EVIDENCE-BASED OTOLARYNGOLOGY; RESEARCH AND PRACTICE IN MANAGING PATIENTS WITH CHRONIC RHINOSINUSITIS

NINA KAPER

537940-L-sub01-bw-Kaper
Processed on: 20-12-2019

Cover design by Nora Louise Hoekstra
Printing and thesis layout: Gildeprint, Enschede

ISBN 9789464020090

Printing of this thesis was kindly supported by:
Stichting ORLU, ACTA, Jeroen Bosch Ziekenhuis, Ziekenhuis Gelderse Vallei, K.H. de Jong's Beleggingsmaatschappij B.V., Allergy Therapeutics, Specsavers Hoortoestellen, Rentmeester F. Nijpjes VOF, Beter Horen, ALK, Atos Medical, Chipsoft, MediTop, DOS Medical and Mylan.

EVIDENCE-BASED OTOLARYNGOLOGY; RESEARCH AND PRACTICE IN MANAGING PATIENTS WITH CHRONIC RHINOSINUSITIS

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het college voor promoties ingestelde
commissie, in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 31 januari 2020, te 12.00 uur

door

Nina Marie Kaper
geboren te Hilversum

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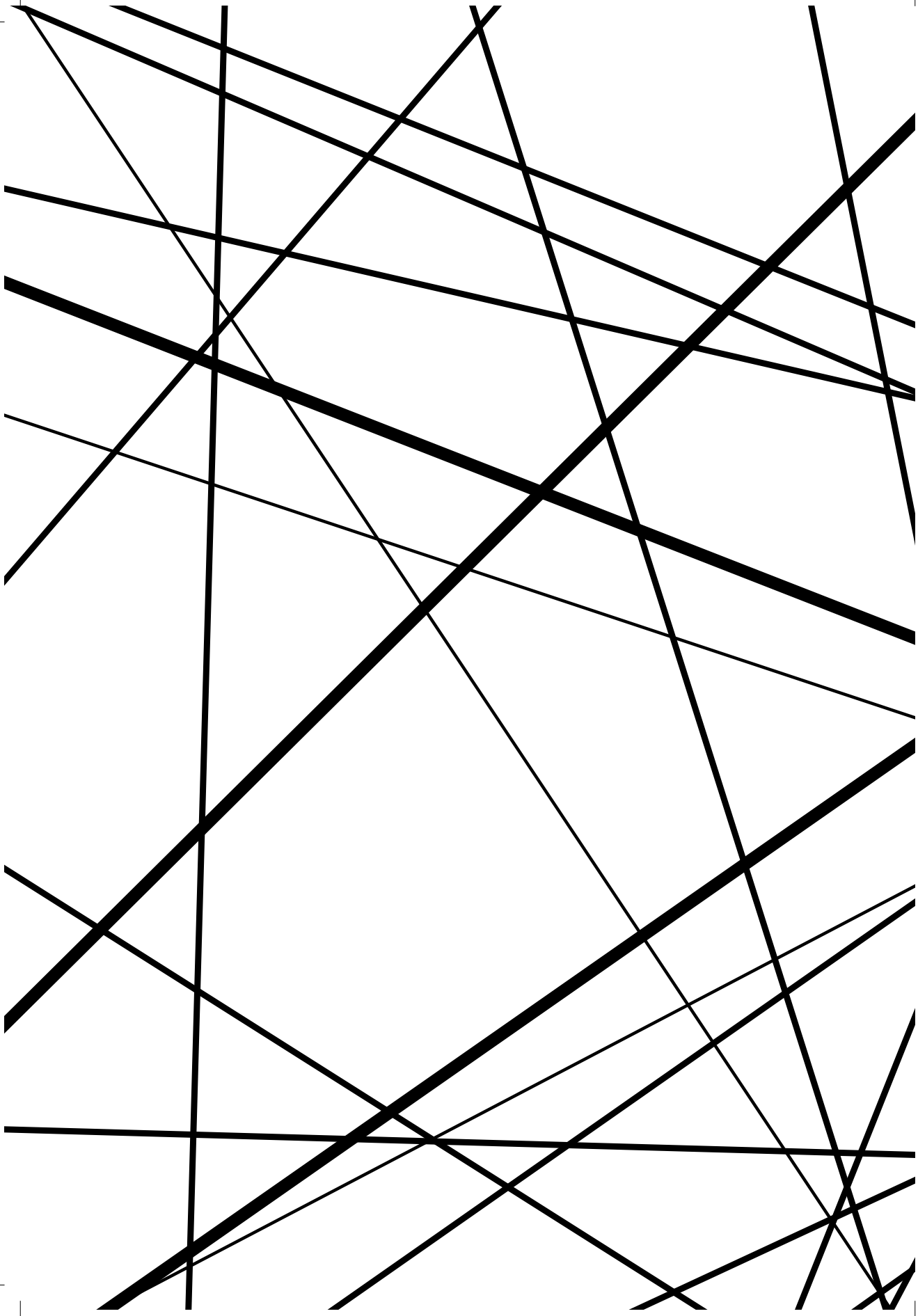
It always seems impossible until it’s done. Nelson Mandela

CONTENTS



CHAPTER 1

General introduction and thesis outline

INTRODUCTION

The term evidence-based medicine was introduced in 1991 and originally focused on a problem-solving approach that resulted in formulating an explicit clinical question. This question should then be answered by a systematic evaluation of available medical research, rather than the traditional modus operandi, i.e. looking for an answer in medical textbooks, using pathophysiological principles, or asking senior doctors for advice.[1] Up to that point, healthcare was based on professional dominance and craftsmanship, with reliance on oral communication and expert opinion.[2]

Based on large unexplained practice variation, side effects and harm on top of unproven benefits of established medical therapies, the call for evidence-based medicine emerged.[2] This concept has evolved over the years into evidence-based practice (EBP), which has become standard of care.[3] EBP is a process of decision making in healthcare, which is based on the best available research evidence, combined with patients' preferences and doctors' experiences. Healthcare decisions should be made together with those receiving care, after being informed by both tacit and explicit knowledge from their clinicians.[3]

To be able to apply EBP, clinicians must acquire knowledge and skills to perform the five steps of EBP, which are an ongoing process.

1. translate a clinical case scenario into a research question.
2. systematic retrieval of the best available evidence.
3. critical appraisal of evidence for clinical relevance, validity and applicability.
4. application of results in practice, integrate with own experience and patients' preferences.
5. evaluate the performance and improve if necessary.[3]

EBP has the potential to improve patient outcomes and reduce unwarranted practice variation, i.e. variation in healthcare that cannot be explained by patients' preferences or factors, such as differences in disease prevalence, risk factors for disease or disease severity.[3,4]

The effective integration of research evidence into healthcare has been challenging, resulting in a clear gap between research and practice. It is estimated that 30–40% of patients do not receive care according to the best available research evidence and 20–25% of provided care is not needed or potentially harmful.[5] Various methods to close this gap have been developed. Predominantly, summarizing and appraising individual studies from the large and expanding evidence pool have been promoted, to make the available evidence more accessible for clinicians. Haynes describes these as part of the 5S model,

537940-L-sub01-bw-Kaper
Processed on: 20-12-2019

i.e. systems (computerized decision-support systems), summaries (evidence-based clinical practice guidelines), synopses (summary and critical appraisal of a study, with a recommendation) and synthesis (systematic reviews and meta-analysis, e.g. Cochrane reviews) of individual studies.[6]

The steps from research to practice have been described in different subsequent steps. These can be visualized as an evidence pipeline, based on the Pathman guideline implementation model (aware, agree, adopt and adhere).[7,8] With each step there is some leakage possible, through which a part of the evidence fails to make it into practice.[8]

1. Awareness; to know the valid and relevant evidence from the expanding research pool
2. Agreed to; when being aware, will there be agreement with the evidence?
3. Acceptance; when agreeing, is there willingness to change routines and practice?
4. Available and able; the abilities and circumstances required should be available to allow for the use of the evidence
5. Applicable; the evidence should be applied correctly and appropriately in relevant circumstances
6. Acted on; actually change practice habits
7. Adhered to; stick to such change

Barriers and facilitators of EBP have been studied widely and are numerous. They can arise at the level of the individual professional (mind-set, EPB competencies), at team and organization level, at an environmental level, or with evidence and clinical practice guideline (CPG) characteristics.[9] For example, the type of health problem influences compliance (e.g. better implementation of guidelines for acute versus chronic care). Better quality of evidence increases compliance. The uptake of evidence is also facilitated by recommendations corresponding with existing values, recommendations that diminish complex decision-making, concrete description of the recommendations and limited need for new skills and organizational change.[5]

In this thesis, the gap between research and practice in otolaryngology will be assessed at various stages of the evidence pipeline (**Thesis outline**). The focus will be on the management of patients with chronic rhinosinusitis (CRS), a disease which is defined by infection of the nasal and paranasal mucosa for a minimum of 12 weeks.[10] Patients may present with different symptoms, notably, nasal obstruction, rhinorrhea (anterior or posterior), facial pain/pressure and loss of smell. Two or more of these symptoms should be present for the diagnosis of CRS, of which one should be either nasal obstruction or rhinorrhea (anterior/posterior). The diagnosis is confirmed by signs of inflammation at anterior/posterior rhinoscopy and/or pathological findings on CT.[10] There is a distinction

between CRS with and without nasal polyps. CRS is a common disease, estimated to affect 2% to 11% of the adult population.[10] Its impact on quality of life is considerable, equaling other chronic conditions such as chronic back pain, congestive heart disease and chronic obstructive pulmonary disease.[11] There is an extensive evidence base for CRS, with over 12.000 publications in Pubmed (more than 700 clinical trials), 12 Cochrane reviews and multiple (inter)national CPG's.[12,13]

OVERALL AIM OF THIS THESIS

In this thesis we aim to find out whether current available evidence in otolaryngology in the broader sense and CRS guidelines specifically serve the uptake of medical knowledge from research evidence into daily otolaryngology practice, also known as EBP. Also, the compliance of Dutch otolaryngologists to CRS guidelines and practice variation for CRS are further evaluated.

THESIS OUTLINE

In part one EBP behavior is assessed in various ways. In **Chapter 2** the development and validation of an inventory to measure barriers and facilitators for EBP among clinicians are presented. This is a framework for future studies and is ultimately intended for healthcare teams and organizations to assess local conditions for EBP, to aim efforts at improving or maximizing EBP. In Chapters 3 and 4 guideline compliance is assessed using different methods. In **Chapter 3**, guideline adherence for CRS is measured with a nationwide survey among Dutch otolaryngologists. In **Chapter 4**, healthcare utilization, guideline follow-up and practice variation for CRS are measured using health care reimbursement claims.

In part two, the quality of the evidence base for otolaryngology in general is assessed. In **Chapter 5**, the different publication types from major otolaryngology and medical journals are presented. In the context of EBP, systematic reviews and original publications concerning therapy, diagnosis, prognosis and etiology are found to be most relevant. In **Chapter 6** the risk of bias of the therapeutic publications identified in Chapter 5 is critically assessed.

In part three the quality of the evidence base for CRS is further assessed. **Chapter 7** displays three clinical questions for CRS, that are answered based on the best available evidence, using a systematic search for evidence and critical appraisal of the selected literature. **Chapter 8** shows a quality assessment and comparison of 10 (inter)national clinical practice guidelines for CRS.

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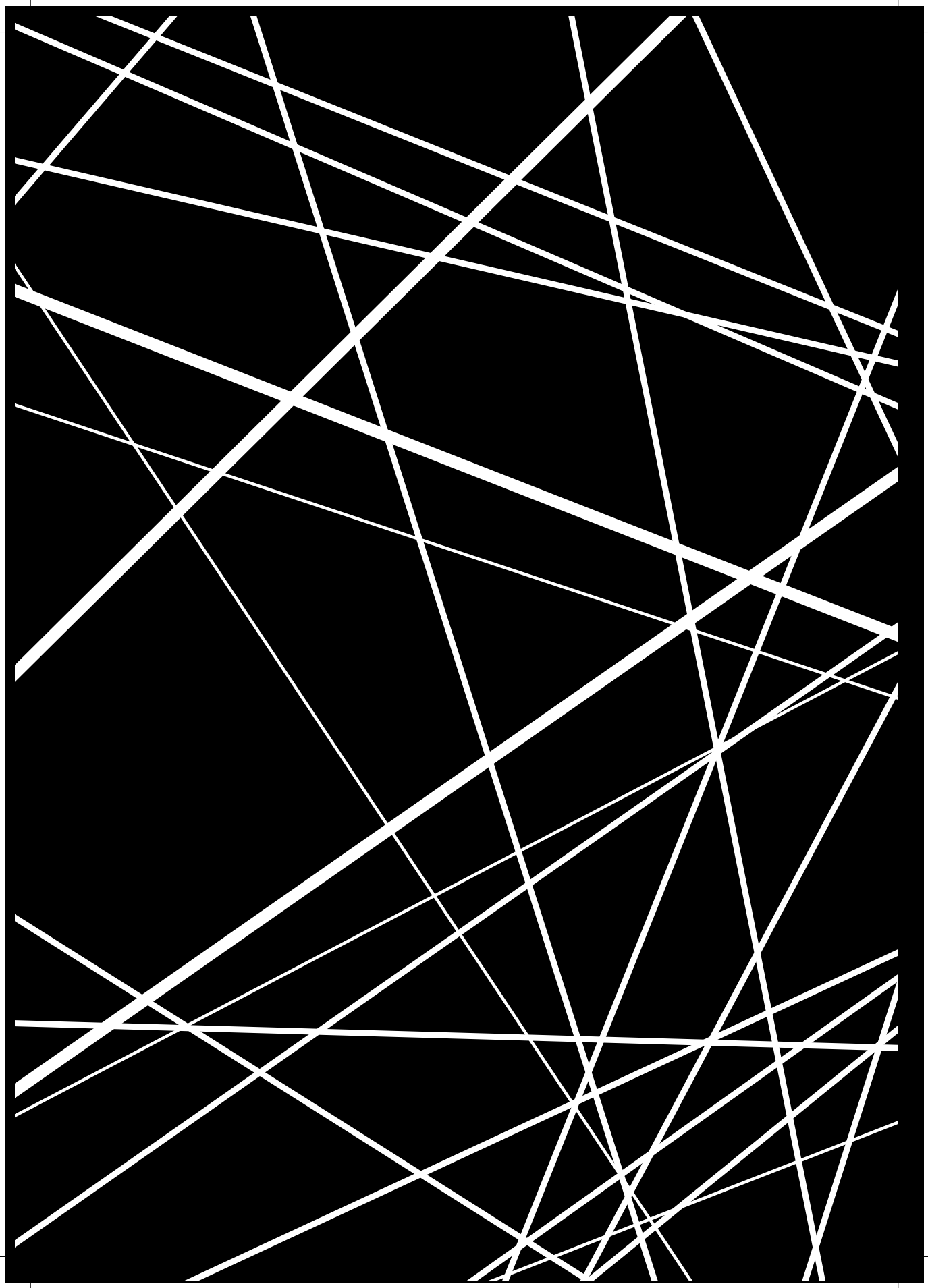
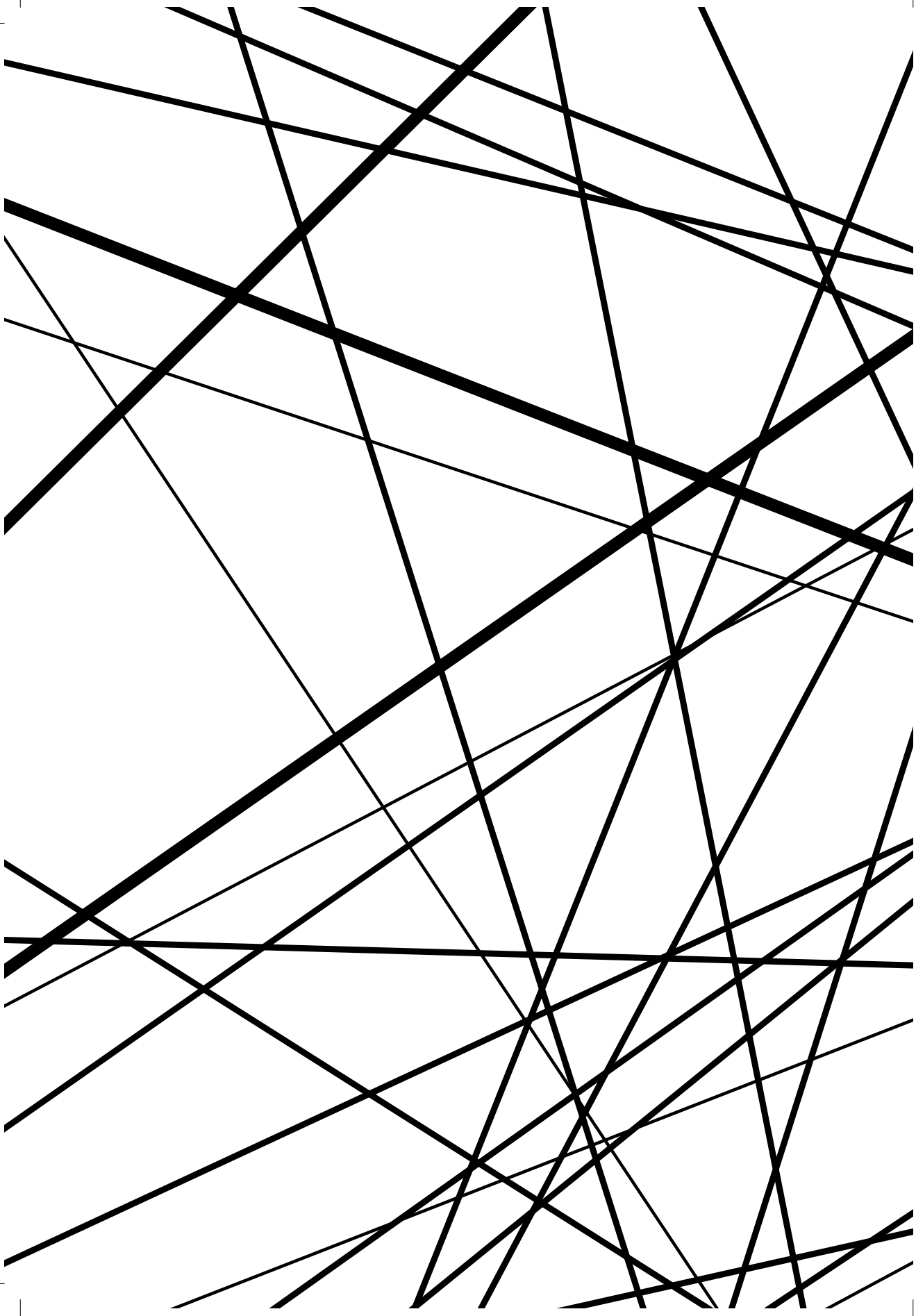


PART 1

Evidence-based practice behavior, guideline awareness and adherence



CHAPTER 2

The "evidence-based practice inventory": reliability and validity was demonstrated for a novel instrument to identify barriers and facilitators for Evidence-Based Practice in health care

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*Both authors contributed equally to first authorship

J Clin Epidemiol. 2015;11:1261-9

Author contributions

Kaper NM: Questionnaire survey, Analysis and interpretation of data, Drafting figures and tables, Drafting of the manuscript, Final approval of the version to be published.

Swennen MH: Questionnaire development, Delphi study, pilot study, Analysis and interpretation of data, Drafting figures and tables, Drafting of the manuscript, Final approval of the version to be published.

van Wijk AJ: Design of study, Analysis and interpretation of data, Revision of the manuscript, Final approval of the version to be published.

Kalkman CJ: Analysis and interpretation of data, Revision of the manuscript, Final approval of the version to be published.

van Rheenen N: Questionnaire development, Delphi study, pilot study, Revision of the manuscript, Final approval of the version to be published.

van der Graaf Y: Design of study, Analysis and interpretation of data, Revision of the manuscript, Final approval of the version to be published.

van der Heijden GMJG: Design of study, Analysis and interpretation of data, Drafting of the manuscript, Final approval of the version to be published.

ABSTRACT

Objective: To design and validate a practical questionnaire for clinicians, to identify barriers and facilitators for evidence-based Practice (EBP), that is, the use of research evidence in patient care. The inventory is ultimately intended for departments to assess local conditions for EBP, to aim and evaluate efforts at improving or maximizing EBP.

Methods: We derived candidate items from existing EBP scales, psychology and behavioral economics. In an online Delphi study, 537 international expert clinicians, researchers, teachers and policymakers interested in EBP identified items with sufficient face and content validity. We piloted and validated the resulting draft inventory among 127 clinicians from various specialties and career stages.

Results: The Delphi study started with 114 candidate items and resulted in a draft inventory with 29 items in five dimensions. During the pilot, the draft inventory was easy to complete within 15 minutes and the items showed sufficient response variation. In four of five dimensions test-retest reliability was substantial to almost perfect and the power to discriminate between groups with different expertise was adequate, whereas internal consistency showed that the items generally measured the same construct. On the basis of internal consistency and factor analysis we excluded three items. The final EBP inventory consists of 26 items in five dimensions: decision making, subjective norm, attitude, perceived behavior control and intention and behavior.

Conclusion: The EBP inventory was developed with support of EBP experts and validated among various academic clinicians. It shows adequate face and content validity, internal consistency, test-retest reliability, discriminative power, and completion will take <15 minutes. We recommend further evaluation of its value in field trials.

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INTRODUCTION

Providing evidence-based care is recognized as an essential competence for clinicians.[1] Health care decisions based on the available research evidence have considerable potential to improve patient outcomes and reduce unwarranted variations in clinical decisions.[2] However, implementation of research evidence into practice remains a challenge and wide unexplained variations exist in the extent to which clinicians use research evidence to inform their decisions.[3] This gap between research evidence and clinical practice highlights the importance of evidence-based practice (EBP).[1] EBP is a problem solving approach intended to improve the quality of health care by informing clinical decision making in patient care by current best evidence. Creating a setting that facilitates EBP remains a key challenge for those wishing to provide high quality health care.[4] A number of studies have addressed barriers and facilitators that are important for the implementation of research evidence in patient care. Besides the characteristics of the evidence or clinical practice guideline itself, the major barriers and facilitators seem to relate to the individual mind-set, professional group norms, competencies in EBP, the balance between confidence and critical reflection, and managerial collaboration.[4-6]

To date, there is no comprehensive instrument to assess barriers and facilitators for EBP.[7-9] This article describes the design and validation of a short inventory aimed at identifying barriers and facilitators for EBP across a variety of clinician and setting characteristics. The Inventory can be used by health care departments to assess EBP culture under local conditions and may provide mirror information on barriers and facilitators, and thereby give clues for strategies to improve and evaluate EBP.

METHODS

Questionnaire development

Item generation

On the basis of face validity, that is, whether items appear relevant as a barrier or facilitator for adherence to EBP, we derived candidate items from the literature. We consulted both the conceptual framework of EBP and from existing scales in EBP, psychology and behavioral economics.[7,10-30] If necessary, we rephrased items to the context of EBP, and to prevent socially desirable responses, we phrased them neutrally. On the basis of theoretical considerations regarding barriers and facilitators for the adherence to EBP, we specified seven dimensions and assigned candidate items to these by their face and content validity, that is, the extent to which the

537940-L-sub01-bw-Kaper
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items cover the most important aspects of EBP. This process was carried out by two independent authors (M.S. and N.R.) and discussed with a third author (G.H.) until agreement was reached.

Item reduction

During an online Delphi study of 2 rounds (August 2010 to October 2011), we used a judgmental approach that was aimed at maximizing the face and content validity of the EBP inventory. To include a diverse range of views on EBP we invited 537 clinicians, teachers, researchers and policy makers from our EBP network to participate (Appendix 1). In Delphi round 1 we asked respondents to select any number of items that they considered to represent important barriers or facilitators for adherence to EBP and weigh their importance (1=marginally important to 5=extremely important). In Delphi round 2 we asked respondents to select 15 items considered important barriers or facilitators for identifying variability in the adherence to EBP and weigh their importance for that in the same manner. During both Delphi rounds we invited respondents to comment on grammar and phrasing in order to improve uniform interpretation of items and prevent socially desirable responses, and we asked them whether they wanted to add items or dimensions.[29-31]

For each round we calculated the relative item weights by dividing the mean of the item by its standard deviation. We then ranked items by their relative item weight twice: once for all items together and once for items grouped per dimension. For each ranking we then marked items when their weight exceeded the mean of item weights for all items together as well as per dimension. Items marked twice were selected for the second Delphi round and for inclusion in the draft version. For items marked only once we discussed selection, during which we considered the number of items already selected for a dimension, to balance the number of items per dimension.

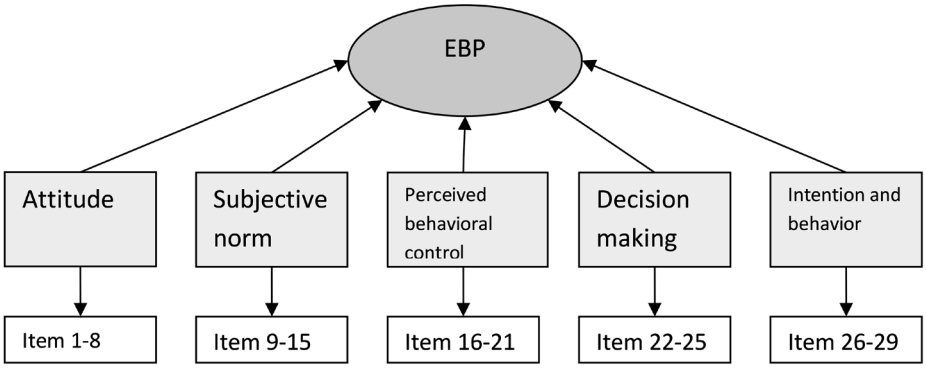
Draft version

We worded items neutrally and defined their response scale ranging from 1 to 6. Wording of scale extremes was chosen per item topic, with a positive phrasing for the high scale extreme and a negative phrasing for the low scale extreme. For items with two extremes, not necessarily positive or negative, we phrased the item in such a way that it was balanced between one and another extreme. According to the reflective measurement model theory the item scores are considered 'effect indicators' that denote their dimension within the conceptual framework of the EBP Inventory. As such, we sum item scores to measure their dimension.[27,28] (Figure 1, bottom part) These dimension scores are deemed 'causal indicators' which together capture EBP as construct. Hence, and according to the formative measurement model theory, we do not total dimension scores. [27,28] (Figure 1, upper part)

In addition, we defined the frequently used terms “EBP” and “clinical decision” to standardize their interpretation, as these are concepts central to the EBP Inventory. Finally, we also identified items for documenting demographic, personal and setting characteristics that we considered relevant for variation in EBP.

To finalize the draft version of the EBP Inventory we invited comments from the expert panel in a third Delphi round on the content validity, that is, the extent to which the draft covers the most important aspects of EBP, phrasing of items and item response scales, as well as on both definitions, and items on demographic, personal and setting characteristics.

Figure 1. Combined formative and reflective measurement model for EBP.



Legend:
EBP, evidence-based practice

Pilot of draft

We piloted the draft version of the EBP Inventory in the department of otolaryngology of the University Medical Center Utrecht, the Netherlands (26 October 2011) and in the department of Pediatrics (6 March 2012) of the Isala Clinics, Zwolle, the Netherlands. We assessed ease of use and duration of completion and explored the discriminative ability of items. We evaluated whether the item response distributions satisfied Gaussian ‘normality’ assumptions by the proportion of respondents with scores higher than half a standard deviation above the mean, and the proportion of respondents with a score lower than half a standard deviation below the mean. In addition, we looked for floor effects, that is, item response mean was lower than 1 (lowest possible item score) plus the standard deviation, and ceiling effects, that is, item response mean was higher than 6 (highest possible item score) minus the standard deviation.

We explored internal consistency, that is, whether items measured the same construct of their dimension, where Cronbach's α of 0.7 to 0.8 is considered satisfactory, 0.8 to 0.9 is good, and >0.9 is excellent.[32] After this pilot testing we invited final comments from experts in a fourth Delphi round on the content and phrasing of items and response scales, and dimensions of the EBP Inventory.

Performance testing

Between July 2012 and April 2013 we tested the validity and reliability of the EBP Inventory among staff of the departments of Radiology, Pediatrics, Otolaryngology and among staff of the general practitioners (GP) training program of the University Medical Center Utrecht. Participants were asked to complete the EBP Inventory twice, the first time during general or education meetings, the second time at least 3 weeks later during a subsequent meeting or by means of an online survey. As a rule of thumb, we aimed at a sample size of three respondents for each item evaluated.[33]

Under Dutch law (Wet Medisch-Wetenschappelijk Onderzoek bij Mensen), a waiver for informed consent applied. The approval to collect and analyze data was obtained from the heads of the departments. We informed clinicians on the confidential use of data and all filled out the Inventory voluntarily and anonymously.

Distribution of responses

We planned to exclude items and respondents with ≥10% missing values and imputed remaining missing values with conditional imputation of means, taking into account age, gender, career stage (resident or consultant) and specialty.[34,35] We examined the distribution of responses and looked for items with floor and ceiling effects.

Validity

We assessed structural validity, that is, whether items within the same predefined dimension show a unidimensional factor structure. For this, we assessed whether the highest factor loading on the first factor exceeds 0.4 during an exploratory factor analysis, and used the data collected at the first completion.[36]

We also assessed construct validity, that is, the extent to which a particular measure is related to other measures in a manner that is consistent with hypotheses derived from the conceptual framework of EBP concerning the phenomenon that is measured.[36] For this, we anticipated the EBP Inventory dimensions to discriminate well between a priori hypothesized groups. We assessed whether score distributions for pre-specified EBP Inventory dimensions differ between theoretical a priori subgroups and used a criterion of 10% difference between groups of proportions with high scores, that is, above mean

plus half the standard deviation, and with low scores, that is, below mean minus half the standard deviation. As such we evaluated these differences for the dimensions "attitude" and "intention & behavior" in teachers of EBP (yes / no); for the dimension "subjective Norm" in adepts of shared learning (yes / no); for the dimension "perceived behavioral control" in those who received EBP training in medical school (yes / no); for the dimension "decision making" in those with significant clinical experience (yes / no).[28] For this assessment of the construct validity we used the data collected during the first completion.

Reliability

The internal consistency of the EBP Inventory was assessed by calculating Cronbach α, which was considered to be acceptable when it exceeds 0.7 and is lower than 0.9.[28]

The usefulness of individual items was evaluated by assessing the impact on the internal consistency of the EBP Inventory when individual items were excluded one at a time (Cronbach α when item deleted). Potentially redundant items are those for which removal would raise internal consistency.[32] For this assessment of internal consistency we used the data collected the first completion.

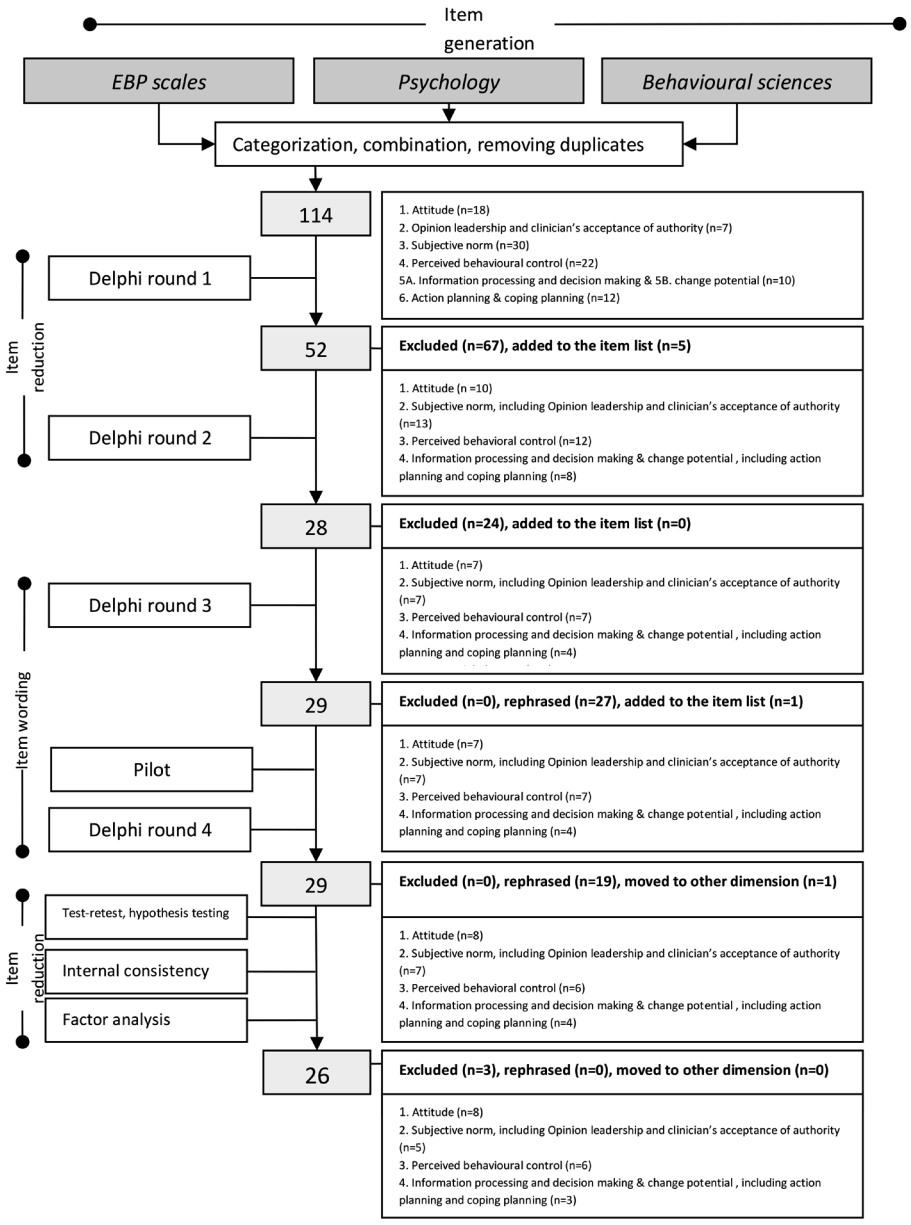
We calculated the two-way mixed model with absolute agreement intraclass correlation coefficient (ICC), with to assess test-retest reliability (0 to 0.20; slight agreement, 0.21 to 0.40; fair agreement, 0.41 to 0.60; moderate agreement; 0.61 to 0.80 substantial agreement; 0.81 to 1.00 almost perfect agreement).[37] Calculations of ICC were based on the data collected during the first and second completion.

On the basis of results of validity and reliability testing, two authors (M.S. and N.R.) decided on expert suggestions for adding and excluding items or moving items to another dimension (Fig. 2). They also incorporated the final responses of experts on the need for rephrasing of items, response scale, wording and rephrasing of demographic items and definitions. A third author (G.H.) decided when they could not reach agreement.

Software

We used software NETQ 6.0 (NETQuestionnaire, Nederland BV; 2007) for data collection of responses during the Delphi study. We used SPSS version 20.0 (IBM Corp.; Armonk, NY) and Microsoft Office Excel 2003 (Redmond, WA) for analyses of the Delphi study data and validity and reliability testing.

Figure 2. Flow diagram of the consecutive stages in the development of the EBP Inventory.



Legend:
EBP, evidence based practice
n, number of items

RESULTS

Questionnaire development

A total of 114 items, pre-assigned to 7 dimensions were identified. Of these, 52 items grouped in 5 dimensions (Text box 1) remained after the first Delphi round. Thereafter, 29 items (on a six-point response scale) grouped in 5 dimensions resulted for the final version (Figure 2).

Text Box 1. EBP inventory dimensions and their definitions

Dimension 1 - attitude Item numbers 1-8

A clinician's individual evaluation of EBP [20-23]

Overall; 'Do I believe EBP to be good?'

Instrumental; 'Does my use of EBP achieve something?'

Experiential; 'How does it feel when I apply EBP?'

Dimension 2 - subjective norm (including Opinion leadership and acceptance of authority) Item numbers 9-15

A clinician's own estimate of the social pressure to perform or not to perform EBP behaviour [20-23]

Opinion leadership

A doctor's expression (and thereby visibility) of his or her opinions, and the perceived impact of these opinions on others

Acceptance of authority:

A doctor's acknowledgement of the recommendations or instructions of others (*related to 'motivation to comply'*)

Opinions of important individuals or groups ('Do they want me to apply EBP?')

Motivation to comply ('Do I think it is important to comply with these opinions?')

Pressure to comply ('Do I feel pressured to comply with these opinions?')

Dimension 3 - perceived behavioural control Item numbers 16-21

The extent to which a clinician feels able to enact EBP behaviour [20-23]

Self-efficacy

Knowledge and skills ('Am I able to apply EBP?')

Self-confidence ('Am I confident that I am able to apply EBP?')

Controllability:

Autonomy on performance of behaviour ('Is my use of EBP all up to me?')

Factors in the clinical setting ('Am I enabled to apply EBP?')

Dimension 4 – Decision making (including information processing and decision making, Item numbers 22-25 change potential of behaviour; action planning and coping planning

Text Box 1. Continued

The extent to which new information reshapes the clinician's current understanding and (habitual) behaviour [20-23]

A clinician's balance between using intuition or reasoning when handling information in order to make clinical decisions
We made parallels between intuition and using clinical experience, and between reasoning and using research evidence

Intuition

An implicit unconscious process, that is fast, automatic and based on pattern recognition and habits. This process is very difficult to change or manipulate

Reasoning

An explicit conscious process, that is slower and controlled. This process is much more volatile, being subject to conscious judgments and attitudes

The clinician's ability to plan, initiate and maintain intended EBP behaviour [24-26]

Action planning

The specification of when, where and how to act. Action planning helps to make the leap from behavioural intention to actual behaviour

Coping planning:

Detailed planning of responses to anticipate and cope with personal risk situations that endanger the performance of newly initiated behaviour

Dimension 5 - Intention and behaviour Item numbers 26-29

The clinician's aim and actual response, respectively, to apply EBP [15-17, 20-23]

Intention: the clinician's aim to enact EBP behaviour and his expectation to actually do so

Aim ('Am I committed to apply EBP?')

Expectation ('Do I expect that I will actually apply EBP?')

Behaviour: The clinician's manifest, observable EBP behaviour in clinical practice

EBP behaviour: doctors who repeatedly compare and adopt their own clinical decisions to latest best standards. For making well-informed decisions a clinician would need to translate both latest best research evidence and clinical experience to the preferences and clinical needs of individual patients

Respondents

In the first Delphi round 3 (1%) of the 537 addressees refused participation and for 21 (4%) the e-mail address was not valid. Of the remaining 513 invited EBP experts, 148 (29%) responded in the first Delphi round and 151 (29%) responded in the second Delphi round. Of the later, 122 respondents (81%) indicated to be willing to participate in the following Delphi rounds. Of these 79 (65%) of 122 addressees responded in the third round, whereas 59 (75%) of these 79 did so in the fourth round. The respondent characteristics are displayed in Appendix 2.

Pilot study

In our pilot among 43 clinicians, all completed the draft EBP Inventory within 15 minutes, without questions or further comments (Appendix 3). There was sufficient variation in responses, score "1" was used least. We observed no floor or ceiling effects. The overall internal consistency was excellent (0.93), although internal consistency for dimensions was good or excellent except for "Decision Making" (0.51).

Content validity

After final comments of experts on the content and phrasing of items and response scales, and dimension, the EBP Inventory consisted of 29 items (on a six-point response scale) in five dimensions, accompanied by 13 demographic items and definitions of "EBP" and "clinical decision".

Performance testing

We invited 128 staff members to complete the EBP Inventory, with a response rate of 100% the first time and 74% for the second time. For each completion we deleted one respondent due to >10 % missing values, resulting in 127 and 93 respondents for respectively the first and second completion. Comparison of characteristics revealed no apparent differences between non-responders and responders (Appendix 4). We imputed missing values (<2% of all responses).

Distribution of responses

Responses ranged from 1 to 6, response option 5 was used most and 1 was used least. All items showed sufficient variation: overall their mean was 4.2 (standard deviation of means 1.0), whereas the item standard deviation ranged between 0.8 and 1.3. There were no floor or ceiling effects, but the distribution of responses for the dimensions "attitude" and "subjective norm" was skewed towards higher scores. For the 93 participants completing the EBP Inventory twice we found no apparent differences in scores between the first and second time.

Structural validity

All items in the dimensions "attitude", "perceived behavioral control" and "intention and behavior" showed high single factor loadings. Items from the dimension "subjective norm" did not show a unidimensional factor structure, items 9 and 10 showed their highest factor loading on the second factor. This suggests an additional dimension "role models" within the dimension "subjective norm". In the dimension "decision making" item 25 showed only a weak factor loading (0.30).

Construct validity

Table 1 displays the dimension scores, with between-subgroup differences and the accompanying 95% confidence intervals. All dimensions, except "perceived behavioral control" showed the minimal expected difference.

Table 1. Results of testing for anticipated differences for specific groups

Dimension	Groups with anticipated difference	N	*n*, high score[a] (%)	*Δ* (95%CI)	*n*, low score[b] (%)	*Δ* (95%CI)
Attitude	Teacher of EBP					
	Yes	19	8 (42)	12 (11,14)	3 (16)	3 (2,4)
	No	108	32 (30)		20 (19)	
Subjective norm	Shared EBP learning					
	Yes[c]	52	26 (50)	31 (30,33)	5 (10)	24 (22,25)
	No[d]	75	14 (19)		25 (33)	
Perceived behavioural control	EBP training in medical school					
	Yes	85	28 (33)	0 (0,1)	20 (24)	0 (0,1)
	No	42	14 (33)		10 (24)	
Decision making	Significant clinical experience					
	Yes[e]	50	15 (30)	11 (10,12)	13 (26)	16 (14,17)
	No[f]	77	15 (19)		32 (42)	
Intention & behaviour	Teacher of EBP					
	Yes	19	9 (47)	28 (26,30)	1 (5)	35 (33,38)
	No	108	21 (19)		44 (41)	

Legend:
N, total number of respondents
Δ, difference
CI, confidence interval
EBP, evidence based practice
GP, general practitioner
[a] number of respondents with a score > (mean+0.5 standard deviation)
[b] number of respondents with a score <(mean-0.5 standard deviation)
[c] Otolaryngology & Paediatrics
[d] GP & Radiology
[e] Resident
[f] Consultant

Reliability

Cronbach α was good or excellent for all dimensions, except "decision making" (0.60). Only after excluding item 25 Cronbach α increased significantly.

The ICC showed moderate agreement for "attitude" (0.53), substantial agreement for "subjective norm", "decision making", "intention and behavior" (0.63, 0.71 and 0.76, respectively) and almost perfect agreement for "perceived behavioral control" (0.83).

EBP Inventory

The final version of the EBP Inventory is displayed in Text Box 2. The introduction to the inventory can be found in Appendix 5. The final version of the baseline data and demographics of respondents is displayed in Appendix 4. On the basis of insufficient validity and reliability we decided to exclude items 9, 10 and 25 (see Text box 2).

Text Box 2. Evidence based practice inventory – the questionnaire

Attitude
I feel that EBP is *useless* ① ② ③ ④ ⑤ ⑥ *useful* to improve my patients' outcomes.
I feel that EBP is an *unimportant* ① ② ③ ④ ⑤ ⑥ *important* feature of high-quality patient care.
I feel that EBP *worsens* ① ② ③ ④ ⑤ ⑥ *improves* the quality of my clinical decisions.
I feel that EBP *disregards* ① ② ③ ④ ⑤ ⑥ *respects* my clinical experience.
I feel that EBP *disregards* ① ② ③ ④ ⑤ ⑥ *respects* individual differences between my patients.
EBP makes me feel *constrained* ① ② ③ ④ ⑤ ⑥ *autonomous* in my clinical decisions.
EBP *hinders* ① ② ③ ④ ⑤ ⑥ *helps* me in making better clinical decisions.
I feel that clinical guidelines in my own discipline *hinder* ① ② ③ ④ ⑤ ⑥ *help* me in making decisions.
Subjective norm
My colleagues *discourage* ① ② ③ ④ ⑤ ⑥ *encourage* me to apply EBP principles in my clinical decisions.
In my department we pay *no* ① ② ③ ④ ⑤ ⑥ *a lot of* attention to applying EBP principles in our clinical decisions.
Managers in my department *hinder* ① ② ③ ④ ⑤ ⑥ *support* me to apply EBP principles in my clinical decisions.
My colleagues and I *rarely* ① ② ③ ④ ⑤ ⑥ *frequently* discuss and challenge how we make our clinical decisions.
My colleagues and I *rarely* ① ② ③ ④ ⑤ ⑥ *frequently* discuss research evidence from literature.
* Clinicians whom I respect most are *opponents* ① ② ③ ④ ⑤ ⑥ *advocates* of EBP.
* Clinicians whom I respect most *rarely* ① ② ③ ④ ⑤ ⑥ *frequently* use research evidence to account for their clinical decisions.
Perceived behavioural control
I feel that I am *incapable* ① ② ③ ④ ⑤ ⑥ *capable* of applying EBP principles in my clinical decisions.

