	.005	1.76	1.19	2.60
Excess bronchial secretions in the child at 2 months	.031	1.65	1.04	2.59
Logistic regression 2 taking non-wheezers vs persistent wheezers as the dependent variable.				
Variable	**p-value**	**ORa**	**Confidence Interval**	
Gender (males* vs females)	<0.001	.63	.49	.81
Number of siblings categories (compared to no siblings)	<0.001			
1 sibling	<0.001	2.19	1.65	2.90
2 siblings	<0.001	2.23	1.53	3.24
3 or more siblings	0.03	1.92	1.06	3.46
Reflux in the child at 2 months	.001	1.55	1.18	2.02
Maternal history of asthma	.029	1.46	1.04	2.04
Maternal smoking during pregnancy	.002	1.57	1.18	2.08
Nocturnal cough in the child at 2 months	<0.001	5.20	3.91	6.92
Respiratory distress in the child at 2 months	<0.001	4.10	2.96	5.67
Excess bronchial secretions in the child at 2 months	<0.001	3.47	2.41	4.98
Logistic regression 3 taking non-wheezers vs incident wheezers as the dependent variable.				
Variable	**p-value**	**ORa**	**Confidence Interval**	
Gender (males* vs females)	<0.001	.61	.55	.66
Cutaneous rash in the child at 2 months	.037	1.13	1.01	1.28
Reflux in the child at 2 months	.001	1.20	1.08	1.34
Maternal history of asthma	<0.001	1.41	1.23	1.61
Paternal history of asthma	<0.001	1.32	1.16	1.49
Maternal smoking during pregnancy	.012	1.16	1.03	1.30
Maternal history of hay fever or eczema	.016	1.13	1.02	1.24
Nocturnal cough in the child at 2 months	<0.001	1.22	1.09	1.36
Excess bronchial secretions in the child at 2 months	.063	1.10	.99	1.21

* Reference group

-Variables entered in the models: maternal history of asthma, maternal history of eczema or hay fever, paternal history of asthma, maternal smoking during pregnancy, type of delivery, gender, number of siblings categories, rash on the child's skin at 2 months, reflux in the child at 2 months, age of the mother at the child's birth, educational level of the mother, nocturnal cough in the child at 2 months, respiratory distress in the child at 2 months, excess bronchial secretions in the child at 2 months.

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Discussion

In this large ELFE cohort, we found a high prevalence of respiratory symptoms in as early as two months. We also assessed different risk factors and respiratory symptoms associated with persistent wheezing at one year.

The percentage of children with respiratory symptoms at age two months and at one year old was higher compared to the Columbia Center for Children's Environmental Health (CCCEH) (20.4 percent at age one) [26] and the ALSPAC [17] cohorts (26 percent at 18

months old). A nocturnal cough, signs of respiratory distress, and excess bronchial secretion symptoms continued to increase from two months old to one year. To our knowledge, no other cohort has evaluated these three symptoms with the development of respiratory symptoms at age one. Time will reveal the association between each of these symptoms and asthma at a later stage of these children's lives. While all these symptoms are associated with an increased risk of having persistent wheeze at one year, it's interesting to note also that nocturnal cough at the age of 2 months is also associated with an increased likelihood of incident wheeze at one year.

Nocturnal cough at two months, respiratory distress signs at two months, excess bronchial secretions at two months increased the likelihood of persistent and incident wheezing in the multivariate analysis. These symptoms could be due to allergenic inflammation, or inflammation related to environmental exposure to irritants in children exposed to a detrimental environment. These symptoms could also be due to viral infection, or to bacterial infection although endotoxin and other components of bacteria have been found to have a protective effect for asthma at an older age (hygiene hypothesis) [27]. Furthermore, the same respiratory symptoms may have different biological etiology.

Maternal smoking was associated with persistent wheezing (from two months to one year) and incident wheezing at one year, in agreement with what was found in previous cohorts [6]. The association between maternal smoking and transient early wheezing may be mediated, at least in part, by narrower airways in the children of women who smoke [6].

Parental asthma is thought to influence the risk of asthma in children [28]. However, hereditary patterns are multifaceted with many important questions remaining unanswered, such as heredity effects at different ages [6, 29], and the potential additional effect of having relatives with asthma. Our results indicate that a mother's history of hay fever, eczema or asthma was associated with an increased risk of persistent wheezing in children, corroborating previous findings [30].

Furthermore, the increased number of siblings was associated with a decreased odds of persistent wheezing compared to intermittent wheezing, which might be explained by a higher risk of viral infection or contamination in children sharing their room with siblings. Indeed, previous findings suggest that the increased number of children puts the entire household at increased risk for infection with viruses that cause colds, flu, and other respiratory illnesses [31]. In addition, an increase in childhood asthma may predispose to severe RSV infection [32]. Meta-analyses have shown that delivery by caesarian section is associated with an increased risk of asthma in the offspring [33, 34], with a close and bilateral link between hospitalization for respiratory syncytial virus and asthma [35, 36].

The relationship between gastroesophageal reflux disease (GERD) and asthma in children has been investigated, although the nature of the association (if any) between them is unclear [37]. A clinical study showed that GERD is highly predominant in children with asthma, with estimations reaching as high as 80 percent, but nearly half of the children were asymptomatic; a finding in agreement with ours [38].

We have defined a priori three wheezing phenotypes, similar to those of Spycher et al. [39]. In the ALSPAC and PIAMA cohorts, six and five phenotypes were identified respectively [40]. A recent latent class analysis including respiratory symptoms (wheeze, night cough, and rhinitis) and atopy in children aged 18 months from the Pollution and Asthma Risk Infant Study identified a mild, a non-atopic severe and an atopic severe phenotype, respectively [41]. At age one, we also defined a transient wheezing phenotype (intermittent wheezing), consistent with the findings of Tucson [6]; since this phenotype is associated with having siblings, we can hypothesize that it is possibly linked to viral infections.

The strengths of our study include the early prospective documentation of respiratory symptoms and wheezing in a large nationally representative cohort with adjustment for key confounders including maternal asthma, exposure to smoking and maternal education and number of siblings. The use of parental reporting to identify respiratory symptoms and wheezing is a limitation, although we used an internationally standardized questionnaire. A selection bias is possible because of the refusal rate and the exclusion criteria. Indeed, a premature child or one from multiple pregnancies may exhibit respiratory or worse health at birth. In this case, the associations between phenotypes and severity criteria could be underestimated. In the French context, our inclusion criteria may have led to a selection bias with younger parents more often born abroad and having a lower occupational status being excluded from the study. Such women are more often single mothers and have a lower level of education than the parents in our sample. This may have led to an under-estimation of the number of less healthy children in our sample since children of such underprivileged mothers could have been under-represented in our sample. Furthermore, we cannot rule out an information bias since we used parent reporting. Another limitation of our study was the lack of viral measurement by PCR, which was not possible in this large population of newborn children, or even in a subsample of children because of the cost aspect.

However, the questionnaires were tested during pilot surveys, thus minimizing the information bias. Further, a follow-up of the ELFE cohort is underway, including respiratory symptoms, pulmonary function testing, and formal examination at age 10. These assessments will facilitate extended evaluation of the association between earlier wheezing phenotypes and subsequent respiratory health.

Conclusion

We found a high prevalence of respiratory symptoms in early life with an increase in incident wheezing at age one. Other respiratory symptoms (cough, respiratory distress, and excessive bronchial secretion) were significantly associated with a higher risk of persistent wheezing. Smoking exposure during pregnancy remains a known risk factor of persistent wheezing. Longer follow-up with symptoms, lung function and atopy markers are needed to derive wheezing phenotypes throughout childhood and assess the relationships of these early-life symptoms with asthma onset.

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ORGINAL ARTICLE
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Association between Caregiver Exposure to Toxics during Pregnancy and Childhood-onset Asthma: A Case-control Study

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ABSTRACT

The aim of this study was to evaluate the associations between caregiver-reported use of medications, alcohol, cigarette and/or waterpipe (WP), and exposure to pesticides/detergents during pregnancy with childhood-onset asthma.

The study design consisted of a case-control study, conducted between December 2015 and April 2016, recruited 1503 children, aged between 3-16 years old. A questionnaire assessed the sociodemographic characteristics (age, gender, education level of both parents), the family history of asthma, and other known risk factors of asthma (heating system at home, child history of recurrent otitis, humidity in the house, child went to a daycare, smoking and drinking alcohol during pregnancy, exposure to pesticides and detergents).

The multivariate analysis showed that children living in North and South Lebanon and the children living in areas where pesticides are frequently used had an increased risk of asthma (ORa=1.625, CI 1.034-2.554, p=0.035, ORa=13.65, CI 3.698-50.385; p<0.001 and ORa=3.307, CI 1.848-5.918, p<0.001 respectively). Smoking WP during pregnancy and cigarette during lactation would increase the risk of asthma in children (ORa=6.11; CI 1.244-30.008; p=0.026 and ORa=3.44; CI 1.024-11.554; p=0.046 respectively).

