

Chapter 9

General discussion and summary

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This thesis shows the results and patient characteristics of three studies. One study was part of the Dutch Mite Avoidance Study (DUMAS): Effectiveness and effect modification of encasings in house dust mite allergy. The two other studies were two different studies with asthmatic patients recruited from and performed at the asthma centre Heideheuvel. Patient recruitment of the Heideheuvel study took place in the same geographical region in the period 1995-1997; the DUMAS study in 1997 and 1998.

In the DUMAS study patients were selected by using questionnaires where particular atypical core questions were addressed, together with a positive intradermal test or skin prick test for house dust mite. Patients were diagnosed as having reported AR, AA and/or AD on basis of this questionnaire. Then patients were randomised and stratified by age and recruiting centre. After randomisation patients were tested for AA with lung function tests (methacholine, adenosine, histamine)¹; for AR, using nasal provocation tests with HDM and the nasal-score²; and for AD, using the LSS^{3,4} for symptom grading and disease extent together with tests for allergen load and immunological and quality of life (QoL) variables. A difference in diagnoses was made by using questionnaires solely (reported diagnoses) and using questionnaires in combinations with clinical tests (clinical diagnoses). A difference between reported and clinical diagnoses was found in 84 out of 325 patients (25.8 %)(Chapter 2). There was a reported atypical comorbidity of 235 out of 325 patients (72.3 %) and a clinical atypical comorbidity of 177 in 325 patients (54.4 %).

Chapters 3, 4 and 5 show the effects of encasings on clinical, immunological and QoL variables. There was a lack of improvement of AD and AA in the active treatment groups despite a significant decrease in Der p1 and Der p1 + f1 exposure.

Lack of clinical effect in the active treatment groups is difficult to explain. Low baseline concentrations of Der p1 or Der p1 + f1 could result in little change of HDM allergen levels after intervention. Higher and lower baseline concentrations of HDM were reported.⁵⁻¹⁵ Recent Dutch studies reported comparable levels of Der p1 or Der p1 +f1. In the DUMAS AD group the baseline data Der p1 in the mattresses (841 and 945 ng per gram dust, placebo and treatment group respectively) are in the same range as earlier reported by Cloosterman et al.¹⁶ So this lower concentration of Der p1 per gram dust might be representative for the Dutch population study.

The Der p1 geometric mean concentration in the mattress after twelve months intervention in the DUMAS AD study decreased to 446 ng Der p1 per gram dust and the Der p1 + f1 to 1319 ng per gram dust. Some high altitude studies reported lower geometric means for Der p1 + Der f1 of 360 ng per gram dust and 180 ng per gram dust for Der p1 in mattresses.^{17,18} There seems to be some room for improvement left in the active treatment group in the DUMAS study, but it is doubtful if encasings alone can decrease the concentration of Der p1 + Der f1 to this extent.

Van Strien et al.¹⁹ reported an allergen load in the placebo group of 1851 (607-3957) ng Der p1 + f1 per gram dust and in the active treatment group of 1676 (419-5609) ng Der p1 + f1 per gram dust before intervention, that decreased after twelve months intervention to 1676 (419-5602) ng per gram dust and 1018 (465-3179) ng per gram dust, respectively.

In the DUMAS AD population the baseline levels of Der p1 + f1 were in the same range (< 10.000 ng): 3388 (1913-6000) ng per gram dust in the placebo group and 4069 (2573-6437) ng per gram dust in the active treatment group, increasing to 3749 (1921-7315) in the placebo group and decreasing significantly to 1319 (851-2046) Der p1 + f1 ng per gram dust in the active treatment group after 12 months intervention.

Surprisingly, in both Heideheuvél studies the geometric mean values were above 15000 ng Der p1 per gram dust. Patients in the Heideheuvél study were recruited 2 years earlier than the patients in the DUMAS study. Whether the high Der p1 exposure could be explained by the recruiting period or by specific patient characteristics within these relatively small groups of AA patients (27 and 38 respectively) compared to the 77 patients of the AD DUMAS study and 157 patients of the Cloosterman study¹⁶, is not clear.

Nevertheless, lowering the Der p1 in both Heideheuvél studies with a factor 10 did not lead to improvement of clinical symptoms in the active treatment group of AA (Chapter 4, 5).

Another reason why the decrease in allergen exposure did not result in clinical improvement might be that the sleeping period in which the decrease in concentration of Der p1 or Der p1 + Der f1 in mattress and bedroom is experienced is just a part of the total exposure time. Patients might still be exposed to higher HDM levels outside the bedroom. Also other allergens in- and outside the domestic environment might have aggravated and maintained AD. Reduction of allergens in other environments (working place, school, and outdoors) might be equally important to improve AD.