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Text Box 2. Continued

I feel that I am *incapable* ① ② ③ ④ ⑤ ⑥ *capable* of translating my information needs into relevant and feasible clinical questions.
I feel that I am *incapable* ① ② ③ ④ ⑤ ⑥ *capable* of searching for research evidence in literature.
I feel that I am *incapable* ① ② ③ ④ ⑤ ⑥ *capable* of critically appraising research evidence from literature.
I feel that I am *incapable* ① ② ③ ④ ⑤ ⑥ *capable* of translating research evidence to the care of my individual patients.
I feel *incapable* ① ② ③ ④ ⑤ ⑥ *capable* of regularly keeping up with latest research evidence from literature.
Decision making
I give *low* ① ② ③ ④ ⑤ ⑥ *high* priority to a thorough understanding of the background of the answers to my clinical questions.
I *dislike* ① ② ③ ④ ⑤ ⑥ *like* using numbers, tables and other quantitative information for supporting my clinical decisions.
When making clinical decisions, I prefer to use *my intuition and experience* ① ② ③ ④ ⑤ ⑥ *facts and arguments.*
Intention and behaviour
I *rarely* ① ② ③ ④ ⑤ ⑥ *frequently* use research evidence to support my clinical decisions. *When research evidence does not support my trusted clinical routines, I feel *uncomfortable* ① ② ③ ④ ⑤ ⑥ *comfortable* to change them
I prefer to use *my own experience* ① ② ③ ④ ⑤ ⑥ *research evidence* for making my clinical decisions.
I tend to *ask colleagues* ① ② ③ ④ ⑤ ⑥ *search the literature* to find answers to my clinical questions.
I *rarely* ① ② ③ ④ ⑤ ⑥ *frequently* seek out available research evidence to answer my daily clinical question.
Clinical decision, the choice made on what action to take in patient care after evaluation of information on alternative options. *Evidence-based practice* (EBP), a problem-solving approach used for making clinical decisions that integrate the current best research evidence with clinical experience and individual patients' characteristics, preferences, and values. *Discarded in the final EBP inventory.
Demographic and baseline information: age, gender, year of finishing medical school, career stage (not in residency training, resident, certified medical specialist), regular training and supervision of medical students (yes/no), regular training and supervision of residents (yes/no), managerial duties (yes/no), received training in EBP (in medical school/during residency training/after becoming a certified medical specialist/never/other), training comprises (Theoretical lectures/ supervised practical training/practical skills acquired during daily work/other/not applicable), level of EBP training (Introductory/intermediate/advanced/not applicable), teaching of EBP to other disciplines (yes/no), writing of scientific articles (yes/no), access to EBP resources in my immediate workspace (yes/no)

INTERPRETATION

Our purpose was to design and validate a short and practical questionnaire to identify and evaluate barriers and facilitators for adherence to EBP, that is, the use of research evidence in patient care. Our aim was to comprehensively include competences (knowledge and skills), attitude and behavior, and to address local conditions for EBP in various clinical settings factor in aspects on departmental setting, information processing and decision making.

In a Delphi study of four rounds we consulted a large international panel of EBP experts on the comprehensiveness and relevance of the items included, thereby ensuring face and content validity in the evaluation of barriers and facilitators for adherence to EBP. We assessed the performance of the EBP inventory in a sufficient sized group of clinicians, who are active in patient care in different medical specialties and in various stages of training. We show that the EBP Inventory can be completed within 15 minutes, and has sufficient structural and construct validity, discriminative power, internal consistency and test-retest reliability.

With regard to the general content of the EBP Inventory, we add the following remark. The conventional framework of EBP is described by five steps: Step 1- ask, step 2- acquire, step 3- appraise, step 4- apply, step 5 – audit. The items of the EBP inventory do not concern step 4 and 5.[38]

Probably because of skewed distribution of data, the dimension “perceived behavioral control” did not discriminate well between a priori hypothesized groups. The test-retest reliability for the dimension “attitude” showed moderate agreement. We believe that this is due to learning effects related to the sequential completion of the EBP inventory.[39]

During finalizing the EBP Inventory we removed three items from the EBP inventory (Text Box 2) based on validity and reproducibility testing. Although the consulted EBP experts considered these items important, the validity of these three items was somehow limited by the distributions of item scores and dimension scores in our population. Nevertheless, when the content of EBP inventory is subsequently further changed by adding or removing items this would probably affect its performance.[39]

Although other currently available instruments in the field of EBP assess either competence (knowledge and skills), attitude, behavior, or a combination thereof, they in particular address knowledge reproduction in educational settings and focus of learning effects among students or postgraduate trainees.[7,9] We instead use a judgement approach

in the evaluation of barriers and facilitators for adherence to EBP. In completion of the EBP inventory we rely on self-report by clinicians. For perceived knowledge and skills we thereby probably only provide a crude estimate for their actual knowledge and skills. We deliberately included other concepts in the EBP inventory, in particular for barriers and facilitators for adherence to EBP, notably attitude, behavior, information processing, decision making and department setting conditions. For these concepts objective measures or external references clearly are not available, and so we relied on self-report by clinicians.[40] Our inventory does not allow evaluation of the actual integration of evidence with clinicians' expertise and patients' preferences. Thus, in view of the intention performance gap, there might be a difference between the outcome on our inventory and the actual EBP performance.

We conclude that the EBP inventory is a comprehensive, valid and reliable instrument for identification and evaluation of barriers and facilitators for adherence to EBP, that is, the use of research evidence in patient care. The EBP inventory is designed to differentiate in the adherence to EBP among clinicians of different specialties, in various stages of career and vocational training, and with different background and experience in EBP.

We suggest to evaluate the performance and validity of the EBP inventory further by comparing settings with known high and low complexity of care, known high and low variation in care, and known high and low quality of care outcomes. Ultimately the EBP inventory could be used in field studies to evaluate the impact of efforts of implementing and maximizing EBP.[41] But before applying the EBP Inventory in this context the appraisal of its responsiveness is warranted.

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APPENDICES

Appendix 1. Groups of addressees on the mailing list for the online Delphi study

Steering committees and attendees of the EBHC conferences in Sicily 2005 – 2009;
Members of the GRADE working group;
Members of the GIN board of trustees;
Employees from departments within the Julius Centre (part of the University Medical Centre Utrecht; The Netherlands);
Employees from departments within IQ Health (part of the University Medical Centre Nijmegen; The Netherlands);
Employees from departments within the Dutch Institute for Healthcare Improvement CBO;
Employees from departments within the Centre of EBM (part of Oxford University, UK);
Employees from departments within the National Institute for Health and Clinical Excellence (that is, NICE; United Kingdom);
Employees from departments within the National Prescribing Centre (that is,, NPC, United Kingdom);
Employees from departments within the Netherlands Organisation for Health Research and Development (that is, ZonMw);
Fellows Implementation and their mentors, sponsored by the Netherlands Organisation for Health Research and Development (that is, ZonMw);
Members and bureau of the Dutch Council for Quality of Healthcare (that is,, Regieraad), established by the Minister of Health, Welfare and Sport;
Authors from various scientific papers on the implementation of (aspects of) EBP or on specific EBP dimensions;
Authors of books on EBP, e.g., “How to practice and teach EBM” (1997-2005); “Using Evidence, How research can inform public services” (2007); “Getting research findings into practice” (2002); “Essential Decision Making and Clinical Judgement for Nurses” (2009); “Evidence-based Medicine toolkit” (2006);
A sample of participants of the mailing list of EVIDENCE-BASED-HEALTH@JISCMAIL.AC.UK;
Individuals from our own network with particular interest in EBP.

Appendix 2. Respondent characteristics (Delphi rounds 1, 2 , 3 and 4)

Professional background[a,b]	Total		Medicine		Nursing		Clinical epide-miology		Physio-therapy		Socio-logy		Psycho-logy	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Round 1	148	100	72	49	8	5	39	26	10	7	4	3	4	3
Round 2	151	100	71	47	11	7	41	27	9	6	5	3	4	3
Round 3	79	100	42	53	7	9	24	30	7	9	2	3	2	3
Round 4	59	100	29	49	7	12	19	32	5	8	0	0	1	2

Legend:
a, Details are only provided for the six professional backgrounds that were most common in web survey 1
b, Numbers add up to more than the total number of respondents, since respondents can have more professional backgrounds and can be involved in more activities
n, number of respondents
%, percentage

Appendix 3. Respondent characteristics of the pilot study

Clinician characteristics		Year (min; max) or No (%)
Mean age (0% missing)		35 (22; 58)
Specialty	Paediatrics	23 (53)
	Otolaryngology	20 (47)
Sex	Male	20 (47)
(0% missing)	Female	23 (53)
Career stage	Still in medical school	7 (16)
(7% missing on year of graduation)	Graduated from medical school	33 (77)
		2000 (1980; 2011)
	Not in residency training (yet)	4 (9)
	In residency training	11 (26)
	Certified medical specialist	18 (42)
	Nurse practitioner	3 (7)
Training / supervision of medical students (0% missing)	Yes	35 (81)
Training / supervision of residents (0% missing)	Yes	20 (47)
Managerial duties (0% missing)	Yes	16 (37)
Timing of EBP training#	Yes	39 (91)
(0% missing)	In medical school	21 (49)
	During residency training	12 (28)
	After becoming medical specialist	10 (23)
	Other	3 (7)
Type of EBP training[a]	Yes	40 (93)
(0% missing)	Theoretical lectures	34 (79)
	Supervised practical training	21 (49)
	Informal; practical skills acquired during daily work	22 (51)
	Other	4 (9)
Level of EBP training	Introductory	19 (44)
(0% missing)	Intermediate	18 (42)
	Advanced	6 (14)
Teacher in EBP (0% missing)	Yes	6 (14)
Author of scientific paper(s) (0 % missing)	Yes	26 (60)
Access to EBP resources (0% missing)	Yes	40 (93)

Legend:
EBP, Evidence Based Practice
a, numbers add up to more than the total number of respondents that have received training in EBP, since respondents could choose more than one response option
%, percentage

Appendix 4. Respondent characteristics of the EBP Inventory survey

		a. First survey (n=127)	b. Second survey (n=93)
Clinician characteristics		Year (min; max) or No (%)	Year (min; max) or No (%)
Specialty	Otolaryngology	32 (25)	29 (31)
	Radiology	41 (32)	20 (22)
	Paediatrics	20(16)	18 (19)
	General practitioners (GP)	34(27)	26 (28)
Mean age		37 (25; 64)	36 (25; 63)
Sex	Female	70 (55)	53 (57)
Career stage	Still in medical school	0 (0)	0 (0)
	Year of graduation	2001 (1972;2012)	2002 (1976; 2012)
	Not in residency training	11 (9)	9 (10)
	In residency training	66 (52)	48 (52)
	Certified medical specialist	50 (39)	36 (39)
Training of medical students	Yes	77 (61)	58 (62)
Training of residents	Yes	53 (42)	40 (43)
Managerial duties	Yes	38 (30)	32 (34)
EBP training	Yes	115 (89)	89 (94)
Timing of EBP training#	In medical school	85 (67)	64 (69)
	During residency training	69 (54)	55 (59)
	After becoming medical specialist	23 (18)	19 (20)
	Other	7 (6)	4 (4)
Type of EBP training[a]	Theoretical lectures	105 (83)	80 (86)
	Supervised practical training	77 (61)	62 (67)
	Practical skills acquired during daily work	56 (44)	42 (45)
	Masters degree in Epidemiology	5 (4)	1 (1)
	Other	4 (3)	4 (4)

Appendix 4. Continued

		a. First survey (n=127)	b. Second survey (n=93)
Clinician characteristics		Year (min; max) or No (%)	Year (min; max) or No (%)
Level of EBP training	Introductory	38 (30)	31 (33)
	Intermediate	62 (49)	50 (54)
	Advanced	19 (15)	10 (11)
Teacher in EBP	Yes	19 (15)	14 (15)
Author of scientific paper(s)	Yes	89 (70)	63 (68)
Access to EBP resources	Yes	123 (97)	90 (97)

Legend:
EBP, Evidence Based Practice
No, number
%, percentage
a, numbers add up to more than the total number of respondents that have received training in EBP, since respondents could choose more than one response option

Appendix 5. Introduction to the evidence-based practice inventory

Introduction

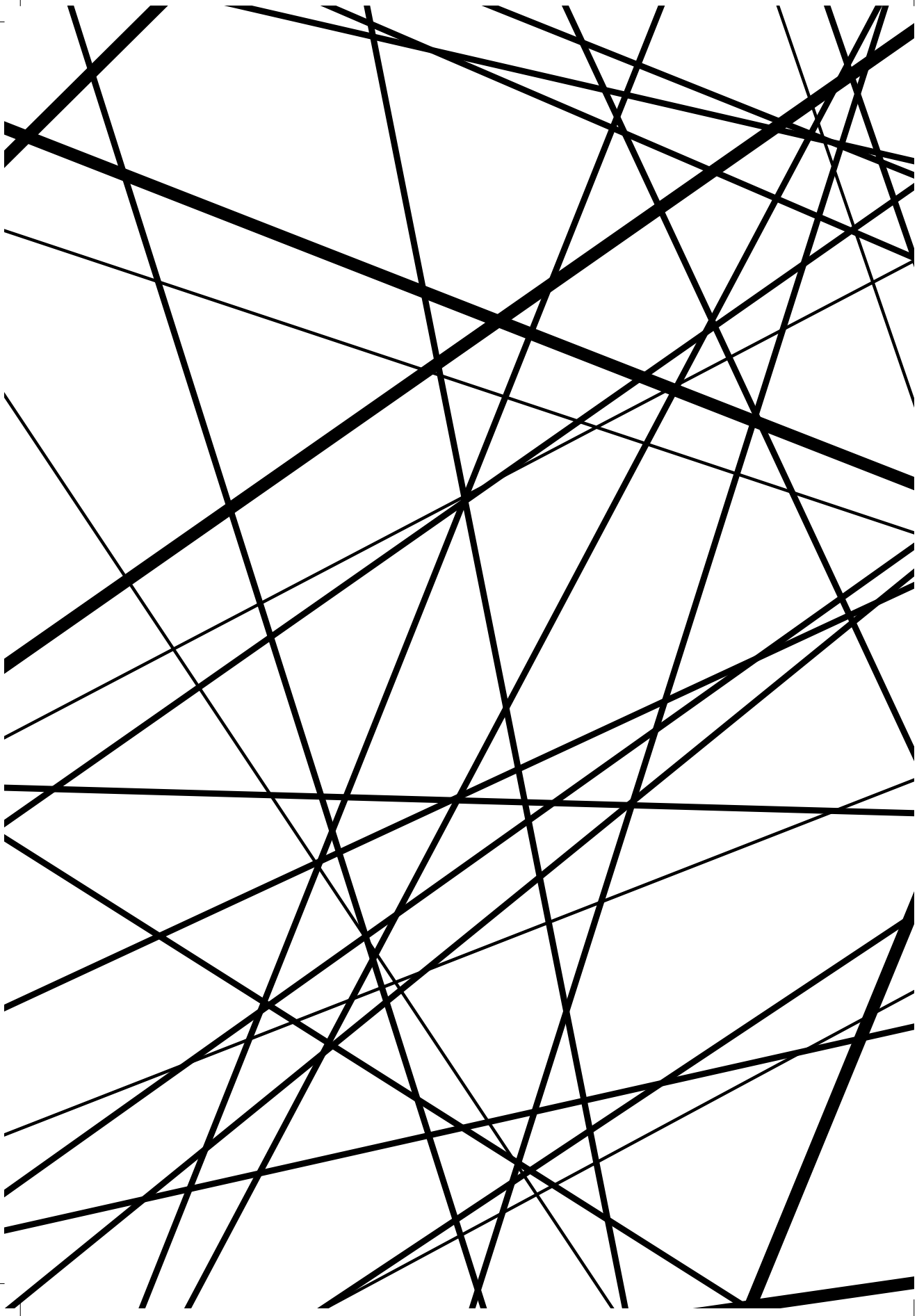
As a doctor, you make many clinical decisions for your patients each day.
To clarify the process of how doctors make their decisions in daily practice, this survey was designed.
Answers to the questions below should reflect the way you typically make your decisions.
There are no right or wrong answers, we only ask you to provide your personal point of view.
Thank you for your participation. Your responses will be treated anonymously and confidentially.
Before proceeding to the survey, please carefully read our definitions on “clinical decision” and “evidence-based practice”.
These terms will be used in the survey.

Definitions

CLINICAL DECISION
- The choice made on what action to take in patient care after evaluation of information on alternative options.

EVIDENCE BASED PRACTICE (EBP)
- A problem solving approach used for making clinical decisions that integrates the current best research evidence with clinical experience and individual patients’ characteristics, preferences and values.

Now please read each question carefully and cross the number of your choice



CHAPTER 3

Otolaryngologists adhere to evidence-based guidelines for chronic rhinosinusitis

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Eur Arch Otorhinolaryngol. 2019;4:1101-1108

Author contributions

Kaper NM: Design of study, Analysis and interpretation of data, Drafting figures and tables, Drafting and revision of the manuscript, Final approval of the version to be published.

Aarts MCJ: Design of study, Analysis and interpretation of data, Drafting figures and tables, Drafting and revision of the manuscript, Final approval of the version to be published.

van Benthem PPG: Design of study, Analysis and interpretation of data, Drafting figures and tables, Drafting and revision of the manuscript, Final approval of the version to be published.

van der Heijden GMJG: Design of study, Analysis and interpretation of data, Drafting of the manuscript, Final approval of the version to be published.

ABSTRACT

Objective: To assess awareness of, opinion about and adherence to evidence-based guidelines on chronic rhinosinusitis among Dutch otolaryngologists.

Methods: We assessed implementation of two guidelines, one Dutch (CBO 2010) and one European (EPOS 2012), that are both intended for diagnosis and treatment of patients with chronic rhinosinusitis. We invited 485 otolaryngologists to fill out a questionnaire and report on their opinion on and adherence to the guidelines. The adherence was further tested by 4 clinical case scenarios, derived from guideline recommendations.

Results: 166 (34%) completed the questionnaire. 99% of the respondents was aware of one or both guidelines. Most respondents (90%) consider the guidelines as directing or supportive for their clinical practice based on the clinical case scenarios, between 62 and 99% of the respondents act according to guidelines. Concerning diagnosis, CT-imaging is performed more and allergy testing less than recommended. Where multiple treatment options are recommended, the responses are more heterogeneous as a result of this. Nonetheless, high recommended treatment was chosen more often. Otolaryngologists were reluctant in surgical treatment as a first option, which is according to the guidelines.

Conclusions: Overall, both the EPOS and CBO guideline are well known among Dutch otolaryngologists and 90% indicates that the guideline is important in their daily practice. Adherence to the guidelines is sufficient to high. If multiple treatment or diagnostic options are recommended this leads to a more heterogeneous response pattern. Recommendations with a high grade of recommendation were followed up most often.

INTRODUCTION

Otolaryngologists are both encouraged and expected to incorporate available evidence-based clinical guidelines in daily practice.[1] Their use has become standard of care in most hospitals. For many conditions in otolaryngology (inter)national guidelines have been developed, however, the publication of a clinical practice guideline does not immediately result in implementation of the use of the guideline in daily practice.[2-4] In 1996, a Pathman et al. developed a model for different steps in the implementation of guidelines. Clinicians must be aware of the guideline, agree, adopt the guidelines in clinical practice for their patients, and then actually adhere to the guideline at appropriate times. With each step there is a risk of losing clinicians in the process of implementing a guideline.[5] After implementation the guideline can be integrated in a shared decision making approach with integration of patient specific circumstances or values.[6] Numerous barriers and facilitators of guideline implementation have been identified, that consist of patient, physician, environmental and guideline-related factors.[7-11]

The self-reported adherence to evidence-based guidelines among Dutch otolaryngologists has been previously assessed in 2010 and is considered rather high.[2] That is, 62% indicated that their daily practice was supported by guidelines and 32% stated that guidelines guided their clinical practice.

In this article, we will focus only on guidelines concerning chronic rhinosinusitis (CRS), which is a common disease in otolaryngology practice, with a reported prevalence ranging from 2 to 11%.[12,13] For this condition, multiple guidelines have been developed.[14-17]

In the Netherlands the Dutch Society of Otolaryngology and Head & Neck Surgery initiates and maintains evidence-based guidelines for otolaryngologists.[18] They recommend the use of the Dutch guideline CBO.[15] However, the authors suspect from their own experience that the European guideline, EPOS, is also widely used.[16] The guidelines are available for free on the internet since 2010 and 2012.

In our study we evaluated the self-reported awareness of the CBO and EPOS guidelines among Dutch otolaryngologists, their opinion on these guidelines and the implementation of these guidelines based on clinical scenarios.[15,16]

METHODS

Compliance with ethical standards

This study does not involve patients. The otolaryngologists were approached without obligation and filled out the questionnaire anonymously.

National survey

Between May 2017 and December 2017 we performed a survey among Dutch otolaryngologists. We sent a questionnaire to 485 otolaryngologists by e-mail and mail, and the request was repeated twice. The questionnaire took respondents 10–15 min.

General questions

The first part of the questionnaire related to respondent characteristics, i.e. gender, PhD grade, training in evidence-based practice, time registered as otolaryngologist, area(s) of interest and how often they read publications related to CRS. We further asked them about the awareness and opinion of both guidelines, the self-reported adherence to the guidelines and reasons not to apply the guidelines (Appendix 1).

Clinical case scenarios

The second part of the questionnaire existed of four clinical case scenarios concerning diagnosis and treatment of patients with CRS. We posed questions on clinical decisions that they would make in these cases and compared their answers to the content and recommendations of the two guidelines, with the intention to provide further insight into the adoption of and adherence to the guideline. The clinical case scenarios were designed to be representative for patients encountered in daily practice.

The recommendations, with corresponding grade of recommendation (GoR), for CBO and EPOS were extracted from the guidelines and compared.[19] EPOS only provides recommendations on treatment options, CBO provides recommendations on both diagnosis and treatment. Therefore, we included questions about both treatment and diagnosis in our clinical case scenarios. For the EPOS guideline, advice regarding diagnosis was retrieved from the full text of the guideline.[16]

The clinical case scenarios are based on patients with (cases 1 and 4) and without nasal polyps (NP) (cases 2 and 3), with (cases 3 and 4) or without (cases 1 and 2) prior treatment. There are four questions concerning diagnosis (1.1, 1.2, 1.3, and 2.1) and four concerning therapy (1.4, 2.2, 3.4, and 4.4).

If provided, the GoR (high, medium, moderate, and low) was extracted from the guideline.[19] The corresponding type of research evidence can be found in Appendix 2. We incorporated questions that were based on different GoR, since we expect that responses might be divert. For recommendations with a high GoR, we expect that most respondents will adhere to the guideline, and therefore, clinical practice will show probably little variation. For a lower GoR, we expect less adherence and more variation in adherence to the guideline and in clinical practice. We expect a similar outcome for questions based on contradicting GoRs.

Table 1. Clinical case scenarios

Clinical case 1
Male, 51 years, presents with decreased smell, purulent rhinorrhea and facial pain in the past 4 months (VAS 4, moderate). The general practitioner has not yet started treatment
1.1 Which anamnestic symptom(s) are a prerequisite to confirm the diagnosis rhinosinusitis?[a]
1.2 Which additional question(s) should you ask your patient?[a]
The patient has no other complaints. Nasal endoscopy shows polyps medial to the middle turbinate
1.3 Which additional examination(s) should you perform?[a]
1.4 How would you treat this patient?[a]
Clinical case 2
A 45-year-old female has complaints of nasal obstruction, post nasal drip and facial pressure in the past 4 months. She has mild complaints and the general practitioner has not yet started treatment. At nasal endoscopy, there are no signs of mucosal disease
2.1 Which additional test(s) should you perform?[a]
2.2 How would you treat this patient?[a]
Clinical case 3
45-year-old female, with complaints of nasal obstruction, post nasal drip and facial pressure in the past 4 months. Despite 6 weeks' course of intra nasal steroids, her complaints persist. Nasal endoscopy shows purulent discharge medial tot the middle turbinate. Computed tomography shows partially clouded ethmoid and maxillary sinus with obstruction of the osteo-meatal complex
3 How would you treat this patient?[a]
Clinical case 4
The 51-year-old patient with nasal polyps from case 1 has underwent functional endoscopic sinus surgery. However, after 6 weeks, his com- plaints have returned. On nasal endoscopy, polyps and purulent discharge are visible lateral to the middle turbinate
4 How would you treat this patient?[a]

Legend:
a, multiple answers possible

See Table 1 for clinical case scenarios and accompanying questions. See complete questionnaire in Appendix 1 for all answer options. Data were analyzed using SPSS (version 21).[20]

RESULTS

General questions: respondent characteristics

Of the 485 contacted otolaryngologists, 166 (34%) replied. Five respondents indicated that their discipline was only head and neck surgery. In total, 161 (33.2%) completed the questionnaire, their baseline characteristics did not differ and can be found in Table 2. Respondents could indicate their area of interest (multiple options possible). The results are described in Table 3.

Table 2. Characteristics of respondents compared to all invited Dutch otolaryngologists

	Respondents (161) *n* (%)	All otolaryngologists[a] (485) *n* (%)
Gender; male	107 (66)	334 (69)
Registry time (years)		
< 10	65 (40)	201 (41)
10–20	53 (33)	156 (32)
20–30	31 (19)	105 (22)
> 30	12 (7)	23 (5)
PhD grade	77 (48)[b]	247 (51)

Legend:
n, number
%, percentage
a, as provided by the Dutch Society of Otolaryngology and Head & Neck surgery
b, 1 response is missing

General questions: evidence-based practice behavior

138 respondents (86%) have had training in evidence-based practice. 61 respondents (39%) indicate that they read publications on rhinosinusitis once a month or more, the remaining respondents read publications on rhinosinusitis less than once a month.

General questions: awareness of, opinion on, and self-reported adherence to the guidelines

Of the 161 respondents, 1 respondent (1%) was not aware of any guideline. 154 (96%) were aware of the CBO guideline and 119 (74%) of the EPOS guideline. 111 respondents (69%) were aware of both guidelines. Two respondents (1%) were aware

of guidelines beside CBO and EPOS, namely, the guideline by Rosenfeld.[14] Of the 154 otolaryngologists aware of the CBO guideline, the guideline is used daily by 60 respondents (39%), 2 - 3 times a week by 36 respondents (23%), and once a week or less by 41 respondents (27%). Of the 119 respondents aware of the EPOS guideline, 35 (29%) uses it every day, three (2%) 34 (29%) 2–3 times a week, and 45 (39%) uses it once a week or less.

Table 3. Area of interest

Description	***N* (%)**
Rhinology	85 (53)
Facial plastic surgery	33 (20)
Otology	86 (53)
OSA/snoring	48 (30)
Pediatrics	45 (28)
Laryngology	17 (11)
Vestibulogy	5 (3)
Skull base surgery	3 (2)

Legend:
n, number of respondents
%, percentage
OSA, obstructive sleep apnea

The CBO guideline is directing practice for 37 (24%) respondents, supportive for 100 (65%) and impeding for three (2%). Of the remaining respondents; three (2%) do not know, two (1%) think of the guideline as "an opinion", and 5 (3%) state that it should be revised. The EPOS guideline is directing practice for 34 respondents (29%), supportive for 72 (61%) and impeding for 5 respondents (4%). Three respondents (3%) state that the guideline should be revised. The opinion of the respondents on the content of the guideline can be found in Table 4. For CBO guideline, 115 (75%) respondents think that it is most or partly based on clearly traceable sources, for EPOS this is similar, 91 respondents (76%).

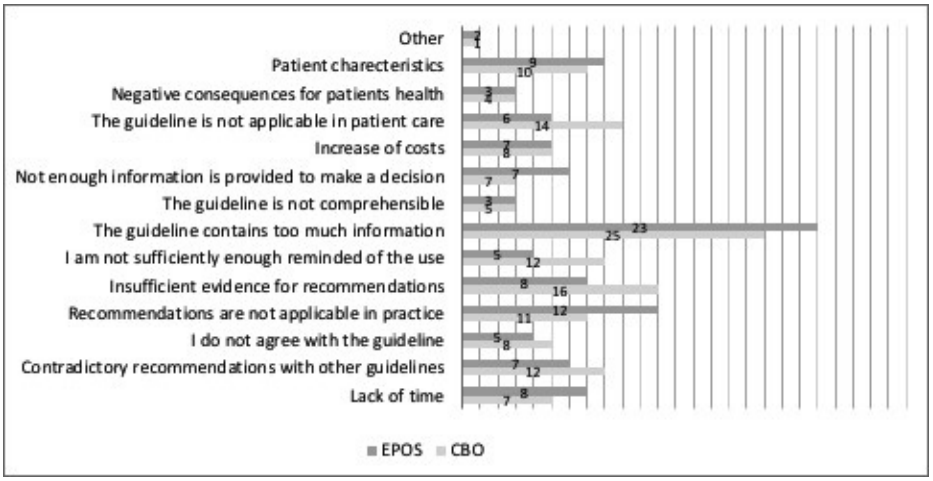
To provide more insight in the opinion of the respondents on the two guidelines, we asked them to indicate barriers to application of the guideline (despite being aware of it) and their answers can be found in Figure 1. There are no differences between the guidelines. All selected barriers play a role, but the largest barrier experienced by our respondents is the amount of information provided in the guidelines.

Table 4. Opinion on the content of the guideline

Recommendations are based on clearly traceable sources	**CBO n (%)**	**EPOS n(%)**
Yes	69 (45)	50 (42)
Partly	46 (30)	41 (34)
No	8 (5)	4 (3)
Don't know	31 (20)	24 (20)

Legend:
n, number of respondents
%, percentage
For CBO total amount of respondents is 154, for EPOS 119

Figure 1. Barriers to guideline application (respondents could choose multiple answers).



Clinical case scenarios

The clinical case scenarios with accompanying questions can be found in Table 1. The answers to the questions were compared to both guidelines. For question 1.1, EPOS and CBO use the exact same definition (Appendix 3), and they do not provide a grade of recommendation to this definition. As expected, most respondents (143; 89%) use the correct definition of anamnestic symptoms and there was not much variation in answer options.

For question 1.2 the responses can be found in Table 5. For symptoms that both guidelines advise to check (asthma, allergy, smoking), most respondents comply. The symptoms not mentioned by one or two guidelines (passive smoking and viral

infections), are far less frequently asked. Note that reflux is not recommended to ask by both guidelines; nevertheless, one-third of respondents asks this anyway.

Question 1.3 (Table 1) is on diagnostics tests for a patient with complaints of CRS, with polyps seen by nasal endoscopy. The guidelines give multiple recommendations, with varying GoR, and we also see variation in answers between respondents. 73 respondents (45%) would per- form no additional tests, corresponding to both guidelines. 46 (29%) would perform a CT scan, even though it is not advised by both guidelines (EPOS; no GoR, CBO; moderate/ low). It is advised only pre-operative or when in doubt about diagnosis in patients with persistent complaints. Allergy testing is advised by both guidelines for patients with anamnestic symptoms of allergy (EPOS: no GoR, CBO: moderate), and 66 (41%) of respondents would perform the test for this patient. No respondent would perform an X-ray or a maxillary sinus culture, and this corresponds with the advice of both guidelines (EPOS: no GoR, CBO moderate). 11 respondents (7%) would perform a nasal culture. This is not mentioned by EPOS and not advised by CBO (GoR medium). In total, 114 (71%) of respondents act according to the guideline(s).

Question 1.4 (Table 1) discusses treatment options for a patient with CRS and nasal polyps. Answers and guideline recommendations can be found in Table 6. Both guidelines advise intranasal steroids with high recommendation, which is followed by 93%. In total, 141 (88%) respondents act according to the guideline(s). Striking is that nasal saline irrigation is applied by 79% of respondents, while it is only mentioned by 1 guideline with a low GoR.

Clinical case 2 concerns a patient with CRS without mucosal disease at nasal endoscopy (Table 1). For question 2.1, the respondents indicate the diagnostic test(s) that they would perform. The guidelines recommend multiple diagnostic strategies and we see this reflected in the varied response. 68 respondents (42%) would not perform additional testing. 56 (35%) would perform a CT scan. 57 (35%) would perform allergy testing. According to the guidelines all these choices are justified. The recommendations are identical for question 1.3. One (1%) respondent would perform an X-ray, one (1%) a maxillary sinus culture, one (1%) an X-OPT, and two (1%) a nasal culture. This does not correspond with both EPOS or CBO (see question 1.3 for recommendations). In total, only 3% would perform diagnostic tests that were not advised by the guidelines.

For question 2.2, the answers are displayed in Table 6. In total, 107 (66%) of respondents act according to the guideline(s). Most respondents chose the answer option with a high GoR (intranasal steroids and saline irrigation).

Clinical case 3 concerns a patient with CRS without nasal polyps, confirmed by both nasal endoscopy and CT, that has been treated with intranasal steroids. For guidelines recommendations see Table 6 (2.2). Note that this patient can be considered as having an exacerbation. There are multiple treatment options according to the guidelines. This is reflected in a varied response. Most respondents chose 3 or more treatment modalities. 60 (37%) would start nasal saline irrigation, 98 (61%) would start short-term antibiotics and 22 (14%) long-term. Concerning long-term antibiotics, the guidelines provide a contradicting recommendation. 99 (62%) would continue intranasal steroids and 49 (30%) would start systemic steroids. All these treatment options are considered valid according to the guidelines. 24 (15%) would start decongestants (in combination with another treatment option) and 29 respondents (18%) would choose FESS, both treatment options are not according to guideline recommendations. In total 113 (62%) of respondents act according to the guideline(s).

Clinical case 4 concerns a patient with CRS and nasal polyps that has been operated but still has complaints with signs of disease at nasal endoscopy. For guidelines recommendations, see Table 6 (1.4). Note that this patient can be considered as having an exacerbation. Multiple treatment options are possible according to the guidelines and this is reflected by a varied response. Most respondents choose a combination of 3 or more treatment options. 124 (77%) would treat this patient with saline irrigation and 137 (85%) with intranasal steroids). 63 (39%) would start short-term antibiotics and 28 (17%) long-term. 96 (60%) would start systemic steroids. All these treatment options correspond to the guideline(s) (except for long-term antibiotics according to CBO). High recommended treatment was chosen more often, while treatment option with moderate, low or contradicting recommendations is chosen less often. 2 (1%) opt for revision surgery. Both guidelines state that revision surgery is reserved for patients failing maximal conservative therapy (EPOS: no GoR, CBO: Moderate GoR). In total, 159 (99%) of respondents act according to the guideline(s).

Table 5. Answers to question 1.2 (multiple answers possible)

Symptoms	GoR	Guideline	n (%)
Symptoms related to asthma (+)	NP	EPOS	142 (94)
	Medium	CBO	
Symptoms related to Allergy (+)	NP	EPOS	158 (98)
	Moderate	CBO	
Reflux (-)	NP	EPOS	46 (29)
	Moderate	CBO	
Smoking (+)	NP	EPOS	114 (71)
	Moderate	CBO	
Passive smoking (+)	NA	EPOS	45 (30)
	NA	CBO	
Viral airway infections (+)	NP	EPOS	47 (29)
	NA	CBO	

Legend:
+, advised to ask
-, advised not to ask
n, number of respondents
%, percentage
GoR, grade of recommendation
Medium, one study of A2 or at least two independent studies of B
Moderate, one study of B or C. (Appendix 1)
NP, advised in guideline, grade of recommendation not provided (Since EPOS does not provide recommendations for diagnosis, the answers are retrieved from the text and do not have a GoR)
NA, not mentioned in guideline

Table 6. Treatment for patients with CRS with and without nasal polyps

		1.4 CRS (with nasal polyps)			2.2 CRS (without nasal polyps)		
Treatment option	**Guide-line**	**Recom-menda-tion**	**GoR**	**n (%)**	**Recom-menda-tion**	**GoR**	**n (%)**
None	EPOS	NA	NA	1 (1)	NA	NA	5 (3)
	CBO	NA	NA		NA	NA	
Nasal saline irrigation	EPOS	+	Low	127 (79)	+	High	123 (76)
	CBO	NA	NA		+	High	
Short course of antibiotics	EPOS	+	Moderate	52 (32)	- [a]	Medium	13 (8)
	CBO	- [a]	Moderate		- [a]	Moderate	
Long-term course of antibiotics	EPOS	+	Moderate	9 (6)	+	Moderate	0
	CBO	-	Moderate		-	Moderate	
Intranasal steroids	EPOS	+	High	150 (93)	+	High	142 (88)
	CBO	+	High		+	High	
Systemic steroids	EPOS	+	High	67 (42)	+	NP	2 (1)
	CBO	+	High		NA	NA	
Decongestants	EPOS	-	Low	10 (6)	-	Low	10 (6)
	CBO	-	Medium		-	Medium	
FESS[b]	EPOS	-	NP	4 (2)	-	NP	1 (0,6)
	CBO	-	Moderate		-	Moderate	
Antihistamines[c]	EPOS	-	Medium	8 (5)	-	Medium	0
	CBO	-	Low		-	Low	
Other[d]	Polyp extraction			1 (1)	"		0
	Nasal ointment			1 (1)	"		1 (1)
	Await CT result			0	"		5 (3)
	Coblation of inferior turbinate			0	"		1 (1)

Legend:
+, treatment is recommended
-, treatment is not recommended
GoR, grade of recommendation
n, number of respondents
%, percentage of total
NP, advised in guideline, grade of recommendation not provided
NA, not mentioned in guideline.
High, research based on A1 or two independent A2 studies
Medium, one study of A2 or at least two independent studies of B
Moderate, one study of B or C; Low, expert opinion. (Appendix 1)
a, only recommended for acute exacerbations
b, FESS is only recommended after failure of conservative treatment by both guideline (both with and without polyps)
c, antihistamines are only recommended in patients with positive allergy testing (both with and without polyps)
d, not mentioned in both guidelines

DISCUSSION

Synopsis of key findings

Guidelines on CRS are very well known by Dutch otolaryngologists. The guideline recommended by the Dutch Society of Otolaryngology and Head & Neck Surgery, the CBO guideline is best known, but also the EPOS guideline is very well known, as we expected in advance.[15,16] Most respondents (99%) are aware of one or two guidelines and the majority indicates that they have confidence in the guideline. The self-reported adherence to the guideline is high; 60% of respondents uses the guideline every day or 2–3 times a week and 90% indicates that the guideline is leading or supportive in their daily practice. Concerning the clinical case scenarios, 62–99% responded according to the guidelines which we consider to be sufficient to good adherence. For the diagnosis of CRS with nasal polyps, CT-imaging is performed more and allergy testing less than recommended. It is also noticeable that if multiple or contradicting treatment options are recommended, the overall response is more heterogeneous as a result of this. Nonetheless, high recommended treatment was chosen more often. In general, surgical treatment is not chosen as first option, which is according to both guidelines.

Limitations of the study

Some limitations can be addressed. First, our response rate was 34%, which means that a selection of otolaryngologists has responded. This could be a selection that known the topic and guideline(s) very well and is positive about the use, or vice versa. We believe that our sample is representative of all Dutch otolaryngologists, since their baseline characteristics do not differ (Table 2). When we look at the specific interest of our respondents (Table 3), this shows a varied group which is also a resemblance of Dutch otolaryngologists.

Second, we tried to assess adherence to the guideline according to questions based on clinical case scenarios. Overall, 62–99% respondents responded according to the guidelines, which we consider to be sufficient to good adherence. This might not reflect their actual clinical behavior, since there is the possibility of socially desirable answers, and since it was possible for respondents to check the guideline for the right answers while filling out the questionnaire. The actual adherence could be lower than we found in this study. In clinical practice, less participants might act according to the guidelines.

Third, this study focusses on the question if the recommendations of the guidelines are implemented. The actual purpose of the guideline, i.e. whether it has led to better treatment outcomes, has not been studied by us.[3] This is a different research question and could be interesting for further research on this topic.

Comparison to other studies

In the study of Aarts et al., 61% of Dutch otolaryngologists reported to have accurate knowledge of the CBO guideline, our results show adherence has improved since then. Other studies on the implementation of CBO or EPOS have not been performed.[2] A study on the implementation of the guideline by Rosenfeld based on retrospective chart review of 10 otolaryngologists showed that adherence to recommendations on rhinosinusitis ranged from 4 to 88% and concluded that adherence was overall rather low.[14,21] Our results show better adherence, but it needs to be considered that self-reported adherence and clinical practice might not correspond.[3]

Implications for future guideline development

Based on the results of our survey, we formed recommendations for the future development or revisions of the guidelines. As we expected from the previous literature, we also found multiple and various barriers to the use of the guidelines.[7-11] Of our respondents 60% indicated reasons not to apply the guidelines (Figure 1). For both the CBO and EPOS guidelines the most important barrier was that they contain too much and too detailed information. Therefore, authors of guidelines have to watch for concise information, clear recommendations and a manageable guideline.

Because of the regularly expected need for actualization, guidelines have an “expiry date”, after that date, the guideline is no longer valid.[22] This could apply to both guidelines, since they date from 2010 to 2012. Recommendations could be outdated or overtaken by new publications. We therefore advise authors to update the guideline regularly with a maximum of 5 years.[22]

In advance, we expected that on topics where the guideline was very clear and directive, there would be little variation in answers. For topics where the guidelines give multiple options or are contradictive, we expected more variation in response. With a few exceptions our results mostly confirmed this. Therefore, we recommend authors to formulate their recommendations in a way that the content and intention are clear to the reader. Authors should also take into account the fact that recommendations with lower GoR might be followed up less than recommendations with high GoR.

We found contradictive recommendations between guidelines, e.g. long-term antibiotics for the treatment of CRS. It is not desirable that there are differences between guidelines, since this is confusing for its reader. Our results show that, in case of contradicting recommendations, we found more variation in practice and less adherence. Authors of guidelines should compare their recommendations with those of other guidelines (if available) to check for contradictions.

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APPENDICES

Appendix 1. Complete questionnaire (translated from Dutch)

Survey on chronic rhinosinusitis
This survey consists of two parts. The first part is about your background and your opinion on the current guidelines for chronic rhinosinusitis. The second part concerns short clinical case scenarios on chronic rhinosinusitis with corresponding questions about diagnosis and treatment.

Background information
What is your gender?
○ Male
○ Female

How long have you been an otolaryngologist?
○ 0-10 years
○ 10-20 years
○ 20-30 years
○ Longer

Do you have a PhD?
○ Yes
○ No

Were you trained in "evidence-based practice"?
○ Yes
○ No

What is your subspecialty/which area is of particular interest to you? (multiple answers possible)
○ Rhinology
○ Facial plastic surgery
○ Head and neck surgery
○ Otology
○ Obstructive Sleep Apnea and snoring
○ Pediatric ENT
○ Other (please give further explanation);
……

How often do you read recent scientific publications on rhinosinusitis?
○ Every day
○ 2-3 times a week
○ Once a week
○ Once a month
○ Once every 3 months
○ Less than once every 3 months

Questions about your use of the guideline(s)
Which evidence-based guidelines on chronic rhinosinusitis do you know?
○ Chronic rhinosinusitis and nasal polyps (CBO 2010, Dutch guideline)
○ European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012)
○ Other (please give further explanation);
……

What are your reasons not to apply the recommendations from the CBO 2010 guideline? (multiple answers possible)
○ I do not use the guideline
○ I don't have enough time to read the guideline
○ The recommendations conflict with other guidelines
○ I don't agree with the guideline
○ The recommendations are not applicable in daily practice
○ There is insufficient evidence for the recommendations
○ I am not sufficiently reminded of the use of the guideline
○ The guideline contains too much information
○ The guideline is incomprehensible
○ Too little information is provided to make a decision
○ Working according to the guideline increases patient costs
○ The guideline is not applicable in patient care
○ The recommendations have negative health consequences for patients
○ Other (please give further explanation);
……

What are your reasons not to apply the recommendations from the EPOS 2012 guideline? (multiple answers possible)
○ I do not use the guideline
○ I don't have enough time to read the guideline
○ The recommendations conflict with other guidelines
○ I don't agree with the guideline

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○ The recommendations are not applicable in daily practice
○ There is insufficient evidence for the recommendations
○ I am not sufficiently reminded of the use of the guideline
○ The guideline contains too much information
○ The guideline is incomprehensible
○ Too little information is provided to make a decision
○ Working according to the guideline increases patient costs
○ The guideline is not applicable in patient care
○ The recommendations have negative health consequences for patients
○ Other (please give further explanation);
……

What is your opinion about the recommendations in the guideline CBO 2010?
○ Contains clearly retrievable sources for most the recommendations
○ Contains clearly retrievable sources for part of the recommendations
○ Contains unclear sources for most the recommendations
○ Other (please give further explanation);
……

What is your opinion about the recommendations in the guideline EPOS 2012?
○ Contains clearly retrievable sources for most the recommendations
○ Contains clearly retrievable sources for part of the recommendations
○ Contains unclear sources for most the recommendations
○ Other (please give further explanation);
……

What is your opinion about the guideline CBO 2010?
○ The guideline is directing in my practice
○ The guideline supports my practice
○ The guideline impedes my practice
○ Other (please give further explanation);
……

What is your opinion about the guideline EPOS 2012?
○ The guideline is directing in my practice
○ The guideline supports my practice
○ The guideline impedes my practice
○ Other (please give further explanation);
……

How often do you use the guideline CBO 2010?
○ Every day
○ 2-3 times a week
○ Once a week
○ Less than once a week
○ Other (please give further explanation);
……

How often do you use the guideline EPOS 2012?
○ Every day
○ 2-3 times a week
○ Once a week
○ Less than once a week
○ Other (please give further explanation);
……

In case you are using a different guideline, how often do you use it?
○ Every day
○ 2-3 times a week
○ Once a week
○ Less than once a week

Clinical case scenarios

Clinical case 1

Male, 51 years old, presents with decreased smell, purulent rhinorrhea and facial pain in the past 4 months (VAS 4, moderate). The general practitioner has not yet started treatment.

