

## **NRS Roadmap Sleep apnoea report**

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### **1. Inventory of Dutch research efforts in this field over the past five years**

Dutch research efforts in the field of sleep apnoea over the last 5 years were assessed as follows. A literature search was performed using PubMed and ISI Web of Knowledge, using the following search criteria: “sleep apnea” OR “sleep disordered breathing” OR “sleep apnoea” AND date 2007-2013. Acquired references were grouped according to topic (with topics including at least 5 references). In addition, citations were analysed using Web of Knowledge.

#### *Summary*

The top-10 of most cited papers found using the described search strategy, did not pertain to sleep apnoea per se for the most part, but dealt with topics such as obesity and risk factors for cardiovascular disease.

The estimated number of sleep apnoea-related Dutch papers over the last 5 years was 87. The largest categories were: oral-appliance therapy (n=18 papers, with 13 papers from the UMCG group and 4 papers from the Slotervaart hospital), surgical treatment (n=8, all from the Lucas Andreas Hospital), position therapy (n=7, Lucas Andreas Hospital), and “apnoea diagnosis” (n=9, various groups). A total of 22 papers dealt with sleep apnoea in other medical disorders (e.g. craniosynostosis (n=11) and Prader-Willi syndrome (n=4)). A total of 25 papers could not be grouped under a specific topic, and several of these papers were not apnoea specific.

In summary, Dutch research on sleep apnoea over the last 5 years has been largely dominated by the group of Hoekema at the UMCG (on oral-appliance therapy) and the group of de Vries at the Lucas Andreas Hospital (on surgical treatments and position therapy).

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

Areas with good visibility	Areas with less visibility
Therapy medical	Biological mechanisms
Therapy non-medical	Prevention
Central sleep apnea	Biobanking
Oral appliance therapy	Implementation and care
COPD and sleep	Animal models
Upper airway surgery	Basic research
Position therapy	Cardiometabolic
Pediatric	

## 3. Research needs

### *Facts and Figures:*

Prevalence of OSAS in the Netherlands is probably around 2-3 % of the entire population. A recent study under employees of the Philips company shows even >6%, Currently around 80,000 patients are being treated with CPAP or MRA which means that at least 250,000 people in the Netherlands are not being treated while they do have OSAS. (LAN 2013<sup>3</sup>). Based on the Philips data, the latest estimations are 500,000 patients with OSAS in the Netherlands. This means that still a great number of patients are not diagnosed, which may be due the fact that the knowledge of sleep apnoea is insufficient in the community. General practitioners encounter this problem as well in referring these patients. As a clear picture of a sleep apnoea patient is not present it is therefore difficult to recognize these patients. Based on the above several unmet needs can be extracted:

- We need data on population screening tools to increase the detection rate of patients having sleep apnoea.
- Further validation of diagnostic tools like polysomnography (PSG) and polygraphy (PG) in different situations are needed.
- Further phenotyping of apnoea patients is necessary: by detailing the broad spectrum of signs and symptoms we might link this to possible severity indicators
- Better insight is needed on optimal treatment. While different treatment modalities are available it is unknown what treatment suits the best for an individual patient.
- We have to explore the role of Drug Induced Sleep Endoscopy in finding the correct treatment option for MRA versus surgery.

*Unmet needs:(extracted from: LAN verkenning 2010<sup>3</sup>)*

### *References*

- <sup>1</sup> Feiten en cijfers 2013 Chronische Longziekten, LAN 2013
- <sup>2</sup> Maatschappelijke kosten voor astma, COPD en respiratoire allergie. RIVM Rapport 260544001/2012
- <sup>3</sup> Feiten en cijfers Chronische Longziekten, LAN 2010

#### 4. Summary SWOT analysis

Results of the web-based SWOT

<p><b>Strengths</b></p> <ol style="list-style-type: none"> <li>1. Research experience on several topics (such as oral-appliance therapy, position therapy etc).</li> <li>2. Several clinical research groups with an interest in sleep apnoea.</li> <li>3. Several groups with a good track record in general sleep medicine, as well as sleep biology and psychology</li> </ol>	<p><b>Weaknesses</b></p> <ol style="list-style-type: none"> <li>1. No research collaboration</li> <li>2. No specific academic support</li> <li>3. No tradition in research</li> </ol>
<p><b>Opportunities</b></p> <ol style="list-style-type: none"> <li>1. National working group on breathing problems during sleep ( WAS) can serve as a network</li> <li>2. Large number of untreated patients.</li> <li>3. Experience with general sleep medicine can be used to broaden sleep apnoea research.</li> </ol>	<p><b>Threats</b></p> <ol style="list-style-type: none"> <li>1. Lack of funding options</li> <li>2. Focus on other topics in many academic centres</li> </ol>

