The role of IgG and IgE in the development of allergy and asthma
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Chapter 1

General Introduction
INTRODUCTION

Atopic diseases are common in childhood. Despite our increasing understanding of these diseases, it is still unknown why a child develops IgE antibodies to usually harmless proteins. We know that it is determined by a combination of genetics and environment and that it starts early in life. However, in order to establish whether a child will become allergic and asthmatic, we need indicators that recognize in early childhood or infancy that a child’s immune system is sensitive and the child is likely to become sensitized in the future. This will enable us to respond adequately or even try to prevent the disease to develop. In this study, we investigated whether IgG to foods could be such an indicator.

Furthermore, to be able to start (early) treatment, we need predictors that can distinguish symptomatic children who will go on developing asthma from symptomatic children in whom the symptoms prove to be transient. In early childhood there is a high proportion of children with asthma-like symptoms that will not develop asthma in the future. For GPs it is difficult to identify in which young children airway symptoms will persist into childhood asthma. It would be interesting to define a variable that could be used to identify young children who will continue to be symptomatic at school age. In this study, we focussed on IgE sensitization as such a factor in the prediction of asthma.

This thesis focuses on the development and prediction of allergy and asthma in childhood, with a special reference to general practice. Most studies on allergy and asthma in young children have been performed in cohorts in the general population or in specialists’ hospitals. In general practice children present with a different distribution of symptoms than in a clinical/specialist setting because of the GP filter and its influence on the frequency of clinical presentations [1]. Results from cohort studies in the general population cannot be applied straightforwardly to the primary care situation. Therefore,
it is important that research is carried out in general practice itself, based upon consultation with the GP.

As an introduction to this thesis, this chapter deals with several topics on the background of this study. We will start assessing definitions of allergy and asthma. Secondly, the immunologic mechanisms of IgG will be considered. In more detail, we will examine whether IgG levels to foods are increased prior to the development of sensitization to airborne allergens and, if so, might be used as indicators of increased activity of the immune system. After that, the prevalence of asthma and allergy will be discussed. In addition we will consider the prognosis of asthma. Finally, we will discuss the guidelines on treatment of allergy and asthma.

Definitions

For research it is important to be as precise as possible about the abnormality we have studied [2]. For instance, depending on the definition used, prevalences for asthma will be different.

The term atopic diseases has been adopted for the group of disorders and syndromes which include asthma, allergy, atopic dermatitis, infantile eczema, and hay fever. These diseases have in common that immunoglobulin E (IgE) against environmental allergens is present. Furthermore, atopy is inherited [3], which means that atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhino-conjunctivitis, or eczema/dermatitis [3].

Allergy is a hypersensitivity reaction initiated by immunologic mechanisms [3]. It is an exaggerated immune response which develops after repeated
exposures to common environmental antigens [4]. Antigens that stimulate hypersensitivity (allergy) are referred to as allergens [3].

It should be noted that allergy/sensitization, i.e. the presence of IgE antibodies, does not necessarily point to (the presence of) a clinical disease. Only some subjects will develop allergic sensitization and of these sensitized subjects, not everyone will develop (clinical) allergic disease. For clarity’s sake, sensitization will be used to indicate the presence of IgE antibodies, and allergy when (also) clinical disease is implied.

There is no agreed definition for asthma in young, i.e. pre-school children [5,6]. As long as we do not know (more about) the pathogenesis of asthma, it can only be defined as abnormalities at several levels: clinical, physiological, pathological, immunological and cellular [7]. Which of these abnormalities is selected depends on the purpose for which it is used [8].

Physiologists define asthma in relation to airflow limitation (induced or spontaneous), which is reversible either spontaneously or with treatment, whereas pathologists define asthma in terms of inflammation and cellular infiltrates of mast cells, T lymphocytes, and eosinophils.

Immunologists use objective criteria for their definition of atopy, including skin prick tests, measurements of total serum IgE and allergen specific IgE antibodies, and eosinophil activation proteins such as eosinophilic cationic protein (ECP). Clinicians usually incorporate the presence of persistent cough and wheeze, particularly at night and evoked by triggers such as allergens, exercise, or infection. Associations with allergic disorders (allergic rhinitis, atopic eczema/dermatitis, and food allergy) are also usually sought [8].