1.1 Which anamnestic symptom(s) are a prerequisite to confirm the diagnosis rhinosinusitis? (multiple answers possible)
○ Nasal obstruction or rhinorrhea (anterior and/or posterior)
○ Rhinorrhea (anterior and/or posterior)
○ Nasal obstruction
○ Facial pain/pressure
○ reduction or loss of smell
○ Coughing

1.2 Which additional question(s) should you ask your patient, before you proceed to physical examination? (multiple answers possible)

○ Symptoms resembling asthma
○ Symptoms resembling allergy
○ Symptoms resembling GERD/reflux
○ Smoking
○ Passive smoking
○ The occurrence of viral airway infections

Clinical case 1, continuation

The patient has no other complaints. Nasal endoscopy shows polyps medial to the middle turbinate.

1.3 Which additional examination(s) should you perform? (multiple answers possible)

○ None
○ Computed tomography of the nasal sinuses
○ X-ray of the nasal sinuses
○ Culture from the middle nasal passage
○ Maxillary sinus culture
○ Allergy test
○ Other (please give further explanation);

……

1.4 How would you treat this patient? (multiple answers possible)

○ No treatment required
○ Nasal saline irrigation
○ Short course of antibiotics (<4 weeks)
○ Long term course of antibiotics (>12 weeks)
○ Intranasal corticosteroids
○ Systemic corticosteroids
○ Local decongestants
○ FESS (Functional endoscopic sinus surgery)
○ Antihistamines
○ Other (please give further explanation);

……

Clinical case 2

A 45-year-old female has complaints of nasal obstruction, post nasal drip and facial pressure since 4 months. She has mild complaints and the general practitioner has not yet started treatment. At nasal endoscopy, there are no signs of mucosal disease.

2.1 Which additional test(s) should you perform? (multiple answers possible)

○ None
○ Computed tomography of the nasal sinuses
○ X-ray of the nasal sinuses
○ Culture from the middle nasal passage
○ Maxillary sinus culture
○ Allergy test
○ Other (please give further explanation);

……

2.2 How would you treat this patient? (multiple answers possible)

○ No treatment required
○ Nasal saline irrigation
○ Short course of antibiotics (<4 weeks)
○ Long term course of antibiotics (>12 weeks)
○ Intranasal corticosteroids
○ Systemic corticosteroids
○ Local decongestants
○ FESS (Functional endoscopic sinus surgery)
○ Other (please give further explanation);

……

Clinical case 3

45-year-old female, complaints of nasal obstruction, post nasal drip and facial pressure in the past 4 months. Despite 6 weeks' course of intra nasal steroids, her complaints persist. Nasal endoscopy show purulent discharge medial tot the middle turbinate. Computed tomography shows partially clouded ethmoid and maxillary sinus with obstruction of the osteo-meatal complex.

3.1 How would you treat this patient? (multiple answers possible)

○ No treatment required
○ Nasal saline irrigation
○ Short course of antibiotics (<4 weeks)
○ Long term course of antibiotics (>12 weeks)

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○ Intranasal corticosteroids
○ Systemic corticosteroids
○ Local decongestants
○ FESS (Functional endoscopic sinus surgery)
○ Other (please give further explanation);
……

Clinical case 4

The 51-year-old patients with nasal polyps from casus 1 has underwent endoscopic sinus surgery. However, after 6 weeks, his complaints have returned. On nasal endoscopy, polyps and purulent discharge are visible lateral to the middle turbinate.

4.1 How would you treat this patient? (multiple answers possible)
○ No treatment required
○ Nasal saline irrigation
○ Short course of antibiotics (<4 weeks)
○ Long term course of antibiotics (>12 weeks)
○ Intranasal corticosteroids
○ Systemic corticosteroids
○ FESS (Functional endoscopic sinus surgery)
○ Other (please give further explanation);
……

Thank you for your cooperation!

Appendix 2. Ratings of two evidence-based guidelines for level of evidence and grade of recommendation into a uniform rating

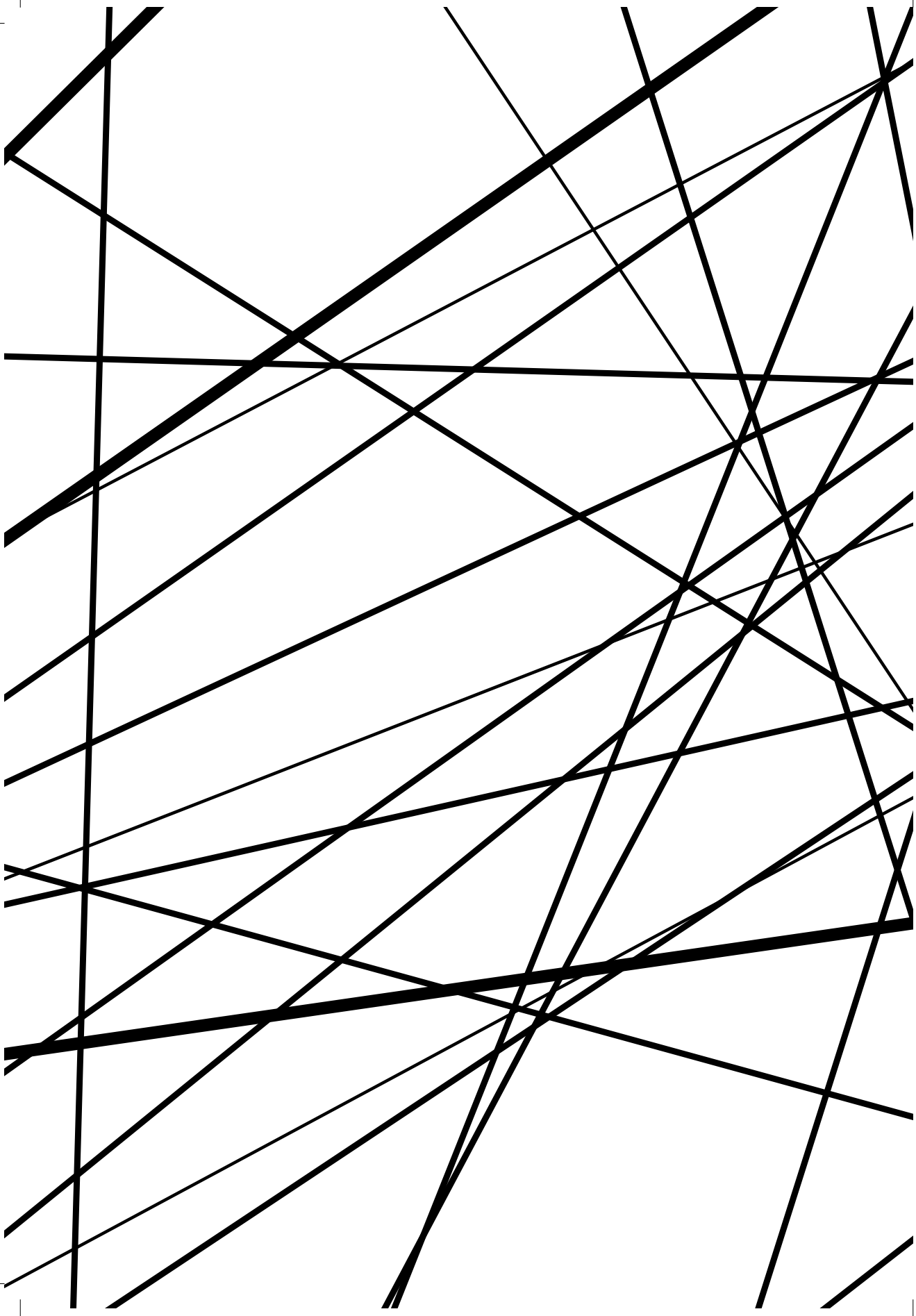
EPOS 2012[16]	**CBO 2010**[15]	**Uniform**		
Level of evidence				
Ia = Evidence from meta-analysis of randomized controlled trials Ib = Evidence from at least one randomized controlled trial IIa = Evidence from at least one controlled study without randomization IIb = Evidence from at least one other type of quasi-experimental study III = Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies IV = Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both	A1 = Systematic review of at least two independent executed research of level A2 A2 = For intervention a randomized controlled trial, double blind, and good quality. For diagnostic, the use of a golden standard and a large enough research population. For prognosis and etiologies, a prospective cohort study with restricted follow-up, controlled for confounding and a large enough research population. B = For intervention a comparative study, but without the point noted in A2. For diagnoses a comparative study, but not the golden standard. For others a prospective cohort study, but without the points noted in A2. C = Non-comparative studies. D = Expert opinion.	Ia	A1	Excellent
		Ib	A2	High
		IIa, IIb	B	Medium
		III	C	Moderate
		IV	D	Low
Grade of recommendation				
A = Directly based on category I evidence B = Directly based on category II evidence or extrapolated recommendation from category I evidence C = Directly based on category III evidence or extrapolated recommendation from category I or II evidence D = Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence	1 = Research based on A1 or two independent A2 studies. 2 = One study of A2 or at least two independent studies of B. 3 = One study of B or C. 4 = Expert opinion.	A	1	High
		B	2	Medium
		C	3	Moderate
		D	4	Low

Appendix 3. Definition of CRS

Chronic Rhinosinusitis (with or without NP) in adults is defined as:
Presence of two or more symptoms one of which should be either nasal blockage/ obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
± facial pain/pressure;
± reduction or loss of smell;
for ≥12 weeks;

and either
• endoscopic signs of:
- nasal polyps, and/or
- mucopurulent discharge primarily from middle meatus
and/or
-edema/mucosal obstruction primarily in middle meatus

and/or
• CT changes:
- mucosal changes within the osteo-meatal complex and/
or sinuses



CHAPTER 4

Healthcare utilization, follow-up of guidelines and practice variation on rhinosinusitis in adults; a health care reimbursement claims study in the Netherlands

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Clin Otolaryngol. 2019 Oct 3; epub ahead of print

Author contributions

Kaper NM: Design of study Analysis and interpretation of data, Drafting figures and tables, Drafting and revision of the manuscript, Final approval of the version to be published.

Stokroos RJ: Design of study Analysis and interpretation of data, Drafting and revision of the manuscript, Final approval of the version to be published.

Aarts MCJ: Design of study Analysis and interpretation of data, Drafting figures and tables, Drafting and revision of the manuscript, Final approval of the version to be published.

van der Heijden GMJG: Design of study, Analysis and interpretation of data, Drafting of the manuscript, Final approval of the version to be published.

ABSTRACT

Objective: To provide insight into healthcare utilization of rhinosinusitis, compare data with clinical practice guideline recommendations and assess practice variation.

Methods: Anonymized data from claims reimbursement registries of healthcare insurers were analyzed from January 1st, 2016 until December 31st, 2016. Patients ≥ 18 years with diagnostic code "sinusitis" in secondary and tertiary care in the Netherlands were included. Main outcome measures were healthcare utilization (prevalence, co-morbidity, diagnostic testing, surgery), costs, comparison with guideline recommendation and practice variation.

Results: We identified 56,825 patients; prevalence was 0.4%. Costs were € 45,979,554.- that is 0.2% of total hospital-related care costs (€21,831.3 x 106). Most patients were <75 years with a slight female preponderance. 29% had co-morbidities (usually COPD/asthma). 9% underwent skin prick testing, 61% nasal endoscopy, 2% X-ray and 51% CT. Surgery rate was 16%, mostly in daycare. Nearly all surgical procedures were performed by endonasal approach which concerned the maxillary and/or ethmoid sinus. 7 recommendations (25%) could be (partially) compared to the distribution of claims data. Except for endoscopy, health care utilization patterns were in line with guideline recommendations. We compared results for three geographical regions and found generally corresponding rates of diagnostic testing and surgery.

Conclusions: Prevalence was lower than reported previously. Within the boundaries of guideline recommendations, we encountered acceptable variation in healthcare utilization in Dutch hospitals. Health reimbursement claims data can provide insight into healthcare utilization, but they do not allow evaluation of the quality and outcomes of care and therefore results should be interpreted with caution.

INTRODUCTION

Rhinosinusitis (RS) is defined as symptomatic inflammation of the nasal cavity and paranasal sinuses. Acute rhinosinusitis (ARS) lasts less than 4 weeks, chronic rhinosinusitis (CRS) >12 weeks. Patients with 4 or more episodes of ARS per year without symptoms in between are classified as recurrent acute rhinosinusitis (RARS). Patients with a prolonged or complicated course (e.g. meningitis, brain abscess, orbital cellulitis, and orbital abscess) can also be distinguished.[1,2] Two or more symptoms should be present, one of which should be either rhinorrhea in ARS and RARS (anterior/posterior or both) or nasal blockage in CRS. Facial pain-pressure-fullness or loss of smell can also be present. For ARS and RARS the diagnosis is confirmed by symptoms, for CRS by signs of inflammation at anterior/posterior rhinoscopy and/or pathological findings on CT.[1,2] There is a distinction between CRS with nasal polyps and without nasal polyps.[1,2] Worldwide, RS is a common disease, with a reported incidence of around 12%.[1] Of RS, ARS is most common and patients usually present themselves in primary care, at their general practitioner.[1] For CRS a prevalence of 2% (defined with ICD-9 codes for primary care and referral centers) to 11% (defined by self-reporting) is reported, although there is a deficit in studies describing the prevalence of CRS in European countries.[2,3,4] RARS is less common, with a reported incidence of 0,03%.[5]

Multiple clinical practice guidelines (CPG) have been developed to guide and support clinical practice for RS, reduce practice variation, and ultimately lead to better treatment outcomes.[6] In the Netherlands, a national CPG is available (CBO 2010), providing recommendations only on CRS.[7] Previous research shows that this CPG is used by most Dutch otolaryngologists.[8,9] In 2010, 61% of them reported being familiar with the CBO CPG.[8] More recently, research showed that 96% of Dutch otolaryngologists are aware of this CPG with sufficient to good adherence to its recommendations.[9] However, data concerning actual CPG compliance in daily practice are lacking.[9] Despite CPGs that drive health care utilization patterns, local or regional practice variations may exist, or systematic deviation from the CPG may occur.

In this study we will use data from healthcare reimbursement claims registries of Dutch healthcare insurers to provide insight into the volume and cost of the RS related healthcare utilization in Dutch hospitals. We will compare results between different hospital types and regions to detect practice variation. In a previous study health care reimbursement claims data have been used to assess non-adherence to guideline recommendations. Therefore, we will compare our data to Dutch recommendations from the CBO 20120 guideline on CRS to detect potential deviations from protocol.[7,10]

METHODS

Ethical considerations

Under Dutch Law for Medical Research with Humans it is allowed to process personal data for statistical and scientific analysis and provided data are not traceable to individuals.[11] Data were provided, processed and analyzed by Vektis, which is the national business intelligence center of the Dutch healthcare insurers.[12] Data safety and security were guaranteed by Vektis. Since we had no access to individual patient data, patient anonymity was guaranteed.

Utilization of health care for rhinosinusitis

Data extraction

We obtained data from Vektis, which collects and analyzes health care reimbursement claims from almost all Dutch healthcare insurers, with coverage of >99% of healthcare providers.[12] The reimbursement procedure for healthcare insurance is the same across the Netherlands. Medical conditions, including RS, are invoiced as diagnostic codes, based on ICD-10 codes.[13,14] Healthcare providers invoice all activities linked to this diagnostic code (e.g. diagnostic procedures, surgical interventions) to the insurer of the patient. Under Dutch Law basic health insurance is legally required for all citizens and all RS related healthcare is covered by this insurance.

In September 2018 we obtained data for the year 2016 (January 1st, 2016 to December 31st, 2016), for patients ≥18 years (determined on June 30, 2016) from secondary and tertiary healthcare. We received data on all reimbursement claims for the diagnostic code "sinusitis", filed until May 31st, 2018. The reimbursement claims coding system does not distinguish between different subtypes of RS, so ARS, RARS, CRS and complicated RS are all covered by this code.

Data on age, gender and comorbidity were obtained. To identify patients with comorbidities we used a nationwide registration system on the use of pharmaceuticals (FKG).[15] Insured persons with a chronic condition were identified based on reimbursement claims of certain medication that is known to be used in a chronic condition. We extracted data on chronic obstructive pulmonary disease (COPD), asthma, diabetes mellitus and cardiac conditions since these are co-morbidities known to influence decisions on surgical treatment strategy.

We obtained data on nasal endoscopy, allergy testing (skin prick), radiographic imaging (CT and X-ray), the number and type of surgical procedures and related hospital admissions.

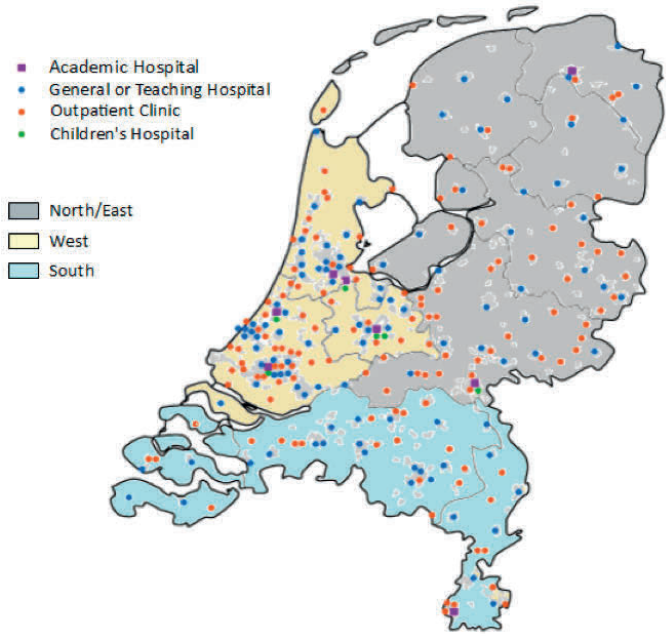
Comparison with Dutch CPG

We extracted 28 recommendations on the diagnosis and treatment of CRS for adults (Appendix 1) and compared these to our data.

Practice variation and comparison between hospitals

We compared practice patterns between different hospital types in the Netherlands and between three regions; South, North/East and West. (Table 1).[16] North/East and South both have large rural areas, whereas West is more urbanized and densely populated. (Figure 1)

Figure 1. Hospitals and regions in the Netherlands



Data analysis

Performed in Microsoft Excel 2010.[17] Due to the large number of patients, 95% and even 99% confidence intervals are narrow, which results in differences of 1% already being statistically significant.[18] Since this is principally a descriptive study of the volume and the costs of care for RS in Dutch Hospitals, we will neither go beyond presenting the data distributions nor provide data on test statistics from statistical analyses.

RESULTS

Utilization of health care for rhinosinusitis

We found a total of 56,852 patients with RS, i.e. a prevalence of 0.4% (total population ≥18 years of 13,585,073).[19] This accounts for 8% of patients that visited an otolaryngologist in the year 2016.[20] Costs of RS were €45,979,554.- which is 0.2% of total hospital related healthcare (€21,831.3 x 10^6).[21] Characteristics of patients can be found in Table 1. There was a slight female preponderance. Most patients were below 75 years old. Patients without co-morbidity were substantially younger than patients with co-morbidity (mean age respectively 49 versus 61 years of age). COPD and/or asthma was more common than diabetes and/or cardiac conditions.

Table 1. Characteristics of patients with rhinosinusitis in 2016

		Hospitals	Patients	Prevalence[b] (%)	Male n (%)	Age (mean, SD)	Co-morbidity[c] n (%)	Costs[d] (%)¶	Costs[e]
Hospital type	General	46	24.781	NP	12.019 (49)	52 (16)	7.175 (29)	19,0 (41)	768
	Teaching	25	25.318	NP	12.180 (48)	52 (16)	7.282 (29)	20,4 (44)	805
	Academic	8	4.376	NP	2.260 (52)	51 (16)	1.728 (39)	4,6 (10)	1048
	Private	8	3.052	NP	1.371 (45)	51 (15)	676 (22)	2,0 (4)	654
Region	West	NP	24.806	0,39	NP	52 (16)	6.996 (28)	19,1 (42)	769
	South	NP	14.814	0,50	NP	52 (16)	4.249 (29)	12,1 (26)	817
	North/East	NP	17.465	0,41	NP	52 (16)	5.478 (31)	14,8 (32)	847
Total		87	56,852[a]	0,42	27.502 (48)	52 (16)	16,643 (29) *-13,026 (23[f] -3,617 (6)[g]*	46,0	809

Legend:
n, number of patients
%, percentage of total
a, total patients is lower than the sum of the above data, since 103 patients(<1%) visited multiple hospitals and 233 patients (<1%) were treated in multiple regions
b, total population North/East: 4209597, West 6435258, South 2940218 (Source: CBS Statline[16])
NP, not provided
SD, standard deviation
c, patients with either COPD and/or asthma or diabetes and/or cardiac conditions, or both; d, total costs in million euro's
e, average cost per patient in euros
f, COPD and/or asthma
g, diabetes and/or cardiac conditions

On average, patients visited the outpatient clinic 1.3 times, with 44% visiting three times or more. For results of diagnostic testing, see Table 2. Details of surgical versus non-surgical patients can be found in Table 3. Surgery claims can be found in Table 4. Surgery was usually limited to the maxillary and ethmoid sinus; the frontal and sphenoid sinus were rarely operated. External sinus surgery was performed in <1% of cases. It was not possible to differentiate between solitary procedures, combined procedures (e.g. maxillary sinus and ethmoid surgery) and revision surgery. The majority of procedures were performed within daycare (Table 5).

Table 2. Diagnostic testing for all patients with rhinosinusitis in 2016 (n=56.852[a])

Diagnostic test	**N (%)**
Skin prick test	5,336 (9)[b]
Nasal endoscopy (1 or more)	34,659 (61)
X-ray	1,201 (2)
CT-scan	29,148 (51)
CT-scan (twice or more)	1,704 (3)
Endoscopy + CT	17,866 (31)

Legend:
N, number of patients
%, percentage
a, sum of patients with diagnostic testing is higher, since 103 patients(<1%) visited multiple hospitals
b, mean age 43 years
CT, computed tomography

Table 3. Surgical versus non-surgical care for all patients with rhinosinusitis seen in 2016 (n=56.852[a])

	Surgery (N=9.396)	**No surgery (N=47.564)**
Age (mean (SD))	50 (16)	52 (26)
Comorbidity[b] N (%)	2.577 (27)	14.097 (30)

Legend:
n, number of patients
%, percentage
SD, standard deviation
a, sum of operated/non-operated patients is higher, since 103 patients (<1%) visited multiple hospitals
b, COPD and/or asthma, diabetes and/or cardiac conditions

Table 4. Surgical procedures (multiple interventions per patient)

Surgical procedure	**Claims (%)**
Endonasal maxillary and/or ethmoid	14,300 (82.0)
Polyp extraction	1,484 (8.0)
Endonasal (or radical) frontal, or sphenoid sinus[b]	982 (5.5)[a]
Antral lavage	588 (3.0)
External frontal or ethmoid sinus	97 (0.6)[‡]
Radical maxillary sinus[c]	44 (0.3)
Total	17,495
Per patient	1,8
Range	1-21

Legend:
%, percentage
a, <1% of data missing
b, e.g. Halle, Mosher, Vacher
c, Caldwell-Luc

Table 5. Peri-operative care (n= 9,396)

		N (%)
Hospital admission	Daycare	6,125 (65)
Hospital stays	1 night	155 (2)[a]
	2 nights	2,806 (30)
	3 nights or more	332 (4)

Legend:
n, number of operated patients
%, percentage
a, <1% missing data

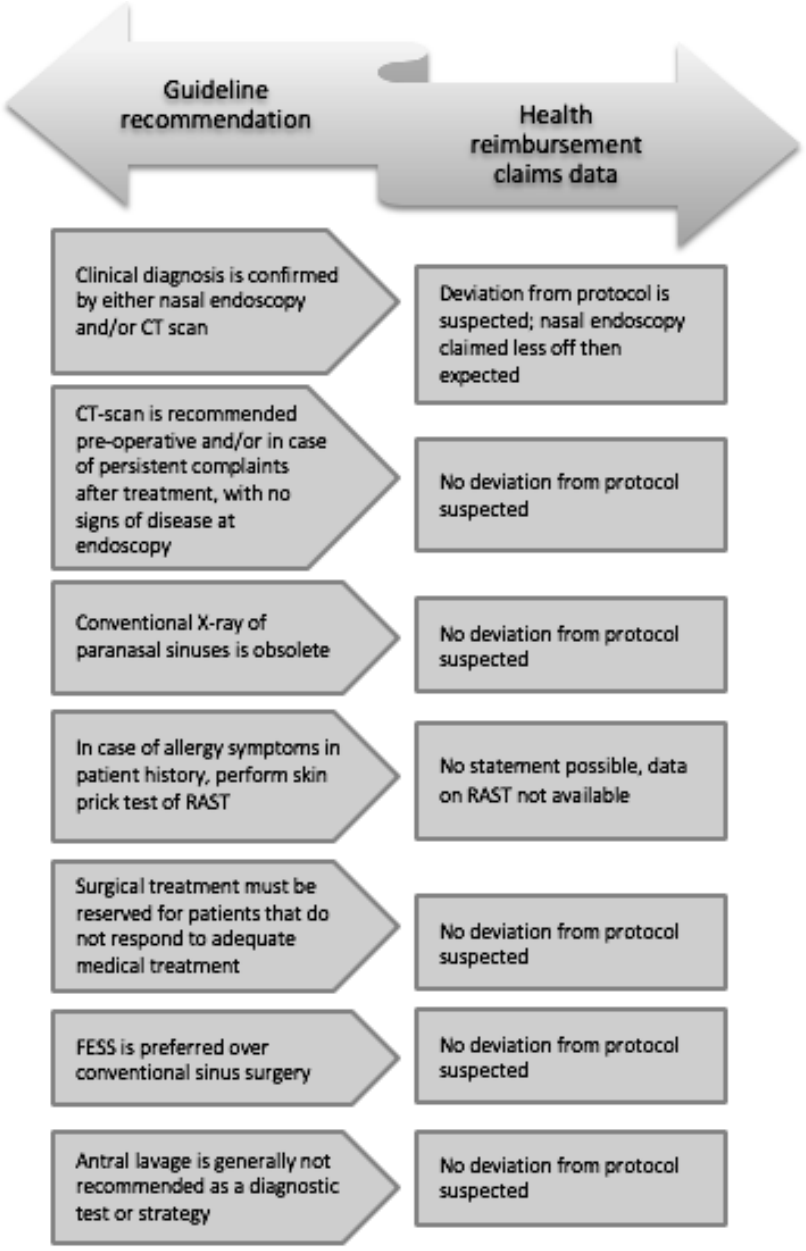
Comparison with Dutch CRS guideline[7]

7 recommendations (25%), could be (partially) compared to the distribution of claims data (Figure 2).

Healthcare utilization compared by hospital and region

Patient characteristics can be found in Table 1. Most patients were treated in general/ teaching hospitals and in the Western region, which reflects population density and hospital distribution in the Netherlands (Figure 1). Prevalence was similar across regions with comparable patient population (based on age and co-morbidity), while costs per patient were lower in the denser Western region.

Figure 2. Guideline recommendations compared to health reimbursement claims



Diagnostic testing compared by hospital and region

We found no important differences in claims for allergy testing by hospital type or region. Nasal endoscopy was claimed most often in academic hospitals (75%) and private clinics (65%) and the least in general/teaching hospitals (60%). Nasal endoscopy was claimed somewhat more frequently in North/East and South (65% and 61%) compared to West (57%). CT scanning was claimed least in academic hospitals (27%) and was similar for other hospital types (49%). Claims for CT scans slightly varied across regions: North/East 44%, West 49% and South 52%. (Appendix 2).

Surgical procedures compared by hospital and region

Surgical procedures were claimed least by private clinics (12%) and more often in other hospital types (teaching 17%, general 16%, academic 14%). Co-morbidity was present in 37% of operated patients in academic hospitals, versus 20% in private clinics. Surgery rates varied slightly between regions (West 15%, North/East 17% and South 18%), while co-morbidity of operated patients did not differ. In academic hospitals, relatively many external, sphenoid and frontal sinus surgeries were performed (24%, versus 0,5%-6% in other hospitals) and antral lavage was performed more often (7% versus 1%-3% in other hospitals). There were no differences in type of surgical claims between regions. Except for academic hospitals, the majority of surgeries was performed within daycare. In the Western region, 77% of surgery was performed within daycare, whereas in the North/East and South this was respectively 53% and 61%.

DISCUSSION

Synopsis of key findings

We set out to assess healthcare utilization and costs of RS for patients ≥18 years in secondary and tertiary care, based on healthcare reimbursement claims data, with a coverage of >99% of all healthcare providers. We discovered a lower prevalence than expected from previous studies.[1-4] Our study population was overall relatively young and healthy, which is comparable to previous studies.[1-4] Costs were less than one percent of all Dutch hospital-related healthcare. For 25% of the recommendations in the Dutch CPG on CRS, diagnostic and treatment patterns could be (partially) compared using these data.[7] Except for endoscopy, healthcare utilization patterns showed no structural deviation from CPG recommendations, which is corroborated by limited regional practice variation.[7] However, our study shows major limitations, and on top of that, reimbursement claims are based on financial parameters and therefore do not allow evaluation of the quality and outcomes of healthcare.

Comparison with other studies

Previous studies reported a higher prevalence of RS, although with the use of different methods. Less stringent definitions were used, studies were performed in primary care, or relied on self-reported symptoms.[1-4] Age and gender distribution corresponded to previous studies.[2,22,23] Allergy testing was encountered less than expected based on literature, but data on RAST are missing and allergy testing is probably invoiced using the diagnostic code "allergic rhinitis" which was not included in our study.[2,7,13,14]

Results on nasal endoscopy are consistent with a study performed in the US (concerning community and academic practice).[24] Nasal endoscopy is registered by Dutch otolaryngologists themselves which might lead to under-registration due to limited time and lack of financial incentive. However, this only partially explains the low number of registered endoscopies.

Surgery rate was comparable to a study in the US.[23] Previous studies showed much higher surgery rate variation, that is, in the US up to three times, in Finland up to four times, and in Canada up to two times higher.[25-27]

Variation by hospital type and region

In the Netherlands, most patients visit general and teaching hospitals; private clinics are not very common. There are eight academic hospitals in the country; these have an important function as referral centers for other hospital types (tertiary care), and therefore perform more complex care, which is reflected by our results.

We found little variation in the geographical prevalence of RS, which was to be expected since the geographic area of the Netherlands is small. For diagnostic testing, we found acceptable differences ranging from 1% to 8%. For surgery rate differences were even smaller, being 2% or less. We did find a remarkable variation in the number of patients treated within daycare, which can be explained by the fact that in some regions patients generally live further away from the hospital.

Strength & Limitations

We had access to a large database that covered more than 99% of patients in the Netherlands, therefore we can present an almost complete overview of all RS related care. Our study is the first to assess healthcare reimbursement claims data for RS in the Netherlands. However, major limitations have to be addressed.

First, the data are derived from reimbursement claims, which are financial outcome measures. In addition, incorrect registration might have occurred, therefore, the data show an approximation of the actually delivered care. Besides, the data represent healthcare at a population level and are too limited to assess treatment patterns our outcomes.

Second, we compared our data to recommendations from a CPG on CRS, while we included patients in secondary and tertiary care based on the diagnostic code "sinusitis". This code encompasses patients with ARS, RARS, CRS, patients with a duration of complaints between 4 and 12 weeks and patients with complicated RS. Due to the healthcare structure in the Netherlands, we can argue that the majority of patients in Dutch otolaryngology practice probably suffer from prolonged RS or CRS. Patients with complaints of RS must always first present to their GP and only after referral they may visit an otolaryngologist. According to their CPG, GPs only refer patients with 3 or 4 episodes of ARS, patients with a suspected complicated course of disease and patients with duration of complaints of 8 weeks or more.[28] Therefore patients with ARS will rarely be referred unless RARS or a complication is suspected, which is known from previous literature to be very rare.[1,2,5] Consequently, we felt that the recommendations of the CPG on CRS could be compared to our claims data.

Third, we might have missed patients with RS that were registered under a different diagnostic code, e.g. "allergic rhinitis".[13,14]

Fourth, due to our cross-sectional design it was not possible to track the course of disease for individual patients, so patients visiting the hospital in 2016 might have undergone diagnostic testing or surgery in 2015 or 2017. Therefore, an underestimation of diagnostic testing and surgery cannot be precluded.

Fifth, since the Dutch healthcare structure varies from those in other countries, our results might not be extrapolated to other countries.

Sixth, since adherence to the Dutch CPG is evaluated in the context of a 5-year quality assessment of Dutch otolaryngologists, this might have influenced our results and explain the limited practice variation.

Finally, our research neither evaluates whether the care invoiced was actually provided, nor whether it was needed. To assess what healthcare was delivered to the patients and whether diagnostic tests and interventions were indicated according to CPG recommendations, extensive chart review by field specialists would have to be performed.

Implications

The general public and especially patients visiting an otolaryngologist, can benefit from the new insights of this study and be reassured by the fact that we found little structural deviation from CPG recommendations.

Otolaryngologists can use our results for a better understanding of RS related healthcare and comorbid diseases. Also, it shows in what way reimbursement claims can be used to assess healthcare. In the future, they should be aware that secondary use of reimbursement claims data might increase and therefore adequate registration remains important.

Outcomes of this study can help CPG authors and board members in designing new or improved methods for healthcare delivery and registration in RS, from which patients eventually will benefit. For example, further embedding guideline adherence as an evaluation tool in quality assessments might increase the adoption of evidence- based CPGs. Methods to assign these quality benchmarks have been recently developed.[29]

For healthcare insurers and policymakers, it is important to realize that healthcare reimbursement claims data are too limited to assess quality of care or evaluate treatment outcomes. Our results also indicate the effects of market forces used to decrease health care costs. In line with competition between hospitals is higher in the Western region, we found decreased costs per patient, further contributing to a decrease of the total healthcare budget. Also, the low prevalence of RS in secondary/tertiary care, compared to the higher prevalence in previous studies (situated at population level or in primary care), implies that most patients with RS are treated by their GP and not by an otolaryngologist.[1-4] This demonstrates a high level of cost-effectiveness of the Dutch healthcare system.

For researchers, these results add to the existing knowledge about RS and can be used as a foundation for formulating research priorities. Our study can also serve as an example for future studies on healthcare reimbursement claims.

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APPENDICES

Appendix 1. Recommendations on diagnosis and treatment for adults with CRS, extracted from the CBO 2010 guideline (n=28)

Number	Recommendation[a]	Level of evidence[b]	Grade of recommendation[b]	Comparable to Vektis data
1.	In patients with suspected CRS, patient history should be carefully considered, including symptoms, duration and severity of the complaints.	C	3	-
2.	In patients with nasal polyps and complaints of CTS, it is advised to perform nasal endoscopy when symptoms last longer than three months and are severe.	C	3	+
3.	In patient with complaints of CRS and no signs of disease at nasal endoscopy, a CT scan should be considered when symptoms persist.	C	3	-
4.	An olfactory test can be helpful in patients with CRS and nasal polyps.	*D*	4	-
5.	Before starting antibiotic treatment in patients with CRS, a culture from the middle nasal passages can be considered, especially when a patient has undergone surgery. It is possible to start with an empirical antibiotic that can be adjusted if necessary.	B	2	-
6.	When surgery is considered in patients with CRS, a pre-operative CT-scan should be mad with the aim of visualizing the anatomy and assess risks.	D	4	-
7.	When radiographic imaging is indicated in patients with CRS, CT-scanning is the method of choice.	*C*	3	+
8.	When making a pre-operative CT-scan in patients with CRS, the lowest radiation exposure possible should be chosen.	C	3	-
9.	In patients with CRS and anamnestic symptoms of allergy, further diagnosis with RAST or skin prick test is indicated, because allergic rhinitis may be a contributing factor.	C	3	+/-

Appendix 1. Continued

Number	Recommendation[a]	Level of evidence[b]	Grade of recommendation[b]	Comparable to Vektis data
10.	NO measurement does not yet play a role in patients with CRS and nasal polyps, since there are no studies showing the added value of NO measurement for these conditions.	B/C	3	-
11.	Since the gold standard is invasive and laborious, NO measurement can be used in diagnosis primary ciliary dyskinesia.	B/C	3	-
12.	The work-up of patients with CRS should not consist of diagnosing gastro-esophageal reflux.	C	3	-
13.	In all patients with CRS, anamnesis should target lower airway disease.	B	2	-
14.	Uncomplicated CRS should not be treated with short-term antibiotics (<14 days), unless in case of an acute exacerbation, then it can be considered.	B/C	3	-
15.	There is insufficient evidence to make a recommendation on long-term antibiotic treatment (3 months) as an alternative to FESS, in patients that do not respond to local corticosteroids. The possible effect does not outweigh the risk of antibiotic resistance.	B	3	-
16.	Local corticosteroids are first line treatment in patients with CRS, with or without nasal polyps.	A2	1-2	-
17.	If there are no contra-indications, patients with CRS can be treated effectively with systemic steroids during 14 days.	A2	1-2	-
18.	Is there is doubt to whether the loss of smell is sensory or mechanical, a diagnostic course of systemic corticosteroids for 14 days can be applied.	B	3	-
19.	Due to a lack of randomized, controlled studies showing a relationship between GER and CRS, there is currently no place for anti-reflux treatment in CRS.	*C*	3	-

Appendix 1. Continued

Number	Recommendation[a]	Level of evidence[b]	Grade of recommendation[b]	Comparable to Vektis data
20.	In patients with CRS without nasal polyps, it is desirable to start rinsing with isotonic saline.	A2	1	-
21.	Treatment with antihistamines in patients with CRS and nasal polyps is only effective in patients with allergy	A2 B	2	-
22.	There is no place for the use of decongestives in patients with CRS	A2	2	-
23.	There may be a place for a trial treatment with anti-leukotrienes in CRS patients who also have asthma	B	2	-
24.	CRS should initially be treated with extensive medical treatment. Surgical treatment should be reserved for patients not who do not respond adequately to medical treatment.	B	3	+
25.	If CRS is treated surgically, FESS is the treatment of choice, rather than conventional open surgery	C	3	+
26.	If there is an indication for diagnostic culture in patients with CRS, endoscopic culture of the middle meatus is preferred instead of antral lavage.	A2	2	+/-
27.	Antral lavage is not recommended as a treatment in CRS	B	2	+
28.	In patients with therapy resistant CRS and insufficient improvement on medical therapy, revision surgery can be considered.	C	3	-

Legend:
a, translated from Dutch
b, for details on level of evidence and grade of recommendation, see guideline[4]
+, yes
-, no
+/-, partially

4

Appendix 2. Results for hospital type and region

		Age groups (years)					*Comorbidity*	*Diagnostic testing*[a]						
		18-30	***31-45***	***46-60***	***61-75***	***>75***	***n***	***A***	***NE (total)***	***NE (mean)***	***NE 1***	***NE 2***	***NE ≥3***	***CT 1***	***CT ≥2***	***NE+ CT***
Hospital type	*General*	2,916 (12)	5,443 (22)	7,826 (32)	6,829 (28)	1,767 (7)	19,020,335 (41)	1,044 (4)	14,798 (60)	1.8	8,621 (58)	3,719 (25)	2,458 (16)	12,292 (49)	587 (2)	7,976 (32)
	Teaching	3,066 (12)	5,888 (23)	8,048 (32)	6,717 (27)	1,599 (6)	7,282 (29)	1,348 (5)	14,607 (60)	1.7	8,847 (61)	3,724 (25)	2,036 (14)	12,351 (49)	739 (3)	7,828 (31)
	Academic	571 (13)	1,008 (23)	1,428 (33)	1,178 (27)	191 (4)	1,728 (39)	278 (6)	3,272 (75)	2.3	1,411 (43)	905 (28)	956 (29)	1,195 (27)	54 (1)	1,017 (23)
	Private	346 (11)	759 (25)	999 (33)	763 (25)	185 (6)	676 (22)	91 (3)	1,982 (65)	1.6	1,314 (66)	433 (22)	235 (12)	1,492 (49)	62 (2)	1,045 (34)
Region	*West*	2,137 (12)	3,803 (22)	5,550 (32)	4,787 (27)	1,188 (7)	6,996 (28)	1,190 (5)	14,055 (57)	1.66	8,661 (62)	3,295 (23)	2,099 (15)	11,788 (48)	578 (2)	7,279 (29)
	South	2,866 (12)	5,862 (24)	7,943 (32)	6,549 (26)	1,586 (6)	4,249 (29)	609 (4)	9,089 (61)	1.65	5,546 (61)	2,227 (25)	1,316 (14)	7,664 (52)	522 (4)	5,176 (35)

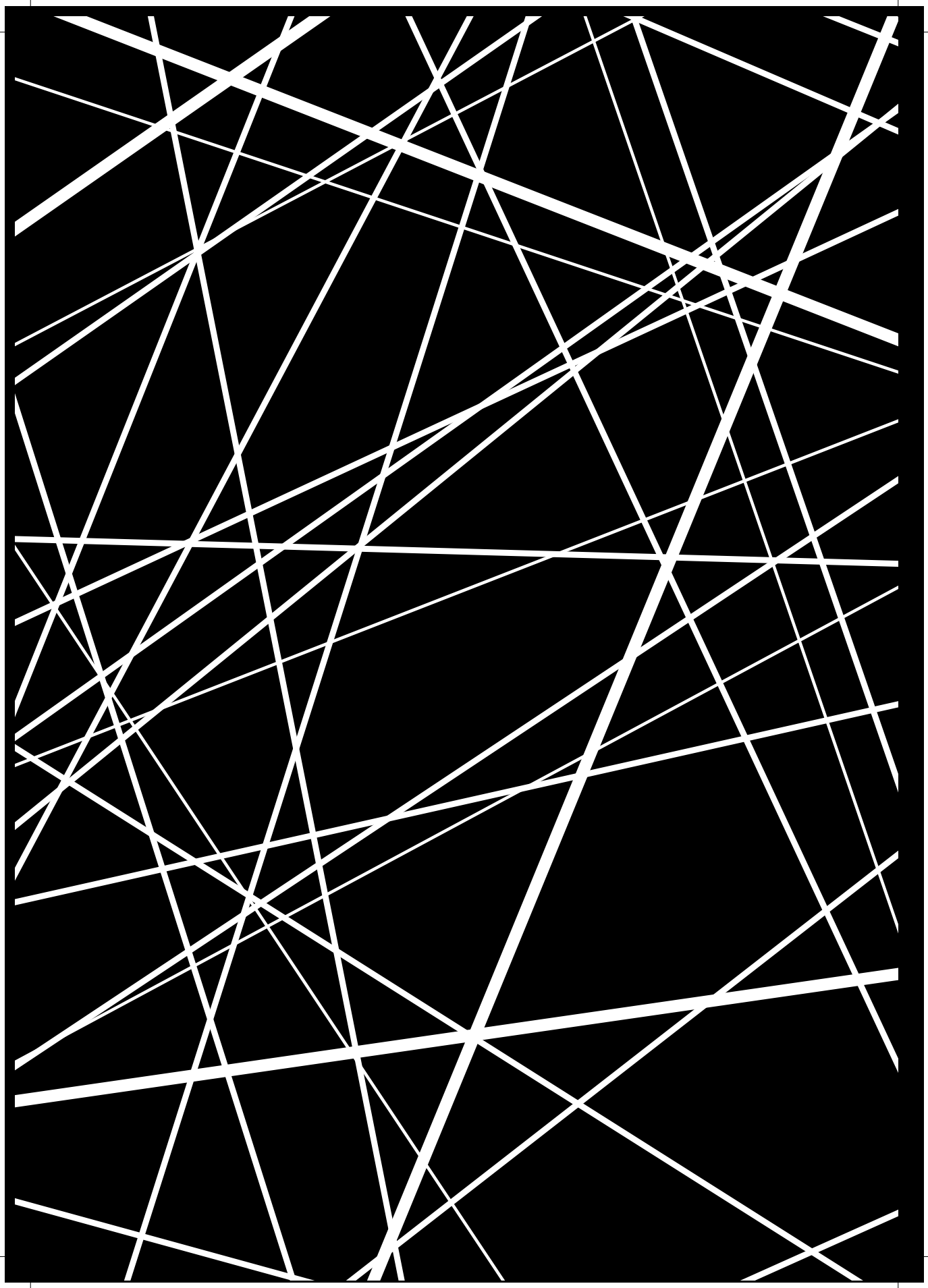
	Outpatient clinic visits[a]						No surgery			Surgery				Admission days (surgery)[a]					Intervention pp
	M	*1*	*2*	*3*	*4*	*≥5*	*n*	*Age (mean)*	*Comorbidity*	*n*	*Age (mean)*	*Comorbidity*	*NE+ CT*	*mean*	*0*	*1*	*2*	*≥3*	*mean*
	1.6	4.292 (17)	9,998 (40)	5,061 (20)	2,502 (10)	2,928 (12)	20,692	53	6,110 (30)	4,042 (16)	50	1,043 (26)	2,018 (50)	2.2	3043 (75)	12 (0.3)	920 (23)	67 (2)	1.8
	1.6	4149 (16)	10,133 (40)	5,096 (20)	2,624 (10)	3,316 (13)	20,894	52	6,022 (29)	4,369 (17)	50	1,239 (28)	2,161 (49)	2.2	2572 (59)	24 (0.5)	1,659 (38)	114 (3)	1.7
	1.9	707 (16)	1,518 (35)	899 (21)	505 (12)	747 (17)	3,729	51	1,492 (40)	630 (14)	50	231 (37)	306 (49)	3.3	2,057 (41)[b]	<10 (<1)	227 (36)	146 (23)	2.3
	1.5	731 (24)	1,175 (39)	616 (20)	257 (8)	273 (9)	2,667	52	605 (23)	377 (12)	46	70 (19)	239 (63)	1.4	258 (69)	119 (32)	<10 (<1)	<10 (<1)	1.5
	1.6	4,186 (20)	9,758 (39)	5,147 (21)	2,494 (10)	3,221 (13)	21,053	52	5,961 (21)	3,692 (15)	50	1,015 (27)	1,812 (50)	2.3	2,841 (77)	134 (4)	614 (17)	103 (3)	1.7
	1.6	2,422 (20)	5,946 (40)	3,061 (21)	1,555 (11)	1,830 (12)	12,138	52	3,511 (29)	2,650 (18)	49	727 (27)	1,538 (58)	2.2	1,404 (53)[b]	<10 (<1)	1,132 (43)	114 (4)	1.7