Decreasing the 'wrong' allergens could also cause the lack of clinical effect. Several studies showed that HDM is one of the most important risk factors of sensitisation and inducing atopic symptoms.²⁰⁻²² Grading of allergens according to the prevalence of sensitisation within a population with AR, AA and/or AD revealed the following prevalences: HDM 68.4 %; cat 66.7 %, grass-pollen (GP) 64.9 %; making cat allergen the second most important indoor allergen.²⁰ The independent risk odds ratios (OR (95 % CI)) for HDM were 2.19 (0.92-5.17); 8.07 (4.6-14.14); and 1.95 (1.04-3.66) for AR, AA and AD respectively.^{20;22} A study performed by Carswell et al.¹² showed that applying encasings and acaracides in houses without cats lowers the cat allergen Fel d1 from 24 (0-2240) ng per m³ to 0 (0-0) ng per m³, using a Casella air sampler. In houses with cats and in the placebo group no decrease in Fel d1 was seen. In the AD DUMAS study population the Fel d1 allergens were not measured. In this population 52 out of 73 AD patients were sensitised to cats, 52 to dogs. No cats and/or dogs were allowed during the study when patients were sensitised to these allergens. Presence of Fel d1 allergen in the study group homes is likely, the study of Carswell et al.¹² suggests

however that together with the decrease of Der p1 + f1 the Fel d1 would also have decreased in the active treatment group.

Multiple triggers

Exacerbation of atopic diseases is a complex process. It requires interactions between genotype and environmental conditions. This thesis deals with allergen specific triggers. But other non-allergic triggers can play an important part. Triggers for AA for instance consists of cold air, hyperventilation, exercise, psychological stress, β -blockers, oesophageal reflux, viral airway infections, tobacco smoke, air pollution etc.²³ Non allergic triggers for AD are psychological stress, contact irritants, climate, microbial and fungal agents.^{24;25} Allergens form a part of these multiple triggers cumulating to a particular threshold level or gradually increasing the AR, AA and/or AD symptoms dependent of the cumulative trigger load. Lowering the major trigger could initially lead to an improvement of clinical symptoms, but at the same time it increases the relative contribution of other triggers. Not dealing with these other triggers could stop further improvement of symptoms.

Effect of genotype and environment on phenotype

As already stated, atopic diseases could be caused by interaction of multiple genes and environmental factors. It is possible that three major areas concerning atopy, inflammation and organs (nose, lungs, skin) at gene level interact with each other and induce the atopic prone genotype, combined with environmental factors results in a particular atopic phenotype.²⁶ Figure 1 shows the current state of affairs concerning discovered gene clusters that are associated with atopy (genotype box). Three gene clusters are associated with at least two atopic phenotypes: 5q31-32²⁷⁻³¹; 11q13^{32;33}; 12q13-24^{34;35}. These three gene clusters code for several proteins that regulate and control the immune response: interleukines; colony stimulating factors; interferon gamma, which are inflammation specific proteins, and the beta subunit of the high-affinity receptor for IgE which is an atopy specific protein.²⁶⁻³⁶ Concerning organ (skin) specific genes, an association between psoriasis and AD genes has also been found.³⁷ Surprisingly, Becker et al.³⁶ showed that the same gene clusters were involved not only in atopic but also in autoimmune diseases. These diseases did not always map to the same loci within the same gene. Probably a delicate balance concerning activation of gene clusters is necessary to prevent either atopic or autoimmune diseases. These data suggests that rigorous allergen avoidance measures solely will have a limited effect on prevention and exacerbation of atopic diseases.

Also, multiple atopy inhibiting and inducing triggers in the environment can influence the balance between Th1 and Th2. Strachan reported for the first time a reciprocal relation between hay fever, hygiene and household size.³⁸ Other studies reported quickly thereafter that respiratory, gastrointestinal pathogens, the commensal flora of gastrointestinal tract and bacterial cell-wand products could regulate the allergic specific immune responses towards a Th1- and inhibiting a Th2- profile, e.g. “reset” the Th2 prone individuals to a common Th1 profile. Absence of particular bacterial and viral infections, due to more westernised hygienic conditions, could result in individuals with a Th2 (allergy-prone) profile, this was called the

hygiene hypothesis.^{39-43;43-50} Not all viral and bacterial pathogens cause a Th1- profile. Respiratory syncytial virus (RSV) and lower respiratory infections are associated with an increase in asthmatic symptoms and a Th2-profile.^{41;44;50} Figure 1 gives a summary of environmental Th1 and Th2 inducing triggers (environment box).