We conclude that asthma may originate from the environmental exposure to toxics such as pesticides and tobacco (cigarettes and WP) or to alcohol and prescribed medications during pregnancy and lactation. Spreading awareness by health professionals about these preventable causes can help educate the parents and children to prevent asthma and its exacerbation.

Keywords: Asthma; Children; Cigarette smoking; Environmental exposure; Lebanon; Pesticides; Pregnancy; Waterpipe smoking

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INTRODUCTION

Many risk factors are linked to asthma in children, including familial history of asthma in one or both of the parents, smoking, exposure to pesticides and use of medications during pregnancy. The effect of parents' smoking, either in early life (pregnancy)[1-3] or active smoking,[4] on children is a well-established trigger to express childhood-onset asthma. There is convincing evidence that maternal smoking during pregnancy and breastfeeding, leading to in utero and perinatal exposures to environmental tobacco smoke, are associated with increased risk of asthma.[3] In Lebanon, similar results were shown in a post-hoc analysis, where passive exposure to mother's smoke from cigarettes and from waterpipe was associated with asthma and allergic diseases in children.[5] On the other hand, the role of alcohol consumption during pregnancy in triggering asthmatic responses in the child at birth has not been well described. One study showed that approximately one third of asthmatic outpatients reported a worsening of asthma symptoms after alcohol consumption.[6] Another study showed that alcoholic drinks, and particularly wines, appear to be important triggers for asthmatic responses, possibly attributable to the sensitivity to the sulfite additives[7] and yeast in wines.[8]

Children of parents working with pesticides may be exposed from occupational sources (storing working equipment in the house, contamination of clothes).[9-12] Residing near pesticide treated areas or in agricultural regions, or having home and yard treated with pesticides also contribute to children exposure.[11-15] Direct indoor application of pesticides contaminates the house and exposes its occupants to volatile ingredients and residues. Salameh et al also found that exposure to pesticides was associated with chronic respiratory symptoms and asthma in children.[16] Domestic use of cleaning products, in particular, those in spray form, has been also suggested as a risk factor for asthma.[17,18]

Moreover, an association has been found between in utero exposures to several xenobiotics and increased risk of asthma. The literature is replete with evidence of a relationship between prescribed medications' intake by the mother during pregnancy and asthma in children.[19-21]

While we know that exposures to toxics are common during pregnancy among Lebanese women,[22] in utero and young childhood exposures to these toxics have not been fully assessed in Lebanon. A previous pilot study revealed that waterpipe, smoking and alcohol intake during pregnancy, recurrent otitis and humidity at home seem to be significantly correlated with asthma in children.[23] Although composition details may differ by culture, tobacco waterpipes most often seen in Lebanon have a fired-clay head, metal body, glass or acrylic water bowl, and leather or plastic hose. The bowl is partially filled with water and the head is filled with moistened tobacco upon which a lit piece of charcoal is placed (tobacco and charcoal are often separated by perforated aluminum foil). The smoker inhales through the hose, thus drawing air over the burning charcoal, heating the tobacco, and producing smoke that travels through the body of the waterpipe, the water, and the hose to the user. The objective of this study is to evaluate the associations between caregiver-reported use of medications, alcohol, cigarette and/or waterpipe, and exposure to pesticides/detergents during pregnancy and childhood-onset asthma, hoping that our results will help set up educational and awareness programs to protect our children.

MATERIALS AND METHODS

Ethical Aspect

The Institutional Review Board of the University Faculty of Pharmacy waived the need for an approval based on the facts that it was an observational study that respected participants' autonomy and confidentiality and induced minimal harm to them.

Study Design

This case-control study was conducted between December 2015 and April 2016. In addition to cases (asthmatic) and controls (healthy), a third group of participants (undiagnosed/ probable asthma) was defined as the presence of respiratory symptoms (wheezing, cough, excess bronchial secretions, respiratory distress), but without a physician diagnosis of asthma.

Participants' Characteristics

Controls were chosen using a sample of healthy Lebanese students, from schools in all districts of Lebanon, including children from different socioeconomic levels. Directors of the schools were contacted to take the permission to enter classrooms to distribute the questionnaires. Children were then given the questionnaire to be filled at home by their parents after a parental written informed consent. Classification into a control (healthy child) requires a double absence of a diagnosis of a respiratory disease by a physician and absence of respiratory symptoms (wheezing,

cough, dyspnea).

As for cases, they were taken mainly (85%) from a specialized center for the treatment of asthma in children, which provides free services to children with respiratory diseases from all areas of the country. Children came to the center either as new patients or for follow-up visits on their asthma symptoms, and not for any other reason. After the administration's approval, the questionnaire was distributed in the Asthma Center to asthmatic children's parents after a written informed consent was obtained. Classification into the diagnosed asthma group was defined as the child having asthma-related symptoms (chronic wheezing, cough, and dyspnea), as well as an affirmative answer to the question "Have your doctor ever told you that your child has asthma?". We note that some asthmatic children encountered in schools and fullfilling the case criteria were also enrolled in the study as cases (15%); this allowed an increase in the sample size and the power of the study.

A third group of participants that had a state of "probable asthma" was suggested for children in schools, having chornic respiratory symptoms but no physician confirmation of asthma diagnosis. They were neither cases nor controls. "Probable asthma" was thus defined as the presence of one of the following symptoms: a recurrent wheezing during the day, the evening, the night, the whole day or at exercise, a recurrent cough during the day, the evening, the night, the whole day or at exercise, a history of more than one dyspnea plus wheezing episode treated by a doctor.

Children with diagnosed asthma and those with probable asthma constituted the mixed group of children with "respiratory problem". Finally, no matching was done for cases and controls regarding any variable.

Questionnaire and Variables

A self-administered questionnaire adapted to local Arabic language (the native language of the country) from the standardized and validated American Thoracic Society chronic respiratory disease questionnaire, was used.[24] The same conditions were applied for questionnaires for all participants, to evaluate the diagnosis of asthma and respiratory symptoms. The standardized international study of asthma and allergies in childhood (ISAAC) questionnaire was translated into Arabic and back translated into English to ensure the accuracy of questions.[25] Questions regarding wheezing and night cough without having a cold were also taken from the ISAAC questionnaire.[25] More details about the used questionnaire can be found in previous studies.[23,26-28]

This questionnaire assessed the socio-demographic characteristics, including age, gender, region, the number of rooms and the number of persons living in the house, the level of education for both parents, the family history of asthma, and other known risk factors of asthma (i.e. the heating system used at home, child history of recurrent otitis, humidity inside the house defined as molds seen on the house's walls, the presence of pets at home, if the child went to a daycare, breastfeeding).

Questions about smoking or alcohol intake during pregnancy and during breastfeeding, the kind of smoking or alcohol along with the quantity were included, in addition to the use of any prescribed medication during pregnancy or lactation, occupational, regional, local, and domestic pesticides exposures and cleaning products use. For pesticide exposure, information was recorded using the following questions: i.e. ''Have you ever used pesticides in your work?'' ''Have you ever used pesticides out of your work (for house or garden treatment)?'' ''Do you live in a region heavily treated by pesticides?'' ''Do you live in the proximity of a heavily treated field by pesticides?'' along with the duration of exposure during work and the number of times the house or the garden get sprayed by pesticides per week or per year. Active smoking was determined by several questions (i.e. number of daily cigarettes, weekly waterpipes smoked, other nictotine/tobacco use), categorizing subjects in non-smokers or current smokers. Passive smoking will be characterized by the number of smokers at home.

Detergents use was determined by questions about who uses these products at home, the type of detergents and if there is any mixture of these products or not (the use of 2 or more detergents simultaneously). Education level was quantified according to the number of years of studying. Information about the heating system used at home, the presence of an air conditioner and a dehumidifier, the presence of humidity or mold at home as seen on walls, the child's history of recurrent otitis, tonsillectomy, cardiac problems, premature birth, and kindergarten were also recorded.

Sample Size Calculation

Using the Gpower 3.1.9.2 software for the calculation of the minimal sample size needed for our study, with a 1-β=0.8, a proportion $p2$=0.05 (5% reflects the percentage of the mothers that smoked

during pregnancy in the healthy children group) according to the pilot study that was done last year[23] and considering a ratio of 4 controls for every case and an odds ratio OR=2, the results showed that we need 296 cases versus 1184 controls.[29]

Statistical Analysis

Data analysis was performed using SPSS version 23 (IBM, USA). Percentages were shown for qualitative variables, while means and standard deviation were given for quantitative variables.

Two sided statistical tests were used to compare between group percentages and Student's t test for quantitative variables of normal distribution and homogeneous variances. Moreover, two multivariable backward logistic regressions were applied taking healthy children versus asthmatics and healthy children versus those with respiratory symptoms (probable asthma) as the dependent variables respectively; the independent variables taken into the multivariable analysis were those that showed a $p<0.2$ in the bivariate analysis. A $p<0.05$ was considered significant.

RESULTS

Socio demographic and socio economic characteristics

Out of 1680 questionnaires distributed in schools, 1503 (89.46%) were collected back from parents of the children aged between 3-16 years old. There were missing values in our results since not all questions were answered by all parents. The sample included 527 children having respiratory problems (35.1%; 95% CI 32.65-37.48), with 300 having diagnosed asthma (20%; 95% CI 17.937-21.983) and 227 having probable asthma (15.1%; 95% CI 13.29-16.92) respectively.