Appendix 2. Continued

	Age groups (years)					*Comorbidity*	*Diagnostic testing*[a]								
	18-30	***31-45***	***46-60***	***61-75***	***>75***	***n***	***A***	***NE (total)***	***NE (mean)***	***NE 1***	***NE 2***	***NE ≥3***	***CT 1***	***CT ≥2***	***NE+ CT***
Region															
North/East	1,850 (12)	3,325 (22)	4,657 (31)	4,049 (27)	933 (6)	5,478 (31)	961 (6)	11,314 (65)	1.97	5,799 (51)	3,189 (28)	2,326 (21)	7,716 (44)	411 (2)	5,397 (31)

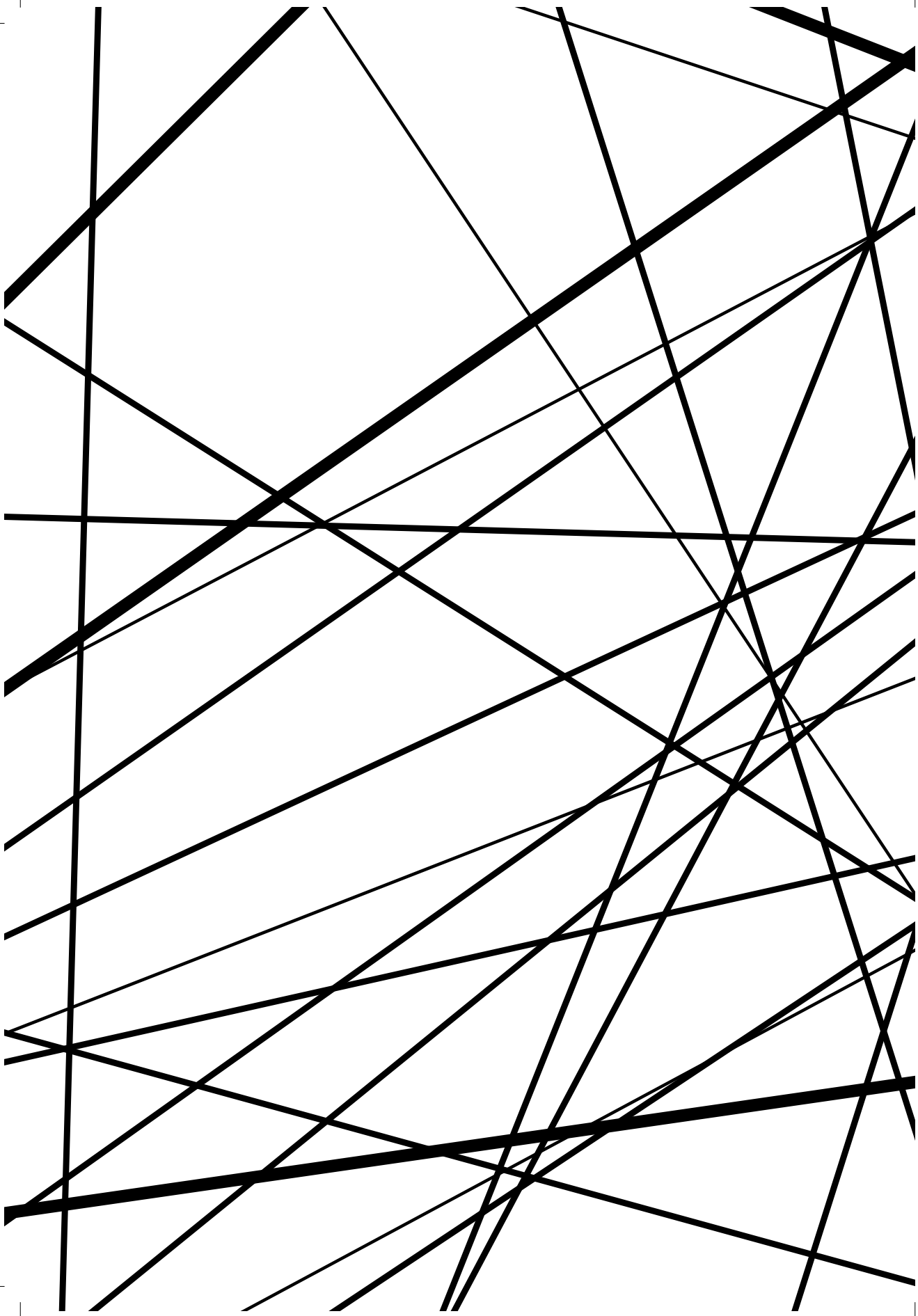
Legend:
n, number of patients
a, allergy testing (skin prick test)
NE, nasal endoscopy
CT, computed tomography scan of paranasal sinuses
a, no differences in mean age for region or hospital, with the exception of allergy: patients in academic hospitals were older (46) than patient in other hospitals (42 years for general/teaching and 43 years for private clinics). For admission days, mean age was not provided
b, <1% of data missing
pp, per patient

	Outpatient clinic visits[a]						*No surgery*			*Surgery*			*Admission days (surgery)*[a]					*Intervention pp*
	M	***1***	***2***	***3***	***4***	***≥5***	***n***	***Age (mean)***	***Comorbidity***	***n***	***Age (mean)***	***Comorbidity***	***NE+ CT***	***mean***	***0***	***1***	***2***	***≥3***	***mean***
	1.7	3,094 (22)	6,903 (40)	3,386 (19)	1,824 (10)	2,258 (13)	14,373 14.373	52	4,625 (32)	3,054 (17)	50	835 (27)	1,415 (46)	2.3	1,862 (61)	18 (0.6)	1,059 (35)	115 (3)	2.0



PART 2

Quality of evidence in otolaryngology



CHAPTER 5

Publications on clinical research in otolaryngology - A systematic analysis of leading journals in 2010

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Front Surg. 2019;6:18

Author contributions

Kaper NM: Conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the article, final approval of the version to be submitted and any revised version.

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van der Heijden GJMG: Conception and design, analysis and interpretation of data, drafting and revising the article, final approval of the version to be submitted and any revised version

ABSTRACT

Objective: We wanted to asses and characterize the volume of otolaryngology publications on clinical research, published in major journals.

Methods: To assess volume and study type of clinical research in otolaryngology we performed a literature search in high impact factor journals

We included 10 high impact factor otolaryngology journals and 20 high impact factor medical journals outside this field (2011). We extracted original publications and systematic reviews from 2010. Publications were classified according to their research question, that is therapy, diagnosis, prognosis or etiology.

Results: From otolaryngology journals (impact factor 1.8 to 2.8) we identified 694 (46%) publications on original observations and 27 (2%) systematic reviews. From selected medical journals (impact factor 6.0 to 101.8) 122 (2%) publications related to otolaryngology, 102 (83%) were on original observations and 2 (0,04%) systematic reviews. The most common category was therapy (40%).

Conclusion: Half of publications in otolaryngology concerns clinical research, which is higher than other specialties. In medical journals outside the field of otolaryngology, a small proportion (2%) of publications is related to otolaryngology. Striking is that systematic reviews, which are considered high level evidence, make up for only 2% of publications. We must ensure an increase of clinical research for optimizing medical practice.

INTRODUCTION

Clinicians strive to provide evidence-based patient care.[1] According to the principles of evidence-based medicine (EBM), they should evaluate all available research for the best evidence and combine this with their experience and patients' preferences.[1,2] Therefore clinicians are in need of publications reporting on health outcomes in patients, that provide answers to clinical research questions. These studies are addressed to as clinical research and have therefore a direct possibility to influence clinical practice.[1,2] Other research types, such as biological experiments or individual clinician's experiences can also be important, but their impact on clinical practice is often limited.[2]

We initiated this study because we wanted to asses and characterize the volume of otolaryngology publications on clinical research. Four important categories in clinical research can be distinguished (Table 1), on which we will emphasize in this study.[3]

Besides original publications, systematic reviews are also important for decision making in patient care. They collect and summarize all existing publications and are considered the highest quality, i.e. level 1a evidence.[4]

In the past, similar studies have been performed, showing a constant amount of 77% clinical research in '69, '79 and '89 in four major otolaryngology journals.[5] In 1999, clinical research accounted for 72% of publications in four major journals.[6] Six major otolaryngology journals were reviewed for the years 1993 and 2003, showing an increase in clinical research from 72% to 73%.[7]

The purpose of our study is to provide insight in the volume and type of clinical research that is published in one year, in the field of otolaryngology. In addition, we compare leading otolaryngology specialty journals to journals outside this field, based on their impact factor.[8]

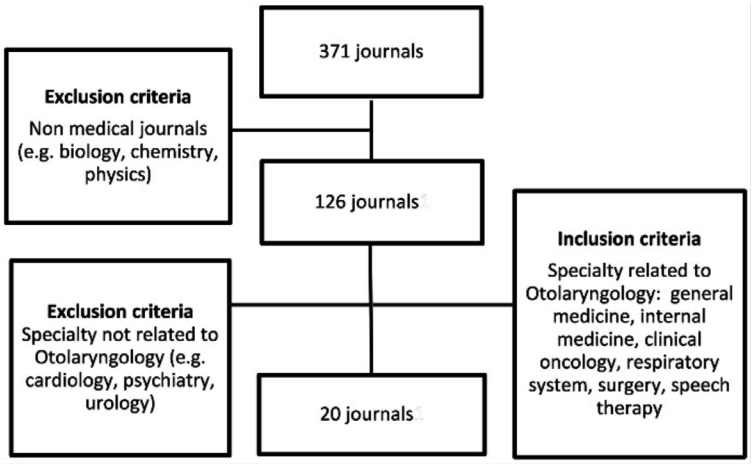
METHODS AND MATERIALS

Selection of journals

Data collection was carried out in February 2012. We identified leading journals by their impact factor. We selected the top 10 impact factor otolaryngology journals, using the 2011 impact factor.[8] We then searched for medical journals outside the field of otolaryngology. We used the 2011 impact factor to rank journals from high to low and selected the first 20 journals that were likely to publish articles related to otolaryngology.

The journals were selected based on their scope. The in- and exclusion criteria can be found in Figure 1. The overview of all reviewed journals can be found online (Appendix 1). Two authors independently selected journals; initial disagreement was resolved by consensus. (N.K. and G.R.)

Figure 1. Selection of journals



Selection of publications

We retrieved full texts of all citable articles, that is, peer-reviewed articles from the selected otolaryngology journals. From the selected medical journals two authors independently retrieved full texts of all citable articles concerning otolaryngology based on title or abstract, initial disagreement was resolved by consensus. (N.K. and G.R.)

We selected all original publications on health outcomes in patients, with a determinant or outcome considered relevant for patient care.[3] (Table 2) We also selected systematic reviews and meta-analyses that were based on original publications, relevant for patient care. Case reports were excluded.[4]

The selected studies were further classified based on the purpose of their research question, e.g. therapy, diagnosis, prognosis or etiology (Table 1).[3]

Two authors (N.K. and G.R.) independently retrieved and reviewed all publications. Initial disagreement on selection and categorization of articles was discussed with a third author (G.H.) until agreement was reached; the selection is therefore based on a full consensus.

Table 1. Publication topic

	Description
Therapy	Causally explains and predicts the course of disease as given by an intervention for therapy (including adverse effects studies), prevention, rehabilitation, quality improvement, or continuing medical education and clinical or non-clinical profile
Diagnosis	Content pertains directly to using a tool to arrive at a diagnosis of a disease or condition.
Prognosis	Content pertains directly to the prediction of the clinical course or the natural history of a disease or condition with the disease or condition existing at the beginning of the study.
Etiology	Determines if there is a causal relation between an exposure and a disease or condition.
Other	Costs and economics, Qualitative, Test development and validation, Descriptive study, Product development

Table 2. Publication types

	Definition
Citable article	All peer-reviewed publications (letters, editorials and symposium reports were excluded)
Original publication	Authors report first-hand observations
Clinical study	Study conducted in living healthy or affected patients, or in tissue/ body fluids of living humans, with a determinant and outcome relevant for patient care, reporting outcomes for 10 or more patients
Systematic review (and meta-analysis)	Authors systematically select, assess and synthesize all relevant original publication on a particular topic
Case report	Original publication that identifies personalized data (less than 10 patients)

RESULTS

Journals

The 10 selected otolaryngology journals can be found in Table 3 (impact factor 1.8 to 2.8). The scope of these journals can be found online (Appendix 2), two did not publish clinical evidence. The 20 selected medical journals had an impact factor varying from 6.0 to 101.8 (Table 3). A complete list of all evaluated medical journals is available online (Appendix 1). The selection process is shown in Figure 1. The titles of the selected journals can be found in Table 3.1 (otolaryngology journals) and Table 3.2 (medical journals).

Table 3.1 Results 1. Type of research in otolaryngology journals.

Journal title	IF	Citable articles (% of total)	Clinical research (% of citable articles)	Systematic reviews (% of citable articles)	Therapy	Diagnosis	Prognosis	Etiology	Other
Journal of the Association for Research in Otolaryngology	2,8	49 (3)	0 (0)	0 (0)	0	0	0	0	0
Hearing Research	2,7	178 (13)	20 (11)	0	2	0	1	4	13
Ear and hearing	2,6	80 (5)	50 (63)	0	4	1	2	4	39
Audiology & Neurotology	2,5	44 (3)	19 (43)	0	7	1	1	3	7
Head & Neck	2,4	209 (14)	129 (62)	6 (3)	61	19	34	4	11
Clinical Otolaryngology	2,4	54 (4)	38 (70)	7 (13)	15	3	4	1	15
Rhinology	2,3	118 (8)	82 (69)	1 (1)	28	5	10	22	17
Laryngoscope	2,0	422 (28)	214 (51)	7 (2)	89	10	22	42	51
Otology & Neurotology	1,9	260 (17)	142 (55)	6 (2)	56	2	14	15	55
Current Opinion in Otolaryngology	1,8	86 (6)	0	0	0	0	0	0	0
Total		1500	694 (46)	27 (2)	262 (38)	41 (6)	88 (13)	95 (14)	208 (30)

Legend:
IF, impact factor
%, percentage

Table 3.2 Results 2. Type of research in selected medical journals

Journal title	IF	Citable articles	Clinical research[a] (% of citable articles)	Systematic reviews (% of citable articles)	Therapy	Diagnosis	Prognosis	Etiology	Other
CA a cancer journal for clinicians	101.8	18	0	0	-	-	-	-	-
New England journal of medicine	53.3	345	1 (0,3)	0	0	0	1	0	0
Lancet	38.3	271	0	0	-	-	-	-	-
JAMA	30.1	233	3 (1,3)	1 (0,4)	2	0	0	0	1
Lancet Oncology	22.6	108	3 (2,8)	0	3	0	0	0	0
Journal of Clinical Oncology	18.4	784	21 (2,7)	0	11	4	5	0	1
Annals of Internal Medicine	16.7	167	0	0	0	0	0	0	0
Plos Medicine	16.3	99	0	0	-	-	-	-	-
British Medical Journal	14.1	312	1 (0,3)	0	1	0	0	0	0
Journal of the National Cancer Institute	13.8	135	1 (0,7)	0	1	0	0	0	0
Archives of Internal Medicine/ JAMA Internal Medicine	11.5	204	0	0	0	0	0	0	0
American Journal of Respiratory and Critical Care Medicine	11.1	310	6 (1,9)	0	1	0	0	4	1
Journal of Allergy and Clinical Immunology	11.0	336	14 (4,2)	1 (0,3)	6	0	0	7	1
Canadian Medical Association Journal	8.2	123	0	0	-	-	-	-	-
Clinical Cancer research	7.7	629	18 (2,9)	0	5	0	9	3	1
Annals of Surgery	7.5	291	2 (0,7)	0	0	0	1	0	1

Table 3.2 Continued

Journal title	IF	Citable articles	Clinical research[a] (% of citable articles)	Systematic reviews (% of citable articles)	Therapy	Diagnosis	Prognosis	Etiology	Other
American Journal of Clinical Nutrition	6.7	389	2 (0,5)	0	2	0	0	0	0
Annals of Oncology	6.4	445	12 (2,7)	0	6	1	3	0	2
Allergy	6.1	185	18 (9,7)	0	2	0	2	8	6
BMC Med	6.0	78	0	0	0	0	0	0	0
Total (%)		10967	102 (0,9)	2 (0,02)	40 (39)	5 (5)	21 (21)	22 (22)	14 (14)

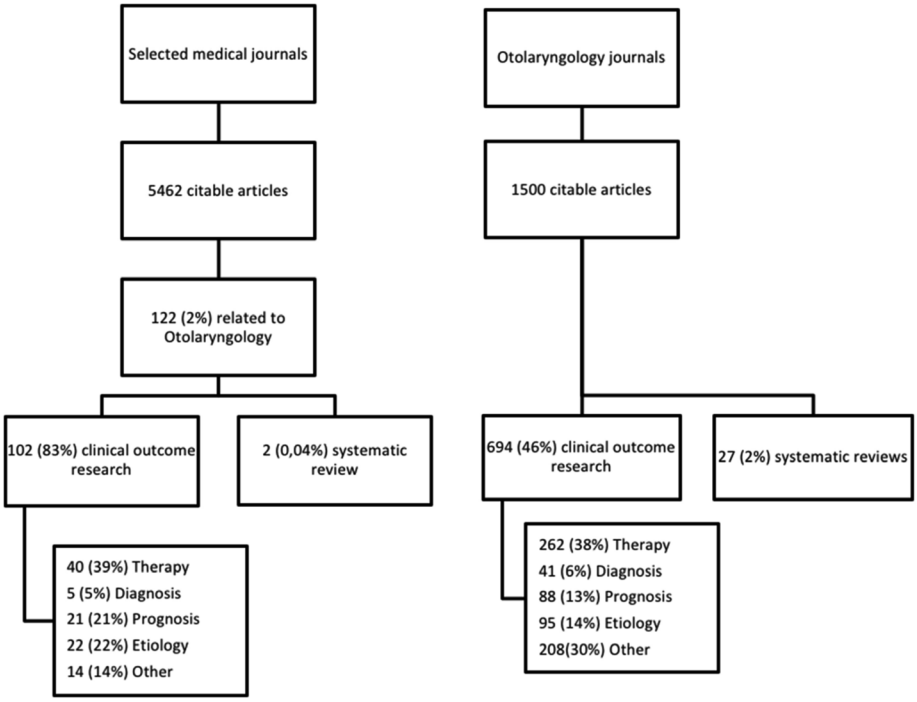
Legend:
IF, impact factor
a, related to otolaryngology
%, percentage

Publications

From 1500 articles in otolaryngology journals, we identified 694 (46%) original publications on clinical research and 27 (2%) systematic reviews. (Figure 2). Of 5462 citable articles in selected medical journals, 122 (2%) were related to otolaryngology. Of these, 102 (83%) were original publications and 2 (0,04%) were systematic reviews.

The different research questions are shown in Figure 2. Most publications concern therapy, followed by prognosis and etiology. Least represented is diagnosis. The proportion of publications on prognosis and etiology research is lower in otolaryngology journals. For diagnosis and therapy there are no differences. The results per journal can be found in Table 3.1 and 3.2. The variation in the proportion of clinical research between journals could be explained by the different scopes of the journals; JARO only publishes basic research and Current Opinion in Otolaryngology only publishes (non-systematic) reviews (Appendix 2). If we exclude these journals from the analysis, the proportion of clinical research increases to 51%.

Figure 2. Selection of publications



DISCUSSION

Synopsis of key findings

We set out to find the amount of clinical research in otolaryngology, published both in leading otolaryngology journals and in medical journals outside this field. Two percent of otolaryngology related research is published in journals outside the field of otolaryngology. In selected otolaryngology journals, 46% (95% confidence interval 44;49) of publications relates to clinical research. The proportion increased to 51% (95% confidence interval 48;53) after excluding two journals that do not publish clinical research. We found that the impact factor of medical journals outside the field of otolaryngology (6.0 to 101.8) is higher than the impact factor of otolaryngology journals (1.8 to 2.8). Regarding research questions, 40% of publications was related to therapy.

Comparison to previous studies

The proportion of clinical research in otolaryngology is lower than the 75% reported previously.[5-7] The difference may be explained by selection of different journals (the only identical journal included in the previous studies was the Laryngoscope), by our use of possible more stringent definitions than in previous research. It could also indicate an actual decrease in clinical evidence.

Compared to other specialties, otolaryngology journals achieve similar or higher rates of clinical evidence. For example, previous studies found an amount of clinical evidence in urology journals of 35% (2002-2010)9, 53% in anesthetics (2000-2009), 11% in plastic surgery (2002) and 24% in ophthalmology (2002).[10-12]

Limitations of our study

We used the impact factor of 2011, which relates to publications from 2010 and 2011, but for this study we only selected publications from 2010. We selected 30 medical journals and reviewed over 300 journals. These journals were selected retrospectively, therefore selection bias could have occurred. The selected publications can be judged outdated. However, it takes some time for studies to become available full text and to be indexed. Then it also takes several years before studies are adopted in daily practice.[13] When we look at clinical practice guidelines, it is common to find references of studies of 2010 and before. Therefore, our results are still important and informative.

We selected articles based on the impact factor of the journal they were published in, since we wanted to show results for leading journals, since they are often read and looked to for relevant research. With this selection approach, we systematically evaluated almost 12.500 articles. However, we might have missed publications with our search strategy, so the actual amount of clinical outcome research could be either lower or higher.

Implications for clinicians and researchers

For otolaryngology journals, it is striking that some high impact factor journals do not strive to publish clinical research. In addition, our results show that 2% of otolaryngology related clinical outcome research is published in journals outside the field of otolaryngology. These findings support results from different specialties, i.e. that important clinical studies are often not published in specialty journals.[14] Moreover, otolaryngology related research of substantial quality might be published in medical journals outside the field of otolaryngology, since higher impact factors can be achieved. Doctors should therefore look beyond their specialized journals when searching for evidence.

40% of publications we found, report about therapy, which is a similar result to previous studies.[7] Studies concerning etiology, prognosis and diagnosis are less common. This implies that the emphasis of researchers and journals is more on therapy than diagnosis, prognosis or etiology. Yet they should realize that these purpose categories are also important for clinical practice.[3]

Our results show a limited number of systematic reviews (both in and outside of otolaryngology journals). Systematic reviews are of high importance since they sum op the results of existing studies.[4] Therefore, we highly recommend that the amount of systematic reviews should increase, both in- and outside of otolaryngology journals.

For evidence-based practice, clinical original studies are also of vital importance.[1,2] We must therefore also ensure an increase of this type of research to improve and optimize medical practice.[15] This applies particularly to otolaryngology journals since journals outside the field of otolaryngology showed a better balance between clinical and fundamental research (50% versus 83%).

The amount of clinical evidence is predominantly determined by the scope of a journal and the choice of the editors and reviewers, but also by amount of studies that are conducted and submitted.[15] On one hand, this implies that editors and reviewers of journals should watch for balance between publication of clinical and fundamental research. On the other hand, researchers and doctors involved in research, are encouraged to publish clinical evidence.[15]

537940-L-sub01-bw-Kaper
Processed on: 20-12-2019

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APPENDICES

Appendix 1. List of all journals listed in the InCites Journal Citation Reports 2011, with impact factor ranging from high to low[11]

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
CA-A CANCER JOURNAL FOR CLINICIANS	**101.8**	**yes**	**yes**
NEW ENGLAND JOURNAL OF MEDICINE	**53.3**	**yes**	**yes**
ANNUAL REVIEW OF IMMUNOLOGY	52.8	yes	no
REVIEWS OF MODERN PHYSICS	42.9	no	-
CHEMICAL REVIEWS	40.2	no	-
NATURE REVIEWS MOLECULAR CELL BIOLOGY	39.1	no	-
LANCET	**38.3**	**yes**	**yes**
NATURE REVIEWS GENETICS	38.1	no	-
NATURE REVIEWS CANCER	37.5	no	-
ADVANCES IN PHYSICS	37.0	no	-
NATURE	36.3	no	-
NATURE GENETICS	35.5	no	-
ANNUAL REVIEW OF BIOCHEMISTRY	34.3	no	-
NATURE REVIEWS IMMUNOLOGY	33.2	no	-
NATURE MATERIALS	32.8	no	-
CELL	32.4	no	-
ENERGY EDUCATION SCIENCE AND TECHNOLOGY	31.7	no	-
SCIENCE	31.2	no	-
NATURE REVIEWS NEUROSCIENCE	30.4	no	-
JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	**30.0**	**yes**	**yes**
NATURE PHOTONICS	29.3	no	-
NATURE REVIEWS DRUG DISCOVERY	29.0	no	-
CHEMICAL SOCIETY REVIEWS	28.8	no	-
NATURE NANOTECHNOLOGY	27.3	no	-
PHYSIOLOGICAL REVIEWS	26.9	no	-
CANCER CELL	26.6	no	-
ANNUAL REVIEW OF ASTRONOMY AND ASTROPHYSICS	26.5	no	-
NATURE IMMUNOLOGY	26.0	yes	no
ANNUAL REVIEW OF PLANT BIOLOGY	25.96	no	-
ANNUAL REVIEW OF NEUROSCIENCE	25.7	no	-

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
CELL STEM CELL	25.4	no	-
BEHAVIORAL AND BRAIN SCIENCES	25.1	no	-
PROGRESS IN POLYMER SCIENCES	24.1	no	-
LANCET NEUROLOGY	23.5	yes	no
LANCET BIOTECHNOLOGY	23.3	no	-
NATURE BIOTECHNOLOGY	23.3	no	-
LANCET ONCOLOGY	**22.6**	**yes**	**yes**
NATURE MEDICINE	22.5	yes	no
ANNUAL REVIEWS OF GENETICS	22.2	yes	no
ACCOUNTS OF CHEMICAL RESEARCH	21.6	no	-
ANNUAL REVIEW OF PHARMACOLOGY AND TOXICOLOGY	21.6	no	-
IMMUNITY	21.6	yes	no
NATURE REVIEWS MICROBIOLOGY	21.2	no	-
ANNUAL REVIEW OF PHYSIOLOGY	20.8	no	-
NATURE CHEMISTRY	20.5	no	-
PHYSICS REPORTS	20.4	no	-
ANNUAL REVIEW OF PATHOLOGY	20.0	yes	no
ENDOCRINE REVIEWS	19.9	yes	no
NATURE CELL BIOLOGY	19.5	no	-
NATURE METHODS	19.3	no	-
NATURE PHYSICS	19.0	no	-
JOURNAL OF CLINICAL ONCOLOGY	**18.4**	**yes**	**yes**
PROGRESS IN MATERIALS SCIENCE	18.2	no	-
ECOLOGY LETTERS	17.6	no	-
LIVING REVIEWS IN RELATIVITY	17.5	no	-
LANCET INFECTIOUS DISEASES	17.5	no	-
ANNUAL REVIEW OF PSYCHOLOGY	16.8	yes	no
ANNALS OF INTERNAL MEDICINE	**16.7**	**yes**	**yes**
ANNUAL REVIEW OF MARINE SCIENCE	16.5	no	-
PLOS MEDICNE	**16.3**	**yes**	**yes**
CLINICAL MICROBIOLOGY REVIEWS	16.1	yes	no
ALDRICHIMICA ACTA	16.1	no	-

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
ANNUAL REVIEW OF CELL EN DEVELOPMENTAL BIOLOGY	15.8	no	-
TRENDS IN ECOLOGY&EVOLUTION	15.8	no	-
NATURE NEUROSCIENCE	15.5	no	-
NANO TODAY	15.4	no	-
MATERIALS SCIENCE & ENGINEERING R-REPORTS	15.0	no	-
ANNUAL REVIEW OF GENOMICS AND HUMA GENETICS	14.8	no	-
CIRCULATION	14.7	yes	no
NEURON	14.7	no	-
REPORTS ON PROGRESS IN PHYSICS	14.7	no	-
NATURE CHEMICAL BIOLOGY	14.7	no	-
PSYCHOLOGICAL BULLETIN	14.5	no	-
ANNUAL REVIEW OF ECOLOGY EVOLUTION AND SYSTEMATICS	14.4	no	-
ANNUAL REVIEW OF MICROBIOLOGY	14.3	yes	no
TRENDS IN NEUROSCIENCES	14.2	no	
PROGRESS IN ENERGY AND COMBUSTION SCIENCE	14.2	no	-
MOLECULAR CELL	14.2	no	-
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	14.2	yes	no
ANNUAL REVIEW OF PHYSICAL CHEMISTRY	14.1	no	-
BRITISCH MEDICAL JOURNAL	**14.1**	**yes**	**yes**
DEVELOPMENTAL CELL	14.1	no	-
ADVANCED MATERIALS	14.0	no	-
JOURNAL OF EXPIRIMENTAL MEDICINE	13.9	yes	no
JOURNAL OF THE NATIONAL CANCER INSTITUTE	**13.8**	**yes**	**yes**
CELL METABOLISM	13.7	no	-
MOLECULAR PSYCHIATRY	13.7	no	-
GENOME RESEARCH	13.6	no	-
ANNUAL REVIEW OF BIOPHYSICS	13.6	no	-
CELL HOST & MICROBE	13.5	no	-
ASTROPHYSICAL JOURNAL	13.5	no	-
ANGEWANDTE CHEMIE- INTERNATIONAL EDITION	13.5	no	-
NANO LETTERS	13.2	no	-
ANNUAL REVIEW OF MEDICINE	13.1	yes	no

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
ANNUAL REVIEW OF MATERIALS RESEARCH	13.1	no	-
JOURNAL OF CLINICAL INVESTIGATION	13.1	yes	no
MICROBIOLOGY AND MOLECULA BIOLOGY REVIEWS	13.0	no	-
CURRENT OPINION IN CELL BIOLOGY	12.9	no	-
ANNUAL REVIEW OF FLUID MECHANICS	12.8	no	-
NATURE STRUCTURAL & MOLECULAR BIOLOGY	12.7	no	-
ACTA CRISTALLOGRAPHICA	12.6	no	-
TRENDS IN COGNITIVE SCIENCES	12.6	no	-
AMERICAN JOURNAL OF PSYCHIATRY	12.5	yes	no
LIVING REVIEWS IN SOLAR PHYSICS	12.5	no	-
NATURE REVIEWS NEUROLOGY	12.5	yes	no
ANNUAL REVIEW OF CONDENSED MATTER PHYSICS	12.4	no	-
REVIEWS OF GEOPHYSICS	12.4	no	-
TRENDS IN CELL BIOLOGY	12.4	no	-
ANNUAL REVIEW OF BIOMEDICAL ENGINEERING	12.2	no	-
COORDINATION CHEMISTRY REVIEWS	12.1	no	-
ARCHIVES OF GENERAL PSYCHIATRY	12.0	yes	no
NATURE REVIEWS CLINICAL ONCOLOGY	12.0	yes	no
NATURE GEOSCIENCE	11.8	no	-
SURFACE SCIENCE REPORTS	11.7	no	-
GASTROENTEROLOGY	11.7	yes	no
HEPATOLOGY	11.7	yes	no
GENES AND DEVELOPMENT	11.7	no	-
ASTRONOMY AND ASTRPHYSICS REVIEW	11.5	no	-
ADVANCED DRUG DELIVERY REVIEWS	11.5	no	-
ARCHIVES OF INTERNAL MEDICINE	**11.5**	**yes**	**yes**
ANNUAL REVIEW OF ENTOMOLOGY	11.5	no	-
PLOS BIOLOGY	11.5	no	-
FRONTIERS IN NEUROENDOCRINOLOGY	11.4	yes	no
ACS NANO	11.4	no	-
IMMUNOLOGICAL REVIEWS	11.1	no	-
ANNALS OF NEUROLOGY	11.1	yes	no

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE	**11.1**	**yes**	**yes**
TRENDS IN PLANT SCIENCE	11.0	no	no
JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY	**11.0**	**yes**	**yes**
FEMS MICROBIOLOGY REVIEWS	11.0	no	-
TRENDS IN PHARMACOLOGICAL RESEARCH	10.9	no	-
TRENDS IN BIOCHEMICAL SCIENCES	10.8	no	-
PAIN PHYSICIAN	10.7	yes	no
MEDICINAL RESEARCH REVIEWS	10.7	yes	no
PROGRESS IN LIPID RESEARCH	10.7	no	-
STUDIES IN MYCOLOGY	10.6	no	-
AMERICAN JOURNAL OF HUMAN GENETICS	10.6	no	-
CANCER AND METASTASIS REVIEWS	10.6	yes	no
EUROPEAN HEART JOURNAL	10.5	yes	no
MASS SPECTOMETRY REVIEWS	10.5	no	-
TRENDS IN IMMUNOLOGY	10.4	yes	no
JOURNAL OF PHOTOCHEMISTRY AND PHOTOBIOLOGY C-PHOTOCHEMISTRY REVIEWS	10.4	no	-
TRENDS IN MOLECULAR MEDICINE	10.4	no	-
BRAIN RESEARCH REVIEWS	10.3	no	-
EMBO MOLECULA MEDICINE	10.3	no	-
JOURNAL OF CELL BIOLOGY	10.3	no	-
SYSTEMATIC BIOLOGY	10.2	no	-
ADVANCED FUNCTIONAL MATERIALS	10.2	no	-
GUT	10.1	yes	no
QUARTERLY REVIEWS OF BIOPHYSICS	10.1	no	-
TRENDS IN GENETICS	10.1	no	-
SIAM REVIEWS	10.0	no	-
NATURE REVIEWS ENDOCRINOLOGY	10.0	yes	no
LASER PHYSICS LETTERS	10.0	no	-
MOLECULAR ASPECTS OF MEDICINE	10.0	no	-
NATURE PROTOCOLS	10.0	no	-
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY	10.0	no	-
BLOOD	9.9	yes	no

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
ADVANCES IN MICROBIAL PHYSIOLOGY	9.9	no	-
ANNUAL REVIEW OF PHYTOPATHOLOGY	9.9	no	-
CURRENT OPINION IN CHEMICAL BIOLOGY	9.9	no	-
NATURAL PRODUCT REPORTS	9.8	no	-
PROCEEDING OF THE NATIONAL ACADEMY OF THE UNITED STATES OF AMERICA	9.7	no	-
JOURNAL OF THE AMERICAN SOCIET OF NEPHROLOGY	9.7	yes	no
CURRENT BIOLOGY	9.6	no	-
BIOTECHNOLOGY ADVANCES	9.6	no	-
ENERGY AND ENVIRONMENTAL SCIENCE	9.6	no	-
LEUKEMIA	9.6	yes	no
DRUG RESISTANCE UPDATES	9.6	no	-
CURRENT OPINION IN IMMUNOLOGY	9.5	yes	no
CIRCULATION RESEARCH	9.5	yes	no
CRITICAL REVIEWS IN SOLID STATE AND MATERIAL SCIENCES	9.5	no	-
BRAIN	9.5	yes	no
PROGRESS IN RETINAL AND EYE RESEARCH	9.5	yes	no
ANNUAL REVIEW OF NUTRITION	9.4	yes	no
CURRENT OPINION IN STRUCTURAL BIOLOGY	9.4	no	-
COLD SPRING HARBOUR PERSPECTIVES IN BIOLOGY	9.4	no	-
ACTA-REVIEWS ON CANCER	9.4	yes	no
PROGRESS IN INORGANIC CHEMISTRY	9.3	no	-
ACTA BEUROPATHOLOGICA	9.3	no	-
CURRENT OPINION IN PLANT BIOLOGY	9.3	no	-
JOURNAL OF HEPATOLOGY	9.3	yes	no
JOURNAL OF ECONOMIC LITERATURE	9.2	no	-
HUMAN REPORDUCTION UPDATE	9.2	no	-
EMBO JOURNAL	9.2	no	-
CLINICAL INFECTIOUS DISEASES	9.2	yes	no
TRENDS IN BIOTECHNOLOGY	9.1	no	-
PLOS PATHOGENS	9.1	no	-
FRONTIERS IN ECOLOGY AND THE ENVIRONMENT	9.1	no	-
ANNUAL REVIEW OF CLINICAL PSYCHOLOGY	9.1	yes	no

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
BIOLOGICAL REVIEWS	9.1	no	-
ANNUAL REVIEW OF ANALYTICAL CHEMISTRY	9.0	no	-
GENOME BIOLOGY	9.0	no	-
PLANT CELL	9.0	no	-
PROGRESS IN NEUROBIOLOGY	8.9	no	-
CELL DEATH AND DIFFERENTIATION	8.8	no	-
NATURE REVIEWS CARDIOLOGY	8.8	yes	no
SCHIZOFRENIA BULLETIN	8.8	yes	-
ANNALS OF THE REUMATIC DISEASE	8.7	yes	no
PLOS GENETICS	8.7	no	-
NEUROSCIENCE AND BIOBEHAVIOURAL REVIEWS	8.7	no	-
PROGRESS IN SURFACE SCIENCE	8.6	no	-
MOLECULAR SYSTEMS BIOLOGY	8.6	no	-
PHARMACOLOGY AND THERAPEUTICS	8.6	no	-
EUROPEAN UROLGY	8.5	yes	no
ANTIOXIDANT & REDOX SIGNALING	8.5	no	-
NATURE REVIEWS RHEUMATOLOGY	8.4	yes	no
SMALL	8.3	no	-
NEUROLOGY	8.3	yes	no
DIABETES	8.3	yes	no
BIOLOGICAL PSYCHIATRY	8.3	yes	no
CANADIAN MEDICAL ASSOCIATION JOURNAL	**8.2**	**yes**	**yes**
ADVANCES IN COLLOID AND INTERFACE SCIENCE	8.1	no	-
TREND IN ENDOCRINOLGY AND METABOLISM	8.1	yes	no
NATURE REVIEWS GASTROENTEROLOGY AND HEPATOLOGY	8.1	yes	no
DIABETES CARE	8.1	yes	no
CURRENT OPINION IN GENETICS AND DEVELOPMENT	8.1	no	-
NUCLEIC ACIDS RESEARCH	8.0	no	-
CURRENT OPINION IN COLLOID AND INTERFACE SCIENCE	8.0	no	-
NATURE CLINICAL PRACTICE ONCOLOGY	8.0	yes	no
NEURPSYCHOPHARMACOLOGY	8.0	no	-
PHYSIOLOGY	8.0	no	-

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
CURRENT OPINION IN MICROBIOLOGY	7.9	no	-
TRENDS IN MICROBIOLOGY	7.9	no	-
CLINICAL CHEMISTRY	7.9	no	-
ARTHRITIS AND RHEUMATISM	7.9	yes	no
CANCER RESEARCH	7.9	yes	no
CYTOKINE & GROWTH FACTOR REVIEWS	7.8	no	-
SCIENCE TRANSLATIONAL MEDICINE	7.8	no	-
STEM CELLS	7.8	no	-
PSYCHOLOGICAL REVIEW	7.8	no	-
CLINICAL CANCER RESEARCH	**7.7**	**yes**	**yes**
QUARTERLY REVIEW OF BIOLOGY	7.7	no	-
CURRENT OPINION IN BIOTECHNOGLY	7.7	no	-
JOURNAL OF MOLECULAR CELL BIOLOGY	7.6	no	-
CRITICAL REVIEWS IN BIOCHEMISTRY	7.6	no	-
HUMAN MOLECULAR GENETICS	7.6	no	-
NATURE CLINICAL PRACTICE NEUROLOGY	7.6	yes	no
ARCHIVES OF NEUROLOGY	7.6	yes	no
EPIDEMIOLOGIC REVIEWS	7.6	yes	no
NATURE CLINICAL PRACTICE ENDOCRINOLOGY&METABOLISM	7.5	yes	no
CHEMICAL SCIENCE	7.5	no	-
CATALYSIS REVIEWS	7.5	no	-
SCIENCE SIGNALING	7.5	no	-
ANNALS OF SURGERY	**7.5**	**yes**	**yes**
AUTOPHAGY	7.5	yes	no
CURRENT OPINION IN NEUROBIOLOGY	7.4	no	-
ECOLOGICAL MONOGRAPHS	7.4	no	-
BIOMATERIALS	7.4	no	-
MOLECULAR AND CELLULAR PROTEOMICS	7.4	no	-
NATURE COMMUNICATION	7.4	no	-
LASER AND PHOTONICS REVIEWS	7.4	no	-
ISME JOURNAL	7.4	no	-
PHYSICAL REVIEW LETTERS	7.4	no	-
JOURNAL OF AUTOIMMUNITY	7.4	yes	no

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
EMBO REPORTS	7.4	no	-
BASIC RESEARCH IN CARDIOLOGY	7.3	no	-
ANNUAL REVIEW OF CHEMICAL AND BIOMOLECULAR ENGINEERING	7.3	no	-
CHEMISTRY OF MATERIALS	7.3	no	-
AMERICAN JOURNAL OF GASTROENTEROLOGY	7.3	yes	no
PARTICLE AND FIBER TOCICOLOGY	7.3	no	-
ANNUAL REVIEW OF EARTH AND PLANETARY SCIENCES	7.2	no	-
PHYSICS OF LIFE REVIEWS	7.2	no	-
REVIEWS IN MEDICAL VIROLOGY	7.2	no	-
EXPERT REVIEWS IN MOLECULAR MEDICINE	7.1	no	-
JOURNAL OF NEUROSCIENCE	7.1	yes	no
NATURE REVIEWS NEPHROLOGY	7.1	yes	no
INTERNATIONAL JOURNAL OF CARDIOLOGY	7.1	yes	no
CLINICAL PSYCHOLOGY REVIEW	7.1	yes	no
SEMINARS IN LIVER DISEASE	7.1	yes	no
NATURE CLINICAL PRACTICE CARDIOVASCULAR MEDICINE	7.0	yes	no
OBESITY REVIEWS	7.0	yes	no
ENVIRONMENTAL HEALTH PERSEPCTIVES	7.0	no	-
ADVANCES IN ORGANOMETALLIC CHEMISTRY	7.0	no	-
PROGRESS IN QUENSTUM ELECTRONIS	7.0	no	-
NANO RESEARCH	7.0	no	-
MUCOSAL IMMUNOLOGY	7.0	no	-
INTERNATIONAL MATERIALS REVIEWS	7.0	no	-
SLEEP MEDICINE REVIEWS	6.9	yes	no
MOLECULAR THERAPY	6.9	no	-
AMERICAN PSYCHOLOGIST	6.9	yes	no
GLOBAL ENVIRONMENTAL CHANGE	6.9	no	-
CURRENT OPINION IN PHARMACOLOGY	6.9	no	-
THORAX	6.8	yes	no
DRUG DISCOVERY TODAY	6.8	no	-
CHEMS SUS CHEM	6.8	no	-
DIABETOLOGIA	6.8	yes	no

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
PROCEDINGS OF THE IEEE	6.8	no	
JACC-CARDIOVASCULAR INTERVENTIONS	6.8	yes	no
JOURNAL OF MAMMARY GLAND BIOLOGY AND NEOPLASIA	6.7	no	-
ADVANCES IN CANCER RESEARCH	6.7	yes	no
NANOMEDICINE	6.7	no	-
AMERICAN JOURNAL OF CLINICAL NUTRITION	**6.7**	**yes**	**yes**
GONDWANA RESEARCH	6.7	no	-
SEMINARS IN CELL&DEVELOPMENTAL BIOLOGY	6.6	no	-
NEW PHYTOLOGIST	6.6	no	-
AUTOIMMUNITY REVIEWS	6.6	no	-
BRITISH JOURNAL OF PSYCHIATRY	6.6	yes	no
NEUROPSYCHOLOGY REVIEW	6.6	yes	no
KIDNEY INTERNATIONAL	6.6	yes	no
DEVELOPMENT	6.6	no	-
EARTH-SCIENCE REVIEWs	6.6	no	-
CELLULAR AND MOLECULAR LIFE SCIENCES	6.6	no	-
TOPICS IN CURRENT CHEMISTRY	6.6	no	-
CEREBRAL CORTES	6.5	no	-
PLANT PHYSIOLOGY	6.5	no	-
JOURNAL OF CONTROLLED RELEASE	6.5	no	-
SEMINARS IN CANCER BIOLOGY	6.5	no	-
CRITICAL REVIEWS IN BIOTECHNOLOGY	6.5	no	-
RETROVIROLOGY	6.5	no	-
CIRCULATION ARRHYTHMIA AND ELECTROPHYSIOLOGY	6.5	no	-
MUTATION RESEARCH	6.5	no	-
ANNUAL REVIEW OF NUCLEAR AND PARTICLE SCIENCE	6.5	no	-
ACS CHEMICAL BIOLOGY	6.4	no	-
JOURNAL OF THE AMERICAN OF CHILD AND ADOLESCENT PSYCHIATRY	6.4	yes	no
ANNALS OF ONCOLOGY		**yes**	**yes**
HAEMATOLOGICA	6.4	yes	no
ANNUAL REVIEW OF ENVIRONMENT AND RESOURCES	6.4	no	-
INTERNATIONAL JOURNAL OF EPIDEMIOLOGY	6.4	yes	no