Epidemiologists tend to use the symptom of wheeze, as it is assumed that most schoolchildren and adults with this symptom have asthma. Also a ‘doctor’s diagnosis of asthma’ is often used to indicate asthma without any particular agreed-upon definition [9,10]. Furthermore, in epidemiological and clinical research a combination of symptoms and bronchial hyperresponsiveness is used [11].
With increasing age the diagnosis of asthma becomes more and more unambiguous and beyond the age of 6, the definition of asthma as used by the National Heart, Blood, Lung Institute (NHBLI) [6,12] seems to be appropriate: “asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role (mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, epithelial cells). In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.”

**Immunology**

Asthma in children is predominantly an allergic disease. Sensitization to allergens is thought to occur early in life, which may be a reflection of the immaturity of the immune system of infants [13-16].

**Immunologic mechanisms of the induction of IgE**

The cause of the allergic response is the production of IgE to the allergen. Key cells for the development of the IgE mediated allergic immune reactions are T lymphocytes and B lymphocytes [17]. Immunoglobulins are produced by plasma cells, which derive from B-cell precursors in the bone marrow. A plasma cell produces only one type of immunoglobulin [18]. Normally, when a substance enters our body, e.g. in a respiratory allergy through inhalation, our body will defend itself. One of the defences is to produce antibodies and to neutralise intruders. Most of the times, these immunological reactions are beneficial, but sometimes the immune system overreacts and defends itself against an offending substance that poses no
threat [4,19]. In this case, upon allergen sensitization and activation, the T lymphocytes predominantly produce cytokines of the Th2-type, including interleukins (IL-4, IL-5, IL-9 and IL-13) making the B-cells differentiate into IgE secreting plasma cells. The IgE produced by the plasma cells attaches to tissue mast cells and blood basophils. At subsequent allergen exposure, mast cells release mediators and the T lymphocytes secrete Th2 cytokines, which activate other effector cells, such as eosinophils (through IL-5) and B-cells to produce IgE (through IL-4 and IL-13) [17,20,21], thus starting the development of early and late allergic reactions [4,17].

In other situations, the immune system may stimulate immature T-cells to differentiate to Th1 lymphocytes, producing cytokines IL-2 and interferon-gamma (IFN-γ) and inducing B lymphocytes to produce IgG instead of IgE [17,22].

IgE mediated diseases result from interactions between genetic inheritance and environmental exposure to allergens and other variables [3,23-25]. The development of different phenotypes depend largely on genetic regulation and the development of sensitization. Although a genetic predisposition is a strong risk factor, it is probably not enough and not an essential factor for developing allergic disease. In addition, environmental factors and/or living conditions are likely to contribute to the development of allergic diseases.

The predisposition to easily produce IgE antibodies to trivial antigens in the environment (inhalant- and food-antigens) is the fundamental feature of the atopic constitution. What are the mechanisms behind this atopic constitution? Three possible explanations have been suggested:

1. there is a mucosal defect in the gut, which increases the permeability of macromolecules in the gut [26]. This causes less suppression and higher immune reactivity of the T-cells, producing more IL-4. The immune system is too sensitive and the T-cells are activated at lower antigen doses.
2. there is immunological hyperreactivity [27,28].
3. there is immunological cross-reactivity of food antigens with inhalant allergens [29].
The effects of the increased permeability of macromolecules and enhanced immunological hyperreactivity are effective through immunological cross-reactivity [30,31]. It is interesting to know whether IgG hyperreactivity could be used as a surrogate marker of enhanced Th2-activity.

To be able to measure whether a child’s immune system is sensitive in its immune response, a weak antigen is needed to which everyone is exposed but not everyone reacts with an IgE immune response [18,30]. There are indications that children with a classical atopic allergy have an immune system that is more sensitive in its immune responses (both IgE and IgG). This can be shown as follows: when stimulated by a weak antigen, e.g. normal levels of exposure to grass pollen or mite allergens, only the most reactive (i.e. atopic) immune system is triggered, which results in the production of IgE and some IgG1 [18].

Upon continuing stimulation by a moderately potent antigen, e.g. food allergens or animal dander allergens in heavily exposed individuals, everyone will respond by producing IgG antibodies, IgG1 at first and IgG4 later on; only atopic individuals will produce IgE antibodies.

A very strong antigenic stimulus (e.g. parasitic infections, tetanus immunisation, repeated bee stings in bee keepers) will induce IgE as well as IgG1 antibodies in the majority of exposed individuals, atopic as well as non-atopic; upon continued exposure the IgG4 response becomes dominating. This is the case in non-atopic allergies, in which no genetic effects are being found.