Table 1 summarizes the sociodemographic and socioeconomic factors. The results showed that our sample included 1,503 children aged 3-16 years (51.6% boys and 48.4% girls). 55.9% of these children had 1 or 2 person(s) living with them. Parents' university education was 35.8% for fathers and 55.1% of the mothers.

Bivariate Analysis

The bivariate analysis results for the factors that might be associated with the respiratory problem are summarized in Table 2. A significantly greater proportion of asthmatic children (37%) as compared to healthy ones (4.2%) had more respiratory infections ($p<0001$), a higher number of smokers at home (46% vs 44.7%, $p=0.019$), played in the dust (26% vs 8.1%, $p<0.001$), had respiratory problems or eczema before the age of 2 years ($p<0.001$ for both variables), had recurrent otitis (35.2% vs 16.7%, $p<0.001$) and heart problems (2.7% vs 0.6%, $p=0.01$), had humidity in the house as seen on the walls (26% vs 11%, $p<0.001$), parental history of eczema ($p=0.001$), asthma ($p<0.001$) or rhinitis ($p<0.001$). A higher proportion of children with respiratory disease (14.5%) as compared to the healthy ones (8.5%) had pets at home ($p=0.021$).

Table 3 summarizes the bivariate analysis performed concerning the exposure of pregnant mothers and infancy to active smoking, alcohol, prescribed medication intake and detergent mixing. Taking any medication during pregnancy ($p<0.001$) or breastfeeding ($p=0.001$), alcohol during lactation ($p=0.028$), presence of a person at home working with pesticides ($p<0.001$), the child living in an area with pesticide use ($p<0.001$), pesticide use in the interior of the house ($p<0.001$) were all significantly associated positively with the asthma status.

Multivariate Analysis

At first, a multivariate analysis was performed taking children with diagnosed asthma as the dependent variable as compared to all other children. This analysis showed that the boys had a significantly higher risk of having asthma by 36.4% (ORa=0.646, CI 0.489-0.854, $p=0.002$); increasing the age of one year significantly increased the risk of asthma in 62.5% (ORa=1.625, CI 1.034-2.554, $p=0.035$); children living in North and South Lebanon had an increased risk of asthma in 62.5% and 13.6 times respectively (ORa=1.625, CI 1.034-2.554, $p=0.035$ and ORa=13.65, CI 3.698-50.385; $p<0.001$; respectively). The fact that the child lives in an area that has frequent use of pesticides increased the risk of asthma significantly by more than 3 times (ORa=3.307, CI 1.848-5.918, $p<0.001$ respectively). Smoking waterpipe by the mother during pregnancy increased the risk of asthma in children 6 times (ORa=6.11; CI 1.244-30.008; $p=0.026$), while cigarette smoking by the mother during lactation increased that risk by more than 3 times (ORa=3.44; CI 1.024-11.554; $p=0.046$) (Table 4).

A second multivariate analysis performed on children with a respiratory problem (probable asthma or diagnosed asthma) as dependent variable and compared to totally healthy children showed that boys

have a significantly higher risk of respiratory disease 23.1% as compared to girls (ORa=0.769, CI 0.613-0.965, *p*=0.023); children living in North and South Lebanon have a significant risk of respiratory disease 61.4% and 6 times respectively (ORa=1.614, CI 1.087-2.396, *p*=0.018 and ORa=6.335, CI 1.778-22.574; *p*=0.004 respectively). Living in an area with a frequent use of pesticides or pesticide in the house significantly increased the risk of respiratory diseases in children 2.5 times and 29.3% respectively (ORa = 2.48; CI 1.459-4.217; *p*=0.001 and ORa=1.293, CI 1.029-1.626, *p*=0.028 respectively). Taking any medicine during pregnancy and the paternal positive smoking status significantly increased the risk of respiratory diseases in children by 69.7% and 26.5% (ORa=1.697, CI 1.206-2.387, *p*=0.002 and ORa=1.265, CI 1.01-1.584; *p*=0.04) respectively (Table 4).

Table 1. Demographic and socioeconomic factors associated with a child's health status (healthy, probable and diagnosed asthma)

Disease status/ Factors	Total number of subjects N=1503 (100%)	Healthy Subjects N=976 (64.9%)	Probable Asthma N=227 (15.1%)	Diagnosed Asthma N=300 (20%)	*p*-value
Age (in years)	9.92 ± 3.34	9.12 ± 3.43	8.83 ± 3.60	8.83 ± 3.60	<0.0001
Age category					<0.0001
3-6 years	331 (22%)	163 (16.8%)	68 (30.2%)	100 (33.8%)	
7-10 years	337 (22.4%)	208 (21.5%)	56 (24.9%)	73 (24.7%)	
11-13 years	640 (42.6%)	459 (47.4%)	80 (35.6%)	101 (34.1%)	
> 14 years	181 (12%)	138 (14.3%)	21 (9.3%)	22 (7.4%)	
Gender					<0.0001
Male	775 (51.6%)	476 (48.8%)	113 (49.8%)	186 (62.4%)	
Female	726 (48.3%)	500 (51.2%)	114 (50.2%)	112 (37.6%)	
District					<0.0001
Beirut	348 (23.3%)	241 (24.7%)	46 (20.3%)	61 (20.4%)	
Mount Lebanon	637 (42.4%)	416 (42.6%)	100 (44.1%)	121 (40.5%)	
North	189 (12.6%)	98 (10%)	33 (14.5%)	58 (19.4%)	
South	25 (1.7%)	4 (0.4%)	0 (0%)	21 (7%)	
Bekaa	303 (20.2%)	217 (22.2%)	48 (21.1%)	38 (12.7%)	
Education father					0.027
Low *	133 (8.8%)	70 (7.2%)	27 (12.1%)	36 (12%)	
Intermediate **	820 (54.6%)	545 (56.3%)	112 (50%)	163 (54.5%)	
High ***	538 (35.8%)	353 (36.5%)	85 (37.9%)	100 (33.4%)	
Education mother					0.012
Low *	89 (5.9%)	49 (5%)	10 (4.4%)	30 (10.1%)	
Intermediate **	577 (38.4%)	383 (39.4%)	81 (35.8%)	113 (38%)	
High ***	828 (55.1%)	539 (55.5%)	135 (59.7%)	154 (51.9%)	
Number of persons per room					0.844
[0-1]	542 (36.3%)	354 (36.5%)	80 (35.6%)	108 (36.4%)	
[1-2]	849 (56.9%)	550 (56.7%)	133 (59.1%)	166 (55.9%)	
More than 2	101 (6.8%)	66 (6.8%)	12 (5.3%)	23 (7.7%)	

* Low level of education: Education for 8 years or less

** Intermediate level of education: Education for more than 8 years but no university degree

*** High level of education: university degree

Table 2. Bivariate analysis for the factors associated with the health status (healthy, probable and diagnosed asthma)

Disease status/ Factors	Total number of subjects N=1503 (100%)	Healthy Subjects N=976 (64.9%)	Probable Asthma N=227 (15.1%)	Diagnosed Asthma N=300 (20%)	*p*-value
Respiratory infections					<0.0001
No	1324 (88.1%)	935 (95.8%)	200 (88.1%)	189 (63%)	
Yes	179 (11.9%)	41 (4.2%)	27 (11.9%)	111 (37%)	
Number of smokers at home					0.019
0	828 (55.1%)	540 (55.3%)	126 (55.5%)	162 (54%)	
1 or more	675 (44.9%)	436 (44.7%)	101 (44.5%)	138 (46%)	
Pets in the house					0.021
No	1358 (90.4%)	893 (91.5%)	194 (85.5%)	271 (90.3%)	
Yes	145 (9.6%)	83 (8.5%)	33 (14.5%)	29 (9.7%)	
Play in dust					<0.0001
No	1318 (87.7%)	897 (91.9%)	199 (87.7%)	222 (74%)	
Yes	185 (12.3%)	79 (8.1%)	28 (12.3%)	78 (26%)	
Play outside					0.032
No	786 (52.3%)	530 (54.3%)	119 (52.4%)	137 (45.7%)	
Yes	717 (47.7%)	446 (45.7%)	108 (47.6%)	163 (54.3%)	
Play on carpet					<0.0001
No	425 (28.3%)	314 (32.2%)	45 (19.8%)	66 (22%)	
Yes	1078 (71.7%)	662 (67.8%)	182 (80.2%)	234 (78%)	
Pulmonary problems forbidding daily activities					<0.0001
No	1351 (89.9%)	962 (98.6%)	197 (86.8%)	192 (64.2%)	
Yes	151 (10.1%)	14 (1.4%)	30 (13.2%)	107 (35.8%)	
Humidifier at home					<0.0001
No	1190 (79.2%)	781 (80%)	158 (69.6%)	251 (83.7%)	
Yes	313 (20.8%)	195 (20%)	69 (30.4%)	49 (16.3%)	
Respiratory problems before 2 years of age					<0.0001
No	1334 (88.8%)	947 (97%)	212 (93.4%)	175 (58.3%)	
Yes	169 (11.2%)	29 (3%)	15 (6.6%)	125 (41.7%)	
Eczema before the age of 2 years ago					<0.0001
No	1404 (93.4%)	933 (95.6%)	210 (92.5%)	261 (87%)	
Yes	99 (6.6%)	43 (4.4%)	17 (7.5%)	39 (13%)	
Recurrent otitis					<0.001
No	1186 (79%)	813 (83.3%)	180 (79.3%)	193 (64.8%)	
Yes	315 (21%)	163 (16.7%)	47 (20%)	105 (35.2%)	
Heart problems					0.01
No	1487 (98.9%)	970 (99.4%)	225 (99.1%)	292 (97.3%)	
Yes	16 (1.1%)	6 (0.6%)	2 (0.9%)	8 (2.7%)	