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
JOURNAL OF INFECTIOUS DISEASES	6.4	yes	no
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B-BIOLOGICAL SCIENCES	6.4	no	-
DRUG METABOLISM REVIEW	6.4	no	-
AMERICAN JOURNAL OF TRANSPLANTATION	6.4	yes	no
SEMINARS IN IMMUNOLOGY	6.4	yes	no
JOURNAL OF NUCLEAR MEDICINE	6.4	no	-
ALZHEIMERS AND DEMENTIA	6.4	yes	no
JOURNAL OF BONE AND MINERAL RESEARCH	6.4	no	-
ONCOGENE	6.4	no	-
ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY	6.4	no	-
JOURNAL OF MEDICAL GENETICS	6.4	no	-
STRUCTURE	6.3	no	-
CRITICAL CARE MEDICINE	6.3	yes	no
GREEN CHEMISTRY	6.3	no	-
JOURNAL OF PATHOLOGY	6.3	no	-
JOURNAL OF INVESTIGATIVE DERMATOLOGY	6.3	yes	no
IEEE COMMUNICATION SURVEYS AND TUTORIALS	6.3		-
CIRCULATION HEART FAILURE	6.3	yes	no
PSYCHOTHERAPY AND PSCYHOSOMATICS	6.3	yes	no
POLYMER REVIEWS	6.3	no	-
SEMINARS IN IMMUNOPATHOLOGY	6.3	no	-
TRENDS IN ANALYTICAL CHEMISTRY	6.3	no	-
ALLERGY	**6.3**	**yes**	**yes**
CRITICAL REVIEWS IN MICROBIOLOGY	6.3	no	-
AGING CELL	6.3	no	-
AIDS	6.2	yes	no
WORLD PSYCHIATRY	6.2	yes	no
JOURNAL OF PHYSICAL CHEMISTRY LETTERS	6.2	no	-
HYPERTENSION	6.2	yes	no
NEUROBIOLOGY OF AGING	6.2	no	-
AGEING RESEARCH REVIEWS	6.2	no	-
ACADEMY OF MANAGEMENT REVIEW	6.2	no	-

Appendix 1. Continued

Journal Title	IF	Medical journal	Subspecialty related to otolaryngology
CHEMICAL COMMUNICATIONS	6.2	no	-
EMERGING INFECTIOUS DISEASES	6.2	yes	no
PLANT JOURNAL	6.2	no	-
PSYCHOLOGICAL MEDICINE	6.2	yes	no
EUROSURVEILLANCE	6.2	yes	no
SOCIAL COGNITIVE AND AFFECTIVE NEUROSCIENCE	6.1	yes	no
JOURNAL OF CELL SCIENCE	6.1	no	-
CIRCULATION CARDIOVASCULAR GENETICS	6.1	no	-
BIOTECHNOLOGY FOR BIOFUELS	6.1	no	-
CURRENT OPINION IN LIPIDOLOGY	6.1	yes	no
NATURE CLINICAL PRACTICE NEPHROLOGY	6.1	yes	no
CORTEX	6.1	yes	no
PERSONALITY AND SOCIAL PSYCHOLOGY REVIEW	6.1	no	-
CARDIOVASCULAR RESERACH	6.1	yes	no
ANGIOGENESIS	6.1	yes	no
CIRCULATION CARDIOVACULAR INTERVENTIONS	6.1	yes	no
CANCER TREATMENT REVIEWS	6.1	yes	no
ADVANCED SYNTHESIS & CATALYSIS	6.0	no	-
CLINICAL PHARMACOLOGY AND THERAPEUTICS	6.0	no	no
BMC MEDICINE	**6.0**	**yes**	**yes**

Legend:
IF, impact factor

Appendix 2. Scope for selected otolaryngology journals

Journal Title	Scope (as displayed on website of the journal)
1. Journal of the Association for Research in Otolaryngology (JARO)	JARO is a peer-reviewed journal that publishes research findings focused on the auditory and vestibular systems. JARO welcomes submissions describing original experimental research that investigates the mechanisms underlying problems of basic or clinical significance. Clinical case studies, pharmaceutical screens and methods papers are not encouraged unless they include significant new findings as well. Commentaries and reviews are published at the discretion of the Editorial Board; consult the Editor-in-Chief before submitting
2. Hearing Research	The aim of the journal is to provide a forum for papers concerned with basic peripheral and central auditory mechanisms. Emphasis is on experimental and clinical studies, but theoretical and methodological papers will also be considered. The journal publishes original research papers, review and mini- review articles, rapid communications, method/ protocol and perspective articles. Papers submitted should deal with auditory anatomy, physiology, psychophysics, imaging, modeling and behavioural studies in animals and humans, as well as hearing aids and cochlear implants. Papers on comparative aspects of hearing and on effects of drugs and environmental contaminants on hearing function will also be considered. Clinical papers will be accepted when they contribute to the understanding of normal and pathological hearing functions.
3. Ear and hearing	From the basic science of hearing and balance disorders to auditory electrophysiology to amplification and the psychological factors of hearing loss, *Ear and Hearing* covers all aspects of auditory and vestibular disorders. This multidisciplinary journal consolidates the various factors that contribute to identification, remediation, and audiologic and vestibular rehabilitation. It is the one journal that serves the diverse interest of all members of this professional community - otologists, audiologists, educators, and to those involved in the design, manufacture, and distribution of amplification systems. The original articles published in the journal focus on assessment, diagnosis, and management of auditory and vestibular disorders

Appendix 2. Continued

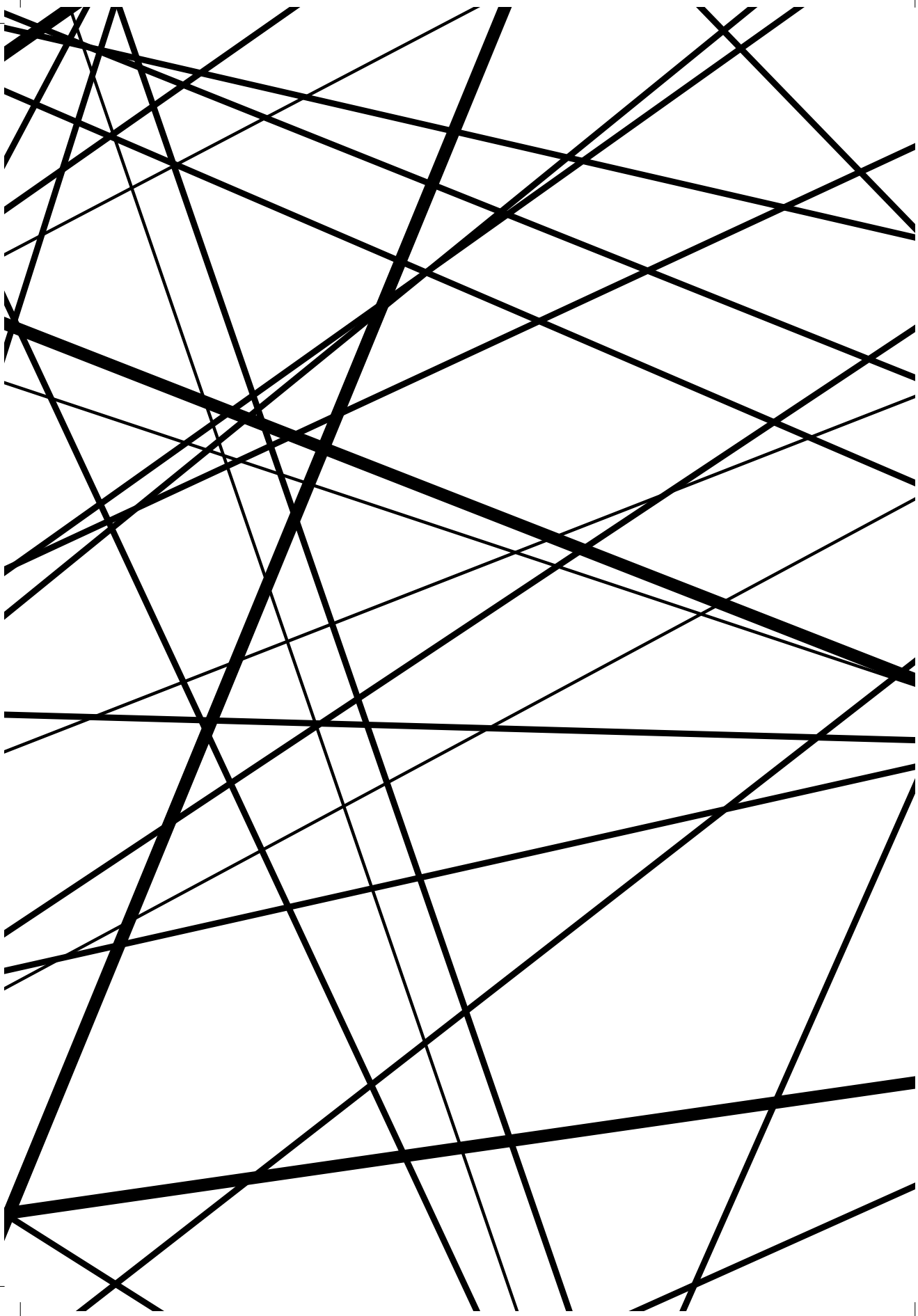
Journal Title	Scope (as displayed on website of the journal)
4. Audiology & Neurotology	Audiology and Neurotology provides a forum for the publication of the most-advanced and rigorous scientific research related to the basic science and clinical aspects of the auditory and vestibular system and diseases of the ear. This journal seeks submission of cutting edge research opening up new and innovative fields of study that may improve our understanding and treatment of patients with disorders of the auditory and vestibular systems, their central connections and their perception in the central nervous system. In addition to original papers the journal also offers invited review articles on current topics written by leading experts in the field. The journal is of primary importance for all scientists and practitioners interested in audiology, otology and neurotology, auditory neurosciences and related disciplines
5.Head & Neck	Head & Neck is an international multidisciplinary publication of original contributions concerning the diagnosis and management of diseases of the head and neck. This area involves the overlapping interests and expertise of several surgical and medical specialties, including general surgery, neurosurgery, otolaryngology, plastic surgery, oral surgery, dermatology, ophthalmology, pathology, radiotherapy, medical oncology, and the corresponding basic sciences. Head & Neck publishes original contributions on clinical and research topics. Each manuscript is submitted to peer review by at least two experts in the field. Comprehensive reviews of topics, particularly in fields subject to rapid change in knowledge, will be included at the discretion of the Editor and on the recommendation of reviewers. Technical notes, descriptions of new technologies, single case reports of unusual interest, and brief preliminary communications are accepted after proper peer review.

Appendix 2. Continued

Journal Title	Scope (as displayed on website of the journal)
6. Clinical Otolaryngology	Clinical Otolaryngology is a bimonthly journal devoted to clinically-oriented research papers of the highest scientific standards dealing with: current otorhinolaryngological practice audiology, otology, balance, rhinology, larynx, voice and paediatric ORL, head and neck oncology, head and neck plastic and reconstructive surgery continuing medical education and ORL training The emphasis is on high quality new work in the clinical field and on fresh, original research. Each issue begins with an editorial expressing the personal opinions of an individual with a particular knowledge of a chosen subject. The main body of each issue is then devoted to original papers carrying important results for those working in the field. In addition, topical review articles are published discussing a particular subject in depth, including not only the opinions of the author but also any controversies surrounding the subject.
7.Rhinology	Review articles Reviews should present an update of the most recent developments in a particular field of rhinologic research research. We encourage the submission of high quality colour pictures and cartoons. Original articles: We welcome high quality original publications dealing with innovative aspects of rhinologic research. As from April 1, 2009, the journal does NOT accept Case reports anymore.

Appendix 2. Continued

Journal Title	Scope (as displayed on website of the journal)
8.Laryngoscope	The Laryngoscope has been the leading source of information on advances in the diagnosis and treatment of head and neck disorders for nearly 120 years. The Laryngoscope is the first choice among otolaryngologists for publication of their important findings and techniques. Each monthly issue of The Laryngoscope features peer-reviewed medical, clinical, and research contributions in general otolaryngology, allergy/rhinology, otology/neurotology, laryngology/bronchoesophagology, head and neck surgery, sleep medicine, pediatric otolaryngology, facial plastics and reconstructive surgery, oncology, and communicative disorders. Contributions include papers and posters presented at the Annual and Section Meetings of the Triological Society, as well as independent papers, "How I Do It", "Triological Best Practice" articles, and contemporary reviews. Theses authored by the Triological Society's new Fellows as well as papers presented at meetings of the American Laryngological Association are published in The Laryngoscope.
9.Otology & Neurotology	Otology & Neurotology publishes original articles relating to both clinical and basic science aspects of otology, neurotology, and cranial base surgery. As the foremost journal in its field, it has become the favored place for publishing the best of new science relating to the human ear and its diseases. The broadly international character of its contributing authors, editorial board, and readership provides the Journal its decidedly global perspective.
10.Current Opinion in Otolaryngology	Current Opinion in Otolaryngology & Head and Neck Surgery is a bimonthly publication offering a unique and wide ranging perspective on the key developments in the field. Each issue features hand-picked review articles from our team of expert editors. With eleven disciplines published across the year – including maxillofacial surgery, head and neck oncology and speech therapy and rehabilitation – every issue also contains annotated references detailing the merits of the most important papers.



CHAPTER 6

Quality of reporting and risk of bias in therapeutic otolaryngology publications

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J Laryngol Otol. 2018;132:22-28

Author contributions

Kaper NM: Conception and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, final approval for publication, accountable for publication.

Swart KMA: acquisition of data, analysis and interpretation of data, revising the manuscript, final approval for publication, accountable for publication.

Grolman W: Conception and design, revising the manuscript, final approval for publication, accountable for publication.

van der Heijden GJMG: Conception and design, analysis and interpretation of data, revising the manuscript, final approval for publication, accountable for publication.

ABSTRACT

Objective: To identify high-quality trials that have the potential to influence clinical practice.

Methods: Ten otolaryngology journals with the highest 2011 impact factors were selected and publications from 2010 were extracted. From all medical journals, the 20 highest impact factor journals were selected and publications related to otolaryngology for 2010 and 2011 were extracted. For all publications, the reporting quality and risk of bias were assessed.

Results: The impact factor was 1.8–2.8 for otolaryngology journals and 6.0–101.8 for medical journals. Of 1500 otolaryngology journal articles, 262 were therapeutic studies; 94 had a high reporting quality and 5 a low risk of bias. Of 10 967 medical journal articles, 76 were therapeutic studies; 57 had a high reporting quality and 8 a low risk of bias.

Conclusion: Reporting quality was high for 45 per cent of otolaryngology-related publications and 9 per cent met quality standards. General journals had higher impact factors than otolaryngology journals. Reporting quality was higher and risk of bias lower in general journals than in otolaryngology journals. Nevertheless, 76 per cent of articles in high impact factor journals carried a high risk of bias. Better reported and designed studies are the goal with less risk of bias, especially in otolaryngology journals.

INTRODUCTION

In order to provide high-quality healthcare, clinicians are expected to have knowledge of the best available research evidence conducted in their field. They should be able to combine this knowledge with their experience and their patient's wishes when making clinical decisions, which is an approach known as evidence-based practice.[1] This means that clinicians should be able to find and select publications that are relevant for clinical practice and which have sufficient methodological quality.[2,3]

There is a large quantity of publications in otolaryngology, of which a major proportion is thought to lack clinical relevance or be of insufficient quality.[4] High-quality research is important because it can change clinical practice, foster patient experiences

and improve healthcare benefits. This study aimed to assess the quality of methods in otolaryngology studies. As most studies published concern the evaluation of treatment effects, and the assessment tools for such intervention studies are well established and accepted, we focused on the quality of such study publications.[5] The quality of a study depends largely on the quality of reporting and the risk of bias of the applied study design. Without adequate reporting, risk of bias cannot be assessed.[6] General standards and conditions for reporting intervention studies and avoiding risk of bias are widely known and available.[7,8] Clinicians rely, among other things, on impact factor to select the best available evidence. The impact factor is widely assumed to be an indicator of the quality of research journals.[9] It is calculated at the end of every year, based on the number of citations in the previous two-year period, relative to the number of publications in this period.[10] Researchers strive to publish in journals with the highest impact factor. Consequently, these journals are seen as the leading and most prestigious journals.[11,12]

For our study, we selected the leading field-specific and general medical journals. We extracted publications on treatment outcomes in otolaryngology and we investigated their quality of reporting and risk of bias. We compared the findings based on the publication source and either selected otolaryngology journals or selected general medical journals. We expected to find a major portion of high-quality otolaryngology publications in the selected general medical journals.

MATERIALS AND METHODS

Publication search and classification

We defined our cohort of publications in the year 2012. Using the most recent impact factors, from 2011, we selected 10 otolaryngology journals with the highest impact factor and searched for citable articles (i.e. peer-reviewed publications) from 2010.[13] We ranked all medical journals in the 2011 Journal Citation Report by their impact factor and selected 20 with the highest impact factor that were likely to publish otolaryngology-related research.[13] We selected journals with a subspecialty related to otolaryngology (e.g. oncology, allergy, respiratory) and journals that transcend multiple disciplines (e.g. The Lancet, The BMJ, PLOS Medicine). Two authors (NK and KS) independently selected journals and searched for otolaryngology-related publications; initial disagreement was resolved by discussion until agreement was reached. We selected journals from both 2010 and 2011, because we expected to find few articles and aimed to include a sufficient number of studies to compare between journals.

Two authors (NK and KS) independently retrieved and reviewed all publications. We selected studies reporting first-hand and original data, conducted on living patients. We selected only clinical research with a determinant and outcome relevant for patient care. We searched for therapeutic studies; that is, studies estimating the effect of an intervention on the course and outcome of a disease. We included all therapeutic intervention studies, both randomized and non-randomized studies, multiple and single group comparisons, and prospective and retrospective trials. Studies reporting on less than 10 patients were excluded.[14] Initial disagreement on the selection and categorization of articles was discussed with a third author (GH) until agreement was reached; the selection is therefore based on a full consensus.

Publication quality assessment

Based on pre-defined criteria, we evaluated the quality of selected articles by their study design. Assessment involved the evaluation of: selection bias, notably the study design characteristic of treatment assignment by (1) random and (2) concealed allocation; information bias, notably standardization of (3) treatments and (4) outcome assessments; performance bias, (5) blinding of outcome assessment, and attrition bias; and (6) completeness of reported data (Table I).[14,15] The Cochrane Handbook includes criteria 1, 2, 5 and 6 in their assessment of bias.[16]

When item information was not provided or not clearly reported, we rated it as insufficient. When item information was clearly reported, it was rated as sufficient. Studies were assigned a high reporting quality for reporting five or six items, a moderate reporting

quality for reporting three or four items, and a low reporting quality for reporting zero, one or two items. For the classification, it did not matter which item was fulfilled: all items were assigned an equal weight.

Table 1. Checklist for assessment of therapeutic publications

Checklist item	Description
Random allocation	Independent set procedure to generate the random allocation
Concealed allocation	Treatment allocation was independent from selection (e.g. central allocation, like telephone service or web-based
Standardization of treatment	Protocolled, uniform treatment & co-treatment (including placebo)
Standardization of outcome	Protocolled, uniform measurement & assessment of outcome
Blinding of outcome assessment	Outcome is measured, obtained & documented without knowledge of the treatment, observers of outcome are blinded to treatment (by blinding or placebo)
Completeness of reported data	*Adequate reporting of all included patients:* timing, amount & reason for loss to follow-up (if known), preferably displayed in flow chart *Number of patients included are reported,* for all treatment groups, with a description of source population & reasons for participant exclusion *Number of patients analysed per* treatment group; loss to follow-up should be ≤ 20%

After determining reporting quality, we assessed risk of bias per item. When the reporting allowed assessment (i.e. when reporting was rated sufficient), we rated the item as either satisfied or not satisfied. When the reporting quality was insufficient, the item was rated as not satisfied. Two authors (NK and KS) independently assessed articles and resolved initial disagreements by discussion.

Because selection bias is most important in therapeutic studies, these items were assigned most weight in terms of risk of bias.[15] Studies that did not satisfy criteria 1 and 2 (random and concealed allocation) were considered to have a high risk of bias, even if they fulfilled all other items. Studies were classified as having a low risk of bias if they satisfied criteria 1 and 2 plus all other study design features. If studies satisfied criteria 1 and 2 but failed on one or two of the other four features, they were rated as having a moderate risk of bias. Studies that failed on more items were classified as having a high risk of bias.

According to current quality standards, studies should have good reporting quality, and moderate or low risk of bias.[17]

Data analysis

We entered and analyzed data using SPSS statistical software, version 23.0 (Chicago, Illinois, USA). We compared ordinal outcomes using the Mann–Whitney U test. Binary outcomes were tested using the chi-square test. We used a Bonferroni post-hoc correction to determine inflated risks of a type 1 error in cases of multiple testing. For prediction of outcomes, ordinal logistic regression was performed.

RESULTS

The 10 selected otolaryngology journals had impact factors ranging from 1.8 to 2.8. The 20 selected medical journals had impact factors ranging from 6.0 to 101.8. For details on the selected journals and their impact factors, see Appendix 1.

Of 1,500 citable articles in the otolaryngology journals, we identified 262 (17%) therapeutic articles. Of these, 94 (36%) had a high reporting quality (Table 2); 7 (3%) had a moderate risk of bias and 5 (2%) had a low risk of bias (Table 3).

Of 10,967 citable articles in the selected medical journals, 183 (2%) were original clinical studies related to otolaryngology. We identified 76 (42%) therapeutic studies, 36 from 2010 and 40 from 2011. There were no statistical differences between the two years. Overall, 57 (75%) had a high reporting quality (Table 2); 10 (13%) a moderate risk of bias and 8 (11%) had a low risk of bias (Table 3).

Table 2. Overall reporting quality

Journal type	Articles (n)	Reporting quality			*P-value*[a]
		High (n (%))	Moderate (n (%))	Low (n (%))	
Selected medical journals	76	57 (75)	19 (25)	0 (0)	<0.05
Otolaryngology journals	262	94 (36)	165 (63)	3 (1)	
Total	338	151 (45)	184 (54)	3 (1)	

Legend:
n, number of articles
%: percentage
a, overall significance calculated using Mann-Whitney U Test. Post hoc tests with a Bonferroni correction showed significant difference between the moderate and high categories

Table 3. Overall risk of bias

Journal type	Articles (n)	Risk of bias			*P-value*[a]
		High (n (%))	Moderate (n (%))	Low (n (%))	
Selected medical journals	76	8 (11)	10 (13)	58 (76)	<0.05
Otolaryngology journals	262	5 (2)	7 (3)	250 (95)	
Total	338	13 (4)	17 (5)	308 (91)	

Legend:
n: number of articles
%: percentage
a: overall significance calculated using Mann-Whitney U Test. Post hoc tests with a Bonferroni correction showed significant difference between the moderate and high categories

The results per checklist item are reported in Table 4. For the selected medical journals, only blinding was remarkably poorly reported. For the otolaryngology journals, both blinding and completeness of data were remarkably poorly reported. Other items were moderately to well reported. Risk of bias items were more often rated sufficient for publications in the selected medical journals. Randomization, concealed allocation and blinding often had a low score, which explains the overall high risk of bias.

Table 5 shows the results of reporting quality against risk of bias. For a low or moderate reporting quality, the probability of low or moderate risk of bias was 0. High reporting quality was therefore a pre-requisite in order to even qualify for a low or moderate risk of bias.

The results per journal are shown in Figure 1 (reporting quality) and Figure 2 (risk of bias). The details can be found in Appendix 2. From the 10 selected otolaryngology journals, one journal did not publish original research. The top three otolaryngology journals published little clinical research (their focus is on fundamental research); the number one otolaryngology journal did not publish any therapeutic studies (Appendix 2).

Table 4. Reporting quality and risk of bias per checklist item

Item	**Reporting quality**		**Risk of bias**	
	Articles (n(%))[a]	OR (95 % CI)[b]	Articles (n(%))[c]	OR (95 % CI)[b]
Random allocation				
Otolaryngology journals	251 (96)	0,2 (0,1-0,5)	19 (7)	5,9 (3,0-11,6)
Selected medical journals	63 (83)		24 (32)	
Concealed allocation				
Otolaryngology journals	240 (92)	0,3 (0,2-0,7)	11 (4)	8,7 (4,0-19,1)
Selected medical journals	60 (79)		21 (28)	
Standardization of treatment				
Otolaryngology journals	209 (80)	3,0 (1,2-7,2)	122 (47)	4,3 (2,4-7,9)
Selected medical journals	70 (92)		60 (79)	
Standardization of outcome				
Otolaryngology journals	211 (81)	8,9 (2,1-37,7)	193 (74)	13,2 (3,2-55,3)
Selected medical journals	74 (97)		74 (97)	
Blinding of outcome				
Otolaryngology journals	27 (10)	7,0 (3,9-12,9)	20 (8)	4,3 (2,2-8,5)
Selected medical journals	34 (45)		20 (26)	
Complete data				
Otolaryngology journals	141 (54)	12,2 (4,8-31,2)	104 (40)	5,3 (3,0-9,5)
Selected medical journals	71 (93)		59 (78)	

Legend:
n, number of articles
%, percentage
a, number of articles that adequately reported the item
b, calculated using the chi-square test
c, number of articles that were rated sufficient
OR, odds ratio
CI, confidence interval

Table 5. Reporting quality against risk of bias

Reporting quality	Risk of bias			Total (n (%))
	Low (n (%))	Moderate (n (%))	High (n (%))	
High				
Otolaryngology journals	5 (2)	6 (2)	83 (32)	94 (36)
Selected medical journals	8 (11)	10 (13)	39 (51)	57 (75)
Category probability[a](%)	8	11	81	
Moderate				
Otolaryngology journals	0	1 (0)	164 (63)	165 (63)
Selected medical journals	0	0	19 (25)	19 (25)
Category probability[a](%)	0	0	100	
Low				
Otolaryngology journals	0	0	3 (1)	3 (1)
Selected medical journals	0	0	0	0
Category probability[a](%)	0	0	100	
Total				
Otolaryngology journals	5 (2)	7 (3)	250 (95)	262 (100)
Selected medical journals	8 (11)	10 (13)	58 (76)	76 (100)

Legend:
n, number of articles
%, percentage
a, probabilities calculated by an ordinal regression model, with $p<0.05$ for fitting of the model (Nagelkerke=0,23, goodness of fit test $p>0.05$ and test of parallel lines $p=0.61$)

Figure 1. Reporting quality per journal according to impact factor

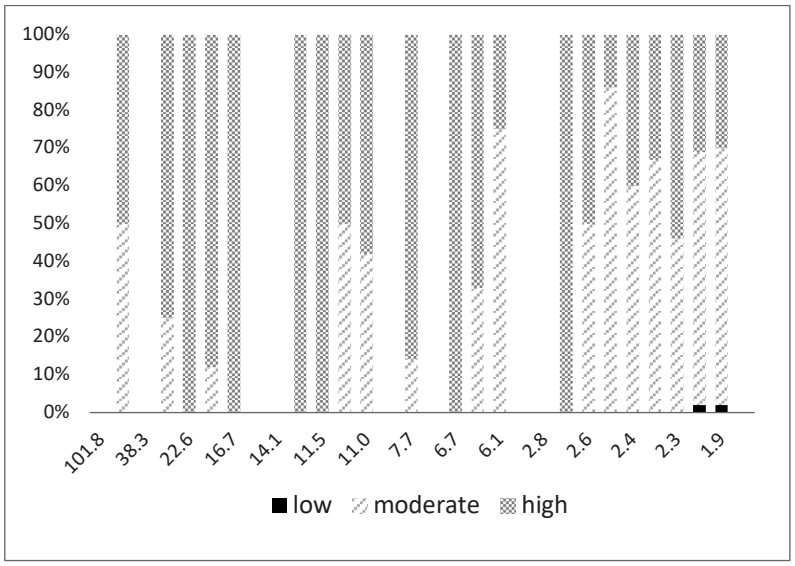
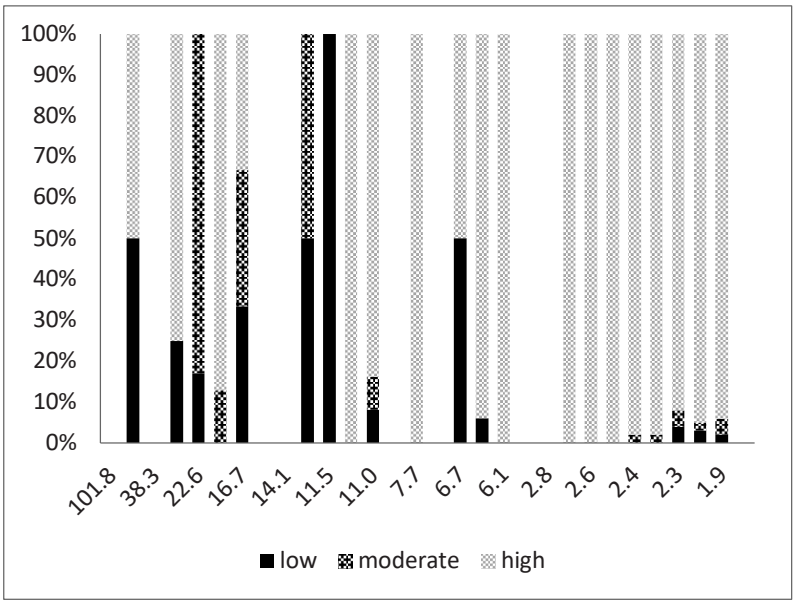


Figure 2. Risk of bias per journal according to impact factor



DISCUSSION

Otolaryngology journals have a relatively low impact factor compared to the selected medical journals. Overall, the reporting standards were met for 45% of therapeutic otolaryngology publications, and 9% met our quality standards (having a low or moderate risk of bias). This is the first time such a study has been carried out in otolaryngology.

As a result of our selection approach, we missed publications, but there is unlikely to be high-quality otolaryngology research published outside of our selected journals. For reasons of efficiency we selected studies from 2010 and assumed that our sample from 2010 would be representative of the studies published in the previous and subsequent year. We therefore presume that including more studies from adjacent years would lead to a reduction in random error, but would not change the outcome of our study. We included studies from the year 2010 because we expected to find most articles available in full text. Publications from 2010 (and even from before that) are still widely used in daily practice and guidelines. This is because it usually takes several years before publications are used in daily practice.[18]

We could have introduced bias in our study because the authors and journals that published the studies we assessed were not blinded. Therefore, the researchers who evaluated the quality of the articles could have been influenced by its authors or by the impact factor of the journal it was published in. However, by performing a systematic evaluation, which was executed independently by two authors, we reduced this risk of bias.

In evaluating the quality of publications, we limited the methodological aspects assessed, to provide an overview of the results. Adding items to the current classification would not change the risk of bias, but it could have an effect on the reporting quality. We believe we chose valid items for our rating, as all are derived from the Cochrane Handbook. We did not include the selective reporting item because we did not compare outcomes between different studies.[16]

There are important differences between otolaryngology journals and the selected medical journals. Our results show that the selected medical journals, which have a high impact factor, have better reporting quality and published considerably higher quality research. However, 76% of the publications in these journals still had a high risk of bias, so a high impact factor is definitely not a guarantee of high quality. It was not possible to compare impact factors between journals, given the small differences in impact factor and the limited number of publications; nevertheless, Figures 1 and 2 show that there is variation between journals.

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There are several explanations for the higher quality of publications in the selected medical journals. Medical journals can select from different research fields and are more attractive for authors to submit their research to, given their high impact factor.[12] As a result, general medical journals have the first and most comprehensive choice when selecting publications. Additionally, high impact factor journals have stricter rules about reporting, and often authors are requested to fulfil checklists (such as the Consolidated Standards of Reporting Trials ('CONSORT')).[7]

Our study provides important information for both research and clinical practice. The results show that the reporting of study designs needs to improve, especially for the lower impact factor otolaryngology journals. Even if not all items for risk of bias can be met, the reporting quality can and should always be high. In order to achieve improvement and help reduce research waste, there is a significant role for authors, reviewers and journals to play.[4] Better reporting of studies and improved methodological quality is warranted. Furthermore, researchers, reviewers and editors can play an important role.

In the context of clinical practice it is important for medical doctors to realize that they should always critically assess an article, even if it is published in a high impact factor journal. It is also important to be aware that relevant otolaryngology articles are not only published in otolaryngology journals, but also in general medical journals. Publications should meet other conditions, besides those concerning reporting and methodological quality. Studies should preferably report original data, and should not simply review or summarize existing data, or express opinions. The study should be relevant and innovative; that is, the outcome should preferably have an impact on current policy. The journal or publication should be open access; furthermore, publishing studies driven by publication rates ('bean counting'), rather than by the above factors, must be avoided.[4,12]

CONCLUSION

The majority of therapeutic research in leading otolaryngology journals does not meet current standards for methodological quality. Selected medical journals, with a considerably higher journal impact factor, tend to publish research of higher quality. Nevertheless, almost half of their publications are of low quality. Both researchers and medical publishers have a responsibility to improve the quality of methods and reporting. Medical doctors should critically assess publications before applying their findings in daily practice and should look outside their specialized literature when searching for high-quality evidence in their field.

537940-L-sub01-bw-Kaper
Processed on: 20-12-2019

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APPENDICES

Appendix 1. Impact factor (2011) for selected journals

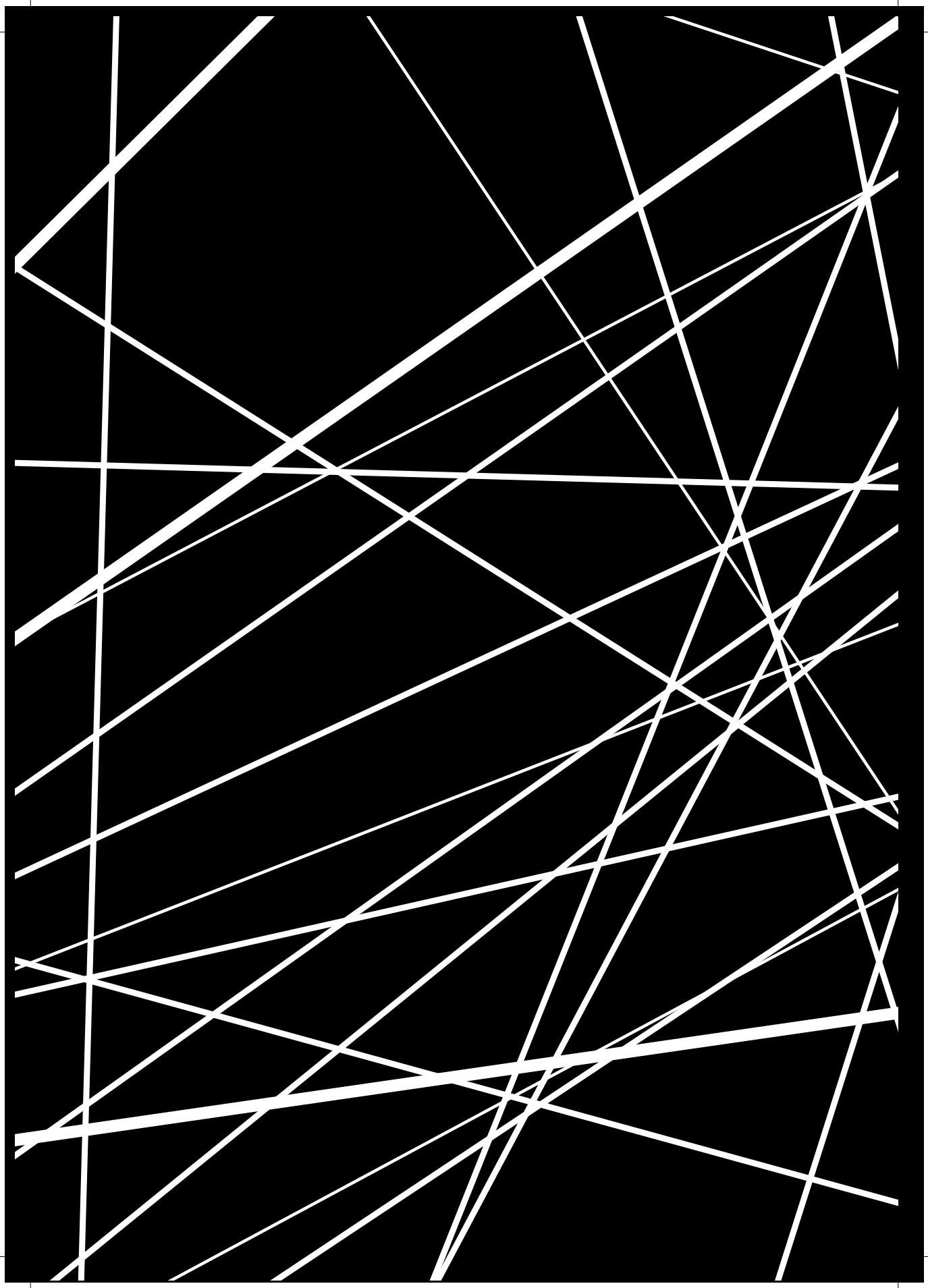
Journals	Impact factor
Medical journals	
CA a cancer journal for clinicians	101.8
New England journal of medicine	53.3
Lancet	38.3
JAMA	30.1
Lancet Oncology	22.6
Journal of Clinical Oncology	18.4
Annals of Internal Medicine	16.7
Plos Medicine	16.3
British Medical Journal	14.1
Journal of the National Cancer Institute	13.8
Archives of Internal Medicine/ JAMA Internal Medicine	11.5
American Journal of Respiratory and Critical care Medicine	11.1
Journal of Allergy and Clinical Immunology	11.0
Canadian Medical Association Journal	8.2
Clinical Cancer research	7.7
Annals of Surgery	7.5
American Journal of Clinical Nutrition	6.7
Annals of Oncology	6.4
Allergy	6.1
BMC Med	6.0
Otolaryngology journals	
Journal of the association for research in otolaryngology	2.8
Hearing research	2.7
Ear and Hearing	2.6
Audiology and Neurotology	2.5
Head and Neck	2.4
Clinical Otolaryngology	2.4
The American Journal of Rhinology & Allergy	2.3
Laryngoscope	2.0
Otology Neurotology	1.9
Current opinion in Otolaryngology	1.8

Appendix 2. Reporting quality and risk of bias per journal

Journals	Articles (n)	Reporting quality (number per category)	Risk of bias (number per category)
Otolaryngology journals			
Journal of the association for research in Otolaryngology	0	–	–
Hearing research	2	2 high	2 high
Ear and Hearing	4	2 moderate 2 high	4 high
Audiology and Neurotology	7	6 moderate 1 high	7 high
Head and Neck	60	36 moderate 24 high	1 moderate 59 high
Clinical Otolaryngology	15	10 moderate 5 high	1 moderate 14 high
The American Journal of Rhinology & Allergy	28	13 moderate 15 high	1 low 1 moderate 26 high
Laryngoscope	90	2 low 60 moderate 28 high	3 low 2 moderate 85 high
Otology & Neurotology	56	1 low 38 moderate 17 high	1 low 2 moderate 53 high
Current opinion in Otolaryngology	0	–	–
Medical journals			
CA a cancer journal for clinicians	0	–	–
New England journal of medicine	2	1 moderate 1 high	1 low 1 high
Lancet	0	–	–
JAMA	3	1 moderate 2 high	1 low 2 high
Lancet Oncology	6	6 high	1 low 5 moderate
Journal of Clinical Oncology	16	2 moderate 14 high	2 moderate 14 high
Annals of Internal Medicine	3	3 high	1 low 1 moderate 1 high

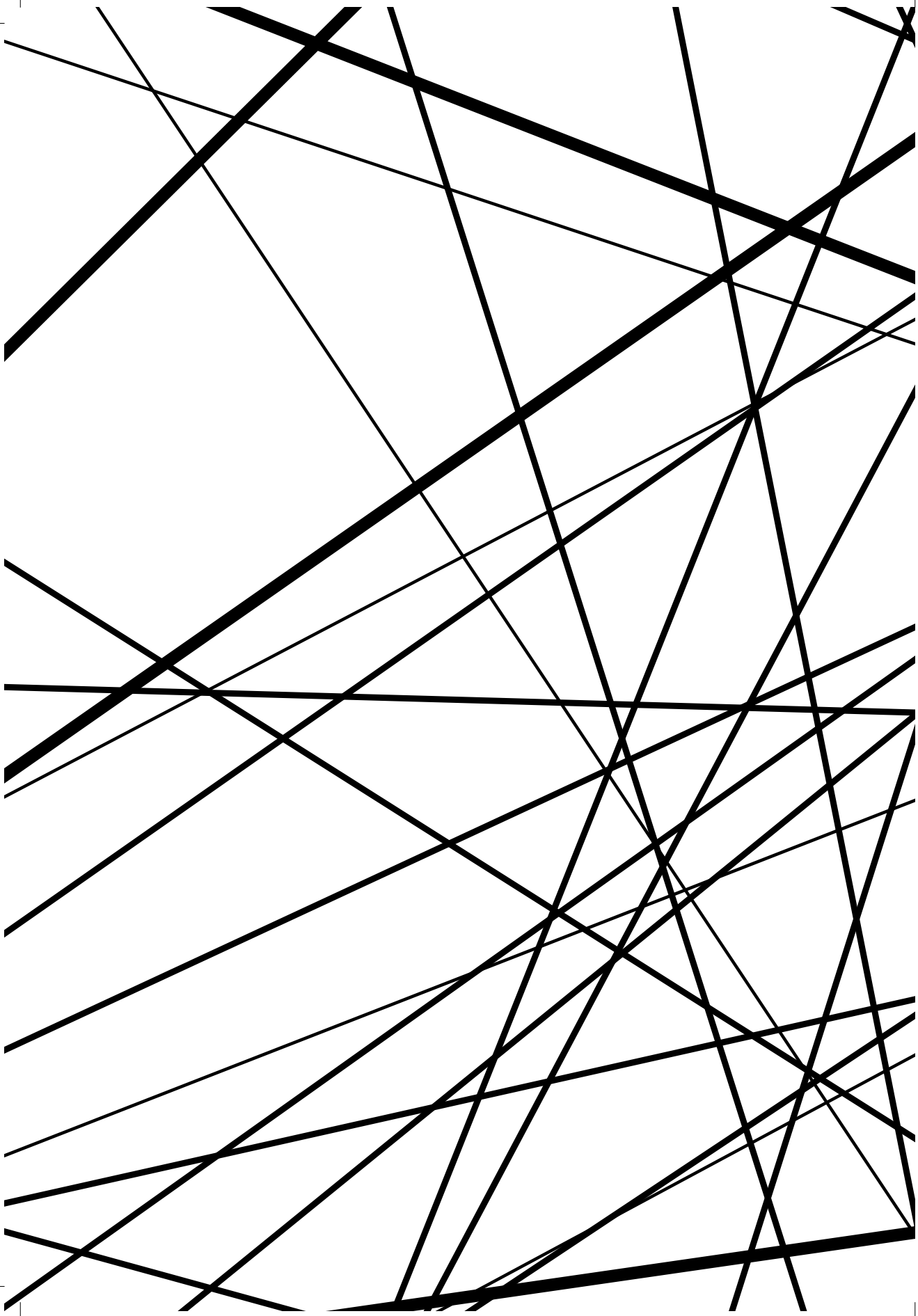
Appendix 2. Continued

Journals	Articles (n)	Reporting quality (number per category)	Risk of bias (number per category)
Medical journals (Continued)			
PlosMedicine	0	–	–
British Medical Journal	0	–	–
Journal of the National Cancer Institute	2	2 high	1 moderate 1 high
Archives of Internal Medicine/ JAMA Internal Medicine	1	1 high	1 low
American Journal of Respiratory and Critical care Medicine	1	1 moderate	1 high
Journal of Allergy and Clinical Immunology	12	5 moderate 7 high	1 low 1 moderate 10 high
Canadian Medical Association Journal	0	–	–
Clinical Cancer research	7	1 moderate 6 high	7 high
Annals of Surgery	-	0	0
American Journal of Clinical Nutrition	2	2 high	1 low 1 high
Annals of Oncology	18	6 moderate 12 high	1 low 17 high
Allergy	3	2 moderate 1 high	3 high
BMC Med	0	–	–



PART 3

Quality of evidence and clinical practice guidelines for chronic rhinosinusitis



CHAPTER 7.1

Nasal endoscopy is recommended for diagnosing adults with chronic rhinosinusitis

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Otolaryngol Head Neck Surg. 2014;3:359-64

Author contributions

Wuister AM, Goto NA, Oostveen EJ, de Jong WU, van der Valk ES: Construction of the search strategy, retrieval of articles, selection of relevant articles, assessment of study quality, extraction of study data, analysis and interpretation of data, drafting figures and tables, drafting manuscript, revision of the manuscript, final approval of the version to be published.