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

	<b>Mean</b>
Phenotyping and Severity	2.33
Biological mechanisms	2.00
Environment and lifestyle	2.50
Development and ageing	1.66
Prevention	1.50
Diagnosis monitoring	2.00
Therapy medical	5.00
Therapy non-medical	4.66
Biobanking	1.00
Data management clinical studies	1.50
Implementation and care	1.50

## 5. Description of the interface of sleep apnoea with other Roadmap areas

Possible opportunities for exchange of knowledge and ideas are for example with paediatrics, difficult asthma and COPD (by definition in the so-called overlap syndrome). In addition, we may be able to 'tap into' the experience with clinical databases in other groups, e.g. oncology. Finally, as in sleep apnoea a multidisciplinary approach is necessary there is almost by definition a good collaboration between ENT, pulmonary diseases, neurology and oral facial surgery. In addition if we consider in this paper central sleep apnoea with a ventilatory problem as well as collaboration with the teams of intensive care and COPD are possible.

## 6. Priorities for Dutch research in your area for 2014-2019

We like to subdivide our priorities in 4 different categories.

### Research network / Database

A very important first step is to develop a research network of physicians who are interested to participate actively in research linked to sleep apnoea. This team has to develop a national database for both obstructive sleep apnoea as well as central sleep apnoea. This is a highly important first step as it will not only provide an indication of the number of diagnosed apnoea patients in the Netherlands, but also on the diagnostic and therapeutic methods that are applied. Most importantly, a multicenter clinical database will be an indispensable tool to enable future clinical research studies.

### Diagnostic tools

As pointed out above we need to further increase the standardisation of our diagnostic procedures and diagnostic criteria. Next to standardisation we need prospective longitudinal studies into the role of diagnostic procedures such as for example DISE to validate therapeutic response and prognosis. Another example for standardisation and validation is the combination of questionnaires and oxymetry, which might help us to detect patients in an adequate manner and treat them effectively.

### Phenotyping

The national data base might be used to phenotype sleep apnoea in more detail. In this way we can prospectively record individual signs and symptoms.

### Therapeutics

Currently different treatment options are available in patients with OSAS. Nevertheless there is no convincing evidence which treatment should be provided to which patient. While CPAP and MRA are more established treatment options, positional therapy and neuromodulation are promising new therapies. Clinical studies are ongoing, and are urgently needed to investigate the effects of the different options. As many patients have complex problems that can not be solved with one option multimodality treatment is a further option as well.

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

Sleep apnoea is a relatively small field in the Netherlands with many interested physicians, however, a strong research history is lacking. First step is to set up a national network and to develop a national data base. Crucial in setting up a national network is to find the physicians with research competence wishing to participate actively next to the team. The implementation of a national clinical database is of the utmost importance to enable future research efforts in virtually every venue. To make this national data base a success we have to develop an infrastructure how data can easily be collected. Cooperation with existing organizations such as Lung Foundation, LAN, NRS, and patient organisations is pivotal to get access to funding.

## **8. What do patients want?**

The Dutch apnea patient association has growing interest in exploring research in this area and wants to facilitate this where possible. Their primary focus is research that will improve early detection of the disease, as there are still many patients who are not being diagnosed. Secondly, they want to increase knowledge on the societal impact of the disease if this is not being treated. Finally, they are interested in exploring the effects of MRA and position training devices as these are the more promising treatment options for the expected future patient population.

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

Theme	Article	Citations	
		Total	Mean/yr
Ventilatory control	Teppema, L.J, Dahan, A . The Ventilatory Response to Hypoxia in Mammals: Mechanisms, Measurement, and Analysis. <i>Physiological reviews</i> 2010; 90: 675-754	36	18.0
Diagnostics	van Houdt, P.J, Ossenblok, P.P.W, van Erp, M.G, et al. Automatic breath-to-breath analysis of nocturnal polysomnographic recordings <i>Medical &amp; Biological Engineering &amp; Computing</i> . 2011; 49: 819-830	5	5.0
MRA	Doff, M.H.J, Hoekema, A, Pruijm, G.J, et al. Effects of a mandibular advancement device on the upper airway morphology: a cephalometric analysis <i>Journal of Oral Rehabilitation</i> . 2009; 36: 330-337	5	1.7
Ventilatory control	Kiwull-Schoene, H, Teppema, L, Wiemann, M, et al. Pharmacological impact on loop gain properties to prevent irregular breathing <i>Journal of Physiology and Pharmacology</i> . 2008; 59: 37-45	5	1.3