Premature birth					0.005
No	1400 (93.1%)	922 (94.5%)	211 (93%)	267 (89%)	
Yes	103 (6.9%)	54 (5.5%)	16 (7%)	33 (11%)	
Humidity at home seen on walls					<0.0001
No	1273 (84.7%)	869 (89%)	182 (80.2%)	222 (73%)	
Yes	230 (15.3%)	107 (11%)	45 (19.8%)	78 (26%)	
Child sent to the kindergarten					0.066
No	863 (57.4%)	581 (59.5%)	118 (52%)	164 (57.4%)	
Yes	640 (42.6%)	395 (40.5%)	109 (48%)	136 (45.3%)	
Smoking father					0.099
No	828 (55.5%)	561 (58%)	113 (50.4%)	154 (51.5%)	
Yes	661 (44.3%)	406 (41.9%)	111 (49.6%)	144 (48.2%)	
Parents respiratory problems					<0.0001
No	1327 (88.3%)	892 (91.4%)	208 (91.6%)	227 (75.9%)	
Father	92 (6.1%)	43 (4.4%)	12 (5.3%)	37 (12.4%)	
Mother	67 (4.5%)	33 (3.4%)	7 (3.1%)	27 (9%)	
Parents with rhinitis problems					<0.0001
No	1290 (85.9%)	887 (90.9%)	185 (81.5%)	218 (72.9%)	
Father	94 (6.3%)	49 (5%)	17 (7.5%)	28 (9.4%)	
Mother	87 (5.8%)	24 (2.5%)	18 (7.9%)	45 (15.1%)	
Both	31 (2.1%)	16 (1.6%)	7 (3.1%)	8 (2.7%)	
Parents history of eczema					0.001
No	1268 (84.4%)	852 (87.3%)	179 (78.9%)	237 (79.3%)	
Father	113 (7.5%)	61 (6.3%)	27 (11.9%)	25 (8.4%)	
Mother	84 (5.6%)	42 (4.3%)	16 (7%)	26 (8.7%)	
Both	37 (2.5%)	21 (2.2%)	5 (2.2%)	1 (3.7%)	
Parental asthma history					<0.0001
No	1270 (84.6%)	859 (88%)	201 (88.5%)	210 (70.2%)	
Father	124 (8.3%)	69 (7.1%)	15 (6.6%)	40 (13.4%)	
Mother	70 (4.7%)	28 (2.9%)	7 (3.1%)	35 (11.7%)	
Both	38 (2.5%)	20 (2%)	4 (1.8%)	14 (4.7%)	
Maid at home					0.051
No	1095 (72.9%)	722 (74%)	171 (75.3%)	202 (67.3%)	
Yes	408 (27.1%)	254 (26%)	56 (24.7%)	98 (32.7%)	
Reflux					<0.0001
No	1379 (91.7%)	940 (96.3%)	197 (86.8%)	242 (80.7%)	
Yes	124 (8.3%)	36 (3.7%)	30 (13.2%)	58 (19.3%)	

Table 3. Association between exposure to toxics during pregnancy and infancy and the health status (healthy, probable and diagnosed asthma)

Disease status/ Factors	Total number of subjects N=1503 (100%)	Healthy Subjects N=976 (64.9%)	Probable Asthma N=227 (15.1%)	Diagnosed Asthma N=300 (20%)	*p*-value
Any drug used by the mother during pregnancy					<0.0001
No	1317 (87.7%)	890 (91.2%)	186 (82.7%)	241 (80.3%)	
Yes	184 (12.3%)	86 (8.8%)	39 (17.3%)	59 (19.7%)	
Any drug used by the mother during breastfeeding					0.001
No	1461 (97.2%)	957 (98.1%)	222 (97.8%)	282 (94%)	
Yes	42 (2.8%)	19 (1.9%)	5 (2.2%)	18 (6%)	
Active smoking mother during pregnancy					0.122
No	1433 (95.3%)	938 (96.1%)	215 (94.7%)	280 (93.3%)	
Yes	70 (4.7%)	38 (3.9%)	12 (5.3%)	20 (6.7%)	
Kind of smoking during pregnancy					0.172
Non smoker	1433 (95.3%)	938 (96.1%)	215 (94.7%)	280 (93.3%)	
Cigarette	47 (3.1%)	26 (2.7%)	7 (3.1%)	14 (4.7%)	
Waterpipe	19 (1.3%)	10 (1%)	3 (1.3%)	6 (2%)	
Active smoking mother during breastfeeding					0.289
No	1436 (95.5%)	938 (96.1%)	216 (95.2%)	282 (94%)	
Yes	67 (4.5%)	38 (3.9%)	11 (4.8%)	18 (6%)	
Kind of smoking during breastfeeding					0.212
Non smoker	1436 (95.5%)	938 (96.1%)	216 (95.2%)	282 (94%)	
Cigarette	45 (3%)	25 (2.6%)	5 (2.2%)	15 (5%)	
Waterpipe	19 (1.3%)	11 (1.1%)	5 (2.2%)	3 (1%)	
Alcohol during pregnancy					0.515
No	1469 (97.7%)	957 (98.1%)	221 (97.4%)	291 (97%)	
Yes	34 (2.3%)	19 (1.9%)	6 (2.6%)	9 (3%)	
Alcohol drinking during breastfeeding					0.028
No	1476 (98.2%)	962 (98.6%)	218 (96%)	296 (98.7%)	
Yes	27 (1.8%)	14 (1.4%)	9 (4%)	4 (1.3%)	
Person at home using pesticides					<0.0001
No	1187 (79%)	770 (78.9%)	154 (67.8%)	263 (87.7%)	
Yes	316 (21%)	206 (21.1%)	73 (32.2%)	37 (12.3%)	
Child living in a region with pesticide use					<0.0001
No	1428 (95%)	947 (97%)	215 (94.7%)	266 (88.7%)	
Yes	75 (5%)	29 (3%)	12 (5.3%)	34 (11.3%)	
Child living near a prairie/field treated with pesticides					0.065
No	1247 (83%)	826 (84.6%)	182 (80.2%)	239 (79.7%)	
Yes	256 (17%)	150 (15.4%)	45 (19.8%)	61 (20.3%)	
Pesticides use at home					<0.0001
No	854 (56.8%)	586 (60%)	105 (46.3%)	163 (54.3%)	
Yes	649 (43.2%)	390 (40%)	122 (53.7%)	137 (45.7%)	
Active smoking father					0.099
No	828 (55.5)	561 (58%)	113 (50.4%)	154 (51.5%)	
Yes	661 (44.3%)	406 (41.9%)	111 (49.6%)	144 (48.2%)	
Father smoking kind					0.054
Non smoker	836 (55.6%)	566 (58%)	114 (50.2%)	156 (52%)	
Cigarette	439 (29.2%)	285 (29.2%)	68 (30%)	86 (28.7%)	
Waterpipe	199 (13.2%)	110 (11.3%)	38 (16.7%)	51 (17%)	
Cigarette&waterpipe	27 (1.8%)	14 (1.4%)	6 (2.6%)	7 (2.3%)	
Detergent mixing					0.004
No	1277 (85%)	849 (87%)	190 (83.7%)	238 (79.3%)	
Yes	226 (15%)	127 (13%)	37 (16.3%)	62 (20.7%)	

Table 4. Multivariable analyses of factors associated with probable and diagnosed asthma

Regression 1: Diagnosed asthma versus healthy children at the dependent variable				
Factors	***p*-value**	**ORa**	**Confidence Interval**	
Gender	0.002	0.646	0.489	0.854
Age	0.035	1.625	1.034	2.554
District*				
Mount Lebanon	0.723	1.067	0.747	1.523
North	0.035	1.625	1.034	2.554
South	<0.0001	13.65	3.698	50.385
Bekaa	0.215	0.743	0.466	1.188
Person using pesticides who lives with the child at home	0.001	0.5	0.337	0.744
Child living in a region sprayed with pesticides	<0.0001	3.307	1.848	5.918
Any drug during pregnancy	0.058	1.462	0.988	2.164
Smoking kind during pregnancy**				
Cigarettes	0.785	0.841	0.243	2.911
Waterpipe	0.026	6.11	1.244	30.008
Smoking kind during breastfeeding**				
Cigarettes	0.046	3.44	1.024	11.554
Waterpipe	0.086	0.154	0.018	1.303