Kaper NM: Formulating clinical question, selection of relevant articles, assessment of study quality, extraction of study data, analysis and interpretation of data, drafting figures and tables, drafting manuscript, revision of the manuscript, final approval of the version to be published.

Aarts MCJ: Formulating clinical question, analysis and interpretation of data, drafting figures and tables, drafting manuscript, revision of the manuscript, final approval of the version to be published.

Grolman W: Analysis and interpretation of data, revision of the manuscript, final approval of the version to be published.

van der Heijden GMJG: Design of study, analysis and interpretation of data, revision of the manuscript, final approval of the version to be published, supervision of study.

ABSTRACT

Objective: To assess the diagnostic value of nasal endoscopic findings in adults suspected of chronic rhinosinusitis.

Methods: A comprehensive search in PubMed, EMBASE, and the Cochrane Library was performed up to March 5, 2013. Articles that assessed the diagnostic value of nasal endoscopy in adults suspected of chronic rhinosinusitis were included. For selected articles, the study design was assessed for applicability and risk of bias. Prevalence, positive, and negative predictive values were extracted from reported data.

Results: Out of 3899 unique publications, we included 3 diagnostic studies with a high applicability and a low or moderate risk of bias for data extraction. They showed a prevalence of chronic rhinosinusitis (diagnosed with computed tomography) of 0.40 to 0.56. Compared with posterior probabilities we found an added value for ruling in chronic rhinosinusitis by a positive nasal endoscopy of 25% to 28% and an added value for ruling out chronic rhinosinusitis by a negative nasal endoscopy of 5% to 30%.

Conclusions: Computed tomography is not considered necessary in case of a positive nasal endoscopy. While nasal endoscopy cannot rule out chronic rhinosinusitis, we advise computed tomography only for patients with a prolonged or complicated course of rhinosinusitis.

CLINICAL SCENARIO

A 33-year-old male visits your ear-nose-throat clinic with complaints of decreased smell, facial fullness and postnasal drip since 6 months. He has healthy and complete dentition, has no relevant medical history and does not use medication. You consider the diagnosis chronic rhinosinusitis and intend to perform a nasal endoscopy. You wonder what the value of such procedure is, in addition to his clinical symptoms, to support the diagnosis and start pharmacological treatment.

BACKGROUND

Chronic rhinosinusitis (CRS) is a common disease with an estimated prevalence varying from 3% to 16%.[1] According to the American Association of Otolaryngology—Head and Neck Surgery (AAO-HNS) 2007 practice guideline, CRS is defined by the presence of at least 2 of the following symptoms for a minimum of 12 weeks: nasal congestion, nasal discharge, facial pain/pressure, and hyposmia. In addition, inflammation should be documented by either nasal endoscopy or radiographic imaging of the paranasal sinuses. Endoscopic findings suspect for CRS are purulent mucus and edema at the middle meatus or ethmoid region or polyps.[2] Nasal endoscopy is a simple, fast, and relatively cheap assessment that carries low patient burden. Currently, computed tomography (CT) scanning of the paranasal sinuses is considered as the reference standard in diagnosing CRS.[3] For radiographic staging of CRS the Lund-MacKay system is recommended.[3] This system produces a numerical value between 0 and 24 reflecting the degree of opacification of the paranasal sinuses.[4] In national and international guidelines nasal endoscopy is either recommended or considered an option for diagnosing CRS; however, the diagnostic value and clinical consequences of either positive or negative findings remain unclear.[1,2,5,6]

METHODS

Searching for Evidence

We systematically evaluated the evidence base on the diagnostic value of nasal endoscopy in adults suspected of chronic rhinosinusitis. That is, given the prior probability (or prevalence) of chronic rhinosinusitis, does the risk of chronic rhinosinusitis change with positive or negative nasal endoscopic findings?

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Processed on: 20-12-2019

Retrieving Studies

Through a comprehensive systematic search (up to March 5, 2013) assisted by our clinical librarian, we retrieved 3899 unique records from PubMed, Embase, and the Cochrane Library. We used the search terms nasal endoscopy and rhinosinusitis with relevant synonyms. The full search syntax is displayed in Appendix 1. Three authors (A.W., N.G., and W.J.) independently screened title and abstract, removed duplicate publications, and selected studies that assessed the diagnostic value of nasal endoscopy in adult patients suspected of chronic rhinosinusitis. Animal or laboratory studies, therapeutic studies, studies in children, case reports, systematic reviews, and opinion papers were excluded. Through full-text screening three authors (A.W., N.G., and E.O.) independently selected articles reporting on nasal endoscopic findings in patients suspected of chronic rhinosinusitis (Figure 1). The article retrieval was completed by cross reference checking in Scopus and Web of Science for selected articles, while citations of retrieved reviews, meta-analyses, and guidelines on rhinosinusitis were screened for omitted studies. The similar procedure was followed to check for eligibility of articles that were thereby retrieved. Initial disagreements on eligibility and selection of articles were resolved by discussion and their inclusion is based on a full consensus.

Assessing Studies

Using predefined criteria, 5 authors (N.G., A.W., E.O., E.V., and N.K.) independently evaluated the design of studies reported in the included articles on applicability and risk of bias (RoB). When item information for the assessment of applicability or RoB item was not or not clearly reported, we rated it as insufficient and considered it as not satisfied. When the reporting allowed assessment, we rated it as either satisfied or not satisfied. Authors resolved their initial disagreements by discussion. Assessment of the applicability involved evaluation of study design characteristics for appropriateness of patients, notably (1) adults suspected of chronic rhinosinusitis; index test(s), notably (2) nasal endoscopy; and the outcome, notably (3) confirmation of chronic rhinosinusitis using a reference test. Studies were classified as highly applicable if they satisfied all the aspects of our 3-part question, moderate if they satisfied 2, and low if they satisfied only 1.

Assessment of the RoB involved evaluation of the study design characteristics for selection bias, notably (1) inclusion of an inception cohort; (2) adequate reference standard and information bias, notably (3) mutual blinding of assessment of index and reference test(s); and standardization of (4) index test(s) and (5) outcome (reference test) and (6) completeness of reported data. Studies were classified as low RoB if they satisfied criteria 1 and 2 plus all other study design features, moderate RoB if they satisfied criteria 1 and 2 but failed on 1 or 2 of the other 4 features, and the remainder was classified as high RoB. We aimed to include studies for data extraction with a high and moderate applicability and low and moderate RoB.

Extraction and Analysis of Study Data

For the included articles 2 authors (W.J., N.K.) independently extracted data. We aimed to extract and recalculate the reported true and false positive and negative results for the index test. From this we (re)calculated the prior probability (or prevalence) and the predictive values for a positive (PPV) and a negative (NPV) index test, with accompanying 95% confidence intervals (95% CI). By comparing the prior and posterior probabilities of a positive (PPV) or negative (NPV) index test, we evaluated whether nasal endoscopic findings are of added value for either confirming or ruling out CRS. We excluded papers from analysis if there were no such data reported, while we present the findings as originally reported if the necessary data could not be (re)calculated.

RESULTS

Retrieving Studies

Our initial literature search yielded 7041 records. After removing duplicates 3899 unique publications remained for title and abstract screening (Figure 1). Of these, 22 articles were identified as potentially eligible for study assessment during screening of title and abstract, and their full texts were retrieved. Cross reference checking revealed no additional articles. Based on full text evaluation, 7 studies were included for study assessment. Citations of excluded articles can be found in Appendix 2.

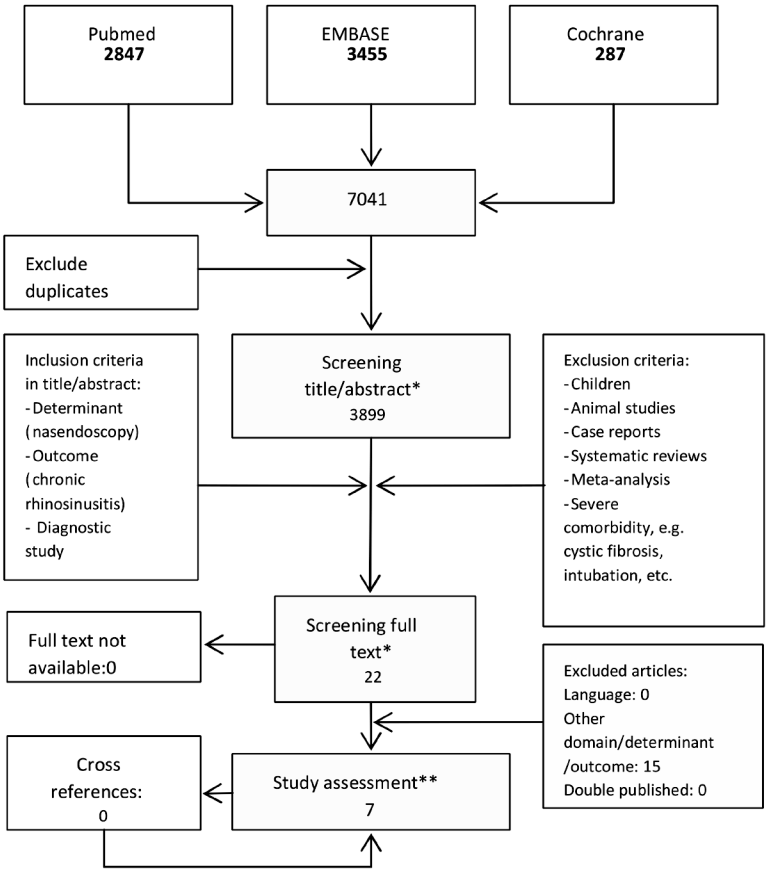
Assessing Studies

Three studies provided moderate applicability, of which 2 were excluded from further analysis because patients were included after previous sinus surgery and 1 was excluded because it failed to report CRS as an outcome.[7-9] One study carried a high RoB and was excluded.[10] Therefore 3 studies remained for extraction and analysis of data: Bhattacharyya et al was rated with a high applicability and a low RoB.[11] Stankiewicz et al and Agius et al were rated with a high applicability and a moderate RoB (Table 1).[12,13]

Extraction and Analysis of Study Data

The data reported in all 3 included studies include or allow to calculate the prior probability (or prevalence) for all study patients and the true and false positive and negative results for the index test. These data are presented in Table 2. We compared the prior probabilities with posterior probabilities of a positive nasal endoscopy (PPV; positive predictive value) or negative nasal endoscopy (NPV; negative predictive value) to evaluate whether nasal endoscopic findings are of added value for either confirming or ruling out CRS (Figure 2).

Figure 1. Flowchart (March 5, 2013)



Legend:
*, based on agreement among 3 independent authors
**, based on agreement among 5 independent authors

For inclusion of 178 patients, Bhattacharyya et al used the definition of CRS according to the AAO-HNS 2007 guideline and included an additional 24 patients who did not meet these criteria.[2,11] All patients were 18 years of age or above, those with prior sinus surgery were excluded. Previous medical treatment was not reported.

CT scans as reference standard were assessed using the Lund-MacKay score for which a score of at least 4 was required to confirm the presence of CRS.[4] Accordingly, CRS was confirmed in 80 of 202 patients, namely, a prior probability (or prevalence) of CRS of 0.40 (95% CI, 0.33-0.46). Nasal endoscopy was positive when pus or polyps were observed. The prevalence of a positive endoscopic finding (or PPV) was 36 out of 55 or 0.65 (95% CI, 0.52-

Table 1. Study assessment

	Applicability				Risk of bias						
Study characteristics	Domain	Index test	Outcome	Overall	Inception cohort	Reference standard	Blinding for index/ Reference test status	Index test standardization	Reference test standardization	Complete data	RoB score
Bhattacharyya et al[11]	•	•	•	H	•	•	•	•	•	•	L
Stankiewicz et al[12]	•	•	•	H	•	•	□	•	•	•	L
Agius et al[13]	•	•	•	H	•	•	□	□	•	•	M
Amine et al[10]	•	•	•	H	○	•	□	□	•	○	H
Ferguson et al[7]	○	•	•	M	•	•	□	•	•	•	L
Rosbe et al[8]	○	•	•	M	•	•	□	•	○	•	M
Kasapoglu et al[9]	•	•	○	M	•	•	□	□	○	•	H

	Applicability
Domain	Included adult patients (≥18 years) with symptoms suggestive for rhinosinusitis ≥12 weeks, no previous sinus surgery
Index test	Nasal endoscopy (flexible or rigid)
Outcome	Confirmation of the diagnosis using a reference test
	Risk of bias
Inception cohort	Inclusion of patients that are initially free of the suspected outcome
Reference standard	Computed tomography
Blinding for reference/index test status	Index test documented without knowledge of reference test status and vice versa
Index test standardization	Protocolled, uniform assessment of index test
Reference test standardization	Protocolled, uniform assessment of reference test
Complete data	Adequate reporting of all included and excluded patients

Legend:
• , satisfied
○ , not satisfied
□ , insufficient information/unclear
RoB, risk of bias
H, high
M, moderate
L, low

0.77), while prevalence of a negative endoscopic finding (or NPV) was 44 out of 147 or 0.30 (95% CI, 0.23-0.38). By comparing prior and posterior probabilities we found an added value for ruling in CRS by a positive endoscopic finding of 25% and for ruling out CRS by a negative endoscopic finding of 30%.

Based on questionnaire results on sinonasal symptoms, Stankiewicz et al included 78 patients of 16 years of age or above.[12] Patients with at least 3 symptoms without prior prolonged antibiotic treatment were included. Prior sinus surgery was an exclusion criterion.

CT scans as reference standard were assessed using the rating system according to Metson and Gliklich, for which at least 1 had to be positive to confirm the presence of CRS.[14] Accordingly, CRS was confirmed in 37 out of 78 patients, namely, a prior probability (or prevalence) of CRS or of 0.47 (95% CI, 0.37-0.58). Nasal endoscopy was considered positive when pus, polyps, erythema, or edema were observed. The prevalence for a positive endoscopic finding (or PPV) was 17 out of 23 or 0.74 (95% CI, 0.53-0.88), while prevalence for a negative endoscopic finding (or NPV) was 20 out of 55 or 0.36 (95% CI, 0.25-0.50). We compared prior and posterior probabilities and found an added value for ruling in CRS by a positive endoscopic finding of 27% and for ruling out CRS by a negative endoscopic finding of 17%.

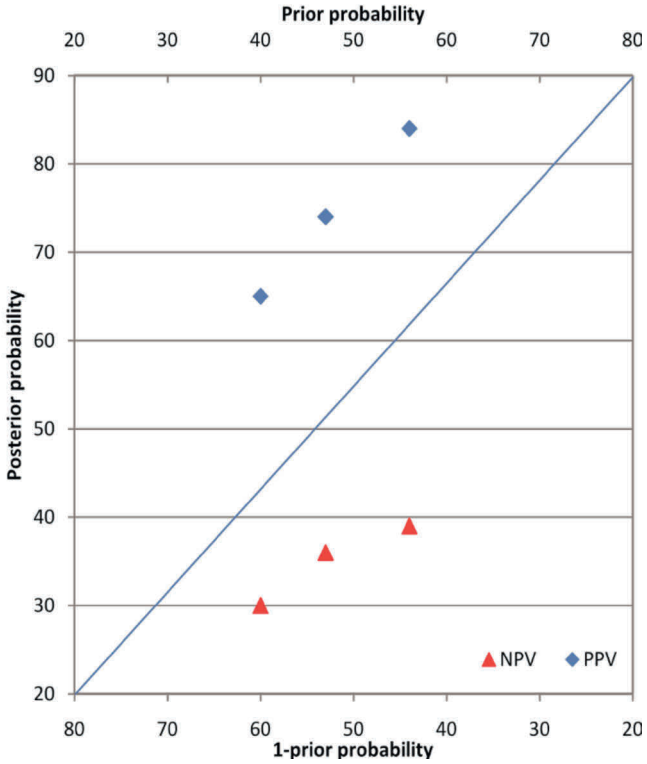
Agius et al included 305 patients of 12 years of age or above, according to the AAO-HNS 1997 definition of CRS while they had no prior sinus surgery.[13,15] All patients failed prior maximal medical therapy. CT scans as reference standard were assessed using the Lund-McKay score, for which a score of at least 2 was required to confirm the presence of CRS. Accordingly, CRS was confirmed in 172 out of 305 patients, namely, a prior probability (or prevalence) of CRS of 0.56 (95% CI, 0.51-0.62). Nasal endoscopy was considered positive if pus or polyps were observed. The prevalence for a positive endoscopic finding (or PPV) was 100 out of 119 or 0.84 (95% CI, 0.76-0.90), while prevalence for a negative nasal endoscopic finding (or NPV) was 72 out of 186 or 0.39 (95% CI, 0.32-0.46). By comparing the prior and posterior probabilities we found an added value for ruling in CRS by a positive endoscopic finding of 28% and for ruling out CRS by a negative endoscopic finding of 5%.

Table 2. Results

Study characteristics	Bhattacharyya et al[11]	Stankiewicz et al[12]	Agius et al[13]
Applicability	H	H	H
Risk of bias	L	L	M
Prior probability (95% CI)	0.40 (0.33-0.46)	0.47 (0.37-0.58)	0.56 (0.51-0.62)
PPV (95% CI)	0.65 (0.52-0.77)	0.74 (0.53-0.88)	0.84 (0.76-0.90)
Added positive value (%)	25	27	28
1-Prior probability (95% CI)	0.60 (0.54-0.67)	0.53 (0.42-0.63)	0.44 (0.38-0.49)
NPV (95% CI)	0.30 (0.23-0.38)	0.36 (0.25-0.50)	0.39 (0.32-0.46)
Added negative value (%)	30	17	5

Legend:
H, high
M, moderate
L, low
CI, confidence interval
PPV, positive predictive value
NPV, negative predictive value

Figure 2. Comparison of prior probability (prevalence of CRS) and 1-prior probability (prevalence of the absence of CRS) with posterior probabilities for positive (PPV) or negative (NPV) nasal endoscopic findings



Legend:

Diagonal indicates no added value of nasal endoscopy

CRS, chronic rhinosinusitis

NPV, negative predictive value

PPV, positive predictive value

COMMENT

We performed a comprehensive systematic search to find the best available evidence for nasal endoscopy in the diagnosis of CRS. Our search yielded 3 articles with a high applicability, which makes the results applicable in daily practice. The risk of bias was low or moderate. For a prevalence of CRS varying from 0.40 to 0.56, a positive nasal endoscopy has an added value for confirming CRS of 25% to 28% and a negative nasal endoscopy has an added value of ruling out CRS of 5% to 30%. Some aspects need further consideration.

First, the prior probabilities differ between studies, this might be due to the use of slightly different inclusion criteria and inclusion of patients failing prior treatment.[13] Our results show that as the prior probability of CRS increases, the added negative value of nasal endoscopy declines (Figure 2).

Second, for the evaluation of nasal endoscopy, we considered edema and erythema (without purulence) nonspecific symptoms of CRS, and we only extracted results on pus and polyps.2 For 1 study it was not possible to make this distinction.[12]

Third, we have to consider that endoscopy is best performed using a rigid scope, as used in 2 studies.[11,12,16] Agius et al. did not report on the type of scope.[13] After contacting the author, he reported that a flexible endoscope was used, which might have had impact on the low added value for ruling out CRS.

Fourth, different cut-off points and grading systems for assessing CT scans to diagnose CRS were used,[11-13] which might explain differences in prevalence and added value of nasal endoscopy.

Finally, CT is the accepted reference standard in the diagnosis of CRS, but has diagnostic impairments, due to false positive results.[3] This could distort our findings and lead to an underestimation of the diagnostic value of nasal endoscopy and especially the NPV of nasal endoscopy.

CONCLUSION AND RECOMMENDATION

With a comprehensive search for the value of nasal endoscopy in the diagnosis of CRS we identified 3 studies with a high applicability and low or moderate risk of bias. All studies used CT scans as a reference standard. Given a prior probability of 0.40 to 0.56, a positive nasal endoscopy has an added value for confirming CRS of 25% to 28%. A negative nasal endoscopy has an added value of ruling out CRS of 5% to 30%. Based on these results, we recommend not to order CT after a positive endoscopy; it is expensive and does not provide conclusive information. While nasal endoscopy cannot rule out chronic rhinosinusitis, we advise computed tomography only for patients with a prolonged or complicated course of rhinosinusitis.

Translating Evidence into Practice

We informed the patient presenting to our clinic with complaints of chronic rhinosinusitis that in case of positive findings on nasal endoscopy, a computed tomography scan is neither conclusive nor necessary. We further explain that in case of negative findings, we want to further evaluate him after 6 weeks only if complaints persist or worsen; then we will decide to order a CT scan.

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13. Agius AM. Chronic sinusitis in Malta-correlation between symptoms and CT scan. Rhinology 2010;48:59-64.
14. Metson R, Gliklich RE, Stankiewicz JA, et al. Comparison of sinus computed tomography staging systems. *Otolaryngol Head Neck Surg* 1997;117:372-379.
15. AAO HNS 1997: Report of the Rhinosinusitis Task Force Committee, Alexandria Virginia, August 17 1996. *Otolaryngol Head Neck Surg* 1997;113:S1-S68.
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APPENDICES

Appendix 1. Search strategy

Database	search	5-3-2013	Hits
Pubmed	1	(sinus[Title/Abstract] OR sinuse[Title/Abstract] OR sinuses[Title/Abstract] OR sinuso[Title/Abstract] OR rhinosinus[Title/Abstract] OR rhinosinuses[Title/Abstract] OR rhino-sinus[Title/Abstract] OR rhino-sinuses[Title/Abstract] OR sinusital[Title/Abstract] OR sinusite[Title/Abstract] OR sinonasal[Title/Abstract] OR sino-nasal[Title/Abstract] OR sinusal[Title/Abstract] OR maxillo[Title/Abstract] OR maxillar[Title/Abstract] OR maxillary[Title/Abstract] OR sinal[Title/Abstract] OR paranasal[Title/Abstract] OR para-nasal[Title/Abstract])	
	2	Nasal [Title/Abstract] OR nose[Title/Abstract]	
	3	cavity[Title/Abstract] OR cavities[Title/Abstract]	
	4	2 AND 3	
	5	1 OR 4	
	6	(infection[Title/Abstract] OR infections[Title/Abstract] OR infect[Title/Abstract] OR infects[Title/Abstract] OR infected[Title/Abstract] OR infectious[Title/Abstract] OR infecting[Title/Abstract] OR inflame[Title/Abstract] OR inflames[Title/Abstract] OR inflamed[Title/Abstract] OR inflaming[Title/Abstract] OR inflammation[Title/Abstract] OR inflammations[Title/Abstract] OR inflammatory[Title/Abstract] OR inflammative[Title/Abstract] OR infective[Title/Abstract] OR infectives[Title/Abstract])	
	7	5 AND 6	
	8	(rhinosinusitis[Title/Abstract] OR rhinosinusitides[Title/Abstract] OR rhinosinusitus[Title/Abstract] OR sinusitis[Title/Abstract] OR sinusites[Title/Abstract] OR sinusitides[Title/Abstract] OR sinusitus[Title/Abstract] OR rhino-sinusitis[Title/Abstract] OR rhino-sinusitides[Title/Abstract] OR rhino-sinusitus[Title/Abstract] OR maxillitis[Title/Abstract] OR pansinusitis[Title/Abstract] OR aerosinusitis[Title/Abstract])	
	9	7 OR 8	

Appendix 1. Continued

Database	search	5-3-2013	Hits
	10	(nasendoscope[Title/Abstract] OR nasendoscoped[Title/Abstract] OR nasendoscopes[Title/Abstract] OR nasendoscopic[Title/Abstract] OR nasendoscopical[Title/Abstract] OR nasendoscopically[Title/Abstract] OR nasendoscopy[Title/Abstract] OR nasendoscopies[Title/Abstract] OR nasoendoscope[Title/Abstract] OR nasoendoscoped[Title/Abstract] OR nasoendoscopes[Title/Abstract] OR nasoendoscopic[Title/Abstract] OR nasoendoscopical[Title/Abstract] OR nasoendoscopically[Title/Abstract] OR nasoendoscopy[Title/Abstract] OR nasoendoscopies[Title/Abstract] OR rhinoscope[Title/Abstract] OR rhinoscoped[Title/Abstract] OR rhinoscopes[Title/Abstract] OR rhinoscopic[Title/Abstract] OR rhinoscopical[Title/Abstract] OR rhinoscopically[Title/Abstract] OR rhinoscopy[Title/Abstract] OR rhinoscopies[Title/Abstract] OR rhinoscopeguided[Title/Abstract] OR rhinoscopia[Title/Abstract] OR rhinoscopic/endoscopic[Title/Abstract] OR sinoscope[Title/Abstract] OR sinoscoped[Title/Abstract] OR sinoscopes[Title/Abstract] OR sinoscopic[Title/Abstract] OR sinoscopical[Title/Abstract] OR sinoscopically[Title/Abstract] OR sinoscopy[Title/Abstract] OR sinoscopies[Title/Abstract] OR sinoscopist[Title/Abstract] OR sinuscope[Title/Abstract] OR sinuscoped[Title/Abstract] OR sinuscopes[Title/Abstract] OR sinuscopic[Title/Abstract] OR sinuscopical[Title/Abstract] OR sinuscopically[Title/Abstract] OR sinuscopy[Title/Abstract] OR sinuscopies[Title/Abstract] OR endoscope[Title/Abstract] OR endoscoped[Title/Abstract] OR endoscopes[Title/Abstract] OR endoscopic[Title/Abstract] OR endoscopy[Title/Abstract] OR endoscopically[Title/Abstract] OR endoscopes[Title/Abstract] OR endoscopies OR scope[Title/Abstract] OR scoped[Title/Abstract] OR scopes[Title/Abstract] OR scopic[Title/Abstract] OR scopical[Title/Abstract] OR scopically[Title/Abstract] OR scopy[Title/Abstract] OR scopies[Title/Abstract])	
	11	9 AND 10	2847
EMBASE	1	(sinus:ti,ab OR sinuse:ti,ab OR sinuses:ti,ab OR sinuso:ti,ab OR rhinosinus:ti,ab OR rhinosinuses:ti,ab OR rhino-sinus:ti,ab OR rhino-sinuses:ti,ab OR sinusital:ti,ab OR sinusite:ti,ab OR sinonasal:ti,ab OR sino-nasal:ti,ab OR sinusal:ti,ab OR maxillo:ti,ab OR maxillar:ti,ab OR maxillary:ti,ab OR sinal:ti,ab OR paranasal:ti,ab OR para-nasal:ti,ab)	
	2	nasal:ti,ab OR nose:ti,ab	
	3	cavity:ti,ab OR cavities:ti,ab	
	4	2 AND 3	

Appendix 1. Continued

Database	search	5-3-2013	Hits
	5	1 OR 4	
	6	(infection:ti,ab OR infections:ti,ab OR infect:ti,ab OR infects:ti,ab OR infected:ti,ab OR infectious:ti,ab OR infecting:ti,ab OR inflame:ti,ab OR inflames:ti,ab OR inflamed:ti,ab OR inflaming:ti,ab OR inflammation:ti,ab OR inflammations:ti,ab OR inflammatory:ti,ab OR inflammative:ti,ab OR infective:ti,ab OR infectives:ti,ab)	
	7	5 AND 6	
	8	(rhinosinusitis:ti,ab OR rhinosinusitides:ti,ab OR rhinosinusitus:ti,ab OR sinusitis:ti,ab OR sinusites:ti,ab OR sinusitides:ti,ab OR sinusitus:ti,ab OR rhino-sinusitis:ti,ab OR rhino-sinusitides:ti,ab OR rhino-sinusitus:ti,ab OR maxillitis:ti,ab OR pansinusitis:ti,ab OR aerosinusitis:ti,ab)	
	9	7 OR 8	
	10	(nasendoscope:ti,ab OR nasendoscoped:ti,ab OR nasendoscopes:ti,ab OR nasendoscopic:ti,ab OR nasendoscopical:ti,ab OR nasendoscopically:ti,ab OR nasendoscopy:ti,ab OR nasendoscopies:ti,ab OR nasoendoscope:ti,ab OR nasoendoscoped:ti,ab OR nasoendoscopes:ti,ab OR nasoendoscopic:ti,ab OR nasoendoscopical:ti,ab OR nasoendoscopically:ti,ab OR nasoendoscopy:ti,ab OR nasoendoscopies:ti,ab OR rhinoscope:ti,ab OR rhinoscoped:ti,ab OR rhinoscopes:ti,ab OR rhinoscopic:ti,ab OR rhinoscopical:ti,ab OR rhinoscopically:ti,ab OR rhinoscopy:ti,ab OR rhinoscopies:ti,ab OR rhinoscopeguided:ti,ab OR rhinoscopia:ti,ab OR rhinoscopic/endoscopic:ti,ab OR sinoscope:ti,ab OR sinoscoped:ti,ab OR sinoscopes:ti,ab OR sinoscopic:ti,ab OR sinoscopical:ti,ab OR sinoscopically:ti,ab OR sinoscopy:ti,ab OR sinoscopies:ti,ab OR sinoscopist:ti,ab OR sinuscope:ti,ab OR sinuscoped:ti,ab OR sinuscopes:ti,ab OR sinuscopic:ti,ab OR sinuscopical:ti,ab OR sinuscopically:ti,ab OR sinuscopy:ti,ab OR sinuscopies:ti,ab OR endoscope:ti,ab OR endoscoped:ti,ab OR endoscopes:ti,ab OR endoscopic:ti,ab OR endoscopy:ti,ab OR endoscopically:ti,ab OR endoscopes:ti,ab OR endoscopies OR scope:ti,ab OR scoped:ti,ab OR scopes:ti,ab OR scopic:ti,ab OR scopical:ti,ab OR scopically:ti,ab OR scopy:ti,ab OR scopies:ti,ab)	
	11	9 AND 10	3016

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Appendix 1. Continued

Database	search	5-3-2013	Hits
Cochrane	1	sinus:ti,ab,kw OR sinuse:ti,ab,kw OR sinuses:ti,ab,kw OR sinuso:ti,ab,kw OR rhinosinus:ti,ab,kw OR rhinosinuses:ti,ab,kw OR rhino-sinus:ti,ab,kw OR rhino-sinuses:ti,ab,kw OR sinusital:ti,ab,kw OR sinusite:ti,ab,kw OR sinonasal:ti,ab,kw OR sino-nasal:ti,ab,kw OR sinusal:ti,ab,kw OR maxillo:ti,ab,kw OR maxillar:ti,ab,kw OR maxillary:ti,ab,kw OR sinal:ti,ab,kw OR paranasal:ti,ab,kw OR para-nasal:ti,ab,k	
	2	nasal:ti,ab,kw OR nose:ti,ab,kw	
	3	cavity:ti,ab,kw OR cavities:ti,ab,kw	
	4	2 AND 3	
	5	1 OR 4	
	6	Infection:ti,ab,kw OR infections:ti,ab,kw OR infect:ti,ab,kw OR infects:ti,ab,kw OR infected:ti,ab,kw OR infectious:ti,ab,kw OR infecting:ti,ab,kw OR inflame:ti,ab,kw OR inflames:ti,ab,kw OR inflamed:ti,ab,kw OR inflaming:ti,ab,kw OR inflammation:ti,ab,kw OR inflammations:ti,ab,kw OR inflammatory:ti,ab,kw OR inflammative:ti,ab,kw OR infective:ti,ab,kw OR infectives:ti,ab,kw	
	7	5 AND 6	
	8	rhinosinusitis:ti,ab,kw OR rhinosinusitides:ti,ab,kw OR rhinosinusitus:ti,ab,kw OR sinusitis:ti,ab,kw OR sinusites:ti,ab,kw OR sinusitides:ti,ab,kw OR sinusitus:ti,ab,kw OR rhino-sinusitis:ti,ab,kw OR rhino-sinusitides:ti,ab,kw OR rhino-sinusitus:ti,ab,kw OR maxillitis:ti,ab,kw OR pansinusitis:ti,ab,kw OR aerosinusitis:ti,ab,kw	
	9	7 OR 8	

Appendix 1. Continued

Database	search	5-3-2013	Hits
	10	nasendoscope:ti,ab,kw OR nasendoscoped:ti,ab,kw OR nasendoscopes:ti,ab,kw OR nasendoscopic:ti,ab,kw OR nasendoscopical:ti,ab,kw OR nasendoscopically:ti,ab,kw OR nasendoscopy:ti,ab,kw OR nasendoscopies:ti,ab,kw OR nasoendoscope:ti,ab,kw OR nasoendoscoped:ti,ab,kw OR nasoendoscopes:ti,ab,kw OR nasoendoscopic:ti,ab,kw OR nasoendoscopical:ti,ab,kw OR nasoendoscopically:ti,ab,kw OR nasoendoscopy:ti,ab,kw OR nasoendoscopies:ti,ab,kw OR rhinoscope:ti,ab,kw OR rhinoscoped:ti,ab,kw OR rhinoscopes:ti,ab,kw OR rhinoscopic:ti,ab,kw OR rhinoscopical:ti,ab,kw OR rhinoscopically:ti,ab,kw OR rhinoscopy:ti,ab,kw OR rhinoscopies:ti,ab,kw OR rhinoscopeguided:ti,ab,kw OR rhinoscopia:ti,ab,kw OR sinoscope:ti,ab,kw OR sinoscoped:ti,ab,kw OR sinoscopes:ti,ab,kw OR sinoscopic:ti,ab,kw OR sinoscopical:ti,ab,kw OR sinoscopically:ti,ab,kw OR sinoscopy:ti,ab,kw OR sinoscopies:ti,ab,kw OR sinoscopist:ti,ab,kw OR sinuscope:ti,ab,kw OR sinuscoped:ti,ab,kw OR sinuscopes:ti,ab,kw OR sinuscopic:ti,ab,kw OR sinuscopical:ti,ab,kw OR sinuscopically:ti,ab,kw OR sinuscopy:ti,ab,kw OR sinuscopies:ti,ab,kw OR endoscope:ti,ab,kw OR endoscoped:ti,ab,kw OR endoscopes:ti,ab,kw OR endoscopic:ti,ab,kw OR endoscopy:ti,ab,kw OR endoscopically:ti,ab,kw OR endoscopes:ti,ab,kw OR endoscopies:ti,ab,kw OR scope:ti,ab,kw OR scoped:ti,ab,kw OR scopes:ti,ab,kw OR scopic:ti,ab,kw OR scopical:ti,ab,kw OR scopically:ti,ab,kw OR scopy:ti,ab,kw OR scopies:ti,ab,kw	
	11	9 AND 10	287

Appendix 2. Reference list of excluded articles

1. Castellanos J, Axelrod D. Flexible fiberoptic rhinoscopy in the diagnosis of sinusitis. J *Allergy Clin Immunol* 1989;83:91-94.
2. Nass RL, Holliday RA, Reede DL. Diagnosis of surgical sinusitis using nasal endoscopy and computerized tomography. *Laryngoscope* 1989;99:1158-1160.
3. Berger G, Steinberg DM, Popovtzer A, Ophir D. Endoscopy versus radiography for the diagnosis of acute bacterial rhinosinusitis. *Eur Arch Otorhinolaryngol* 2005;262:416-422.
4. Kim HN, Kim YM, Choi HS. Diagnostic and therapeutic significance of sinoscopy in maxillary sinusitis. *Yonsei Med J* 1985;26:59-67.
5. Shahizon AM, Suraya A, Rozmnan Z, Aini AA, Gendeh BS. Correlation of computed tomography and nasal endoscopic findings in chronic rhinosinusitis. *Med J Malaysia* 2008;63:211-215.
6. Berger G, Berger RL. The contribution of flexible endoscopy for diagnosis of acute bacterial rhinosinusitis. *Eur Arch Otorhinolaryngol* 2011;268:235-240.
7. Kaplan BA, Kountakis SE. Diagnosis and pathology of unilateral maxillary sinus opacification with or without evidence of contralateral disease. *Laryngoscope* 2004;114:981-985.
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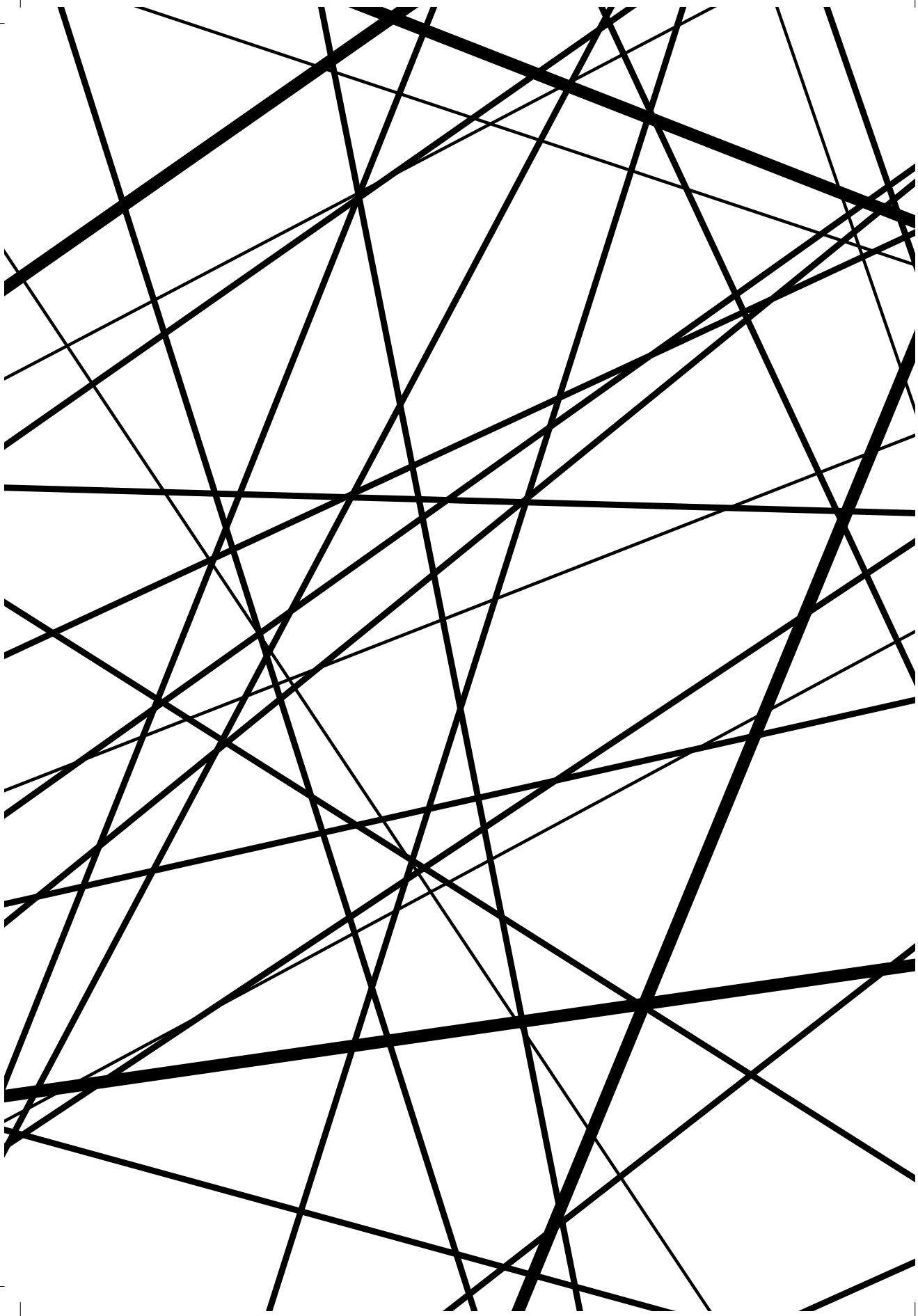
9. Jiang RS, Liang KL, Jang JW, Hsu CY. Bacteriology of endoscopically normal maxillary sinuses. J Laryngol Otol. 1999;113:825-828.
10. Orlandi RR, Terrell JE. Analysis of the adult chronic rhinosinusitis working definition. *Am J Rhinol* 2002;16:7-10.
11. Bera SP, Rao L. Nasal endoscopy in chronic/recurring sinusitis. *Auris Nasus Larynx* 1997;24:171-177.
12. Roberts DN, Hampal S, East CA, Lloyd GA. The diagnosis of inflammatory sinonasal disease. *J Laryngol Otol* 1995;109:27-30.
13. Benninger MS. Nasal endoscopy: its role in office diagnosis. *Am J Rhinol* 1997;11:177-180.
14. Schiappoli M, Le Pera C, Barbieri F, et al. The role of nasal endoscopy in the diagnosis of chronic rhinosinusitis in an allergology setting. *Allergy* 2010;65(Suppl.92):209–682.
15. Vining EM, Yanagisawa K, Yanagisawa E. The importance of preoperative nasal endoscopy in patients with sinonasal disease. *Laryngoscope* 1993;103:512-519.



CHAPTER 7.2

Inconclusive evidence that age predicts a prolonged or chronic course of acute rhinosinusitis in adults: a systematic review of the evidence base

Broeder TP, Grooteman KV, Overdijkink SB, Selhorst CE, Kaper NM, Grolman W, van der Heijden GJMG

Otolaryngol Head Neck Surg. 2014;3:365-70

Author contributions

Broeder TP, Grooteman KV, Overdijkink SB, Selhorst CE: Construction of the search strategy, retrieval of articles, selection of relevant articles, assessment of study quality, extraction of study data, analysis and interpretation of data, drafting figures and tables, drafting manuscript, revision of the manuscript, final approval of the version to be published.

Kaper NM: Formulating clinical question, selection of relevant articles, assessment of study quality, extraction of study data, analysis and interpretation of data, drafting figures and tables, drafting manuscript, revision of the manuscript, final approval of the version to be published.

Grolman W: Analysis and interpretation of data, revision of the manuscript, final approval of the version to be published.

van der Heijden GJMG: Design of study, analysis and interpretation of data, revision of the manuscript, final approval of the version to be published, supervision of study.

ABSTRACT

Objective: To review the evidence whether the risk for a prolonged or chronic course increases with age in adult patients with acute rhinosinusitis.

Methods: A comprehensive literature search in PubMed, EMBASE, and the Cochrane Library was performed on March 24, 2013, and articles were screened and selected using predefined inclusion and exclusion criteria. Articles reporting studies on age as a predictor for the course in patients with acute rhinosinusitis were included. For included articles, the design of reported studies was assessed for applicability and risk of bias. We aimed to extract hazard ratios for age as a continuous variable.

Results: Out of 13,382 unique publications, 3 articles with moderate risk of bias were included, with a maximum follow-up period of 30 days. The reported hazard ratios for recovery at 10, 15, and 30 days are 1.0 (95% confidence interval, 0.9-1.1) for age as a continuous variable, 0.86 (0.66-1.11) for age dichotomized at 38 years, and 0.58 (0.40-0.84) for age dichotomized for an increase with 20 years, respectively.

Conclusions: There is no evidence that age increases the risk for chronic rhinosinusitis in adult patients with acute rhinosinusitis. The literature is inconclusive that age increases the risk for a prolonged course of acute rhinosinusitis and, therefore, does not provide grounds for different management according to age of patients. As such, patients can be managed according to clinical practice guidelines with expectant observation and symptomatic treatment.

CLINICAL SCENARIO

A 68-year-old woman visits your ear-nose-throat outpatient clinic with symptoms of purulent nasal discharge, nasal obstruction, reduced smell, and facial pain for 3 days; she has had a fever in the last 1 day. Anterior rhinoscopy shows purulence, and you diagnose her with acute rhinosinusitis. You tend toward expectant management because of the self-limiting nature of the disease. However, you consider the patient's age might increase her risk for developing a prolonged or chronic rhinosinusitis and wonder whether you should deviate from clinical practice guidelines.

BACKGROUND

Acute rhinosinusitis (ARS) is a common diagnosis in general practice, with an incidence of 8.4% to 12% in Europe and 9% in the United States.[1] The disease is usually self-limiting and resolves within 7 to 10 days, irrespective of antibiotic treatment; therefore, antibiotic treatment is reserved for selected patients.[2-4] Severe complications are rare in untreated patients.[5] Acute rhinosinusitis can last up to 4 weeks; symptoms lasting for more than 4 weeks are referred to as prolonged rhinosinusitis, and symptoms persisting for 12 weeks are referred to as chronic rhinosinusitis (CRS).4 Acute rhinosinusitis and CRS both have significant adverse effects on quality of life.[6,7]

After 14 days, 71% of patients with ARS are cured and disease is recurrent or persisting in 10% to 20% of patients after 60 days.[3,8] After 1 year approximately 2% have chronic complaints.[9]

Predisposing factors for CRS that have been identified are nasal polyps, allergy, asthma and chronic obstructive pulmonary disease.[10] Previous studies show that the incidence of ARS is highest in those aged 25 to 44 years, and the prevalence of CRS is highest in those aged 30 to 60 years.[5,11] We aimed to assess the value of (increasing) age for the prediction of a prolonged or chronic course of ARS. This knowledge could help to identify patients with a worse prognosis, for which deviation from clinical practice guidelines could be considered.

