

NRS roadmap Respiratory Allergy report

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1. Inventory of Dutch research efforts in this field over the past five years (2008-2013) by ISI web of knowledge

We have looked for Web of knowledge articles that comprised key words allerg*, IgE, rhinitis, eczema and sinusitis with more than 90 citations. We included work that was published from 2000 until now. Only original research articles were included in the analysis. The principal investigator, first, second or last author of the original study had to be Dutch. The selection is added as an attachment to this report.

Summary

Top 10 most cited basic research initiated by Dutch groups 2008-2013, defined as that first and last author have a Dutch affiliation (Table 1).

- Air pollution. (Smit H, brunekreef, de Jongste, Koppelman, Postma)
- Dietary patterns. (Tromp, Kiefte-de Jong; de Vries)
- Asthma predicting. (Savenije, Kerkhof, Koppelman, Postma)
- Microbiota. (Van Nimwegen, Penders, Stobberingh)
- Dendritic cells and epithelial cells. (Hammad, Lambrecht)
- Endotoxin exposure and allergy. (Smit, L. Heederik, Doekes)
- Gut microbiota composition. (Penders, Thijs, Van Den Brandt, Kummeling, Snijders, Stelma, Adams, Van Ree, Stobberingh, Gut)

Top 10 most cited clinical research initiated by Dutch groups 2008-2013 (Table 2).

- Tiotropium in severe uncontrolled asthma. (Kerstjens, Disse, Schroeder-Babo)
- Matrass covers. (Terreehorst, De Monchy, Bruijnzeel, Gerth van wijk)

2. Visibility Dutch research judged by international experts (see also appendix)

Areas with good visibility	Less visible
- Phenotyping and Severity	- Immunotherapy for allergic diseases
- Biological mechanisms	- Basic research and experimental studies
- PIAMA consortium	- Diagnosis monitoring
- Parasitic infections	- Therapy Medical
- Genetics in Allergy	
- Environmental factors	

3. Research needs

From 2 years of age and especially during school years, inhalant allergy becomes increasingly important for childhood asthma. Approximately 60% of all school-aged asthmatic children are allergic. The most important allergens vary according to climate, but in all European countries animal dander is among the most frequent allergens in asthma. In a warm and humid climate, house dust mites and moulds are also of major importance, and, depending upon climate, the seasonal allergens (birch, grass and mugwort pollen) play a role. Allergen exposure may cause acute asthma exacerbations, and even in the absence of an exacerbation, may increase airway inflammation and bronchial hyperresponsiveness. In 80% of asthmatics allergy plays a role in the course of the disease¹. Several efforts have been made to prevent the development of asthma. These can be divided into: primary prevention, the aim of preventing symptoms and signs of allergy and asthma from occurring at all; and secondary prevention of asthma in a predisposed child who has, for example, atopic dermatitis. Tertiary prevention is the prevention of symptoms in an affected child. Prolonged feeding with breast milk may prevent respiratory infections but probably not asthma.

In high-risk children, trials have been performed to reduce exposure to allergens, especially house dust mites and animal dander, but the efficacy of such measures remains to be proven. Although allergic sensitisation is related to early allergen exposure, low exposure to animal dander and house dust mite do not seem to reduce the occurrence of bronchial asthma in the general population. (<http://www.erswhitebook.org/>).

Facts and figures

- 20-25% of population has a respiratory allergy in the Netherlands.
- At least 1.2 million people use medication for their allergy based on the number of prescriptions for antihistamines in 2008.
- Between 80-95% of allergic asthma patients has concomitant rhinitis and 30-40% of all allergic rhinitis patients has lower airway symptoms.
- Patients with allergic rhinitis have a 3-fold higher chance to develop asthma.

Euro costs²

- Costs for specific allergy medication (antihistamines and immunotherapy) are approximately €100 million in 2008, and based on a recent publication €103,000,000³. Most costs relate to treatment (88%) and general practice care (10%)³

Unmet needs (extracted from: LAN rapport 2010⁴)

- The link between sensitization and clinical expression.
- Endotype based therapy.
- Integral care for allergy not optimal.
- Preventive measures blocking the allergic march.
- Safer methods of immunotherapy.