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

Theme	Article	Citations	
		Total	Mean/ yr
Epidemiology	Seidell, J.C. Waist circumference and waist/hip ratio in relation to all-cause mortality, cancer and sleep apnea European Journal of Clinical Nutrition. 2010; 64: 35-41	26	13.8
Epidemiology	Schoonderwoerd, B.A, Smit, M.D, Pen, L. et al. New risk factors for atrial fibrillation: causes of 'not-so-lone atrial fibrillation' Europace. 2008; 10: 668-673	46	11.6
Epidemiology	van den Berg, J.F, Neven, A. Knvistingh; Tulen, J. H. M, et al. Actigraphic sleep duration and fragmentation are related to obesity in the elderly: the Rotterdam Study International Journal of Obesity. 2008; 32: 1083-1090	39	9.8
other disorders	Bannink, N, N.E, Wolvius, E.B, et al. Obstructive sleep apnea in children with syndromic craniosynostosis: long-term respiratory outcome of midface advancement International Journal of Oral and Maxillofacial Surgery. 2010; 39: 115-121	16	8.0
Other disorders	de Jong, T, Bannink, N, Bredero-Boelhouwer, H.H, et al. Long-term functional outcome in 167 patients with syndromic craniosynostosis; defining a syndrome-specific risk profile Journal of Plastic Reconstructive and Aesthetic Surgery. 2010; 63: 1635-1641	16	8.0
Treatment CPAP	Hoekema, A, Stel, Stegenga, B, et al. Sexual function and obstructive sleep apnea-hypopnea: A randomized clinical trial evaluating the effects of oral-appliance and continuous positive airway pressure therapy Journal of Sexual Medicine. 2007; 4: 1153-1162	22	4.5
Treatment HCPAP	Richard, W, Venker, J, den Herder, C, et al. Acceptance and long-term compliance of nCPAP in obstructive sleep apnea European Archives of Oto-Rhino-Laryngology. 2007; 264: 1081-1086	20	4.0
Surgery	Richard, W, Kox, D, den Herder, C, et al. One stage multilevel surgery (uvulopalatopharyngoplasty, hyoid suspension, radiofrequent ablation of the tongue base with/without genioglossus advancement), in obstructive sleep apnea syndrome European Archives of Oto-Rhino-Laryngology.	20	4.0

	2007; 264: 439-444		
surgery	van den Broek, E, Richard, W; van Tinteren, H, et al. UPPP combined with radiofrequency thermotherapy of the tongue base for the treatment of obstructive sleep apnea syndrome European Archives of Oto-Rhino-Laryngology. 2008; 265: 1361-1365	15	3.8
Treatment Oral appliances	Hoekema, A, Stegenga, B, Bakker, M,; et al. Simulated driving in obstructive sleep apnoea-hypopnoea; effects of oral appliances and continuous positive airway pressure Sleep and Breathing. 2007; 11: 129-138	17	3.4

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

Theme	Article	Citations	
		Total	Mean/yr
Treatment	Carley, D.W, Olopade, C, Ruigt, Ge.S, et al. Efficacy of mirtazapine in obstructive sleep apnea syndrome Sleep. 2007; 30:35-41	41	8.1
Cardiac complications	Linz, D, Mahfoud, F, Schotten, U, et al. Renal Sympathetic Denervation Suppresses Postapneic Blood Pressure Rises and Atrial Fibrillation in a Model for Sleep Apnea Hypertension. 2012; 60:172-178	8	8.0
Cardiac complications	Linz, D, Schotten, U, Neuberger, H, et al. Combined blockade of early and late activated atrial potassium currents suppresses atrial fibrillation in a pig model of obstructive apnea Heart Rhythm. 2011; 8:1933-1939	3	3.0

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

Theme	Article	Citations	
		Total	Mean/yr
Cognitive function	Lis, S, Krieger, S, Hennig, D, et al. Executive functions and cognitive subprocesses in patients with obstructive sleep apnoea Journal of Sleep Research. 2008; 17:271-280	21	5.0
Diagnostics	Morris, L.G.T, Burschtin, O, Setlur, J, et al. REM-associated nasal obstruction: A study with acoustic rhinometry during sleep Otolaryngology-Head and Neck Surgery. 2008; 139:619-623	1	0.1