IgG to selected foods was thought to be able to act as a surrogate marker of IgE hyperreactivity. Several studies [32-36] have reported that atopic children have higher IgG antibody levels to milk and egg than non-atopic children. Furthermore, in an earlier study [37,38], it was found that high levels of IgG to foods in a high-risk population discriminated between children that will or will not develop IgE antibodies to inhalant-allergens [37,38]. The effects were found for both IgG1 and IgG4 (and even slightly stronger for IgG1 than for IgG4). This was in contrast to what was expected, because
enhanced immunological activity is supposed to be mainly due to enhanced reactivity of the Th2-cells. Th2-cells are necessary for the production of IgE and IgG4. IgE and IgG1/IgG4 ratios can be measured to know whether Th2-cells show enhanced reactivity.

**Mechanisms of asthma**

The above-mentioned definition of the NHBLI/WHO [6] emphasizes that asthma is a chronic inflammatory disorder. This inflammatory response is initiated when mast cells and eosinophils are triggered and an array of inflammatory cells and their mediators including histamine, prostaglandins and leukotrienes are released and contract the smooth muscle [39,40], causing bronchoconstriction and/or bronchial hyperresponsiveness. Furthermore, these factors have the capacity to produce structural changes in the airways or attract inflammatory cells to cause damage to bronchial tissue. Changes in the airways may arise as the result of damage and may lead to remodelling [41], a term used to define complex morphologic changes involving all the structures of the bronchial wall [42]. This may, eventually, lead to permanent reduction in airway function.

The trigger for mast cells and eosinophils to start this cascade of cellular interactions, is usually exposure to allergens, such as dust mites, animal proteins, pollens and fungi while exposure to non-specific irritants usually results in direct bronchoconstriction alone.

Asthma in children and adults is frequently found in association with atopy [43]. There has been, however, discussion whether immunology is needed for airway remodelling or whether allergy is an innocent bystander [44]. The issue is whether bronchial asthma in its pre-clinical stages may cause airway development or remodelling leading to smaller airway diameters and in addition causes wheeze in susceptible children in response to allergen exposure or viral infections [45,46]. Or, alternatively, children who wheeze have smaller airways which might be genetically or prenatally determined, and predisposes them to wheeze early in life with manifestations as viral infections and subsequently or simultaneously to express atopy as wheezing
and bronchial asthma, in which case the allergen is proposed to be an innocent bystander [44,46].

**Prevalence**

The prevalence of allergic/atopic diseases in children varies from less than 1 to 30% in different populations [6]. In general, higher prevalences of asthma and allergy in children are being found in the ‘western’ and ‘westernized’ countries than in children in developing countries. Most studies on asthma and allergies are performed in schoolchildren, although more and more birth cohort studies [47-51] have started recently, either or not with some kind of intervention (Table 1.1 and 1.2).

**Prevalence of specific serum IgE**

IgE antibodies to foods (cow’s milk, hen’s egg) are common in infancy. After sensitization during infancy, most children develop a tolerance to food allergens [52]. Subsequently, sensitization to indoor allergens, like house dust mite, cat and dog dander, increases from the second to fifth year of life, followed by sensitization to outdoor allergens (birch and grass pollen) [53-56]. The sensitization to indoor and outdoor allergens increases with a yearly incidence of 1-3% during the first ten years of life [54].

The most important allergen sources (in the Netherlands) are house dust mite, dander from cats and dogs, birch and grass pollen (causing hay fever) [57].

Table 1.1 shows the prevalences for sensitization (as measured by RAST or skin prick tests) in some recently published birth cohort studies. The prevalences for sensitization to aero-allergens for children aged 1 to 5, range from 0.1% [58] to 17.2% [59], depending on age and population. How often sensitization to aero-allergens occurs in general practice is unknown.
<table>
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<th>study year</th>
<th>number</th>
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<th>intervention</th>
<th>high-risk children</th>
<th>SPT/RAST</th>
<th>allergens</th>
<th>sensitation inhalsants</th>
<th>reference</th>
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<tr>
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<td>1218/981*</td>
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<td>1,2,3,5,7,8,10</td>
<td>19.5</td>
<td>total: 19.4 HDM: 11.9 cat: 5.8 dog: 2.4</td>
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<td>total: 16.4 HDM: 8.9 cat: 8.9 dog: 9.8</td>
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<td>1314</td>
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</tr>
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<td>Age</td>
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<td>17.7</td>
<td>HDM: 9.3</td>
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</table>