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METHODS

Searching for Evidence

We systematically reviewed the evidence base to answer the following question: does (increasing) age in adult patients with acute rhinosinusitis increase the risk of a prolonged or chronic course?

Retrieving Studies

Assisted by our clinical librarian, we retrieved relevant publications from PubMed, EMBASE, and the Cochrane Library (up to March 24, 2013). We used the search terms rhinosinusitis and chronic or prolonged with relevant synonyms. Appendix 1 includes our search strategy.

Four authors (T.B., K.G., S.O., and C.S.) independently retrieved publications, removed duplicates, and screened titles and abstracts for of all unique publications using predefined selection criteria. Articles that reported on studies assessing predictors of a prolonged or chronic course in patients with acute rhinosinusitis were selected. Animal or laboratory studies, studies in immunocompromised patients or patients with acute fungal rhinosinusitis, case reports, systematic reviews and opinion papers were excluded. For final selection, the same 4 authors independently screened full texts of eligible titles in depth and with more detail.

We completed our search by cross-reference checking in Scopus and Web of Science. In addition, we hand-searched references of selected articles, related reviews, meta-analyses, and guidelines. The similar procedure was followed to check for eligibility of articles that were thereby retrieved. Authors resolved their initial disagreements on eligibility and selection of articles by discussion, and the selection is therefore based on a full consensus.

Assessing Studies

Using predefined criteria, five authors (T.B., K.G., S.O., C.S., and N.K.) independently assessed the design of studies reported in the included articles on applicability and risk of bias (RoB). They resolved initial disagreements by discussion. When for the assessment of item information was not available or not clearly reported, we rated it as insufficient and considered it as not satisfied. When the reporting allowed assessment, we rated it as either satisfied or not satisfied.

Assessment of the applicability involved evaluation of patients, notably (1) adults with ARS; the predictor, notably (2) age; and the outcomes, notably (3) a prolonged (4 weeks) or chronic course (12 weeks) of acute rhinosinusitis. Studies provide less direct evidence when they include only a particular subset of patients, assess a proxy for the predictor, or report on a surrogate for the outcome. Therefore, we classified studies as providing a high applicability if they satisfied all the aspects of our 3-part question, moderate if they satisfied 2, or low if they satisfied only 1.

Assessment of the RoB involved evaluation of the study design characteristics for selection bias, notably (1) inclusion of an inception cohort, and information bias, notably (2) blinding of predictor and (3) outcome, (4) standardization of predictor and (5) outcome assessments, and (6) completeness of reported data. The fewer of these aspects are satisfied by a study, the lower the trust we put in the viability of its findings, so we classified studies as low RoB if they satisfied criteria 1 and 4 or 5 of the other study design features and moderate RoB if they satisfied criteria 1 and 2 or 3 of the other 5 features. The remainder were classified as high RoB. We aimed to include studies for data extraction with a high and moderate applicability and low and moderate RoB.

Extraction and Analysis of Study Data

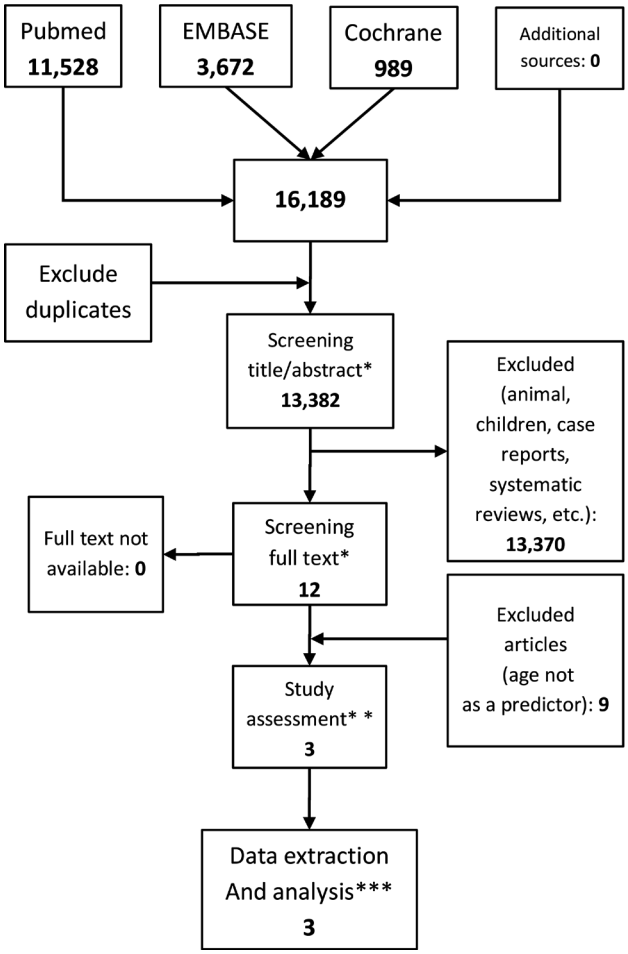
For the included articles, 3 authors (T.B., C.S., and N.K.) independently extracted data. We aimed to extract hazard ratios (HRs) on age as a continuous variable or for different age groups, with accompanying 95% confidence intervals (CI). We excluded studies from analysis if there were no such data reported, while we presented the findings as originally reported if the necessary data could not be (re)calculated.

RESULTS

Retrieving Studies

Our initial search yielded 16,189 articles, resulting in 13,382 unique publications for title and abstract screening. We selected 12 potentially eligible articles, and their full texts were retrieved. No additional articles were found with cross-reference checking. After applying selection criteria to their full texts, 3 articles were included for study assessment (Figure 1).

Figure 1. Flowchart (March 24, 2013)



Legend:
*, based on agreement among 4 independent authors
**, based on agreement among 5 independent authors
***, based on agreement among 3 independent authors

Assessing Studies

All 3 studies matched our research question in terms of evaluation of patients and determinant, but only 1 study reported a sufficiently long enough follow-up period of 30 days and, therefore, provided high applicability.[12] The other 2 studies reported a follow-up period of 15 and 10 days and, therefore, provided moderate applicability.[13,14] The overall RoB of the articles was moderate and therefore, all 3 studies were included for data extraction (Table 1).

Extraction and Analysis of Study Data

All three studies reported HRs for the probability of recovery. These data are presented in Table 2. Lindbæk and Hjortdahl included 86 patients aged 16 to 74 years with symptoms suggestive of ARS, confirmed by computed tomography (CT).[12] The cohort consisted of the treatment arm of a randomized controlled trial (RCT) comparing placebo and antibiotics. Three patients were excluded because they stopped treatment due to side effects. Recovery was defined by patients answering ''no'' to the question of having sinusitis in their diary, and follow-up was 30 days. In multivariate analysis, an increase in age with 20 years (12 standard deviations) was associated with a 42% decrease of recovery at 30 days.

De Sutter et al. included 382 patients 12 years or older with a respiratory tract infection, self-reported purulent rhinorrhea, and unilateral facial pain, pain in upper teeth, or a biphasic illness history.[13] The cohort consisted of both arms of a RCT comparing antibiotics and placebo; 81 withdrew from the study or were otherwise lost to follow-up. Recovery was defined by the patient indicating feeling ''well'' again in the diary. Age was dichotomized at the mean (37 years), and there was no association with the probability of recovery in the 15-day follow-up period.

Stalman et al. included 192 patients aged 15 to 65 years presenting with ARS as defined by the guidelines of the Dutch College of General Practitioners.[14,15] The cohort consisted of both arms of a RCT comparing antibiotics and placebo, and 15 participants were lost to follow-up. Recovery was defined by resolution of facial pain such as indicated by the patient. Age was not associated with the probability of recovery in 10 days.

Table 1. Study assessment

	Applicability						Risk of Bias							
Study Characteristics	Patients	Predictor	Outcome 1	Outcome 2	Follow-up 1	Follow-up 2	Overall	Inception Cohort	Blinding Predictor	Blinding Outcome	Predictor Standardization	Outcome Standardization	Complete Data	RoB
Lindbæk and Hjortdahl(1998) [12]	•	•	•	○	•	○	H	•	□	□	•	•	•	M
Stalman et al (2001)[14]	•	•	•	○	○	○	M	•	□	□	•	•	•	M
DeSutter et al (2006) [13]	•	•	•	○	○	○	M	•	□	□	•	•	•	M

	Applicability
Patients	Included patients >12 years with acute rhinosinusitis
Predictor	Age
Outcome 1	Prolonged rhinosinusitis
Outcome 2	Chronic rhinosinusitis
Follow-up 1	>4 weeks
Follow-up 2	>12 weeks

	Risk of Bias
Inception Cohort	Patients are initially free of outcome of interest
Blinding for Predictor	The observer/assessor of the outcome is blinded for the predictor status
Blinding for Outcome	The observer/assessor of the predictor is blinded for the outcome status
Predictor Standardization	Protocolled, uniform assessment/measurement
Outcome Standardization	Protocolled, uniform assessment/measurement
Complete Data	Adequate reporting of all included patients

Legend:
RoB, risk of bias
H, high
M, moderate
•, satisfied
○, not satisfied
□, insufficient information/unclear

Table 2. Results

Study	Applica-bility	RoB	Age	Follow-up, d	HR[a] (95% CI)	HR[b] (95% CI)
Lindbæk and Hjortdahl[12]	H	M	Dichotomized (120 years[c])	30	—	0.58 (0.40-0.84)
De Sutter et al[13]	M	M	Dichotomized (38 years)	15	0.86 (0.66-1.11)	—
Stalman et al[14]	M	M	Continuous	10	1.0 (0.9-1.1)	—

Legend:
CI, confidence interval
H, high
HR, hazard ratio (for recovery)
M, moderate
RoB, risk of bias
—, data not provided
a, univariate
b, multivariate
c, for patients with a difference of +12 standard deviations, which is an increase of 20 years

COMMENT

With our comprehensive search on age as a predictor for a prolonged or chronic course in patients with ARS we did not identify studies reporting on a chronic course of rhinosinusitis (>12 weeks). We included 3 articles with a moderate risk of bias with a follow-up of respectively 30, 15 and 10 days. The study with the longest follow-up period showed in multivariate analysis that an increase in age of 20 years was a risk factor for a prolonged time until recovery.[12] The studies with shorter follow-up periods did not confirm age as a risk factor.[13,14]

Some aspects of our findings need further consideration.First, Lindbæk and Hjortdahl diagnosed patients not only based on clinical findings but also by CT, which is not used for diagnosing uncomplicated ARS.[4,14] This renders the study less applicable to our patient.

Second, Stalman et al. included patients up to 65 years, so the risk in patients older than 65 years was not assessed.[14] This could influence results, because the increased risk might be present only in the age group older than 65 years, possibly leading to an underestimation of age as a risk factor. Furthermore, De Sutter et al. did not report the distribution of age, so it is unclear in which patients the risk was assessed.[13]

Third, all three studies obtained their study cohort from a RCT. Lindbæk and Hjortdahl included patients from the treatment arm and Stalman et al. and De Sutter et al. pooled data of both the treatment and the placebo-controlled arm.[12-14] The treatment allocation did not influence the prognosis in both studies, so it seems justified to pool these data. However, antibiotic treatment might still have a different effect in elderly patients.

Fourth, there was a substantial difference in duration of symptoms before inclusion. Stalman et al. included 34 patients (19%) with complaints between 14 days and 3 months, and the other studies included patients with complaints up to 30 days.[12-14] Stalman et al. assessed the effect of duration of complaints 14 days before inclusion on recovery and found an HR of 0.7 (95% CI, 0.5-1.0). De Sutter et al. found no significant effect of complaints 7 days at inclusion on recovery.[13]

Finally, Lindbæk and Hjortdahl and De Sutter et al. dichotomized age, using the mean or 2 times the standard deviation. [12,13] This statistical decision can be either data driven or based on existing evidence, but both studies do not discuss the decision. For clinical practice, it is more useful to assess age as a continuous variable or assess risks for different age groups.

CONCLUSION AND RECOMMENDATION

There is no evidence that age increases the risk for chronic rhinosinusitis in adult patients with acute rhinosinusitis. The literature is inconclusive that age increases the risk for a prolonged course of acute rhinosinusitis and, therefore, does not provide grounds for different management according to age of patients. As such, patients can be managed according to clinical practice guidelines with expectant observation and symptomatic treatment.[1,4]

Translating Evidence into Practice

We informed the patient presenting to our clinic with acute rhinosinusitis that to date, there is no evidence that her risk of a prolonged or chronic course of acute rhinosinusitis is increased. We explained that in most patients, symptoms resolve within 14 days and that transition to chronic rhinosinusitis is rare, irrespective of antibiotic treatment. We proposed symptomatic relief for her complaints and asked her to reconsult after 2 weeks if symptoms have not resolved, to which the patient agreed.

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APPENDIX

Appendix 1. Search strategy

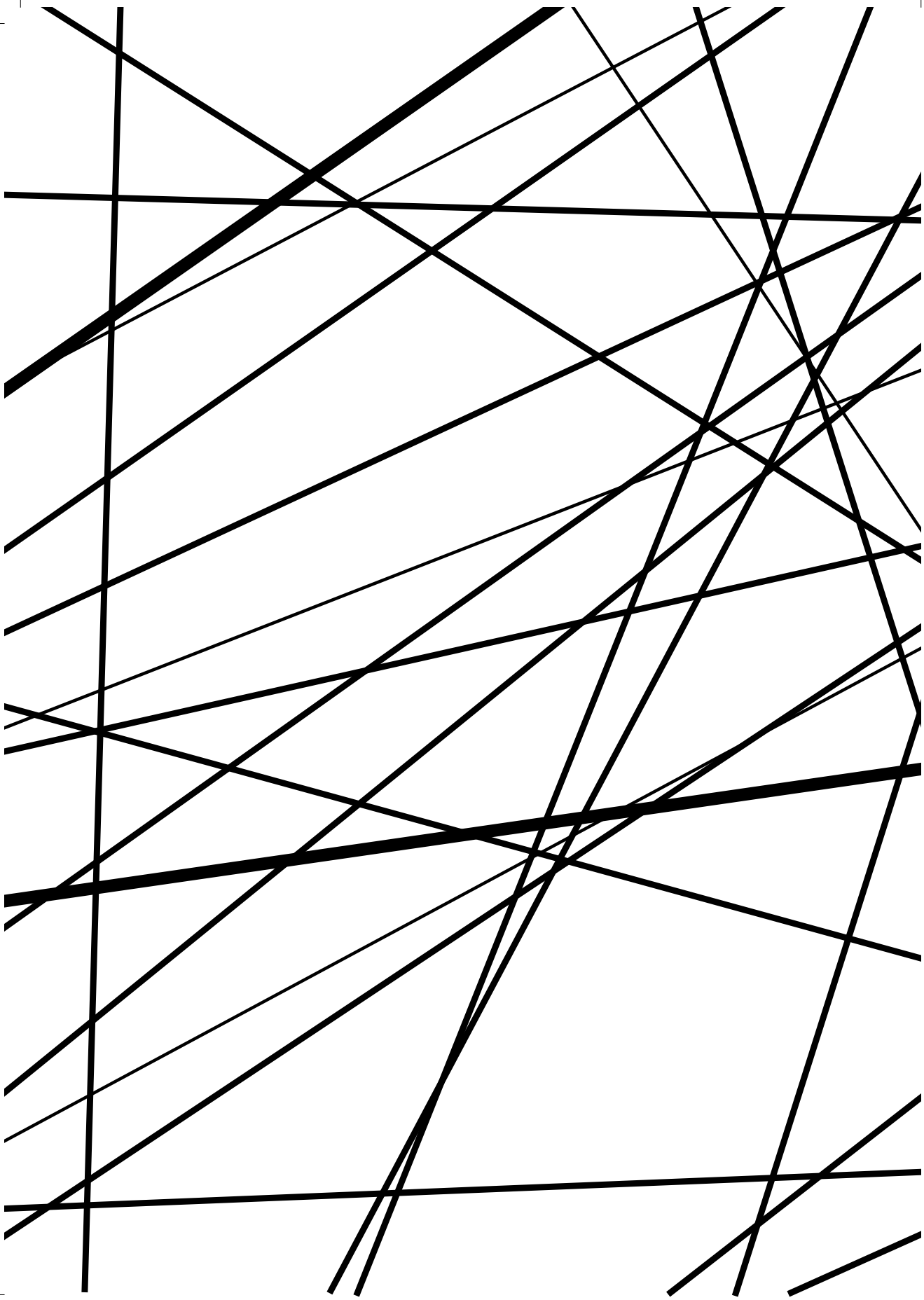
Database	Search	23-4-2013	Hits
Pubmed	1	chronic[Title/Abstract] OR long-lasting[Title/Abstract] OR "long lasting"[Title/Abstract] OR non-remitting[Title/Abstract] OR unremitting[Title/Abstract] OR nonresolving[Title/Abstract] OR non-resolving[Title/Abstract] OR persistent[Title/Abstract] OR chronicity[Title/Abstract] OR duration[Title/Abstract] OR relapsing[Title/Abstract] OR non-recovering[Title/Abstract] OR nonrecovering[Title/Abstract] OR persisting[Title/Abstract] OR persist[Title/Abstract] OR persists[Title/Abstract] OR prolong[Title/Abstract] OR prolonged[Title/Abstract] OR prolongs[Title/Abstract] OR prolonging[Title/Abstract] OR continually[Title/Abstract] OR continuing[Title/Abstract] OR continuous[Title/Abstract] OR continuously[Title/Abstract] OR chronical[Title/Abstract] OR chronically[Title/Abstract] OR lasting[Title/Abstract] OR course[Title/Abstract] OR progression[Title/Abstract] OR progressed[Title/Abstract] OR progress[Title/Abstract] OR progressive[Title/Abstract] OR progresses[Title/Abstract] OR progressing[Title/Abstract] OR progressives[Title/Abstract] OR remitting[Title/Abstract] OR resolving[Title/Abstract] OR recovering[Title/Abstract]	
	2	sinuses[Title/Abstract] OR sinus[Title/Abstract] OR sinonasal[Title/Abstract] OR paranasal[Title/Abstract] OR sinal [Title/Abstract]OR rhinosinus [Title/Abstract]OR rhino [Title/Abstract]OR sinogen [Title/Abstract]OR sinogenic [Title/Abstract]OR "nasal cavity" [Title/Abstract]OR "nasal cavities" [Title/Abstract] OR sinuses[Title/Abstract] OR rhinal[Title/Abstract] OR sinusoidal[Title/Abstract] OR rhino-sinus[Title/Abstract] OR sinusital[Title/Abstract] OR sinusite[Title/Abstract]	
	3	infection[Title/Abstract] OR infected[Title/Abstract] OR infectious[Title/Abstract] OR inflamed[Title/Abstract] OR inflammation[Title/Abstract] OR inflammated[Title/Abstract] OR inflammative[Title/Abstract] OR inflammatory[Title/Abstract] OR infective[Title/Abstract] OR infectives[Title/Abstract] OR infections[Title/Abstract] OR infect[Title/Abstract] OR infects[Title/Abstract] OR infecting[Title/Abstract] OR infectable[Title/Abstract] OR infectability[Title/Abstract] OR Inflame[Title/Abstract] OR inflammations[Title/Abstract] OR inflaming[Title/Abstract] OR inflames[Title/Abstract] OR inflammatories[Title/Abstract]	
	4	2 AND 3	

Appendix 1. Continued

Database	Search	23-4-2013	Hits
	5	rhinosinusitis[Title/Abstract] OR pansinusitis[Title/Abstract] OR aerosinusitis[Title/Abstract] OR sinusitis[Title/Abstract] OR rhinosinusitides[Title/Abstract] OR rhino-sinusitis[Title/Abstract] OR sinusitides[Title/Abstract] OR sinusitises[Title/Abstract]	
	6	4 OR 5	
	7	1 AND 6	11.528
EMBASE	1	(chronic:ti,ab OR long-lasting:ti,ab OR "long lasting":ti,ab OR non-remitting:ti,ab OR unremitting:ti,ab OR nonresolving:ti,ab OR non-resolving:ti,ab OR persistent:ti,ab OR chronicity:ti,ab OR duration:ti,ab OR relapsing:ti,ab OR non-recovering:ti,ab OR nonrecovering:ti,ab OR persisting:ti,ab OR persist:ti,ab OR persists:ti,ab OR prolong:ti,ab OR prolonged:ti,ab OR prolongs:ti,ab OR prolonging:ti,ab OR continually:ti,ab OR continuing:ti,ab OR continuous:ti,ab OR continuously:ti,ab OR chronical:ti,ab OR chronically:ti,ab OR lasting:ti,ab OR course:ti,ab OR progression:ti,ab OR progressed:ti,ab OR progress:ti,ab OR progressive:ti,ab OR progresses:ti,ab OR progressing:ti,ab OR progressives:ti,ab OR remitting:ti,ab OR resolving:ti,ab OR recovering:ti,ab) AND (((sinuses:ti,ab OR sinus:ti,ab OR sinonasal:ti,ab OR paranasal:ti,ab OR sinal :ti,abOR rhinosinus :ti,abOR rhino :ti,abOR sinogen :ti,abOR sinogenic :ti,abOR "nasal cavity" :ti,abOR "nasal cavities" :ti,ab OR sinuses:ti,ab OR rhinal:ti,ab OR sinusoidal:ti,ab OR rhino-sinus:ti,ab OR sinusital:ti,ab OR sinusite:ti,ab) AND (infection:ti,ab OR infected:ti,ab OR infectious:ti,ab OR inflamed:ti,ab OR inflammation:ti,ab OR inflammated:ti,ab OR inflammative:ti,ab OR inflammatory:ti,ab OR infective:ti,ab OR infectives:ti,ab OR infections:ti,ab OR infect:ti,ab OR infects:ti,ab OR infecting:ti,ab OR infectable:ti,ab OR infectability:ti,ab OR Inflame:ti,ab OR inflammations:ti,ab OR inflaming:ti,ab OR inflames:ti,ab OR inflammatories:ti,ab)) OR (rhinosinusitis:ti,ab OR pansinusitis:ti,ab OR aerosinusitis:ti,ab OR sinusitis:ti,ab OR rhinosinusitides:ti,ab OR rhino-sinusitis:ti,ab OR sinusitides:ti,ab OR sinusitises:ti,ab))	3872

Appendix 1. Continued

Database	Search	23-4-2013	Hits
Cochrane	1	(chronic OR long-lasting OR "long lasting" OR non-remitting OR unremitting OR nonresolving OR non-resolving OR persistent OR chronicity OR duration OR relapsing OR non-recovering OR nonrecovering OR persisting OR persist OR persists OR prolong OR prolonged OR prolongs OR prolonging OR continually OR continuing OR continuous OR continuously OR chronical OR chronically OR lasting OR course OR progression OR progressed OR progress OR progressive OR progresses OR progressing OR progressives OR remitting OR resolving OR recovering) AND (((sinuses OR sinus OR sinonasal OR paranasal OR sinal OR rhinosinus OR rhino OR sinogen OR sinogenic OR "nasal cavity" OR "nasal cavities" OR sinuses OR rhinal OR sinusoidal OR rhino-sinus OR sinusital OR sinusite) AND (infection OR infected OR infectious OR inflamed OR inflammation OR inflammated OR inflammative OR inflammatory OR infective OR infectives OR infections OR infect OR infects OR infecting OR infectable OR infectability OR Inflame OR inflammations OR inflaming OR inflames OR inflammatories)) OR (rhinosinusitis OR pansinusitis OR aerosinusitis OR sinusitis OR rhinosinusitides OR rhino-sinusitis OR sinusitides OR sinusitises)) in Title, Abstract or Keywords	989



CHAPTER 7.3

Limited evidence: higher efficacy of nasal saline irrigation over nasal saline spray in chronic rhinosinusitis - an update and reanalysis of the evidence base

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Otolaryngol Head Neck Surg. 2014;3:365-70

Author contributions

van den Berg JW, de Nier LM: Search strategy, retrieval of articles, selection of relevant articles, assessment of study quality, extraction of study data, analysis and interpretation of data, drafting figures and tables, drafting manuscript, revision of the manuscript, final approval of the version to be published.

Kaper NM: formulating clinical question, selection of relevant articles, assessment of study quality, extraction of study data, analysis and interpretation of data, drafting figures and tables, drafting manuscript, revision of the manuscript, final approval of the version to be published.

Schilder AGM: Analysis and interpretation of data, revision of the manuscript, final approval of the version to be published.

Venekamp RP: Formulating clinical question, analysis and interpretation of data, drafting figures and tables, drafting manuscript, revision of the manuscript, final approval of the version to be published.

Grolman W: Analysis and interpretation of data, revision of the manuscript, final approval of the version to be published.

van der Heijden GJMG: Design of study, analysis and interpretation of data, revision of the manuscript, final approval of the version to be published, supervision of study.

ABSTRACT

Objective: To assess the effectiveness of nasal saline irrigation in adult patients with chronic rhinosinusitis.

Methods: A comprehensive search in PubMed, EMBASE, the Cochrane Library. was performed, and 2 authors independently screened publications. The design of selected studies was assessed on applicability and risk of bias.

Results: Of 1596 publications, 1 open-label randomized trial with high applicability and moderate risk of bias was included. In this study, 127 patients were randomly allocated to isotonic nasal saline irrigation or isotonic nasal saline spray, as added to their usual medication. The mean 20-Item Sinonasal Outcome Test (SNOT-20) scores of those treated with nasal irrigation improved more than those allocated to nasal spray. While the authors consider an improvement of 16 or more to be clinically meaningful, the changes from baseline in mean SNOT-20 scores of those treated with irrigation (and the differences with those treated with nasal spray) at 2, 4, and 8 weeks were 12.2 (difference 5.5, [95% confidence interval 20.04 to 11.0]), 16.2 (difference 8.8 [3.2 to 14.4]), and 15.0 (difference 6.5 [0.4 to 12.6]), respectively. Side effects of posttreatment nasal dripping were common but minor and did not lead to discontinuation of treatment.

Conclusions: It should be explained to adult patients with chronic rhinosinusitis that there is limited information on the relative effect of nasal saline irrigation and nasal saline spray on subjective symptom improvement, since there is only 1 trial available with a moderate risk of bias showing limited benefit of irrigation over spray.

CLINICAL SCENARIO

A 33-year-old man visits your ear-nose-throat outpatient clinic with complaints of reduced smell, facial pain, and nasal discharge, lasting for 4 months. Besides purulent discharge in the middle meatus on both sides, nasal endoscopic findings were normal. Computed tomography (CT) scanning of the paranasal sinuses shows mucosal thickening in the maxillary sinuses. Based on these examinations, you conclude that the patient suffers from chronic rhinosinusitis (CRS) without nasal polyposis, and you wonder whether to advise nasal saline irrigation to relieve his complaints.

BACKGROUND

CRS is very common, affecting approximately 5% to 15% of the adult population in both Europe and the United States.[1] Its impact on patient quality of life is considerable, equaling other chronic conditions such as chronic back pain, congestive heart disease, and chronic obstructive pulmonary disease.[2] CRS is defined by the American Association of Otolaryngology - Head and Neck Surgery 2007 practice guideline as the presence of at least 2 of the following symptoms for a minimum of 12 weeks: nasal congestion, nasal discharge, facial pain/pressure, and hyposmia. In addition, inflammation should be documented by purulence or polyps at the middle meatus or radiographic imaging of the paranasal sinuses.[3] In daily practice, nasal saline irrigation is often recommended in addition to topical corticosteroids in patients suffering from CRS.[1,4] It has been suggested to improve sinonasal symptoms by enhancing mucociliary function, decreasing inflammatory mediators, reducing mucosal edema, and clearing mucus.[5] A 2007 Cochrane review concluded that topical saline could be used as adjunctive therapy for symptom relief.[4] However in this review, clinical heterogeneity between studies was substantial as the authors included trials in children and adults with chronic sinus disease as well as trials in patients with allergic rhinitis. The most recent study included in this review was published in 2006. As new evidence may have become available over time, an updated search is warranted. The aim of this systematic review is therefore to provide an update and reanalysis of the available evidence on the effectiveness of nasal saline irrigation in adult patients with CRS.

METHODS

Searching for Evidence

We systematically reviewed the evidence base to answer our research question: What is the effectiveness of nasal saline irrigation in adult patients with CRS, in terms of time to clinical cure, symptom relief, and side effects?

Retrieving Studies

Assisted by our clinical librarian, we retrieved relevant publications from PubMed, EMBASE, and the Cochrane Library (up to March 26, 2013). We used the terms rhinosinusitis and nasal irrigation and relevant synonyms. Appendix 1 includes our search strategy.

Two authors (J.B., L.N.) independently retrieved publications and removed duplicates. They selected articles based on title and abstract screening. Articles that assessed nasal saline irrigation (either as monotherapy or as an adjunct to medical treatment) were included. Further, articles had to compare nasal saline irrigation to either no treatment, placebo, or an active agent. Animal or in vitro studies, studies in children and patients with allergic rhinitis and immunocompromised patients, case reports, reviews, and opinion papers were excluded.

For final selection, the same 2 authors screened full texts of potentially eligible articles for absolute risks for nasal saline irrigation and control treatment or their risk differences. The article retrieval was completed by cross-reference checking in Scopus and Web of Science for selected articles, while citations of related reviews, meta-analyses, and guidelines were screened to identify additional eligible trials. The similar procedure was followed to check for eligibility of articles that were thereby retrieved. Initial disagreements on eligibility and selection of articles between authors were solved by discussion; therefore, the selection is based on full consensus.

Assessing Studies

Based on predefined criteria, three authors (J.B., L.N., and N.K.) independently evaluated the design of included studies on applicability and risk of bias (RoB). They resolved initial disagreements by discussion. When item information for the assessment was not or not clearly reported, we rated it as insufficient and considered it as not satisfied. When the reporting allowed assessment, we rated it as either satisfied or not satisfied.

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Assessment of applicability of the study involved evaluation of patients, notably (1) adults with CRS; treatment comparison, notably (2) nasal saline irrigation; and the outcomes, notably (3) clinical cure or symptom relief. Studies were classified as highly applicable if they satisfied all the aspects of our 3-part question, moderate if they satisfied 2, and low if they satisfied 1.

Assessment of the RoB involved evaluation of selection bias, notably the study design characteristics treatment assignment by (1) random and (2) concealed allocation, and information bias, notably standardization of (3) treatments and (4) outcome assessments, (5) blinding of outcome assessment, and (6) completeness of reported data (Table 1). Studies were classified as low RoB if they satisfied criteria 1 and 2 plus all other study design features, moderate RoB if they satisfied criteria 1 and 2 but failed on 1 or 2 of the other 4 features, and the remainder were classified as high RoB.

We aimed to include studies for data extraction with a high and moderate applicability and low and moderate RoB.

Extraction of Study Data

From selected articles, three authors (J.B., L.N. and N.K.) independently extracted data. We aimed to extract and report absolute risks for nasal saline irrigation and control treatment, plus their risk difference with accompanying 95% confidence intervals (CI). If they were not provided or could not be calculated, we presented the findings as reported in the original article.

RESULTS

7.3

Retrieving Studies

Our initial search yielded 4917 articles. Removing duplicates left 1596 unique articles for screening on title and abstract. Of these, 33 articles were considered potentially eligible, and their full texts were retrieved. No additional studies were found following our iterative cross-reference checking process. Based on full-text evaluation, 4 studies were included for study assessment (Figure 1).

Assessing Studies

One study with high applicability and moderate RoB remained for data extraction (Table 1).[6] We excluded 2 studies because of high RoB.[7,9] One study with moderate RoB included a majority of patients (77%) that underwent previous sinus surgery and was therefore excluded from further analysis.[8]

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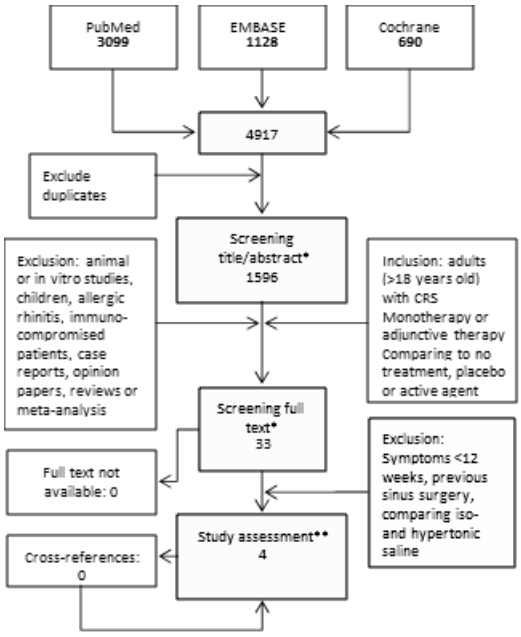
Figure 1. Flowchart of search strategy (March 26, 2013)



Legend:
CRS, chronic rhinosinusitis
*, Based on agreement among 2 independent authors (J.B., L.N.)
**, Based on agreement among 3 independent authors (J.B., L.N. and N.K.)

Extraction of Study Data

In an open-label randomized trial, Pynnonen et al randomly allocated 127 patients aged 18 years and older with 1 or more of the following symptoms: nasal stuffiness, nasal dryness or crusting, nasal congestion, discolored nasal discharge, or thick nasal discharge to either nasal irrigation with an isotonic saline solution (n = 64) or isotonic saline nasal spray (n = 63), twice daily for 8 weeks.[6] Participants were allowed to continue their usual medications. Patients who underwent previous sinus surgery were excluded. Medication use and 20-Item Sinonasal Outcome Test (SNOT-20) scores were recorded for 8 weeks.[10] Time to resolution of symptoms was not assessed.

Duration of symptoms before enrollment varied from 3 to 12 months, with no differences between groups. Baseline mean SNOT-20 scores were similar for both groups (37.6 for irrigation and 35.5 for spray). Of the 127 randomized patients, 120 (94%), 117 (92%), and 114 (90%) were analyzed at 2, 6, and 8 weeks, respectively. At 2, 6, and 8 weeks, mean SNOT-20 scores of patients treated with nasal saline irrigation improved more than of those receiving nasal saline spray (Table 2). The authors also calculated the proportion of patients in both treatment groups with a clinically significant improved SNOT-20 score (defined as a reduction of 16 points or more) and found an absolute risk reduction of 15% for treatment with nasal saline irrigation, corresponding with a number needed to treat of 7.

During follow-up, there was no difference in the number and duration of usual medication use between groups. Medication type and dosage were, however, not reported. Minor side effects were frequently reported in both groups (42% in the irrigation group, 25% in the spray group). Posttreatment nasal saline dripping, an expected side effect, was most commonly reported in both groups (n = 14). No patients discontinued treatment due to side effects, and compliance was about 80%.

Table 1. Study assessment

	Applicability					Risk of Bias						
Study Characteristics	Domain	Treatment	Outcome	Follow-up	Overall	Randomization	Concealed Allocation	Treatment Standardization	Outcome Standardization	Blinding of Outcome	Complete Data	RoB Score
Pynnonen et al. [6]	•	•	•	•	H	•	•	○	•	○	•	M
Heatley et al. [7]	□	•	•	•	M	○	○	○	•	○	•	H
Rabago et al. [8]	○	•	•	•	M	•	•	○	•	○	•	M
Taccariello et al.[9]	○	•	•	•	M	○	○	○	•	○	•	H

Applicability	
Domain	Patients aged 18 years and older with rhinosinusitis symptoms for at least 12weeks, no previous sinus surgery
Treatment	Isotonic or hypertonic nasal saline irrigation (at least once daily)
Outcome	Clinical cure or symptom relieve
Follow up	At least 2 weeks

Risk of Bias	
Randomization	Method of randomization adequately described
Concealed allocation	Concealment of allocation (treatment allocation was independent from selection) adequately described
Treatment standardization	Standardization of co-treatment
Outcome standardization	Protocolled, uniform assessment of outcome
Blinding of outcome	Outcome is documented without knowledge of the treatment status
Complete data	Adequate reporting of all included patients

Legend:
RoB, risk of bias
M, moderate
H, high
•, satisfied
○, not satisfied
□, insufficient information/unclear

Table 2. Reduction in mean SNOT-20 scores from baseline at 2, 4, and 8 weeks.

	Nasal Saline Irrigation (Baseline Mean Score 37.6)		Nasal Saline Spray (Baseline Mean Score 35.5)		
Week	n	Reduction	n	Reduction	D (95% CI)
2	59	12.2	61	6.7	5.5 (–0.04; 11.0)
4	57	16.2	60	7.4	8.8 (3.2; 14.4)
8	55	15.0	59	8.5	6.5 (0.4; 12.6)

Legend:
SNOT-20, 20-Item Sinonasal Outcome Test[10]
CI, confidence interval
D, difference

COMMENT

In this systematic review on the effectiveness of nasal saline irrigation in adult patients with CRS, we identified 1 trial that assessed nasal saline irrigation versus nasal saline spray as an adjunct to usual medical treatment. This trial, with high applicability and moderate RoB, found a larger improvement in subjective symptoms, as measured by the change from baseline in mean SNOT-20 scores, for nasal saline irrigation as compared with nasal saline spray. The absolute benefit of nasal saline irrigation over nasal spray was, however, modest.

We did not identify new trials since the 2007 Cochrane review was published. Because we excluded trials in children, patients with allergic rhinitis, and those who underwent previous sinus surgery, we included only 1 of the studies that were included in the 2007 Cochrane review.[4]

Some aspects of our findings need further consideration. First, the trial included patients based on symptoms, while in daily practice, additional diagnostic procedures (i.e., nasal endoscopy and/or CT scanning) are usually performed.[1,3,6] The effects of nasal saline irrigation may vary across patients with clinically diagnosed CRS, like in this trial, and those in which the diagnosis is confirmed by nasal endoscopy and/or CT scanning as recommended by current clinical guidelines.[1,3] As such, our findings are limited to patients with clinically diagnosed CRS.

Second, patients in both treatment groups were allowed to use their usual medication. Although detailed information regarding medication type, duration of use, and dosage was lacking in the study, no differences were reported in overall medication use between

the groups. As such, the limited benefit of nasal saline irrigation over nasal saline spray regarding symptom improvement may not necessarily result in reduced use of co-medication.

Third, the trial included in our review used an isotonic saline solution.[6] Currently, it has not been established whether the effects differ for isotonic or hypertonic nasal solution. Also, the optimal type of delivery, frequency, and volume of delivery are not yet established, and future studies on this topic are therefore needed.[4]

Fourth, Pynnonen et al found the reduction in mean SNOT-20 score for nasal irrigation to be 5.5 to 8.8 points larger than for nasal saline spray. As the authors considered a change in SNOT-20 score of 16 points clinical meaningful, the difference between nasal irrigation and nasal spray is, although statistically significant, less relevant from a clinical point of view.[6,10]

Finally, we take into consideration that treatment with nasal saline irrigation causes only minor side effects. Furthermore, treatment adherence as measured in clinical trials is moderate to high.[5] Reliable information regarding treatment adherence in daily clinical practice is, however, lacking. Costs of nasal saline irrigation vary but are generally low, especially when patients are instructed to make the saline solution themselves.[5]

CONCLUSION AND RECOMMENDATION

Our systematic review identified 1 open-label randomized trial comparing the effects of nasal saline irrigation to saline nasal spray as an adjunct to co-medication in adult patients with clinically diagnosed CRS. This trial indicates that nasal saline irrigation may provide subjective symptom improvement over nasal saline spray. Although minor side effects such as posttreatment nasal saline dripping were common, no patients in this trial discontinued treatment due to such side effects. However, these results should be interpreted with caution, because RoB was judged moderate. Further methodologically sound trials are needed to draw more definitive conclusions on its use.

Translating Evidence into Practice

We informed our patient with CRS that nasal saline irrigation may provide some improvement for his symptoms. We explained to him that current evidence on the relative effect of nasal saline irrigation and nasal saline spray on the improvement of subjective symptoms is very limited, since there is only 1 trial with a moderate RoB available showing limited benefit of irrigation over spray, against little risk of (minor) side effects.