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

<b>Theme</b>	<b>Article</b>	<b>Total</b>	<b>Citations</b>
Diagnosics	Dirk; A, Ronald M, De Meyer, M. The acoustics of snoring Pevernagie, Sleep Medicine Reviews. 2010; 14: 131-144	20	10.0
Diagnosics	Kezirian, E.J, Hohenhorst, W, de Vries, N. Drug-induced sleep endoscopy: the VOTE classification European Archives of Oto-Rhino-Laryngology. 2011; 268: 1233-1236	13	13.0
Diagnosics	Mathus-Vliegen, E. M. H, Nikkel, D, Brand, H. S. Oral aspects of obesity International Dental Journal. 2007; 57: 249-256	13	2.6
Surgery	Nout, E, Cesteleyn, L.L.M, van der Wal, K.G.H, et al. Advancement of the midface, from conventional Le Fort III osteotomy to Le Fort III distraction: review of the literature International Journal of Oral and Maxillofacial Surgery. 2008; 37:781-789	10	2.5
Diagnosics	Guijarro-Martinez, R, Swennen, G.R.J. Cone-beam computerized tomography imaging and analysis of the upper airway: a systematic review of the literature Guijarro-Martinez, R, Swennen, G. R. J. International Journal of Oral and Maxillofacial Surgery. 2011; 40:1227-1237	8	2.7
ENT	Georgalas, C. The role of the nose in snoring and obstructive sleep apnoea: an update European Archives of Oto-Rhino-Laryngology. 2011; 268:1365-1373	7	7.0
Surgery	de Gijt, J.P, Vervoorn, K, Wolvius, E.B, et al. Mandibular midline distraction: A systematic review Journal of Cranio-Maxillofacial Surgery. 2012; 40: 248-260	2	2.0

## APPENDIX

Opinions of international key opinion leaders:

Questions were sent to international experts in the field about the visibility of Dutch sleep apnoea research.

### Question 1

**Which research topics and groups in Sleep Apnoea research are visible and have impact on pulmonary physicians and researchers outside the Netherland?**

#### Expert 1

W De Backer/ Verbraecken JA (Antwerp): Upper airway physiology, upper airway imaging

A Boudewyns, Van der Veken OM: OSA surgery, oral appliances and hypoglossal nerve stimulation

Wijkstra PJ: Oral appliance/non invasive ventilation

Verhulst SL: Pediatric sleep apnea

Pevernagie D: Central sleep apnea/Positive airway therapies

#### Expert 2

- Central sleep apnea and behavioural hyperventilation. Kempenhaeghe Slaapcentrum.
- Oral appliance therapy in obstructive sleep apnea. Groningen Medisch Centrum; Amsterdam ACTA
- COPD and sleep (less focus on sleep apnea). Groningen Medisch Centrum; Rijnstate Hospitaal Arnhem
- Upper airway surgery in obstructive sleep apnea; pacing in obstructive sleep apnea. Amsterdam St-Lucas ziekenhuis.
- Position therapy in obstructive sleep apnea. Amsterdam St-Lucas ziekenhuis; T wente Medisch Centrum.

#### Expert 3

#### Expert 4

In my opinion the research in sleep apnea in the Netherlands is mainly focused on diagnosis and monitoring. In addition, there is some excellent research in the field of both medical and non-medical therapies for sleep apnea.

## **Question 2**

**Which research topics in Sleep Apnoea research are less visible to physicians and researchers outside the Netherland?**

### **Expert 1**

Cardiometabolic consequences of sleep apnea

Animal models of sleep apnea/basic and mechanistic science in the field of sleep apnea

### **Expert 2**

- Neurocognitive functioning in obstructive sleep apnea after CPAP therapy. Wijk aan Zee Heliomare Rehabilitation.
- Neuroendocrine disorders and obstructive sleep apnea. Leiden University Medical Centre.

### **Expert 3**

To be honest sleep research is not very stimulating worldwide. There are not many open questions yet. The Netherlands is not different from other European countries, there is less basic research in comparison to UK and Italy.

### **Expert 4**

For me, research on phenotyping, biobanking, and development or ageing are less visible and I am not aware of clearly visible research in this area concerning sleep apnea in the Netherlands.

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

Research performed in the Netherlands in the field of **Sleep Apnoea**

0 = no relevant research  
 5 = excellent research international top level

	<b>1</b>	<b>2</b>	<b>3*</b>	<b>4</b>	<b>Mean</b>
<b>Phenotyping and Severity</b>	3	2		2	2.33
<b>Biological mechanisms</b>		2		2	2.00
<b>Environment and lifestyle</b>		3		2	2.50
<b>Development and ageing</b>	3	0		2	1.66
<b>Prevention</b>		1		2	1.50
<b>Diagnosis monitoring</b>		0		4	2.00
<b>Therapy medical</b>		5		5	5.00
<b>Therapy non-medical</b>	4	5		5	4.66
<b>Biobanking</b>		0		2	1.00
<b>Data management clinical studies</b>		0		3	1.50
<b>Implementation and care</b>		1		3	1.50

\* Relevance not given