* District as compared to Beirut taken as a reference

** Smoking during pregnancy or breastfeeding as compared to non-smoking mothers

Regression 2: Respiratory disease versus healthy children at the dependent variable				
Factors	***p*-value**	**ORa*****	**Confidence Interval**	
Gender*	0.023	0.769	0.613	0.965
Age	<0.0001	0.892	0.86	0.924
District **				
Mount Lebanon	0.326	1.159	0.864	1.556
North	0.018	1.614	1.087	2.396
South	0.004	6.335	1.778	22.574
Bekaa	0.851	1.035	0.722	1.485
Child living in a region sprayed with pesticides	0.014	2.709	1.219	6.020
Pesticides use at home	0.016	1.668	1.100	2.527
Any drug use during pregnancy	0.002	2.242	1.355	3.711
Smoking father (cigarette versus non-smoker)	0.012	1.618	1.114	2.351
Alcohol during breastfeeding	0.007	9.961	1.894	52.384

* Male gender as a reference

** District as compared to Beirut taken as a reference

*** ORa= Adjusted Odds Ratio

DISCUSSION

This is a case-control study carried out on schoolchildren in all districts of the country to assess potential risk factors for asthma, respiratory diseases, and allergy, specifically evaluating the effect of exposure to toxic substances during pregnancy and infancy. This type of study has been done before showing similar results,[16,25] however, the originality of the current study was the findings that WP smoking during pregnancy and cigarette smoking during lactation were both significantly associated with the asthma diagnosis in children.

A child living in an area where pesticides are used was significantly associated with both asthma diagnosis and respiratory diseases. A child living with a person that works with pesticides and/or living in a home where pesticides are used was significantly associated with asthma diagnosis and respiratory diseases respectively. Finally, age and gender were both significantly correlated with asthma diagnosis and respiratory diseases while the use of any prescribed medication during pregnancy and the father smoking cigarettes were both positively correlated with respiratory diseases.

We found that age was significantly associated with asthma or allergy but in significant correlation with probable asthma, in line with the observation made by Porsbjerg et al.[30] Living in South Lebanon was significantly associated with a higher risk of asthma and respiratory diseases as compared to all other districts, probably as a consequence of the bombardments during the war in 2006. This finding is opposite to the observation of Salameh et al who found that living in the capital would predispose the child to more respiratory diseases.[16] However, we cannot exclude the fact that healthy families are more likely to leave conflicted zones than families with diseased members and thus the causal relationship may be inverse. Diagnosis of asthma was more frequently done in males compared to females, similar to the results of Waked and Salameh[31] and as shown previously in the literature that male sex is predominant in asthma population in the first decade.[1,32]

Smoking

Our study did show a correlation between waterpipe smoking during pregnancy, cigarette smoking during breastfeeding and asthma on one hand and cigarette smoking in the father and respiratory diseases in children on another hand. This is the first study conducted in Lebanon that shows a positive correlation between waterpipe smoking during pregnancy and asthma in infancy. This could be explained by the fact that a low number of mothers consumed cigarettes during pregnancy maybe due to its known toxicity, while waterpipe's false conception[22] of safety in the Lebanese population induced a higher consumption, the effect of which was easily detected in our study. However, our results showed prominent effects for waterpipe but no significant results for cigarette smoking: These alarming results are to be confirmed by further larger scale studies. Our results were strengthened by other studies done by Neuman et al[33] and Simons et al,[34] showing an increased risk for preschool wheeze and asthma among children exposed to cigarette smoke by their mothers during pregnancy and breastfeeding as well.

Alcohol

Alcohol consumption during lactation, but not during pregnancy, was significantly correlated with respiratory diseases in children. Our results were not in concordance with the results found by Magnus et al[35] that the low levels of alcohol exposure during pregnancy or lactation observed in the cohort study they conducted were not associated with increased risk of asthma.[35] Few studies assess the exposure to alcohol during pregnancy and breastfeeding and the risk of asthma in children, thus more specific studies would be needed for this purpose.

Pesticides, Detergents, Medication Intake

Occupational exposure to pesticides has been associated with respiratory symptoms and chronic respiratory diseases such as asthma.[36] The general population is also exposed to pesticides by domestic use or accidental exposure. Non-occupational chronic respiratory indoor exposure can result in high annual cumulative doses and thus may aggravate or enhance asthmatic symptoms.[37] Child exposure to pesticides (either at home, or in an area surrounding his house, or by living with a person who works with pesticides) was significantly associated with both asthma and respiratory diseases in our study, similarly to the results of Salameh et al that showed that chronic exposure to pesticides in children was associated with chronic respiratory symptoms and diseases, especially asthma.[16]

On the other hand, domestic use of cleaning products, in particular, those in spray form, has been also suggested as a risk factor for asthma.[17,18] Our results did not show any correlation between asthma and detergent use at home by the mother or the maid in the multivariate analysis in opposite to what Vizcaya et al suggested that cleaning workers with asthma or asthma symptoms are characterized by non-reversible airway obstruction and non-eosinophilic inflammation.[38] We hypothesize that mothers clean their home probably when the child is outside the house to avoid exposure; in this way, children may not be exposed to detergents for a long period of time during their life.

Furthermore, the results of this study did show a significant correlation between the use of prescribed medications during pregnancy with respiratory diseases and tended to significance with diagnosed asthma. This goes in line with many studies showing a positive relationship between prescribed medications intake by the mother during pregnancy and asthma in children.[18-20] Further researches might be needed to show the classes of medications that might be implicated in this disease.

Limitations

Our study has several limitations and strength points. The total sample size is acceptable, withdrawn from all districts in Lebanon and might be representative of the whole population. However, a selection bias is still possible because of the ten percent refusal rate. The questionnaire used in our methodology, including ISAAC one, is similar to that used in other case-control studies, which is necessary for international comparisons. This is a case-control study with retrospective reports, and consequently a low level of evidence, due to the possibility of recall bias; parents might have given us wrong information probably because they do not remember what really happened during the pregnancy period or during the childhood period. The use of a questionnaire in parents may not always be accurate: problems in question understanding, recall deficiency and over or under evaluating symptoms as well as a possible underestimation to toxics exposure may still be possible, which can lead to a possible information bias. The study design can only identify associations and whilst agree that evidence from other studies does implicate maternal smoking during pregnancy and pesticides in asthma causation, the authors cannot infer causation since the cotinine levels were not measured in all children. In addition, smoking mothers may be more prone to take other risky behaviors, or that might have low access to healthier lifestyle (alcohol, medications, pregnancy health controls, diet, etc. The frequency of pesticides use in fields nearby living places could not be measured; the answers obtained are subjective by the parents. We did not differentiate between maternal and paternal pesticides use in pregnancy. We did not take into account the season of birth, as this could have an influence on exposure in pregnancy and thus differ between children. Furthermore, we did not assess if the pre- or the postnatal exposure or both had an influence on asthmatic symptoms. Asthmatics were included from all Lebanon, but healthy controls only recruited in schools; this might cause a bias in the results, as there might be less smoking/pesticides in controls. The amounts of alcohol and smoking during pregnancy and breastfeeding are subjective and could not be measured due to the retrospective nature of this study.

Asthma and related diseases seem to be linked to several risk factors in our population of school children across the country. The origin of asthma may be due to the environmental exposure to pesticides, tobacco (cigarettes and waterpipe), alcohol or prescribed medications during pregnancy and lactation. Spreading awareness by health professionals about these preventable causes can help educate the parents and children to prevent asthma and its exacerbation. Additional larger scale studies are necessary to confirm our results, particularly for waterpipe and alcohol exposures.

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Validation of asthma control questionnaire and risk factors affecting uncontrolled asthma among the Lebanese children's population

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ABSTRACT

Objectives: To validate the Arabic version of the Asthma Control Test (ACT) in asthmatic children in Lebanon and identify risk factors that might affect asthma control in these children.
Methods: This study, conducted between December 2015 and April 2016, included 300 children.
Results: A high Cronbach's alpha was found for the full scale (0.959). The correlation factors between each item of the ACT scale and the whole scale ranged between 0.710 and 0.775($p < 0.001$ for all items). Low mother's educational level as well as the history of asthma in the mother and the father would significantly increase the risk of uncontrolled asthma ($p = 0.001$; Beta = 1.862; $p < 0.001$; Beta = 3.534; $p < 0.001$; Beta = 1.885respectively). Cigarette smoking during breastfeeding and waterpipe smoking by the mother during pregnancy were both significantly associated with uncontrolled asthma ($p = 0.005$; Beta = 2.105 and $p = 0.041$; Beta = 2.325 respectively). The high mother's level of education was significantly associated with more asthma control ($p = 0.008$; Beta = −0.715).
Conclusion: The Arabic version of the asthma control questionnaire is a valid tool to use in pediatric patients in the Lebanese population to assess asthma control. Waterpipe smoking during pregnancy and cigarette smoking during breastfeeding, as well as the lower education level are risk factors for uncontrolled asthma. Spreading awareness among health care professionals, as well as reinforcing health education seem to be an important step toward a better asthma control.
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1. Introduction