References

¹ Feiten en cijfers 2013 Chronische Longziekten, LAN 2013

² Maatschappelijke kosten voor astma, COPD en respiratoire allergie. RIVM Rapport 260544001/2012

³ Nederlands Tijdschrift voor Geneeskunde 2013;157:2358-2365

⁴ Feiten en cijfers Chronische Longziekten, LAN 2010

4. Summary SWOT analysis

Results of the web-based SWOT

Strengths 1. Molecular allergology 2. Biological mechanisms 3. Environment and lifestyle	Weaknesses 1. Biobanking 2. Good animal models 3. Clinical studies
Opportunities 1. Epidemiology and omics 2. Translational research 3. Environment and lifestyle	Threats 1. Implementation and care 2. Allergy is a relatively small field 3. Translational research

*Relevance of research judged by 3 international experts (order of importance):
 See Table Relevance of research judged by international experts in appendix*

	Mean
Phenotyping and Severity	4.40
Biological mechanisms	4.60
Environment and lifestyle	3.80
Development and ageing	4.00
Prevention	3.80
Diagnosis monitoring	3.20
Therapy medical	3.60
Therapy non-medical	3.20
Biobanking	3.00
Data management clinical studies	3.80
Implementation and care	3.20

5. Description of the interface of Respiratory allergy with other Roadmap areas

From all areas mentioned in the SWOT analysis, asthma has most overlap. For asthma the numbers of the SWOT analysis are higher and 2 areas of strength are biological mechanisms and environment and lifestyle. Other fields that overlap are pediatric lung disease and infectious diseases. This offers opportunities for cooperation and future research.

6. Priorities for Dutch research in the area for 2014-2019

(Based on literature search and interface with other respiratory fields) would be in order of priority:

- Epidemiology & Omics (extensive work has already be done in this field by Dutch investigators/ These fields are strong in NL; the application of

epigenomics, metabolomics and proteomics to allergy research can bring the field to the forefront).

- Environment and lifestyle (efforts have already been made by researchers in Utrecht, Leiden and Wageningen). There is a clear relationship between western lifestyle and the development of allergic diseases. We need models that intervene in these lifestyles and environments to see whether the development and/or progression of disease can be stopped- strong links with societies in transition?
- Biological mechanisms (protective infections (including microbiome work), allergen structure, innate and adaptive immune responses to allergens).
- Novel treatments, including allergen immunotherapy, basal and clinical research (new areas such as food allergy, safer and more convenient methods of application).
- Biobanking (In the Netherlands we have a tradition of working with patient cohorts and extensive sampling of patients. Although there is not much experience with biobanking yet, this may be a good opportunity for future research).
- Translational research (there is a gap between basic science and clinical practice).
- Focus to explore novel targets for treatment of allergic asthma. (e.g. the role of regulatory B cells to reduce allergic airway inflammation)
- Allergen biotechnology in order to modulate allergenicity

7. What is needed to let the research priorities listed be successful?

- Allergy is a relatively small field in The Netherlands with many practitioners and researchers from different specialties and backgrounds. Necessary conditions for successful research in The Netherlands are establishing and extending current networks, shared focus on current needs, collaboration with primary care and use of eHealth facilities.
- Cooperation with existing organizations such as Lung Foundation, LAN, NRS is pivotal to get access to funding etc.

8. What do patients want?

Allergy is a very fractionated field. Only asthma, food-allergy and eczema patient groups are well organized. We limited our field of interest to respiratory allergy. The lung foundation has asked focus groups of patients on what they thought was needed in research on allergy. This included the following aspects: Cure instead of treatment; Reduction in hayfever attacks; Influence of house dust mite on allergic symptoms; Complementary care and treatment of allergy; Personalized medicine (children, gender, ethnicity) Relation between allergy and exacerbations of COPD; How to control symptoms; Relation indoor air pollution and allergy; A correct early diagnosis and treatment of allergy; Improvement in insights in European epidemiology of allergies. Stimulation of national epidemiologic studies on respiratory allergies, focusing on severity of disease and prevention and cure for children and adults; How does the increase in prevalence of allergies and the transition from mild to severe disease in the current era affects health care policies on a national and European level.

Table 1. Top 10 most cited basic research initiated by a Dutch group:

Theme	Article	Citations	
		Total	Mean/ yr
Immunology	Yazdanbakhsh, M, Kremsner, PG; van Ree, R. Immunology - Allergy, parasites, and the hygiene hypothesis. <i>Science</i> . 2002; 296(5567); 490-494	679	56.6
Innate adaptive immunity	Hammad, H, Lambrecht, B.N. Dendritic cells and epithelial cells: linking innate and adaptive immunity in asthma. <i>Nature Reviews Immunology</i> . 2008 8(3); 193-204	228	38.0
Gut Microbiota	Penders, J, Thijs, C, Van Den Brandt, P.A, Kummeling, I, Snijders, B, Stelma, F, Adams, H, Van Ree, R, Stobberingh, E. Gut microbiota composition and development of atopic manifestations in infancy: The KOALA birth cohort study. <i>Gut</i> 2007; 56(5); 661-667	165	23.6
Air pollution	Brauer, M, Hoek, G, Smit, H. A., et al. Air pollution and development of asthma, allergy and infections in a birth cohort. <i>European Respiratory Journal</i> 2007; 29(5): 879-888	158	22.6
Air pollution	Janssen, NAH, Brunekreef, B, van Vliet, P, et al. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. <i>Environmental Health Perspectives</i> . 2003; 111(12) 1512-1518	205	18.6
Societal impact	Dalstra, JAA, Kunst, AE, Borrell, C, et al. Socioeconomic differences in the prevalence of common chronic diseases: an overview of eight European countries. <i>International Journal of Epidemiology</i> 2005; 34(2): 316-326	147	16.3
Microbiota	van Nimwegen, F.A, Penders, J, Stobberingh, E.E, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. <i>Journal of Allergy and Clinical Immunology</i> . 2011; 128(5); 948-U371	36	12.0
Cohort design	Brunekreef, B, Smit, J, de Jongste, J, et al. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: Design and first results. <i>Pediatric Allergy and Immunology</i> 2002; 13(15): 55-60	136	11.3
Cross reactivity	Aalberse, R.C, Akkerdaas, J, Van Ree, R. Cross-reactivity of IgE antibodies to allergens. <i>Allergy</i> . 2001; 56(6); 478-490	122	9.4
Symptomatology	Caudri, D, Wijga, A, Gehring, U, et al. Respiratory symptoms in the first 7 years of life and birth	37	5.9