Allergens: 1 house dust mite  4 tree pollen  7 egg  10 wheat  2 cat  5 grasses  8 milk  11 egg white  3 dog  6 moulds  9 soy  12 Phadiatop (cat, dog, horse, timothy, mugwort, Dermatophagoides pteronyssinus, Cladosporium)  

Intervention: a: mite covers, b: food, c: mite avoidance, d: breastfeeding, e: other  
High-risk children: substantial part of the population was especially selected because of high-risk  
*number of children for allergy test  
** clinical reactions and sensitization
Table 1.2 Prevalences of current asthma and physician diagnosed asthma

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1: available for analysis  
2: recurrent wheeze (>3 episodes)  
3: wheeze at least once  
4: obvious atopic disease, including asthma  
5: asthma ever  
6: the first centre began its survey in 1991, but most centres undertook the data collection in 1994 and 1995 [9]
**Prevalence of asthma**

*Asthma* is the most prevalent chronic disease in children [77]. Asthma-like symptoms begin during the first years of life [78-80], although only part of the pre-school children with asthma will still have symptoms of asthma at school age [46].

In Table 1.2 asthma prevalences of current asthma in children aged 1 to 5 in recently published birth cohorts are shown. As for pre-school children symptoms, especially (recent or current) wheezing, as a definition for asthma are frequently used, prevalences for recent wheeze (wheeze in the last 12 months) are also shown. Another way of measuring asthma is by asking whether a doctor has (ever) diagnosed asthma. Prevalences for a doctor's diagnosis of asthma are also shown in Table 1.2.

In the early 1990's attempts were made to standardize methodology to be able to compare the prevalences of asthma and allergies in children living in different countries and to obtain baseline measures for prevalence, which resulted in the ISAAC-study (International Study on Asthma and Allergy in Childhood) [81]. The ISAAC-study shows that the prevalence of wheezing in the last 12 months -documented by written questionnaires- among 6 and 7 year old children differs more than fivefold with lowest rates in Indonesia (1.4%) and highest rates in Costa Rica (32.1%) [9] (Table 1.2).

The above-mentioned prevalences are figures from the general population, mostly found by questionnaires. In the Netherlands, there are nine general practice registration systems. The prevalences and incidences in these databases/registrations vary, which can be the result of real differences in the prevalences of asthma in the practice populations. It may also be a result of the method of the registration systems and the way in which diseases are recorded, e.g. some of these registration systems are based on contacts/encounters, others use problem lists [82].

Based on these registrations, the estimated yearly prevalence of asthma (per 1000 patients) in 2000 was 65 for 0-4 year old boys and 44 for 0-4 year old
girls. These prevalences decrease to 59 for 5-9 year old boys and 42 for 5-9 year old girls.
The incidences (per 1000 per year) were 33 and 22 for 0-4 year old boys and girls, respectively, whereas these were 12 and 9 for 5-9 year old boys and girls [83].

**Diagnosis**

Diagnostics are of importance for taking medical decisions with regard to the nature and the seriousness of the complaint, the cause of the complaint, the future clinical course and the prognosis of the illness, the choice of therapy and the effectiveness of therapeutic interventions [1].

An **allergy** can be recognized by the presence of allergen-specific IgE in the patient’s serum or by skin prick tests. Allergen-specific IgE in the patient’s serum can be tested by using RAST (radioallergosorbent test) or EAST (enzyme allergosorbent test). The RAST/EAST measures the amount of IgE that is directed to a specific allergen [19]. In general, RAST and skin prick test have been shown to correlate well [4,84]. One of the advantages of determination of specific IgE in blood over skin prick tests is that it can be used more easily for children. Furthermore, it requires less specialized skill than skin prick testing [85] and is therefore useful in general practice. In the Netherlands, determination of specific IgE by RAST/EAST is a well-accepted procedure to identify allergens involved in sensitization.