Bronchial asthma is a chronic inflammatory syndrome that is highly prevalent worldwide, affecting approximately 300 million individuals of all ages and accounts for 250,000 deaths annually worldwide [1]. According to international guidelines, the primary goal of asthma management is to achieve and maintain asthma control defined as 'no daytime symptoms, no limitations of daily activities, no nocturnal symptoms or awakening, no need for reliever treatment, normal or near-normal lung function results [2] and thus reduce the risk of life-threatening exacerbations and long-term morbidity [3–6]. Nonetheless, in everyday practice, asthma remains poorly controlled in a large proportion of patients [7–10]. Several studies have recognized the profits and advantages of good asthma control on a variety of consequences such as reduced loss of work/school days, a normal and even better quality of life, and reduced risk of exacerbations [11]. Furthermore, several other impacts on children may also be associated with uncontrolled asthma such as a reduced daily activity and a negative impact on cognitive and intellectual functions [11]. Asthma control can be difficult to assess in clinical practice; this might be due to its variation over time and its duplicitous. In an attempt to facilitate this assessment, several simple and easy to use tests have been developed such as the Asthma Control Test (ACT) [12], the Test for Respiratory and Asthma Control in Kids (TRACK) [13] and the Childhood ACT (C-ACT) [14]. The ACT is intended to be used for

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patients 12 years and above [15], while the C-ACT should be used for patients 4–11 years of age [14]. The C-ACT and ACT are 7- and 5-item questionnaires respectively, that assess asthma control (eg, symptom frequency) over the prior month [14,15]. Since the various tests use the same symptoms of asthma (day and night symptoms, limitation of activities and use of rescue medication), the results of these tests are assumed to correlate to some extent with each other and with the GINA definition of asthma control [16]. A study comparing the C-ACT and the ACT tests showed a good agreement between them when detecting poor asthma controlled, as compared to the GINA criteria [17].

Asthma symptoms are influenced by the children's level of perception and the children's daily activities, including sports and social life events and activities. Hence, physical activity is one of the most important causes of symptoms and reliever use in children [18,19]. Furthermore, the risk of future disease- and treatment-related complications, including exacerbations, accelerated decline in pulmonary function, and adverse effects of drugs, should also be considered [2].

On the other hand, multiple socioeconomic and environmental factors contribute to the exacerbation of asthma symptoms. Among these factors, we have the sustainable exposure to triggers and lower educational status [20,21]. One of the most important triggers that the child might be exposed to is tobacco smoking. In particular, household cigarette smoke exposure was the single most significant factor in predicting poor control according to McGhan et al. [22]. In fact, each hour per week of smoke exposure increased the likelihood of poor control by 33% [22]. Additionally, in Lebanon, the prevalence of waterpipe smoking is dramatically increasing, reaching 36.9%, the highest among countries in the region [23]. On the basis of smoking machine data, the amount of water pipe tobacco used in a single smoking session was reported to produce 100-fold more tar, 4-fold more nicotine, 11-fold more CO, and 2- to 5-fold more polycyclic aromatic hydrocarbons than did a single cigarette [24]. Furthermore, a recent study conducted in Lebanon evaluated the acute and chronic effect of 45 min session of waterpipe on the respiratory functions (% Forced Expiratory Volume (FEV) 1, %FEV6 and %FEV1/FEV6). The results showed that there was no statistically significant difference for all the respiratory functions between cigarette and waterpipe tobacco smoking [25]. In addition, Shafagoj and colleagues found that the waterpipe smokers had about 2-fold higher expired CO levels and about 3-fold higher plasma nicotine levels than cigarette smokers [26].

Thus, the objectives of the current study were to use the Arabic version of the ACT in asthmatic children in Lebanon, to check its validity compared to other versions of the questionnaire, as well as identify risk factors that might affect the asthma control in these children.

2. Methods

2.1. Study design

This study was conducted between December 2015 and April 2016. Cases were chosen from a specialized center for the treatment of asthma in children, the Asthma Center, located in Hazmieh, Lebanon. The latter welcomes children, coming from all districts of Lebanon, with respiratory diseases only and are examined by specialized pediatricians free of charge. After the administration's approval, the questionnaire was distributed in the Asthma Center to asthmatic children's parents after a written informed consent was obtained from all parents. Patients included in the study were those with a physician's diagnosis of asthma, whose parents were capable to understand and to complete the questionnaire. The questionnaire was administered at all the study visits to children in those aged 12–16 and to their parents if they were aged 3–11 years, a method similar to the study of Perez et al. [27].

The Lebanese University waived approval of the study since it is an observational non-invasive study that respects participants' autonomy and anonymity; the study followed principles of the Declaration of Helsinki for such types of studies [28].

2.2. Questionnaire and variables

The questionnaire assessed the socio-demographic characteristics, including age, gender, region, number of rooms and the number of persons living in the house, the level of education for both parents, the family history of asthma. The validated questionnaire in Arabic was sent to us by Professor Elizabeth Juniper (Department of Clinical Epidemiology and Biostatistics, McMaster University) to be used in our study.

We decided to choose to use the ACT in our study since the purpose of the study is to check asthma control in all school children from all ages; we could not use the childhood version of this test for children aged more than 11 years. Furthermore, children's parents would be answering the test questions for younger children (4–11 years).

The asthma control questionnaire was composed of 7 questions, asking about the frequency of awakening at night because of the disease (0 for never and 7 unable to sleep because of asthma), the severity of the symptoms upon waking up the next morning (0 for no symptoms and 7 for very severe symptoms), the limitations of the activity due to asthma during the last month (0 for no limitation of activity and 7 for severe limitation), the frequency of shortness of breath (0 for never and 7 for very high frequency) and wheezing (0 for never and 7 for all the time), as well as the number of puffs of a short-acting bronchodilator the patient had to use in the last week because of the disease (0 for never and 7 for more than 16 puffs most of the days) [12]. The answers varied between 0 and 6, with 0 being the answer to no bothering or no symptoms at all and 6 being the answer to very severe symptoms. In addition, the percentage of Forced Expiratory Volume (%FEV) was recorded by a staff member from the Asthma Center, which was categorized into 6 categories according to the original ACT [12]: category 0 refers to an FEV>95%, category 1 between 90 and 95%, category 2 between 80 and 89%, category 3 between 70 and 79%, category 4 between 60 and 69%, category 5 between 50 and 59% and category 6 for less than 50%.

2.3. Sample size calculation

Using the Epi info program for the calculation of the minimal sample size needed for our study, with an acceptable margin of error of 5% and an expected frequency of asthmatic children of 11.7% [29] for a 4 million inhabitants in Lebanon, the results showed that we need 296 cases to be enrolled in the study [30].

2.4. Statistical analysis

Data analysis was performed on SPSS software, version 22. To confirm the asthma quality of life and asthma control questionnaires construct validity in the Lebanese population, a factor analysis was launched for the 15 and 6 items of the two questionnaires respectively, using the principal component analysis technique, with a promax rotation since the extracted factors were found to be significantly correlated. The Kaiser-Meyer-Olkin measure of sampling adequacy and Bartlett's test of sphericity were ensured to be adequate. The retained number of factors corresponded to Eigen values higher than one. Moreover, Cronbach's alpha was recorded for reliability analysis for the total score and for subscale factors.

3. Results

3.1. Socio demographic and socio economic characteristics

Table 1 summarizes the socio-demographic and socioeconomic factors. The results showed that our sample included 300 children between age 3–16 years (62.4% boys and 37.6% girls). The mean age was 8.83 ± 3.60 years; 55.9% of these children had 1 or 2 person(s) living/sleeping in the same room of the house with them. Parents' university education was 33.4% for fathers and 51.9% for the mothers. On the other hand, 8.3% of the children had an asthmatic father, 4.7% had an asthmatic mother, while 2.5% had both parents asthmatic. The mean FEV percentage was 85.96% ± 8.79% while the mean ACT score was 10.84 ± 7.13 among asthmatic children.

Disease status/Factors	Diagnosed Asthma N = 300 (20%)
3-6 years	100 (33.8%)
7-10 years	73 (24.7%)
11-13 years	101 (34.1%)
>14 years	22 (7.4%)
Gender	
Male	186 (62.4%)
Female	112 (37.6%)
District	
Beirut	61 (20.4%)
Mount Lebanon	121 (40.5%)
North	58 (19.4%)
South	21 (7%)
Bekaa	38 (12.7%)
Father's level of education	0.027
Low*	36 (12%)
Intermediate**	163 (54.5%)
High***	100 (33.4%)
Mother's level of education	0.012
Low*	30 (10.1%)
Intermediate**	113 (38%)
High***	154 (51.9%)
Number of persons per room	0.844
[0–1]	108 (36.4%)
[1–2]	166 (55.9%)
More than 2	23 (7.7%)

* Low level of education: Education for 8 years or less.
** Intermediate level of education: Education for more than 8 years but no university degree.
*** High level of education: university degree.