Looking at the protective effect of particular bacterial and viral infections, some authors stated that this effect could be used and that Th2 prone individuals should be vaccinated with Th1 inducing vaccines, for example vaccines derived from Mycobacterium strains. The only antituberculosis vaccine at the moment is based on live, attenuated Bacillus Calmette-Guerin-Myobacterium bovis (BCG).^{39;51} However, retrospective studies show conflicting results concerning atopy preventing effects of BCG vaccination.^{39;52-55}

There is a delicate balance between Th2 and Th1 phenotypes. Several studies show that different autoimmune diseases like rheumatoid arthritis, insulin-dependent diabetes mellitus and multiple sclerosis are associated with a Th1 phenotype.⁵⁶ The presence of autoimmune diseases is associated with a lower prevalence of atopic phenotypes in some studies but not all.⁵⁷⁻⁶¹ Vaccine strategies which aim for a general Th1 phenotype can have an adverse effect with respect to auto-immune diseases. We have to keep the old adage in mind “Primum no nocere” (doing no harm).

While Th1 triggers in the first two years of life might prevent the development of the atopic phenotype, the effect on adult atopic patients could be different. The a-specific non allergic triggers induce chronic inflammation in adult AD patients, resulting in a Th1 response.^{24;62} Prevention of Th2 triggers solely by avoiding environmental allergens could disturb the Th1 and Th2 balance resulting in an increase of AD symptoms by enhancing the chronic inflammation. However, decrease of HDM allergen did not result in an increase of clinical symptoms. Development of effective treatment regimes should be aimed at inhibiting both the acute (Th2) and chronic (Th1) allergic inflammation.

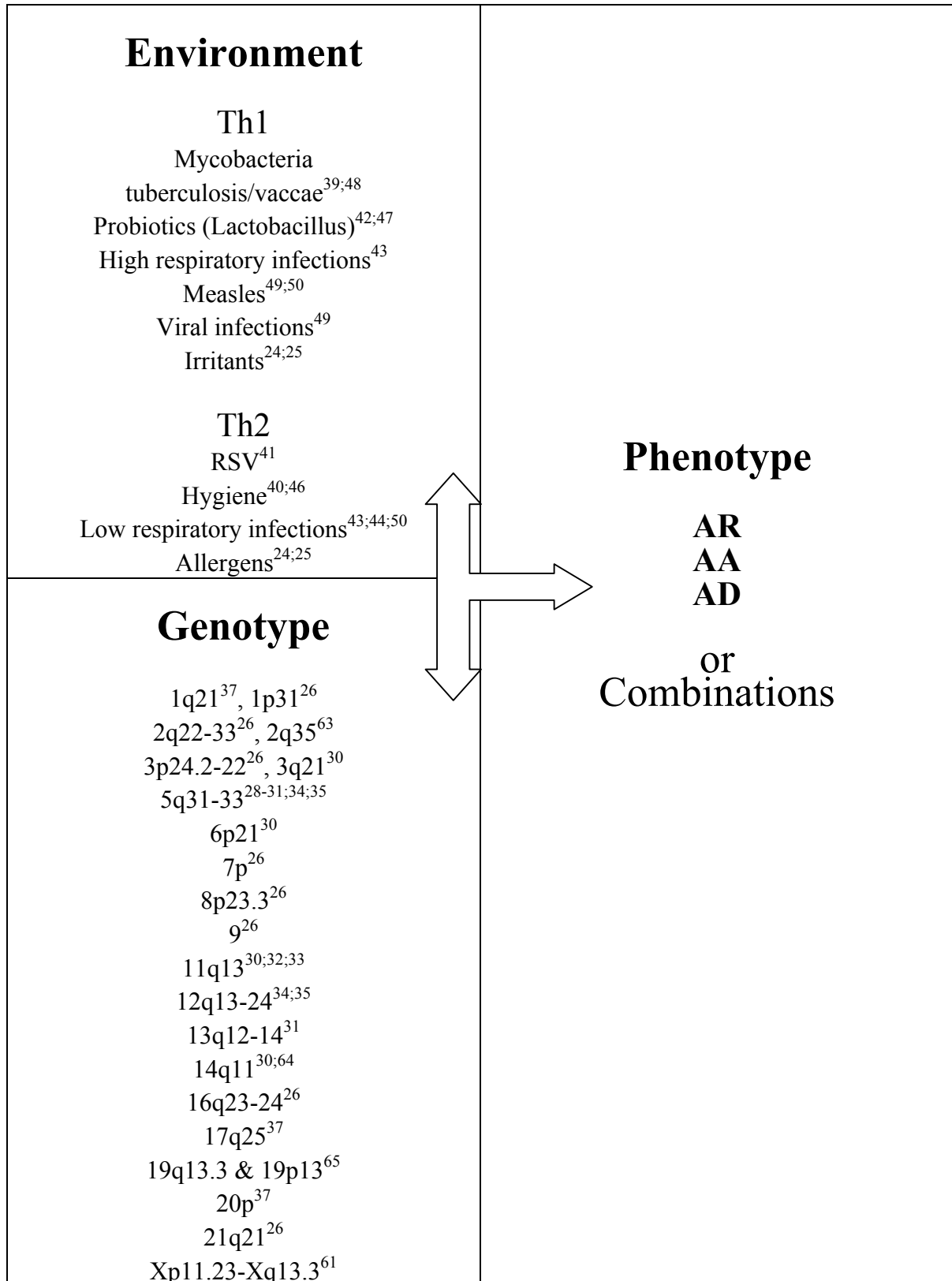


Figure 1: Interactions between genotype and environment resulting in a particular (combined) atopic phenotype.