A diagnosis of **asthma** usually involves assessments of pulmonary function. However, in children younger than 5-6 years of age, lung function tests are not routinely used and furthermore, there are no confirmatory diagnostic blood tests, radiographic or histopathological investigations to diagnose asthma in young children. Therefore, for children younger than six years of age, the physician has to rely upon clinical history and physical examina-
tion. Children aged six and over are able to perform a lung function test, and thus, asthma can be diagnosed.

In the Dutch guidelines for General Practitioners [86], the starting point for a diagnosis of asthma is a child with recurrent coughing, congestion of sputum, wheeze and/or shortness of breath. The symptoms are partly age limited: until the age of four, especially (nocturnal) coughing and -in the first year of life- 'congestion of sputum' and snoring. For children of four years and over, the symptoms are wheeze and shortness of breath. In these children, asthma can be objectified with peakflow or FEV₁ (forced expiratory volume in 1 second) measurements. Also, an allergy test can be performed.

**Prognosis of asthma**

The important symptoms of asthma are wheezing, coughing and shortness of breath. For 36.8% of the children under 5 with a doctor's diagnosis of asthma, the most important reason for an encounter with their GP is a period of coughing [77], compared with 26.4% for shortness of breath and 17.2% for wheezing [77]. Furthermore, in 0-4 year old children, coughing is the symptom a GP is most frequently contacted for [77,87]. It is the reason for encounter for 12.9% of 0-4 year old children and for 8.6% of 5-14 year olds [77]. Wheezing and shortness of breath are reasons for encounter for 1.6% and 1.9% of the 0-4 year olds respectively. Several studies [32,52,88,89] have shown that many children who develop asthma at a later age, have recurrent airway symptoms before the age of 4 and part of them even in the first year of life. However, the opposite is not the case: about half of the children with airway symptoms early in life will not have asthma in later childhood and adolescence [46,79,88,90-93]. Data from a longitudinal registration project in general practice (CMR Nijmegen) [87] showed that of all 0-4 year old children with a doctor's diagnosis of asthma, over 60% was not known with asthma anymore by the GP two
years later. However, data from the same registration showed that of the children with a diagnosis of asthma at the age of 0-4, more than 45% still had asthma at 10 to 23 years of age [94].

The question is, how children with airway symptoms who will go on to develop asthma can be distinguished from the children who will not develop asthma. Answering the question could help clinicians effectively manage children with respiratory illness.

Several follow-up studies have shown that the probability that asthma will persist or remit at an older age depends on several factors and might be influenced by the fact that there are different asthma phenotypes in preschool children, as is proposed by Martinez [46] and others [90,95,96]. These phenotypes include:

- transient early wheezers (wheezing up to age 3 but not thereafter), mostly associated with viral infections and/or small airway size
- non-atopic wheezers (wheezing in toddlers and early school years) and
- persistent wheezers (still wheezing by the age of six) who are at a high risk of developing asthma.

Depending on the type of wheezing, the prognosis of the pre-school child differs. There is evidence suggesting that wheezing in the first three years of life but not thereafter (transient early wheezing) has a good prognosis. It is also suggested that infants and toddlers with wheezing lower respiratory illnesses only have a (abnormal) response to viral infections, a response limited to the first few years of life [97,98]. In infancy, viruses appear to be more important than allergens, but allergens become more important as children get older. According to Martinez et al. [46,99] persistent wheezers are more likely than the children who never wheezed to have a family history of asthma and allergies, to have elevated serum IgE levels early in life, to have normal lung function in the first year of life, and to have elevated serum IgE levels at six years.

Several other studies show that sensitization, with or without clinical symptoms, to common inhalant allergens, particularly to dust mite and pet dander is associated with asthma and persistence of asthma in childhood.
Although few children become sensitized to aero-allergens during the first three years of life, the majority of those who do become sensitized in this age period develop asthma-like symptoms later in life [99,101,104]. Children who become sensitized after the age of 8 to 10 have a risk of developing asthma that is not much higher than that of children who do not become sensitized [105-107].

Despite the fact that there are different types of wheezing, it is impossible to distinguish between these groups during the first few years of life from a clinical point of view, because their symptoms and signs of illness are very similar. In a wheezy child, no accurate prediction can be given whether this wheezing will persist into later life. Nevertheless, a GP cannot wait until the age of 6-7 to know whether the child has indeed asthma. S/he has to act when the child has symptoms. The question is, how these children can be identified.