3.2. Asthma control questionnaire validity checking

Out of all the items asked in the questionnaire, all variables could be extracted from the list, with no items that over-correlated to each other (r > 0.9), having a low loading on factors (<0.3) or because of a low communality (<0.3).

Table 1
Factor analysis of the asthma control questionnaire in the Lebanese population.[a]

Factor	Loading on factor
Waking up due to asthma during the night	0.906
Bad asthma symptoms when waking up in the morning	0.855
Limited activities because of asthma	0.816
Experiencing shortness of breath due to asthma	0.795
Number of times of wheeze due to asthma	0.732
Average number of puffs of a SABA[a]	0.628
FEV category[b]	0.930

c.Cronbach's alpha = 0.959.
[a] SABA= Short Acting Beta Agonist.
[b] FEV= Forced Expiratory Volume.

Table 2
Correlation factor of each item of the scale with the whole scale.

Factor	Correlation factor	p-value
Wake up due to asthma	0.708	<0.001
Bad asthma symptoms when waking up	0.721	<0.001
Limited activities	0.710	<0.001
Shortness of breath from asthma	0.755	<0.001
Wheezing	0.759	<0.001
Average number of puffs of SABA[a]	0.775	<0.001

[a] SABA= Short Acting Beta Agonist.

The factor analysis for the asthma control questionnaire was run over the sample of healthy individuals and asthmatic patients (Total $n = 1503$). The asthma control items converged over a solution of one factor that had an Eigenvalue over 1, explaining a total of 66.34% of the variance. A Kaiser-Meyer-Olkin measure of sampling adequacy of 0.900 was found, with a significant Bartlett's test of sphericity ($P < 0.001$). Moreover, a high Cronbach's alpha was found for the full scale (0.959) (Table 1).

Table 2 displays the correlation factors between each item of the ACT scale and the whole scale. The correlation factors ranged between 0.710 for the limited activities item to 0.775 for the average number of puffs of SABA. To note that all factors were highly significantly correlated with the whole scale with a $p < 0.001$ for all items.

The correlation between the full scale and FEV1 revealed a significant correlation between both items ($p < 0.001$ and $r = -0.682$).

3.3. Relationship between asthma control and FEV

We calculated the regression equation between the FEV1 and the whole scale. We obtained the equation:

ACT score = 50.49-[(0.5*FEV)] with $r = -0.682$ and $p < 0.001$ (Fig. 1). The better the FEV1 (higher scores), the better the asthma control (lower scores).

Fig. 2 shows the mean ACT score in the presence and absence of asthma symptoms (wheezing, allergy, cough or expectoration without flu). The results showed there was a significant difference in the mean ACT score in the absence or presence of all 4 symptoms ($p < 0.001$ for all variables), with a lower ACT score (better control) in the absence of any of these symptoms.

3.4. Multivariable analysis for asthma control as dependent variable

Table 3 summarizes the results of the 2 stepwise linear regressions conducted on asthma control as dependent variable. The results of the first regression conducted on these asthmatic children, with the risk factors as independent variables showed that the low mother's educational level as well as the history of asthma in the mother and the father would significantly increase the risk of uncontrolled asthma by 1.862, 3.534 and 1.885 points respectively ($p = 0.001$; Beta = 1.862; CI 0.766–2.958; $p < 0.001$; Beta = 3.534; CI 2.324–4.744 and $p < 0.001$; Beta = 1.885; CI 0.978–2.793 respectively). Cigarette smoking by the mother during breastfeeding, as well as waterpipe smoking by the mother during pregnancy, were both significantly associated with a lower asthma control by 2.105 and 2.325 points respectively ($p = 0.005$; Beta = 2.105; CI 0.646–3.565 and $p = 0.041$; Beta = 2.325; CI 0.093–4.558 respectively). On the other hand, the high mother's level of education was significantly associated with more asthma control by 0.715 points ($p = 0.008$; Beta = −0.715; CI -1.241 to −0.189).

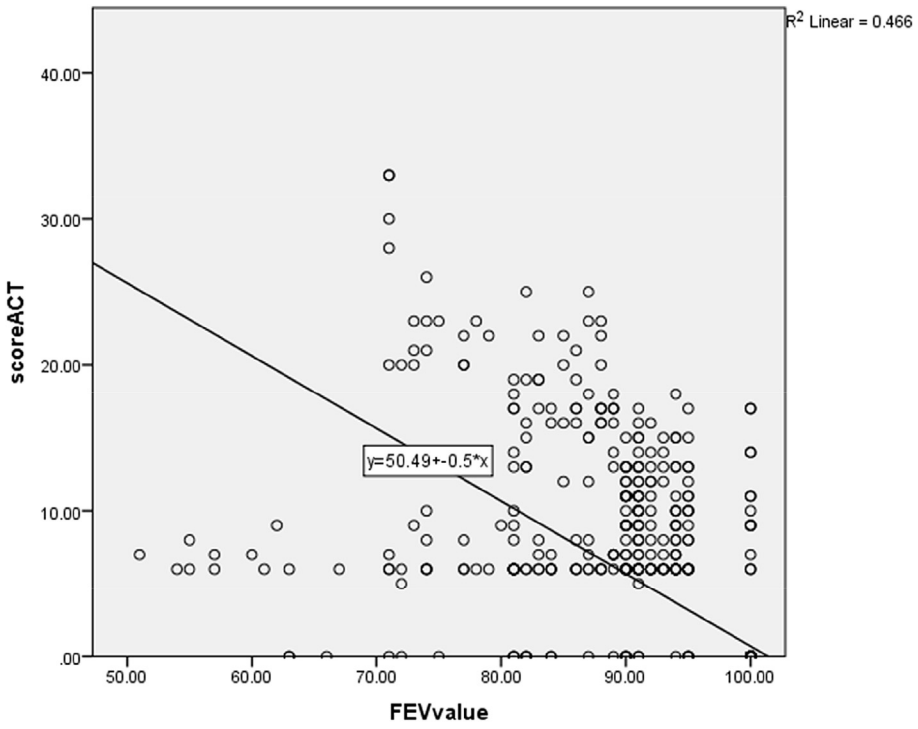


Fig. 1. Scatter plot of FEV value versus ACT score. $R = -0.682$ ($R^2 = < 0.466$); $p < 0.001$; *ACT score* $= 50.49 - [(0.5*\text{FEV})]$.

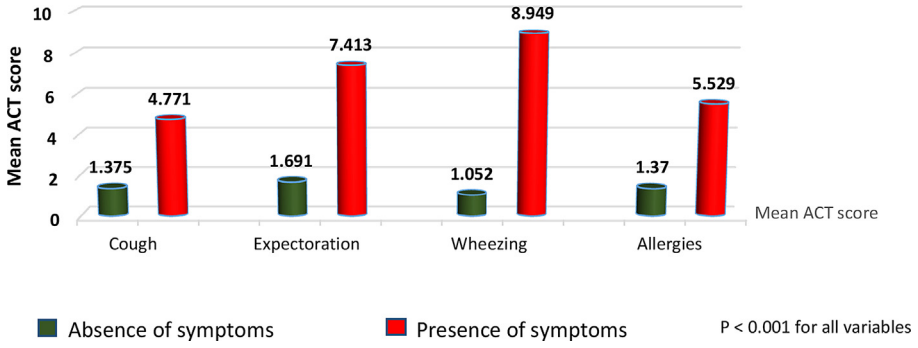


Fig. 2. Difference of mean ACT score in the absence or presence of asthma symptoms.

The second regression conducted, considering the risk factors and the treatment classes as independent variables, showed that treatment with a long-acting beta agonist combined with an inhaled corticosteroid (ICS), treatment with an ICS alone, treatment with a short-acting beta agonist, an inhaled anticholinergic or with a leukotriene inhibitor would significantly increase the asthma control by 11.20, 5.04, 3.02, 2.24 and 1.73 points respectively ($p < 0.001$ for all variables) (Table 3). In addition to that, the moderate and high mother's educational level would significantly increase the asthma control by 0.737 and 1.12 points respectively ($p = 0.024$; Beta $= -0.737$; CI -1.375 to -0.099 and $p < 0.001$; Beta $= -1.12$; CI -1.747 to -0.493 respectively). On the contrary, cigarette and waterpipe smoking by the mother during pregnancy would significantly increase the risk of uncontrolled asthma by 1.457 and 1.714 points respectively ($p = 0.001$; Beta $= 1.457$; CI 0.599–2.315 and $p = 0.013$; Beta $= 1.714$; CI 0.363–3.065 respectively).

4. Discussion

4.1. Validation of the scale

In the current study, we were able to validate the asthma control questionnaire, intended specifically for use among the Lebanese population. Results provided initial evidence supporting the reliability and validity of the scale as a screening instrument for asthma control in the Lebanese children. The one factor identified in the asthma control scale demonstrated good psychometric properties, with excellent internal consistency for the scale. Thus, it can be used in the Lebanese population.

Another way to verify the reproducibility of the questionnaire was to use correlation coefficients, as the one proposed by Kirshner and Guyatt [31]. The correlation coefficients showed high correlation between each item of the ACT questionnaire and the disease.