	weight at term - The PIAMA birth cohort. American Journal of Respiratory and Critical Care Medicine. 2007; 175(10); 1078-1085		
Prediction rules	Savenije, O.E.M, Kerkhof, M, Koppelman, G.H, et al. Predicting who will have asthma at school age among preschool children. Journal of Allergy and Clinical Immunology. 2012 ;130: 325-331	9	4.5

Table 2. Top 10 most cited clinical research initiated by a Dutch group:

Theme	Article	Citations	
		Total	Mean/yr
Treatment tiotropium	Kerstjens, H. A. M.; Disse, B; Schroeder-Babo, W; et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial. Journal of Allergy and Clinical Immunology. 2011 128: 308-314	33	11.0
Bed covers	Terreehorst, I; Hak, E; Oosting, AJ; et al. Evaluation of impermeable covers for bedding in patients with allergic rhinitis. New England Journal of Medicine. 2003; 349(3); 237-246	96	8.7

Table 3. Top 10 most cited collaborative international basic research (excl. reviews, guidelines):

Theme	Article	Citations	
		Total	Mean/yr
Pan-allergen	Asero, R, Mistrello, G, Roncarolo, D, De Vries, S.C., Gautier, M.-F, Ciurana, C.L.F, Verbeek, E, Mohammadi, T, Knul-Brettlova, V, Akkerdaas, J.H, Bulder, I, Aalberse, R.C, Van Ree, R. Lipid transfer protein: A pan-allergen in plant-derived foods that is highly resistant to pepsin digestion. International Archives of Allergy and Immunology. 2000; 122(1); 20-32	192	13.7
Plant glycoallergen	Van Ree, R, Cabanes-Macheteau, M, Akkerdaas, J, Milazzo, J.P, Loutelier-Bourhis, C, Rayon, C, Villalba, M, Koppelman, S, Aalberse, R, Rodriguez, R, Faye, L, Lerouge, P. $\beta(1,2)$ -xylose and $\alpha(1,3)$ -fucose residues have a strong contribution in IgE binding to plant glycoallergens. Journal of Biological Chemistry. 2000; 275(15); 11451-11458	189	13.5
Endotoxin exposure	Smit, L. A. M, Heederik, D, Doekes, G.; et al. Exposure-response analysis of allergy and respiratory symptoms in endotoxin-exposed adults. European Respiratory Journal. 2008; 31(6); 1241-1248	47	7.0
Microbial exposure	Heederik, D, von Mutius, E. Does diversity of environmental microbial exposure matter for the occurrence of allergy and asthma? Journal of Allergy and Clinical Immunology. 2012 ;130 44-	13	6.5
Endotoxin exposure	Smit, L. A. M, Heederik, D, Doekes, G.; et al. Exposure-response analysis of allergy and respiratory symptoms in endotoxin-exposed adults. European Respiratory Journal. 2008; 31(6); 1241-1248	47	7.0
Farm animals	Brunekreef, B, Von Mutius, E, Wong, G.K, et al. Early life exposure to farm animals and symptoms of asthma, rhinoconjunctivitis and eczema: an ISAAC Phase Three Study. International Journal of Epidemiology. 2012; 41: 753-761	4	2.0
Diet	Tromp, I. M, Kiefte-de Jong, J.C, de Vries, J.H, et al. Dietary patterns and respiratory symptoms in pre-school children: the Generation R Study. European Respiratory Journal. 2012; 40(3); 681-689	2	1.0

Table 4. Top 10 Most cited collaborative international clinical research (excl, reviews, guidelines):