Several follow-up studies have been performed trying to assess the prognosis of asthma from early childhood to childhood, adolescence and adulthood. In these studies, prognostic factors that make it more likely that asthma persists or remits are, among others: sensitization to airborne allergens [46,99-105], a family history of atopy [46,90,95,108], presence of other atopic diseases such as eczema [46,90,95,108-110], more severe asthma or wheezing [92,111,112], younger age at presentation [94,108,113,114] and increased airway responsiveness [46,115-119].

Thus, the majority of pre-school children with symptoms, do not have asthma at the age of six. The problem in these young children is that wheezing can be persistent, non-persistent or associated with viral infections. To date, no diagnostic tools are available to distinguish between transient and persistent wheezing at an early age.
Treatment

In case of an allergy, the kind of allergen and the target organ determine the (nature of the) treatment. When the allergens that cause symptoms have been identified, the treatment will be principally aimed at avoiding the factors provoking them [85]. Once a patient’s sensitivity to inhalant allergens has been established, the clinician will be able to recommend specific environmental control measures to decrease exposure.

The guidelines for the Dutch General Practitioners (NHG-guidelines) and international guidelines [6,120,121] give directions for the treatment of asthma in children. The primary goal of treatment as formulated in these guidelines [6,86] is a normal way of living with normal activity levels and reaching and maintaining pulmonary function as close to normal levels as possible without or with as few symptoms as possible, whether or not accompanied by medication in a dose and a frequency of administering as low as possible and with as few side effects as possible.

Both international [6,120,121] and national guidelines [86] recommend a stepwise approach for the treatment of young children, which aims to eliminate symptoms as soon as possible and to optimise peak flow by stepping up treatment as necessary and stepping down when control is good [6,86,120,121]. The number of steps varies, but all guidelines recommend to give inhaled short acting β₂-agonist as required in mild intermittent asthma (step 1) and inhaled steroids as regular therapy (step 2).

Beside therapeutic treatment, education and counselling on how to avoid provoking factors is of the utmost importance. According to the Dutch guidelines [86], the most important non-pharmacological treatment concerns smoking. Smoking by parents or by others in the child’s environment should be avoided. Furthermore, when an allergy for pets is present, it is recommended not to keep pets at home. Taking avoidance measures is useful when an allergy for house dust mite or other indoor allergens is present. Despite indications [46,114,117,122-128] that co-existence of atopy is
related to severity and persistence of asthma, the Dutch guidelines say that children under 4 years of age should not be tested on respiratory allergy (in contrast to the older children who should be tested when there are indications that an allergy could play a role in the child’s asthma). The argument for not recommending allergy testing is that a negative test-result does not rule out allergy in these young children, as the child can still become positive in the future [86]. Although it is obvious that not all young children should be tested for an allergy and treated prophylactically, it is useful to test a selected group of children. When it is known whether a child is sensitized, adequate avoidance measures and/or medication can be directed towards children at risk who will benefit most.

**AIMS OF THE STUDY**

Research shows that children with asthma have symptoms before they are four years of age, sometimes even before their second birthday. However, children with symptoms before the age of three do not necessarily develop asthma at a later age. Three questions can be asked:

– can we identify factors that, at an early age, distinguish children who will develop a respiratory allergy from children who will not?

– to what extent do early airway problems contribute to a subsequent allergy?

– to what extent does a respiratory allergy in symptomatic children contribute to the subsequent development of asthma?

In an earlier study by Calkhoven [38], it was found that an increased sensitivity for food antigens (IgG) distinguished the children that subsequently develop a respiratory allergy (IgE) from the non-sensitized children. That study was performed in a high-risk group of children, which comprised many children with atopic eczema.
The first hypothesis of this study is based on the study of Calkhoven [38]: children with high levels of IgG antibodies to foods have a higher risk of developing IgE antibodies to inhalant-allergens at a later age. During the course of the recruitment phase we found that already many children were IgE positive. This made us wonder whether these IgE positive children would also develop asthma at a later age. And furthermore, whether IgE tests and sensitization could be used in the recognition of pre-school coughing children that will develop asthma in primary care. This gave rise to our next hypothesis: children presenting with complaints of coughing who were found to have specific IgE to house dust mite, cat and/or dog are at a higher risk for developing asthma compared to children with normal levels of specific IgE.

It would therefore be interesting to define variables that could be used to identify coughing children younger than 5 years of age who will continue to be symptomatic at school age.