The association between ACT score and asthma symptoms is

Table 3
Linear regression with uncontrolled asthma as dependent variable.

Regression 1: Regression for risk factors alone on asthmatic children					
Factor	Unstandardized Beta	Standardized Beta	*P*-value	Confidence interval	
History of asthma in the mother	3.534	0.147	<0.001	2.324	4.744
Low mother's educational level	1.862	0.090	0.001	0.766	2.958
History of asthma in the father	1.885	0.105	<0.001	0.978	2.793
High mother's educational level	−0.715	−0.072	0.008	−1.241	−0.189
Cigarette smoking during breastfeeding	2.105	0.074	0.005	0.646	3.565
Waterpipe smoking during pregnancy	2.325	0.053	0.041	0.093	4.558
Regression 2: risk factors and treatment classes on asthmatic children					
Factor	Unstandardized Beta	Standardized Beta	*P*-value	Confidence interval	
Treatment with inhaled corticosteroids (ICS)	−5.041	0.562	<0.001	4.762	5.321
Treatment with short-acting beta agonists	−3.027	0.507	<0.001	2.843	3.210
Treatment with long acting beta agonists associated to ICS	−11.201	0.309	<0.001	10.096	12.307
Treatment with inhaled anticholinergics	−2.247	0.216	<0.001	1.930	2.564
Treatment with leukotriene inhibitors	−1.732	0.160	<0.001	1.403	2.061
Cigarette smoking during pregnancy	1.457	0.053	0.001	0.599	2.315
High mother's level of education	−1.120	-0.112	<0.001	−1.747	-0.493
Waterpipe smoking during pregnancy	1.714	0.039	0.013	0.363	3.065
Moderate mother's level of education	-0.737	-0.072	0.024	−1.375	-0.099

Variables entered in the model for regression 1: person working with pesticides that lives at home, low educational level of the mother, moderate educational level of the mother, high educational level of the mother, body mass index of the child, heart problems in the child, cigarette smoking during breastfeeding, waterpipe smoking during breastfeeding, cigarette smoking during pregnancy, waterpipe smoking during pregnancy, alcohol drinking during pregnancy, breastfeeding of the child, father history of asthma, mother history of asthma, both parents history of asthma.
Variables entered in the model for regression 2: person working with pesticides that lives at home, low educational level of the mother, moderate educational level of the mother, high educational level of the mother, body mass index of the child, heart problems in the child, cigarette smoking during breastfeeding, waterpipe smoking during breastfeeding, cigarette smoking during pregnancy, waterpipe smoking during pregnancy, alcohol drinking during pregnancy, breastfeeding of the child, father history of asthma, mother history of asthma, both parents history of asthma, treatment with LABA + ICS, treatment with ICS alone, treatment with SABA, treatment with anti-leukotrienes, treatment with inhaled anti-cholinergics.

pretty tight. In fact, Juniper et al. originally generated a list of ten symptoms that might be used by clinicians to assess the adequacy of asthma control, including 3 out of 4 symptoms (wheezing, cough, expectoration) assessed in our study [12]. However, the ACT includes the five highest scoring symptoms that most commonly reveal lack of control in the majority of patients, in addition to one question about beta 2 agonist use and another about FEV [12]. Our results showed that the presence of allergies was even related to a worse control of asthma, a factor that was not taken into consideration in Juniper's study.

Furthermore, our results showed a strong correlation between the ACT and the severity of the disease as described by FEV1 value, similar to the results of Perez-Yarza et al. that also showed that patients with more severe symptoms and exacerbations had a worse ACT score, indicating a clear relationship between the ACT score and patients' clinical status [27]. These results are similar to those observed in an earlier study to develop and test an asthma control test for use in adult populations. In that study, the authors also found that the questionnaire discriminated well between patients with different degrees of symptom intensity and frequency [32].

Poor asthma control can result in distressing symptoms including chronic cough, persistent wheezing, annoying nighttime awakenings and difficulty in performing daily activities [17]. This will result in a higher emergency department visits and a higher number of hospitalizations and consequently a lower quality of life [33]. Moreover, patients with inadequately controlled asthma remain at a high risk of serious morbidity and mortality [34]. Despite adequate treatment, continuous exposure to risk factors would still jeopardize asthma control.

4.2. Modifiable risk factors associated with asthma control

4.2.1. Smoking

Constituents of tobacco smoke can cause loss of cilia along with a hypertrophy in the mucus gland in the upper airways. Thus, inflammation, epithelial changes, fibrosis and secretory congestion can occur in the peripheral airways, and alveoli are destroyed with loss of gas exchange surface area and airways flexibility. Indeed, vascular changes to the small arteries and capillaries of the bronchioles and the alveoli also occur [35]. Hence, the nicotine passes through the breast milk of the mother to the baby in an amount of nicotine more than double that transferred to maternal serum [36], and consequently inducing airway inflammation in non-asthmatic smokers without airflow obstruction compared with nonsmokers [37–40].

In our study, mother's waterpipe smoking during pregnancy and cigarette smoking during breastfeeding were associated with more uncontrolled asthma. Results were not significant for cigarette smoking during pregnancy though. Our new finding about waterpipe could be explained by the fact that a low number of mothers consumed cigarettes during pregnancy maybe due to its known toxicity [41], however restarted smoking after delivery. Waterpipe false conception of safety in the Lebanese population induced a higher consumption during pregnancy [42], the effect of which was easily detected in our study. To our knowledge, our study is the first to assess the effect of waterpipe smoking during pregnancy on asthma control in asthmatic children. These alarming results are to be confirmed by further larger scale studies.

4.2.2. Level of education

Low mother's level of education was significantly associated with a poor asthma control, in opposite to the higher educational level significantly associated with a better asthma control. Our results confirm the solid findings of multiple previous studies: it is plausible that parents with high literacy levels were likely to take an active role and intensively engage in the shared decision process, leading to an increase in their satisfaction with shared-decision making [43]. This implies that if physicians improve the interactions with their patient and assure a better patient's

understanding for the asthma treatment plan, the likelihood of achieving good asthma control is high.

From another point of view, it is also credible that parents with a lower level of education are of lower socio-economic status, thus the poor asthma control could also be a result of poor housing, lack of access to good quality healthcare and/or lack of access to medication. In fact, Peters et al. identified low education and household income, as predictive factors of uncontrolled asthma [44]; these 2 factors were consistent and associated with asthma in other populations [45–48].

4.3. Non modifiable risk factors

On the other hand, some other non-modifiable factors such as the history of asthma in the mother and the father, would significantly increase the risk of uncontrolled asthma.

4.4. Parental history of respiratory disease

A history of asthma in either parent was significantly associated with more uncontrolled asthma in the child similar to the findings of Konradsen et al. [49]. There could be a genetic association with asthma related outcomes based on Kondarsen's study; this relationship needs however to be better defined. Another explanation for these findings is the “hygiene hypothesis”. This hypothesis suggests that the young child's environment can be “too clean” to effectively challenge and promote the development of a mature immune system [50]. Parents with a history of asthma may exaggerate in their children's hygiene, which may give an inverse effect and lead to an increase asthma severity.

4.5. Limitations

Our study has some limitations. Since it is an episodic disease, and when properly controlled, the patient may stay asymptomatic for some time. On the other hand, the patient may have extremely severe episodes triggered according to the season of the year or the presence of indoor or outdoor allergens. For these reasons, our patients' answers may not totally reflective of the actual disease status and the actual asthma control. In order to assess the yearly control of the child, longitudinal studies are necessary, along with questions related to events over the whole year (past week, past month, for instance), and to try to determine the intensity and frequency of symptoms at different times of the year. We could not control for the possibility that the same mothers smoking waterpipe during breastfeeding are not also doing so in the present (active waterpipe smoking) and thus active waterpipe smoking acting as a confounder of the relationship “waterpipe smoking during breastfeeding-poor asthma control”; the same applies for cigarette smoking. This is a cross sectional survey with retrospective reports, and consequently a low level of evidence. The possibility of recall bias might be entertained due to the retrospective nature of our investigation. The effect of the recall bias could be differential and lead to the overestimation of effects for some known risk factors. However, for the substances that are not known to be associated with asthma, the bias is non differential, and an underestimation of the association with asthma is to be expected. Prospective studies that override the recall bias are expected to improve the precision of our results. An information bias is also possible since the use of a questionnaire in a young population or for surrogate responders (parents) may not always be accurate: problems in question understanding, recall deficiency and over or under evaluating symptoms may still be possible. The exposure to the different toxics was subjective and was quantified according to the parents' estimation. Unfortunately, there was no possibility to measure the quantity and time of exposure to each toxic.

5. Conclusion

The Arabic version of the asthma control questionnaire is a valid tool that can be safely used in pediatric patients in the Lebanese population to assess asthma control. We were also able to address some factors related to a worse asthma control in asthmatic children. The most significant were waterpipe smoking during pregnancy and cigarette smoking during breastfeeding, as well as the lower education level. Thus, spreading awareness among health care professionals, as well as reinforcing health education seem to be an important step toward a better asthma control.

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Competing interests

None declared.

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