Theme	Article	Citations	
		Total	Mean/yr
Treatment triotropium	Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, Sigmund R, Seibold W, Moroni-Zentgraf P, Bateman ED. N. Tiotropium in asthma poorly controlled with standard combination therapy. N. Engl J Med. 2012; 27;367(13):1198-207	26	13.0

Table 5: Top 10 best cited review and guideline papers with Dutch collaborators:

Theme	Article	Citations	
		Total	Mean/yr
Rhinitis	Bousquet, J, Khaltaev, N, Cruz, A. A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008; 63: 86: 8-+	839	139.8
Rhinitis	Brozek, Jan L, Bousquet, Jean, Baena-Cagnani, Carlos E.; et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision. Journal of Allergy and Clinical Immunology. 2010; 126: 466-476	170	42.5
Occupational asthma	Baur, X, Sigsgaard, T, Aasen, T. B, et al. Guidelines for the management of work-related asthma. European Respiratory Journal. 2012; 39: 529-545	15	7.5
Management	Brakel, T, Flokstra-de Blok, B, van der Molen, T, et al. Developing a decision support system for the management of allergy in primary care: system requirements as reported by general practitioners. Conference: 31st Congress of the European-Academy-of-Allergy-and-Clinical-Immunology (EAACI) 2012	0	0

APPENDIX

Opinions of international key opinion leaders

Question 1

Which research topics and groups in Respiratory Allergy research are visible and have impact on pulmonary physicians and researchers outside the Netherland?

Expert 1

Groningen (asthma)
Amsterdam (asthma, ENT)
Leiden (previously: asthma, currently primary care)
Rotterdam (allergy)
Utrecht (epidemiology)

Expert 2

In my experience the groups led by Dr. Postma in Groningen and Drs. Bel and Sterk in Amsterdam have the greatest impact.

Expert 3

- A very important Dutch consortium is the PIAMA consortium which has generated highly interesting results which are visible all over the world.
- The second group in Allergy research which has generated interesting results is the group by Maria Yazdanbakhsh and Hermelijn Smits working on the relation between parasitic infections and the development of allergy, mostly in children. Also the contribution to the EUROPREVALL project of this group is highly visible.
- Another very visible group concerns the genetics of asthma, in particular Gerard Koppelman in Groningen who has a strong role in various multicentre large consortia such as GABRIEL and EAGLE.
- Peter Sterk and Elisabeth Bel in Amsterdam are very visible in the clinical world for their clinical work on asthma, mostly in adults.
- There is a strong environmental component in the Netherlands which is situated in Utrecht and investigates the role of air pollution and other environmental components such as microbial exposures, represented by Bert Brunekreef and Dick Heederik.

Expert 4

In general, the outreach of research in the Netherlands is very good for basic research in the field of immunotherapy for allergic diseases, as well as basic immunology research in the field of allergy, asthma and general immunology.

From my ENT/Allergology perspective, the following research groups are very much known to me:

- Prof Fokkens and Prof Kapsenberg, AMC, Amsterdam,
- Prof Van Oosterhout, Immunotherapy research group, Groningen

Expert 5

Please see EAACI article “Research needs in allergy” written by more than 110 experts in the EAACI boards. Clin Transl Allergy. 2012 Nov 2;2(1):21. doi: 10.1186/2045-7022-2-21.

Immunogenetics,
Epigenetics
Allergy diagnosis
Specific immunotherapy
Nasal polyps and CRS

Endo and phenotyping
Allergen-SIT
Food Allergy
Immune Tolerance
Biologicals
Epithelial cells
Environment and immune system
Epigenetic regulation of the immune system
DC subsets
T and B cell subsets

Question 2

Which research topics in Respiratory Allergy research are less visible to physicians and researchers outside the Netherland?

Expert 1

Immunotherapy for allergic diseases

Expert 2

I don't know

Expert 3

Basic research and experimental studies.

Expert 4

Clinical research focussed on patient outcomes and guidelines for treatment.

Expert 5

Occupational allergy
NK cells, NK-T cells
Education
Novel Vaccines
Aging and development

Relevance of research judged by international experts (order of importance)

Research performed in the Netherlands in the field of Respiratory **Allergy**

0= no relevant research

5= excellent research international top level

	1	2	3	4	5	Mean
Phenotyping and Severity	4	5	5	4	4	4.40
Biological mechanisms	5	5	4	5	4	4.60
Environment and lifestyle	5	3	5	2	4	3.80
Development and ageing	5	4	3	3	5	4.00
Prevention	4	3	5	2	5	3.80
Diagnosis monitoring	4	4	3	2	3	3.20
Therapy medical	4	3	4	4	3	3.60
Therapy non-medical	3	3	3	4	3	3.20
Biobanking	5	3	3	1	3	3.00
Data management clinical studies	4	4	3	4	4	3.80
Implementation and care	5	3	3	2	3	3.20