Thus, the aims of the thesis are:

- to assess whether or not there is an association between IgG antibody levels to foods and IgE to aero-allergens and if so, whether an increased IgG antibody titre to foods is an indicator for an increased risk to develop an inhalation allergy. In other words: Is a relatively strong (but in itself not pathogenic) immunological reaction to foods more often found in children who develop an allergy for inhaled allergens (allergens of house dust mites and/or pets) at a later age?

- to identify young children with a high or low probability of being sensitized to aero-allergens and to find risk and predictive factors for the development of sensitization in these young children.

- to assess the predictive accuracy for asthma at the age of six of IgE tests to cat, dog and house dust mite in children younger than five years of age presenting with complaints of coughing at the GP’s surgery and to develop a diagnostic prediction rule for children presenting with coughing including readily obtainable parameters from the child’s history, physical
examination and IgE tests in order to distinguish the children who will have asthma at the age of six from those who will not.

The study

To address these aims, a prospective study was designed in which the development of IgE antibodies in initially IgE negative children after two years of follow-up was studied, but was later extended to the follow-up of the IgE positive children and a sample of the IgE negative children until their sixth birthday.

Between February 1995 and February 1997, 136 general practitioners in the North-western part of The Netherlands, recruited 1 to 4 year old children for a study on the development of inhalation allergy in toddlers. Children visiting the participating GPs with complaints of coughing over at least five consecutive days and being known not to have allergic reactions, not to be IgE positive and not to be diagnosed with asthma (by the GP) were eligible. The parents and their children were asked by their GPs to participate in the study. Informed consent was obtained from the children’s parents.

At the same time, drops of blood were drawn from the children (finger prick) and spotted on filter paper for the determination of total IgE and specific IgE for house dust mite, cat and dog. Two groups of children were formed: IgE negative and IgE positive children. Children who were IgE negative on all three allergens were followed up to study the likelihood of their seroconversion after two years. Since this part of the study aimed at seroconversion, the IgE positive children were excluded. The IgE negative children were also tested on their IgG antibody response to foods. After two years of follow-up, these initially IgE negative children were invited to come to the GP’s office for a second blood sample. Again, blood was spotted on filter paper and tested for total IgE and specific IgE for house dust mite, cat and dog.
Children who were IgE positive for at least one of the allergens at baseline, were followed up at the age of six, when their asthma status was determined. These children were tested again for total and specific IgE.

### OUTLINE OF THE THESIS

As an introduction to this thesis, chapter 1 deals with several topics on the background of this study. Chapter 2 provides information on how the children were tested for the presence of specific IgE. As GPs and parents often seem to have objections to venepuncture as blood sampling in young children, we examined whether it was possible to measure total IgE and allergen-specific IgE in capillary blood obtained by a finger prick and absorbed onto filter paper.

Chapters 3 and 4 deal with the first aim of the study, which assumes that young children with a high risk of developing allergy in the future, show an abnormal IgG antibody response to foods before the development of IgE antibodies to inhalant allergens. In these chapters the cross-sectional and longitudinal relation between IgG to foods and IgE to inhalant-allergens is described. In chapter 3 a study is presented on the cross-sectional association between IgG to foods and IgE to inhalants. Furthermore, the development of a sensitive ELISA for determination of IgG antibodies to foods is described in this chapter. In chapter 4 our hypothesis was tested whether IgG antibodies to foods predict the subsequent development of IgE antibodies to inhalant-allergens. Thus, this chapter shows the results of the longitudinal relation between IgG to foods and IgE to inhalant-allergens.

In chapter 5 the results of the inclusion period are shown. Furthermore, this chapter describes the extent to which sensitized pre-school children can be distinguished from non-sensitized children using easily obtainable information.

Chapter 6 focusses on the period between inclusion and second blood sample with respect to the symptoms presented by the children to their GPs.
It describes the results of a medical records’ review which tried to predict allergy and asthma on the basis of information present in the medical records.

Chapter 7 and 8 aim at the third objective of the study. Chapter 7 deals with the core question of this part of the study: can specific IgE be used as an additional test in the diagnosis of asthma in young children? Furthermore, in chapter 8 a short report is presented on the relation between early versus late sensitization and the chances of becoming asthmatic. In chapter 9, some methodological issues on the studies described in this thesis are discussed. Finally, chapter 10 includes an English and a Dutch summary of this thesis.

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INTRODUCTION

CHAPTER 1


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