Quality of life

Patient-assessed health outcomes can be divided in three categories: health status (health-related QoL and functional status); health utilities (patients' values for a particular state of health) and patient satisfaction. QoL is influenced by many factors such as financial status, housing, employment, social support network and health. QoL affected by health and health care, health-related QoL (HRQL) is often used in clinical research. The general QoL encompasses the HRQL.⁶⁶ Because no other QoL factors were assessed in this thesis, the term QoL is used for HRQL.

QoL becomes an important issue in evaluating effects of treatment in patients with chronic diseases. Several disease specific and generic questionnaires have been developed. Disease specific questionnaires assess the severity of particular disease specific (AA and AD) symptoms on patient's life⁶⁶ while generic questionnaires addresses the general "well being". Looking at the prevalence of atopic comorbidity within the selected populations, usage of both kinds of questionnaires is recommended (Chapter 5). The disease specific Quality of Life for Respiratory Illness Questionnaire (QoL-RIQ)⁶⁷ intended for AA and chronic obstructive pulmonary diseases (COPD) was used in the Heideheuvel study. Clinical relevant improvement in QoL was found in both groups and no difference between the active and placebo treatment groups was seen. Suggesting that it might rather reflect the special attention the patients received during the study period. The disease specific Questionnaire of Coping with Skin Diseases (QCSD)⁶⁸⁻⁷¹ was used for AD, together with the generic SF-36⁷²⁻⁷⁵ questionnaire in the DUMAS study. The QCSD could be condensed to a 16 items questionnaire with two dimensions "Feeling hurt" and "Emotional distress", for future research only these items are important to evaluate disease specific QoL, omitting the other 26 items is acceptable. Lack of clinical effect of encasings on AA and AD resulted in a lack in improvement of QoL between the placebo and active treatment groups as measured with disease specific and generic questionnaires in both study populations (Chapter 4, 6, 7). Interestingly, within the AD population the disease specific QCSD and the generic SF-36 questionnaire revealed body-site specific effects of trunk and arms on QoL (Chapter 6, 7).

It is important to know that treatment of chronic diseases can improve QoL without improving clinical symptoms, for example due to better coping. Because of the chronic nature of AR, AA and AD, long lasting clinical improvement might be difficult to reach and it might be better to focus treatment on patient related QoL aspects. Improvement of QoL, due to patient guidance, can be related to disease specific QoL and /or general "well being", as measured with disease specific and generic questionnaires respectively. Combined with the conclusion that the disease specific QCSD and the generic SF-36 questionnaire measure different aspects of QoL (Chapter 5), it is recommendable to use both for evaluating treatment of individual patients in the future.

The background of measuring differences in QoL in evaluating a particular treatment is often to calculate the cost effectiveness of that treatment. Quality of Adjusted Life Year (QALY) is a composite indicator of additional life years gained from an intervention with a patients

judgement concerning the QoL in those years.^{66;76} Improvement of QoL without a difference in gained additional life years between treatment groups could lead to a cost effectiveness of a particular treatment without improving clinical symptoms.

Main conclusions

The decrease in Der p1 + f1 in the Heideheuvel and DUMAS studies and combined lack of clinical improvement of AA and AD shows that there is no experimental basis for prescribing mattress encasings to AA and AD patients.

Questionnaires with atopic disease related items resulted in a good prediction of clinical atopic disease activity within a HDM sensitised population.

Active AD at arms and trunk decreases QoL, as practitioner it is important to keep this in mind when treating the AD patient.

The disease specific and the generic questionnaire should both be used to measure QoL in atopic dermatitis patients, not only do they measure different aspects of QoL but also because treatment of chronic atopic patients could improve different aspects of QoL without improving clinical symptoms.

Recommendations for future research

- 1 In adult atopic patients new treatment strategies should aim for inhibiting both Th1 and Th2 profiles and the effect on Th1 and Th2 cells should be monitored.
- 2 The study shows that using questionnaires with atopic disease related items on atopic patients have a reliability of about 80 % that specific atopic diseases are present. In the future, these items can be used for epidemiological and genetical studies.
- 3 The condensed 16-items QCSD QoL questionnaire should be further evaluated for use in clinical practice.

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