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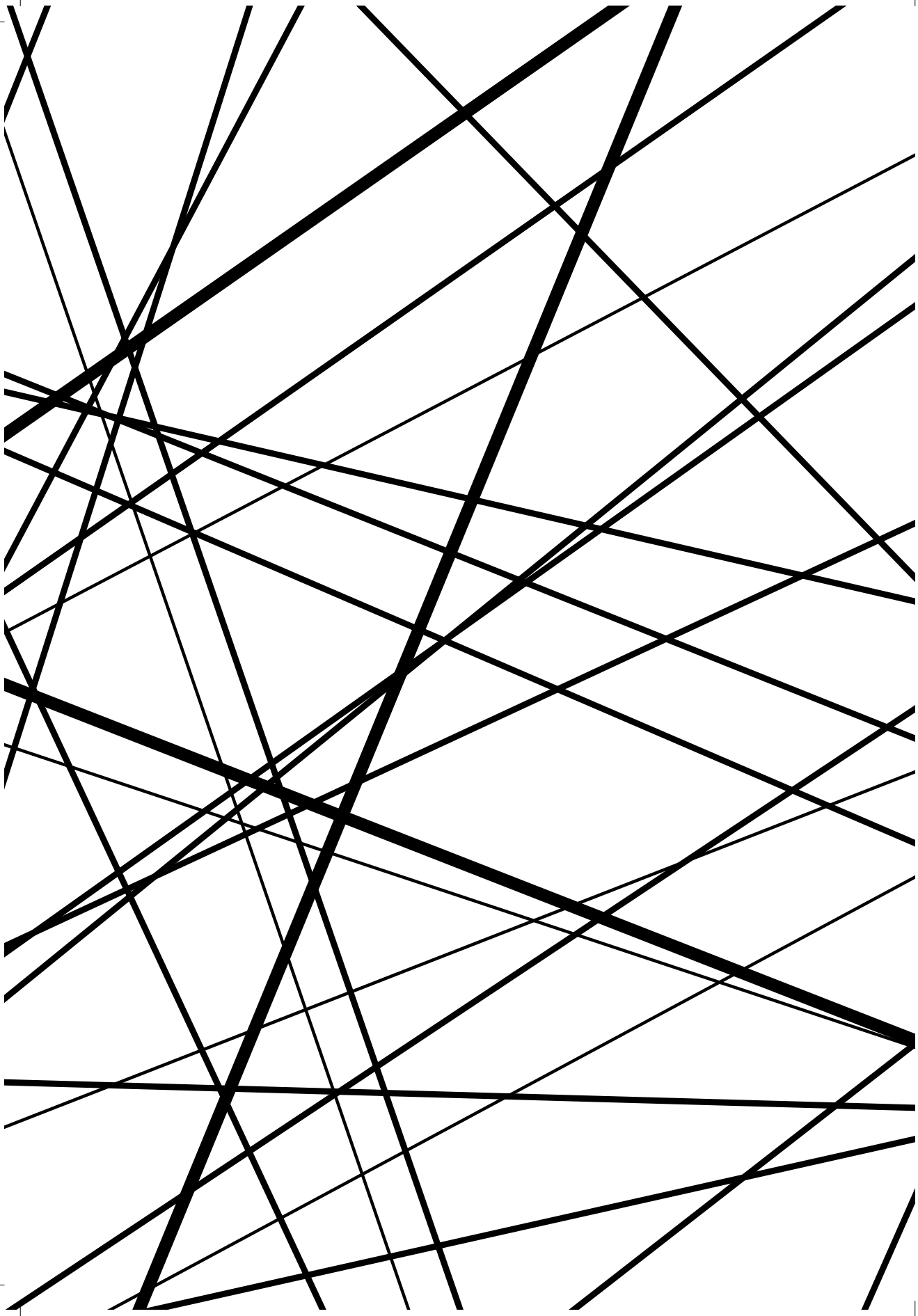
APPENDIX

Appendix 1. Search strategy

Database	Search	(26-03-2013)	Hits
Pubmed	1	(Sinus[tiab] OR Sinuses[tiab] OR Sinusses[tiab] OR Nose[tiab] OR Nasal[tiab] OR Sinal[tiab] OR Sinusoidal[tiab] OR Rhinosinus[tiab] OR Rhinosinuses[tiab] ORRhino[tiab] OR Rhinal[tiab] OR Sinogen[tiab] OR Sinogenic[tiab] OR Sinonasal[tiab] OR Sinusal[tiab] OR Nasosinal[tiab] OR Paranasal[tiab] OR Rino[tiab] OR Rinal[tiab] OR Rhinosinusal[tiab] OR Antral[tiab])	
	2	Infection[tiab] OR Infections[tiab] OR Inflammation[tiab] OR Infectious[tiab] OR Inflammations[tiab] OR Infect[tiab] OR Infected[tiab] OR Inflamed[tiab] OR Inflammated[tiab] OR Inflammatory[tiab] OR Inflammation[tiab] OR Disease[tiab] OR Diseases[tiab] OR Symptom[tiab] OR Symptoms[tiab] OR Inflammative[tiab] OR Infective[tiab] OR Infects[tiab] OR Infecting[tiab] OR Inflame[tiab] OR Inflaming[tiab] OR Inflames[tiab]	
	3	Sinusitis[tiab] OR Sinusites[tiab] OR Sinusitides[tiab] OR Rhinosinusitis[tiab] OR Rhinosinusitides[tiab] OR Pansinusitis[tiab] OR Sinusitus[tiab] OR Sinusites[tiab] OR Aerosinusitis[tiab]	
	4	Lavage [tiab] OR Lavages [tiab] OR Irrigation[tiab] OR Irrigations[tiab] OR Douche[tiab] OR Douches[tiab] OR Douched[tiab] OR Douching[tiab] OR Shower[tiab] OR Showers[tiab] OR Flush[tiab] OR Flushed[tiab] OR Flushes[tiab] OR Flushing[tiab] OR Flushings[tiab] OR Rinsing[tiab] OR Rinsed[tiab] OR Rinsings[tiab] OR Rinse[tiab] OR Rinses[tiab] OR Washing[tiab] OR Washed[tiab] OR Washings[tiab] OR Washout[tiab] OR Washouts[tiab] OR Wash[tiab]	
	5	((#1 AND #2) OR #3) AND #4	3099
EMBASE	1	Sinus:ab,ti OR Sinuses:ab,ti OR Sinusses:ab,ti OR Nose:ab,ti OR Nasal:ab,ti OR Sinal:ab,ti OR Sinusoidal:ab,ti OR Rhinosinus:ab,ti OR Rhinosinuses:ab,ti OR Rhinosinusses:ab,ti OR Rhino:ab,ti OR Rhinal:ab,ti OR Sinogen:ab,ti OR Sinogenic:ab,ti OR Sinonasal:ab,ti OR sinusal:ab,ti OR Nasosinal:ab,ti OR paranasal:ab,ti OR Rino:ab,ti OR Rinal:ab,ti ORRinosinus:ab,ti OR Rinosinuses:ab,ti OR Rinosinusses:ab,ti OR Rhinosinusal:ab,ti OR Antral:ab,ti	

Appendix 1. Continued

Database	Search	(26-03-2013)	Hits
	2	Infection:ab,ti OR Infections:ab,ti OR Inflammation:ab,ti OR Infectious:ab,ti OR Inflammations:ab,ti OR Infect:ab,ti OR Infected:ab,ti OR Inflamed:ab,ti OR Inflammated:ab,ti OR Inflammatory:ab,ti OR Inflammation:ab,ti OR Disease:ab,ti OR Diseases:ab,ti OR Symptom:ab,ti OR Symptoms:ab,ti OR Inflammative:ab,ti OR Infective:ab,ti OR Infects:ab,ti OR Infecting:ab,ti OR Inflame:ab,ti OR Inflaming:ab,ti OR Inflames:ab,ti	
	3	Sinusitis:ab,ti OR Sinusites:ab,ti OR Sinusitides:ab,ti OR Rhinosinusitis:ab,ti OR Rhinosinusites:ab,ti OR Rhinosinusitides:ab,ti OR Pansinusitis:ab,ti OR Sinusitus:ab,ti OR Sinusites:ab,ti OR Rinosinusitis:ab,ti OR Aerosinusitis:ab,ti	
	4	Lavage:ab,ti OR Lavages:ab,ti OR Irrigation:ab,ti OR Irrigations:ab,ti OR Douche:ab,ti OR Douches:ab,ti OR Douched:ab,ti OR Douching:ab,ti OR Douchings:ab,ti OR Shower:ab,ti OR Showers:ab,ti OR Flush:ab,ti OR flushed:ab,ti OR Flushes:ab,ti OR Flushing:ab,ti OR Flushings:ab,ti OR Rinsing:ab,ti OR Rinsed:ab,ti OR Rinsings:ab,ti OR Rinse:ab,ti OR Rinses:ab,ti OR Washing:ab,ti OR washed:ab,ti OR Washings:ab,ti OR washout:ab,ti OR washouts:ab,ti	
	5	((#1 AND #2) OR #3) AND #4	1128
Cochrane	in "Title, Abstract or Keywords"		
	1	Sinus OR Sinuses OR Sinusses OR Nose OR Nasal OR Sinal OR Sinusoidal OR Rhinosinus OR Rhinosinuses OR Rhino OR Rhinal OR Sinogen OR Sinogenic OR Sinonasal OR Sinusal OR Nasosinal OR Paranasal OR Rino OR Rinal OR Rhinosinusal OR Antral	
	2	Infection OR Infections OR Inflammation OR Infectious OR Inflammations OR Infect OR Infected OR Inflamed OR Inflammated ORInflammatory OR Inflammation OR Disease OR Diseases OR Symptom OR Symptoms OR Inflammative OR Infective OR Infects OR Infecting OR Inflame OR Inflaming OR Inflames	
	3	Sinusitis OR sinusites OR Sinusitides OR Rhinosinusitis OR Rhinosinusitides OR Pansinusitis OR Sinusitus OR Sinusites OR Aerosinusitis	
	4	Lavage OR Lavages OR Irrigation OR Irrigations OR Douche OR Douches OR Douched OR Douching OR Shower OR Showers OR Flush OR Flushed OR Flushes OR Flushing OR Flushings OR Rinsing OR Rinsed OR Rinsings OR Rinse OR Rinses OR Washing OR Washed OR Washings OR Washout OR Washouts OR Wash	
	5	((#1 AND #2) OR #3) AND #4	690



CHAPTER 7.4

Epilogue

Kaper NM, Aarts MCJ, van der Heijden GJMG

EBCR METHODOLOGY

In this summary three evidence-based case reports (EBCR) are discussed. EBCRs entail an explicit approach for reliable systematic summaries on best available evidence for specific clinical questions concerning patient management. As such, EBCRs transparently separate evidence from judgment.[1,2] An EBCR starts with a clinical question based on a knowledge gap, so it can be related to differential diagnosis, diagnostic test accuracy, prognosis, treatment, or prevention.[1,2] Such knowledge gap can be encountered in daily practice by a physician, which becomes manifest by a question from a patient or emerge from guideline development. The search strategy for retrieving relevant publications is based on a three-part question consisting of a determinant, domain and outcome. These three elements of the clinical question are used in identification and selection of publications that are considered applicable notably, similarity with domain, determinant and outcome, for answering that clinical question.[2] The applicable publications are appraised for their methodological quality, which concerns the assessment of risk of bias (RoB) and applicability. Those with the highest applicability and lowest RoB are selected for data-extraction on outcomes.[2] After synthesizing the data a recommendation on how to apply the evidence in daily practice is provided.[2] The approach and methods of EBCRs show many similarities to that of systematic reviews, but a few important differences are noteworthy.

Firstly, the research question of an EBCR can be more specific and patient centered in terms of domain, determinant and outcome. For example, an EBCR might focus specifically on patients in secondary care, while systematic reviews assess general patient populations (domain). For the determinant of the research questions, a systematic review often studies multiple interventions, like different types of intranasal steroids for CRS, or decongestants, antihistamines and nasal irrigation for acute sinusitis while EBCR can focus on a single treatment. For the outcome of the research questions, most systematic reviews include multiple outcomes that at best provide indirect or circumstantial evidence, notably surrogate, intermediate or proxy outcomes. For an EBCR the outcomes are selected and restricted based on the applicability of the evidence, notably health outcomes of patients with direct relevance for daily practice. Only when there is no research available providing direct evidence, an EBCR takes indirect or circumstantial evidence into account. For example, a recommendation on prescribing antibiotics in recurrent acute rhinosinusitis, was based on circumstantial evidence, and therefore it also applies to RARS.[3]

Secondly, in contrast to most of the systematic reviews published, the focused questions in EBCRs are not restricted to effect of treatment, but also concern diagnostic and prognostic questions. Diagnostic and prognostic questions constitute frequently recurring knowledge gaps in daily practice.

Thirdly, systematic reviews and meta-analyses on intervention research predominantly select randomized trials. In case of absence of such trials, this might lead to a nihilistic conclusion that evidence is lacking. As an EBCR focuses on questions concerning effects of treatment seek for best evidence, no such restriction applies and an answer to the clinical question can based on reports from non-randomized treatment comparisons.

Fourthly, systematic reviews aim to synthesize pool data all available evidence in a quantitative manner to derive a single estimate of effect from multiple studies, a so-called meta-analysis.[4] An EBCR refrains from such statistical pooling and primarily aims at providing a qualitative synthesis which is restricted of the best available evidence.

Fifth, since not all evidence is created equal, in an EBCR quality evaluation of causal and non-causal research values aspects of RoB assessment differently. While concealed and random allocation only apply to intervention research, blinding of outcome assessment, incompleteness of data and standardization of extraneous factors apply equally to intervention, diagnostic and prognostic research.[4-8]

Finally, estimates of effect reported in an EBCR concern differences in absolute risks, positive and negative predictive values.[4-8] As in systematic reviews and meta-analyses the data for relevant outcome measure are directly drawn or recalculated from the included publications. To explore heterogeneity estimates of effect are tabulated or plotted against their baseline risk. For drawing inferences on the best available evidence data are tabulated or plotted against the risk of bias and applicability of the studies. As in meta-analysis, the unavailability of data due to poor reporting is a major limitation.[5]

EBCRS AND THE CLINICAL PRACTICE GUIDELINE: ADULT SINUSITIS[9,10]

Since 2012, EBCRs are used in undergraduate teaching of medical students at the University of Utrecht. With adequate teaching, and supervision, students show that they are capable to elaborate a systematic approach to answer any clinical question.[2] In collaboration with Otolaryngology-Head and Neck Surgery, the journal of the American Academy of Otolaryngology-Head and Neck surgery, a project with EBCRs on acute, recurrent and chronic rhinosinusitis was carried out in 2012. Clinical questions as entry points for EBCR were formulated based on knowledge gaps for diagnosis, prognosis and treatment, in the 2007 adult rhinosinusitis guideline.[9] These questions served either as entry questions, or addressed topics for supporting information for the 2015 update of the Clinical Practice Guideline: Adult Sinusitis.[10] In consultation with the journal editor chairing the Guideline

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Processed on: 20-12-2019

author group, a total of eight questions (three on treatment, three on diagnosis and two on prognosis) were selected for answering with an EBCR. In this summary, three of those EBCRs are presented.[11-13]

MAIN FINDINGS OF THE THREE EBCRS

Nasal endoscopy – CT scanning of the paranasal sinuses is considered as the reference standard for chronic rhinosinusitis (CRS). However nasal endoscopy is a more simple, faster and cheaper alternative. Our results show that a positive nasal endoscopy confirms the diagnosis of CRS, therefore, and in contrast to conventional practice, a CT scan is (no longer) required. However, with a negative nasal endoscopy one cannot fully rule out CRS, so a CT scan may still be a relevant option in further management of patients with persistent symptoms.[11]

Age as a predictor – Acute and chronic rhinosinusitis occur predominantly in adolescents and adults, and less at old age. The course of disease could deviate in older patients, possibly indicating that they should be handled differently. However, there were no studies or inconclusive evidence for age as a predictor for a prolonged or chronic course of acute rhinosinusitis. Therefore, older patients should not be managed in a separate way.[12]

Nasal saline irrigation – Nasal saline irrigation may provide some improvement of symptoms, as an adjunct therapy for patients with CRS to other medical treatments (e.g. intranasal corticosteroids). It's proclaimed working mechanism is enhancing mucociliary function and clearing mucus. The knowledge gap was based on the Cochrane review on nasal saline irrigation from 2007, that showed large variations in inclusion criteria, since studies also comprised children and patients with allergic rhinosinusitis. Using more stringent criteria, one study with moderate RoB was included, comparing nasal spray or saline irrigation as an adjunct to co-medication, showing limited symptom improvement against little risk of side effects.[13]

STRENGTHS AND LIMITATIONS

As for any study, defining a relevant three-part research question is crucial. For the EBCR project reported in this thesis, clinical questions were based on knowledge gaps from the 2007 guideline on adult rhinosinusitis of the American Association of Otolaryngology – Head & Neck Surgery.[9] Eight clinical questions were selected and approved in advance by the principal guideline author chairing the writing group. To answer questions considered

relevant and pertinent for the guideline update process EBCR's were produced.[10] All eight EBCRs of our project were included in the 2015 update of the rhinosinusitis guideline.[3,11-17] In addition, six of the EBCRs were later also cited by the German guideline on rhinosinusitis.[3,11,13,15-17,18]

In order to keep the EBCRs from this project up to date, they should be revised on a regular and ongoing basis. EBCRs will allow for a modular design of clinical practice guidelines (CPGs), which will improve flexibility and reduce costs of keeping CPGs up to date. As an example, due to a new trial on nasal saline irrigation which has been published in 2015, the EBCR is no longer up to date.[13] Still this new trial did not provide evidence for changing the recommendation.[19]

Since the advent of the EBCR important progress has been made in development and empirical evaluation of standardized approaches to risk of bias assessment for diagnostic and prognostic research.[4-8] As such, the risk of bias assessment in EBCRs could be updated according to the latest insights. For diagnostic reviews the use of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria[6] and for prognostic systematic reviews the QUIPS (prognostic factor) or PROBAST tool (prognostic studies) could be explored.[4,8] For intervention studies, the Cochrane handbook describes items for the risk of bias assessment for intervention studies.[4] Overall, when comparing these existing and novel instruments to the items in the risk of bias assessment in the EBCR, there is a large concordance, so perhaps some minor alterations could be made.

For the process of developing recommendations, the use of the GRADE approach should be considered, resulting in a more transparent presentation how evidence was separated from judgement.[20] According to GRADE, the author(s) should explicitly describe the magnitude of the difference between the desirable and undesirable consequences, quality of the available supporting evidence, certainty about values and preferences of patients, and the resource expenditure associated with the compared management options. After integrating research evidence, patients' values and preferences, and consideration of resource use, a clinical recommendation is formulated, either strong or conditional (weak). However, there are recommendations that should not be 'GRADEd'. This applies only for recommendations with high confidence that indirect evidence undoubtedly supports net benefit and when, in addition, it would be an onerous and unproductive exercise and thus a poor use of the panel's limited resources to collect this evidence.[21]

Overall, EBCRs can be of great importance to answer clinical questions, identify research gaps and assist in development or updating of guidelines, provided that proposed clinical questions are relevant for patient care and robust methodology is used.

IMPLICATIONS

Over the last years, many guidelines have been developed in order to close the gap between research and practice.[22,23] Now we are facing a new challenge, i.e. to keep these guidelines up to date, so health care continues to be based on the most recent best available evidence.[22,23] It appears that there are many guidelines that have not been updated, or updated with time intervals that are considered too wide.[22,23] It seems that standardization of rigorous methods, i.e. an instrument, on when and how to update guidelines is missing.[22,23] Unfortunately, a comprehensive update of a guideline in total, is a very time and resource consuming process. Rather wide search strategies have to be used in order not to miss important studies, which yield large volumes of publications of which only a small part will be included.[22,23] Therefore, a less time consuming modular approach for updating has proposed. This starts with selecting recommendations eligible for updating by a guideline author or preferably multidisciplinary guideline panel. Then the literature search can be restricted to identify more manageable numbers of new publications. After evaluation and synthesizing by field experts a guideline panel decides whether the recommendations should be adapted.[23] Our project producing multiple EBCR's has shown that these limited searches indeed can assist in the updating process of guidelines. Hereby they can aid guideline authors and policy makers in making the process of updating guidelines more efficient. Our EBCR's have been used in the updates of both the American and the German guidelines.[9,10,18] It shows that these limited searches can make the process even more effective, because they can be used to update individual guidelines from different countries.

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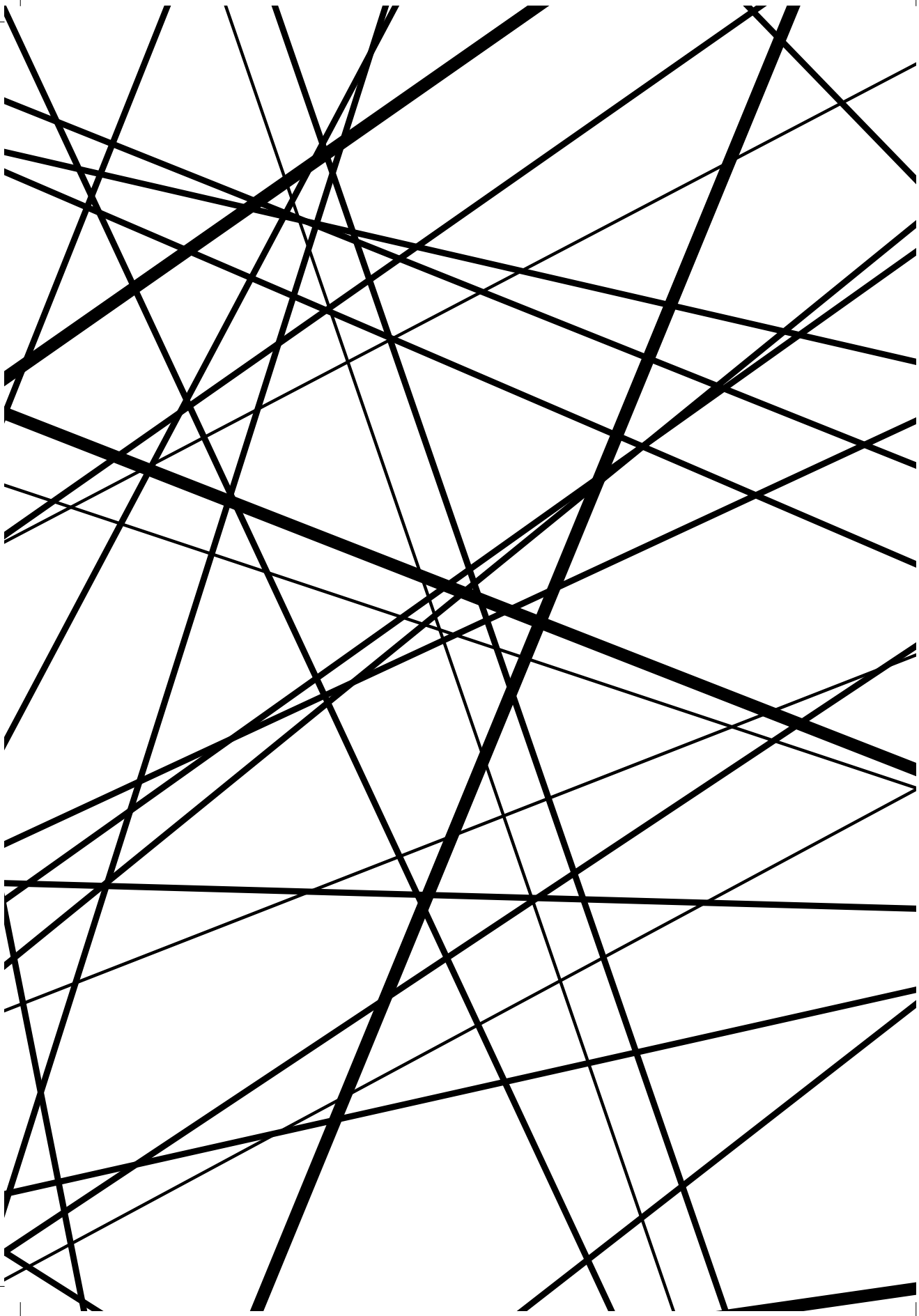

CHAPTER 8

International clinical practice guideline comparison on adult chronic rhinosinusitis shows considerable variability of recommendations for diagnosis and treatment

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Accepted in: *Eur Arch Otorhinolaryngol.*

Author contributions

Kaper NM: Conceived and designed the study, Collected the data, analysis and interpretation of data, drafted manuscript, final approval of manuscript, accountable for publication.

van der Heijden GJMG: Conceived and designed the study, analysis and interpretation of data, revised manuscript, final approval of manuscript, accountable for publication.

Cuijpers SH: Collected the data, analysis and interpretation of data, revised manuscript, accountable for publication.

Stokroos RJ: Analysis and interpretation of data, revised manuscript, final approval of manuscript, accountable for publication.

Aarts MCJ: Conceived and designed the study, analysis and interpretation of data, revised manuscript, final approval of manuscript, accountable for publication.

ABSTRACT

Objective: To compare international clinical practice guidelines on adult chronic rhinosinusitis (CRS).

Methods: An extensive literature search in Embase, Pubmed and the internet (Google, websites of well-known guideline organizations) was performed on November 21st 2018. Main outcome measures were; guideline quality measured by the AGREE II instrument, summary and comparison of recommendations on diagnosis and treatment with harmonized levels of evidence (LoE) and grade of recommendations (GoR).

Results: We selected 10 guidelines on CRS. 5 guidelines were of sufficient to high quality according to AGREE II, the remaining guidelines predominantly did not meet AGREE II criteria. We harmonized all guideline recommendations so we could compare them, although three guidelines did not provide a LoE. Five guidelines provided recommendations on diagnosis, all of them recommended to perform nasal endoscopy, CT scan and allergy testing (with varying GoR's). All 10 guidelines provided recommendations on therapy, one treatment, i.e. the use of intranasal steroids, was recommended by all guidelines (with varying GoR's). Recommendations for surgical treatment of CRS were provided by 5 guidelines.

Conclusions: We performed an extensive search and included 10 (inter)national guidelines on CRS for adults. According to AGREE II, 5 were of good or sufficient quality. Overall, there was much variation between guidelines in recommended diagnostic test or treatment, direction of evidence and GoR. We found consensus for nasal endoscopy, CT scan, allergy testing and intranasal steroids. We argue for standardization of guideline development, to increase their quality and improve comparability.

INTRODUCTION

Evidence-based practice has become standard of care, but due to a the huge quantity of scientific publications in the medical field we are facing a gap between research evidence and clinical practice. Clinical practice guidelines (CPGs) have emerged as one of the solutions to bridge this gap, by collecting and synthesizing the available evidence and translating this evidence into recommendations to support decision making in daily clinical practice.[1] Potentially, CPGs reduce unwarranted practice variation, improve quality of care, lead to better patient outcomes and higher cost-efficiency.[1] In addition, CPG recommendations are increasingly being used as quality benchmarks.[1]

Over the last decade there has been a growing amount of CPGs in the medical field, including in otolaryngology. Besides, many institutes and medical associations (NICE, AAO-HNS, BSACI) have committed to CPG development, which has resulted in more than 6500 CPGs worldwide.[2]

Typically, a CPG is developed by a panel of stakeholders that systematically addresses and reviews all the available evidence on a medical topic and formulates a set of recommendations with corresponding grade of recommendation (GoR), after having addressed both benefits and drawbacks.[1] To develop high quality CPGs, i.e. evidence-based with a rigorous methodology, multiple approaches have been developed, of which AGREE II and GRADE have become widely known and adopted.[3,4] Given that these methods are applied, we expect limited variation between CPGs on similar topics.

In this study we aim to compare CPGs on chronic rhinosinusitis (CRS) by assessing their quality and subsequently comparing recommendations for diagnosis and treatment on direction of evidence and strength of recommendation.

MATERIAL AND METHODS

Ethical considerations

Since this is a literature study it did not involve patients.

Search and selection

We conducted an extensive literature search in Embase, Pubmed, Google and websites of well-known guideline organizations on November 21st 2018, for CPGs on diagnosis and/

or treatment of CRS in adults. For search terms and details, see Appendix 1. Two authors (N.K. and S.C.) independently selected CPGs, on title/abstract and/or on full text. The in- and exclusion criteria can be found in Figure 1. For excluded articles see Appendix 2.

AGREE II

Two authors (N.K., S.C.) independently appraised the selected CPGs with the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument, which consists of 23 items organized in six domains (Table 1).[3,5] For each item, values of 1 (strongly disagree) to 7 (strongly agree) can be given. **1; scope and purpose**; 3 items on the description of the overall objectives, clinical questions, and patients to whom it applies. **2; stakeholder involvement**; 3 items on the degree to which the views of their intended users are represented, whether all relevant professional groups are represented, whether the views and preferences of the target population (e.g., patients, public, etc.) have been sought, definition of target users. **3; rigor of development**; 8 items on the integrity of the development process (search methodology, evidence selection criteria, methods used to formulate recommendations, risk and benefit assessment, links between evidence and recommendations), external review and updating mechanisms. **4; clarity of presentation**; 3 items assessing whether the recommendations are specific and unambiguous, whether different management options are clearly presented, whether key recommendations are easily identifiable, and whether there is support by application tools. **5; applicability**; 4 items on the description of facilitators and barriers of application, considering potential resource implications of applying recommendations, presenting of monitoring or auditing criteria. **6; editorial independence**; 2 items on conflicts of interest, were CPG developers editorially independent from the funding body, reporting of potential conflicts of interest.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain.[5] The domain scores are independent and should not be aggregated into a single quality score.[5] The AGREE II instrument does not provide scores to differentiate between high and low quality guidelines, but leaves this to be determined by its user.[5] We divided domain scores into three groups; high (>67%-100%), sufficient (>33%-67%) and low quality (0%-33%), also see Table 1.

Extracting CPG information, recommendations and harmonizing evidence

We extracted information on publication date, definition of CRS and intended CPG users. Recommendations about diagnosis and treatment were extracted, with corresponding levels of evidence (LoE; defined as low/very low, moderate, high) and GoR (defined as weak, moderate, strong).[4] Since most CPGs use a 3- of 4- points scale we adapted GRADE to enable comparison.[4]

We compared for differences between LoE and GoR per recommendation, to detect upgrading of downgrading of evidence, which without transparent argumentation could potentially indicate bias. According to GRADE, the GoR is separated from the LoE, i.e. not only the quality of the underlying evidence defines the GoR.[6] It's also determined by the magnitude of the difference between desirable and undesirable consequences, certainty about values and preferences of patients, and the resource expenditure associated with the compared options.[6] In the CPG, the approach of up- and downgrading of evidence and formulating a GoR should be explicitly described.

We then compared recommendations between CPGs on topic (conclusions for diagnosis and treatment), direction of evidence (advised to use/not to use) and GoR.

RESULTS

Search and selection

The CPG selection process can be found in Figure 1. We selected 10 CPGs, the results are based on a full consensus (Table 1).[7-16]

Definition

Most CPGs used a definition of CRS based on a combination of symptoms, combined with findings suggestive for CRS at nasal endoscopy and/or CT-scan. (Appendix 3)[7, 9,11,12,15] The Brazilian guideline uses a slightly different symptom combination, DEGAM and Slavin define CRS only by a combination of symptoms.[8,13,16] Dibilidox does not provide a definition for CRS.[14] CBO, EPOS, Scadding and the Brazilian guideline advise to use the VAS score for defining severity of disease.[9,11,15,16] All CPGs maintain a duration of illness of >12 weeks, expect for Slavin (8 weeks).[13] All CPGs distinguish between CRS with or without nasal polyps.[7-16]

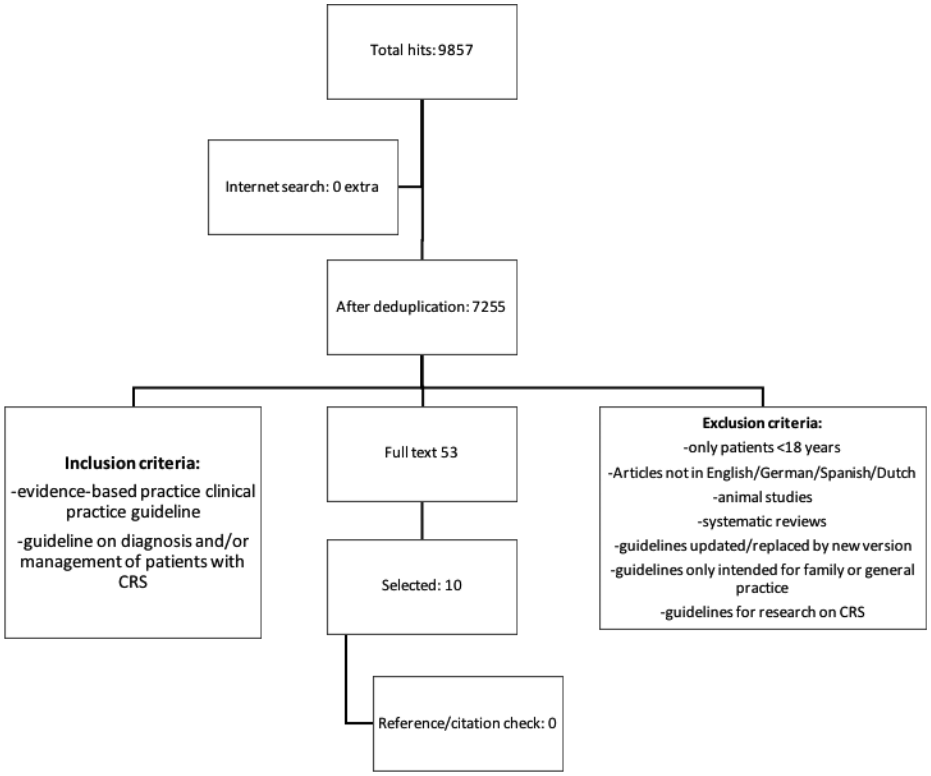
Publication date and country of origin

Publication dates and country of origin can be found in Table 1. DEGAM was published less than 3 years ago and Desrosiers less than 5 years ago.[8,11] All other CPGs were published more than 5 years ago.

Intended users

Rosenfeld, Degam, Desrosies and Dibildox were intended to be used by otolaryngologists.[7,8,11,14] CBO and EPOS by both general practitioners and otolaryngologists.[9,10] Slavin and the Brazilian CPGs were intended for any physician treating patients with rhinosinusitis, Scadding for physicians treating allergic conditions.[13,16,15] Only Bachert did not state it's intended users.[12]

Figure 1. Flowchart



AGREE II

The results can be found in Table 1. There were no differences of more than 2 points per item between the two assessors. Rosenfeld, DEGAM and CBO had an overall good to sufficient score, EPOS and Desrosiers scored sufficient, while the remaining CPGs had predominantly insufficient scores and were therefore classified as insufficient.[7-16] Overall, domain 5 (applicability) was rated lowest. Additional to their low AGREE II score, it is striking that both the Brazilian CPG and Dibildox did not provide literature references.[14,16]

Table 1. AGREE II

	Domain 1	**Domain 2**	**Domain 3**	**Domain 4**	**Domain 5**	**Domain 6**	**Overall**	**Use**
Guideline (publication date, country)	Scope & purpose	Stakeholder involvement	Rigor of development	Clarity & presentation	Applicability	Editorial independence	(min 1, max 7)	
Rosenfeld 2015, USA	89	69	74	86	52	79	7	+
DEGAM 2017, Germany	81	78	73	78	31	83	6	+
CBO 2010, the Netherlands	89	86	69	94	44	21	5	+
EPOS 2012, Europe	75	58	61	75	52	8	4	+/-
Desrosiers 2011, Canada	44	67	52	94	10	67	4	+/-
Bachert* 2014, international	58	36	10	50	6	42	3	-
Slavin 2005, USA	50	39	19	42	15	58	3	-
Dibildox 2012, pan-american	67	36	10	42	2	0	2	-
Scadding** 2008, UK	42	25	31	50	15	21	2	-
Brazilian guideline[a] 2008	44	22	10	28	13	0	2	-
mean	*59*	*50*	*39*	*65*	*20*	*39*		

Table 1. Continued

Legend:
Per domain the total score is reported. The scores are based on sum of scores of 2 assessors (N.K., S.C.). The maximal possible score for each domain is the number of questions multiplied by the number of reviewers multiplied by 7 (i.e., the score for "strongly agree"). The minimal possible score for each domain is the number of questions multiplied by the number of reviewers multiplied by 1 (i.e., the score for "strongly disagree").
Guidelines are arranged from top to bottom according to their AGREE score.
In the black box, guidelines with sufficient to good AGREE II scores are displayed
*, adapted from EPOS 2012
**, adapted from EPOS 2007
a, authors name unknown
Min, minimum score; max, maximum score
■, >67-100% good score; ■, >33-67% sufficient score; ■, 0-33% insufficient score
+, advised to use yes; +/-, advised to use yes, but with modifications; -, advised not to use.

Extracting CPG recommendations and harmonizing evidence

After extracting all recommendations for diagnosis and treatment, we harmonized LoE and GoR for each CPG (Appendix 4). There were different grading systems in use, some CPGs did not describe their grading system.[17,18] DEGAM, Slavin and Scadding did not provide LoE.[8,13,15] For all recommendations with corresponding LoE and GoR, see Table 2. The number of recommendations per guideline varied from 8 to 59, of these, approximately one third had a high GoR. Both for CPGs with good to sufficient quality, as for CPGs with insufficient quality, the distribution of recommendations with a high, moderate and low GoR showed variation (Table 2).

Upgrading of downgrading of evidence

Three CPGs did not provide LoE and could not be included in this analysis.[8,13,15] Of the remaining 7 Rosenfeld, CBO, Desrosiers and EPOS up- or downgraded evidence.[7-10] Up- and downgrading of recommendations was more common in CPGs with sufficient to good quality and all CPGs were transparent on their reasons to up- or downgrade evidence (Appendix 5)

Comparing of recommendations

Overall, there was variation in recommendations on type of diagnostic test or treatment, in direction of evidence and in GoR.

Diagnosis – Four out of five CPGs with sufficient to good quality and one CPG with insufficient quality provided recommendations on diagnosis (Table 3).[7-9,11,13] All five CPGs provided recommendations to perform a nasal endoscopy, CT scan and allergy testing (expect for allergy testing in patients with nasal polyps).[9] For two diagnostic tests (immune testing and maxillary tap) contradicting recommendations were provided. (Table 3)

Table 2. Level of evidence (LoE) and grade of recommendation (GoR)

		Rosenfeld n (%)	Degam n (%)	CBO n (%)	Epos n (%)	Desrosiers n (%)	Bachert n (%)	Slavin n (%)	Dibildox n (%)	Brazilian n (%)	Scadding n (%)	Total n (%)
Level of evidence	High	3 (38)	?	6 (21)	29 (49)	0	7 (50)	?	16 (44)	3 (20)	?	64 (37)
	Moderate	2 (25)	?	6 (22)	8 (14)	5 (31)	0	?	0	0	?	21 (12)
	Low/very low	2 (25)	?	14 (44)	10 (17)	11 (69)	0	?	20 (56)	7 (47)	?	64 (37)
	No data	1 (13)	?	0	12 (20)	0	7 (50)	?	0	5 (33)	?	25 (14)
Grade of recommendation	Strong	1 (13)	1 (5)	3 (11)	24 (41)	5 (31)	7 (50)	0	16 (44)	3 (20)	9 (24)	69 (28)
	Recommen-dation	5 (63)	12 (57)	7 (26)	4 (7)	8 (50)	0	4 (25)	0	0	3 (8)	43 (17)
	Weak	1 (13)	6 (29)	16 (62)	31 (53)	3 (19)	0	8 (50)	20 (56)	12 (77)	25 (68)	122 (49)
	No recommen-dation	1 (13)	2 (10)	0	0	0	7 (50)	4 (25)	0	0	0	14 (6)
	Total	8	21	26	59	16	14	16	36	15	37	249

Legend:
In the black box, guidelines with sufficient to good AGREE II scores are displayed
N, number of recommendations
%, percentage
?, unknown, not described
-, not provided

Treatment– All CPGs provided recommendations on treatment (Table 4), some made distinction between CRS with and without nasal polyps.[7-16] There were few recommendations provided by all CPGs, only treatment types recommended by 6 or more and FESS will be discussed (Table 4). All CPGs recommended the use of intranasal steroids (moderate or strong GoR, except for Slavin).[7-16] Intranasal saline irrigation was also recommended, with strong or moderate GoR, expect for Slavin, which stated that evidence is insufficient.[13] Most CPgs recommended the use of short/long term antibiotics, systemic steroids, antihistamines and leukotriene modifiers, although with different GoR (strong, moderate, weak).[8-16] However, there were also CPGs contradicting these

recommendations, i.e. advising not to use these treatments.[9,15,16] Decongestants were mostly advised not to use, although two CPGs recommended their use (with moderate or weak GoR).[11,14] Topical antibiotics were advised not to use by most guidelines, with GoR ranging from weak to strong. [8,10,14-16] Only 4 CPGs provided recommendations on the performance of FESS and 1 guideline rated the evidence as insufficient.[7-9,11,12] There were large variations (weak versus strong) in GoR for topical/systemic antifungals, bacterial lysates, leukotriene modifiers and prevention measures. (Table 4)

Limiting our results to the 5 CPGs with sufficient to good quality (Rosenfeld, DEGAM, CBO, EPOS and Desrosiers), slightly changed the above results.[7-11] Also here, we notice varying entry questions and contradicting recommendations (i.e. for long term antibiotics, leukotriene modifiers, decongestants, mucolytics and biologicals). However, we found more recommendations with a moderate GoR and differences between GoR were smaller, differing mostly between “weak and moderate” and “moderate and strong”.

Table 3. Diagnostic recommendations (Rosenfeld, Degam, CBO, Desrosiers, Slavin)

	Rosenfeld	Degam	CBO	Desrosiers	Slavin
Distinguish CRS from ARS or other causes	●	-	-	-	-
Take extensive patient history	●	-	●	-	-
Assess for lower airway conditions	●	-	●	-	-
Confirm diagnosis w/					
anterior rhinoscopy (or)	●	-	-	●	●
nasal endoscopy (or)	●	●	● [b]	●	●
CT	●	● [d]	● [c]	●	●
CT with low dose is preferred	-	●	●	●	●
Confirm presence/absence of nasal polyps	●	-	-	-	-
Assess for systemic diseases[a]	●	●	-	-	-
Allergy testing	●	● [e]	○ [f] ●	●	● [g]
Immune function	● [h]	-	-	○ [i]	●
Testing of smell, NO, GERD	-	-	●	-	-
Laboratory testing (general)	-	○	-	-	-
Type of culture					
Middle meatus	-	-	●	●	-
Maxillary tap	-	-	○	● [j]	-
Swab	-	-	-	○	-
In case of therapy failure consider other diagnoses	-	-	-	●	-

Table 3. Continued

Legend:
In the black box, CPGs with sufficient to good AGREE II scores are displayed
•, recommended
○, recommended not to
-, not mentioned in guideline
■, strong
■, moderate
■, weak
■, no grade of recommendation
w/, with
ARS, acute rhinosinusitis
CRS, chronic rhinosinusitis
CT, computed tomography of paranasal sinuses
NO, nitric oxide
GERD, gastro-esophageal reflux disease

a, CF, immunocompromised state, and ciliary dyskinesia
b, for symptoms>3 months and severe
c, symptoms>3 months and normal endoscopy and preoperative
d, before operation
e, without polyps (for postoperative persistent complaints in patients without polyps was a strong recommendation
f, with polyps
g, for uncomplicated course
h, in patients selected on history and physical examination
i, for therapy failure
j, for patients with a complicated course of disease

Table 4. Treatment recommendations (all CPGs)

	Rosenfeld	Degam	CBO	EPOS	Desrosiers
INCS	•	•	•	•	•
Nasal saline irrigation	•	•	• sNP	• sNP / • cNP	•
Long term AB	-	• sNP / • [c] cNP	○	•	•
Short term AB (<14 days)	-	-	•[a]	•[a] sNP / • cNP	•
Systemic steroids	-	•	• cNP	• sNP / • cNP	•
Antihistamines	-	-	•[7]	○	•
Decongestants (topical/systemic)	-	○	○	○	•
Topical AB	-	○	-	○ sNP / ○ cNP	-
Leukotriene modifiers	-	-	•[f]	○ cNP	•
FESS[g]	NR	•[e]	•[d]	-	•
Mucolytics	-	•	-	○	•
Topical AF	○	-	-	○	-
Systemic AF	○	-	-	○	-
Alternative[h]	-	NR	-	○	-
Aspirin desentization	-	• [i] cNP	-	NR	
Proton pump inhibitors	-	-	○	○	-
Prevention measures	-	-	-	• [l] sNP	•[k]
Bacterial lysates	-	-	-	• sNP	-
Biological/ Immunosup-pressant	-	•	-	○	-
Capsaicin	-	-	-	○ cNP	-
Probiotics	-	-	-	○ sNP	-
Antral lavage	-	-	○	-	-
Furosemide	-	-	-	○ cNP	-
ANTI II 5	-	-	-	NR	-
Anti IgE	-	-	-	○ cNP	-
Azelastine	-	-	-	-	-

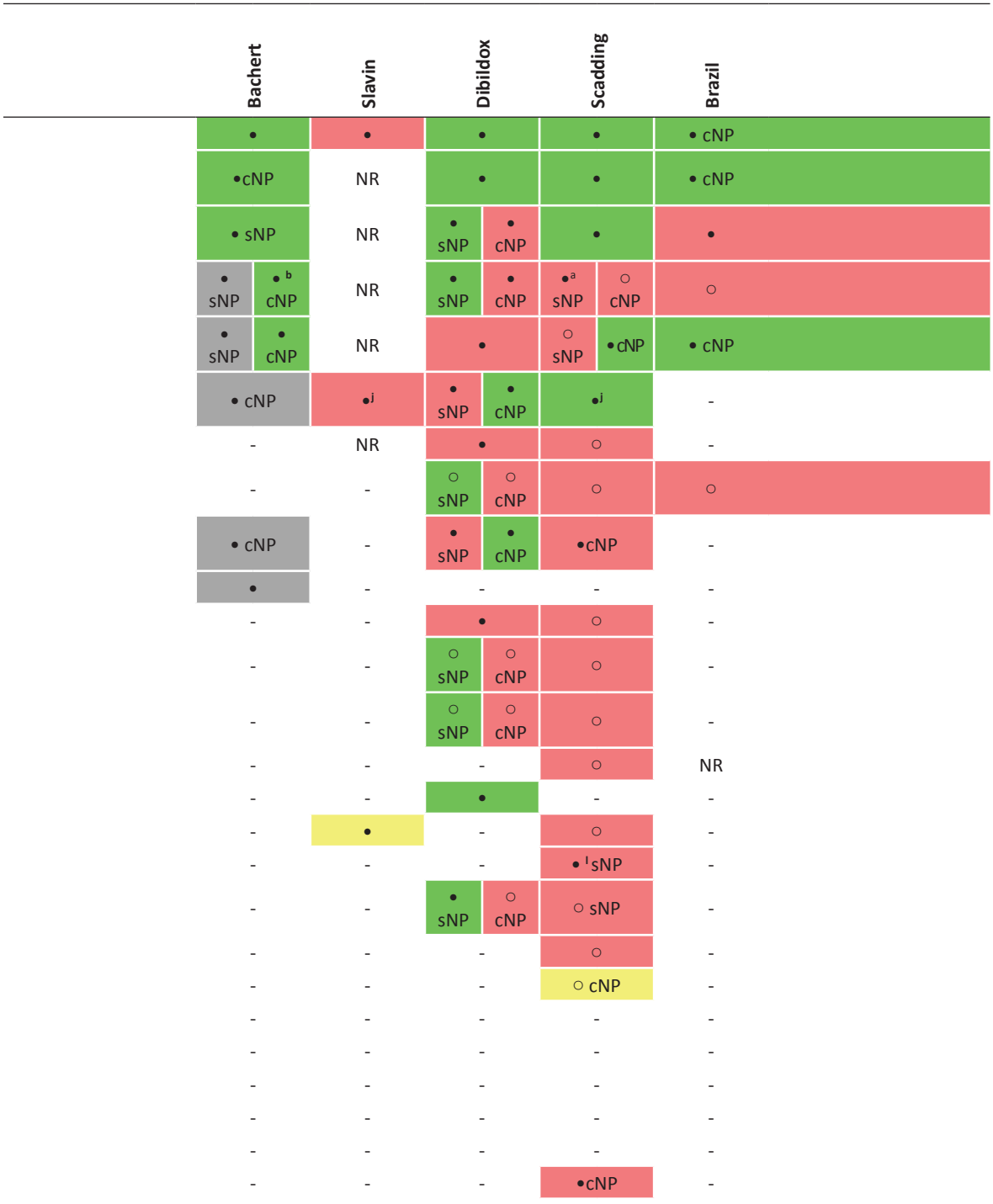

Bachert
Slavin
Dibildox
Scadding
Brazil
• cNP
•cNP
• sNP
NR
• sNP
• cNP
• sNP
• [b] cNP
• [a] sNP
○ cNP
○
• sNP
• cNP
○ sNP
• cNP
• cNP
• [j]
• [j]
-
○ sNP
○ cNP
○
• [l] sNP
○ sNP
○ cNP
NR

Table 4. Treatment recommendations (all CPGs)

	Rosenfeld	Degam	CBO	EPOS	Desrosiers
Long term Tx	-	-	-	-	-
Tx of CRS benefits asthma	-	-	-	-	-
Medical Tx=surgical Tx	-	-	-	-	-
Continuing medical Tx after FESS	-	-	-	• [m]	•

Legend:
No of guidelines, number of guidelines that included this recommendation
In the black box, guidelines with sufficient to good AGREE II scores are displayed
•, recommended
○, recommended not to
-, not mentioned in guideline
NR, no evidence, no recommendation
■, strong
■, moderate
■, weak
■, no grade of recommendation
CRS, chronic rhinosinusitis
sNP, without nasal polyps
cNP, with nasal polyps. If not indicated; recommended for with and without nasal polyps
INCS, intranasal corticosteroids
AB, antibiotics
FESS, functional endoscopic sinus surgery
Tx, therapy
=, is equal to
AF, antifungals

	Bachert	Slavin	Dibildox	Scadding	Brazil
	•sNP	-	-	•	-
	-	•	-	•	-
	-	-	-	•	-
	-		• [m]		• [m]

a, in case of exacerbation
b, doxycycline, initial or after therapy failure
c, for doxycycline, recommendation against macrolides (weak)
d, FESS above conventional surgery (weak GoR)
e, also as primary therapy (weak GoR)
f, for patients with asthma
g, after therapy failure
h, alternative treatments; Acupuncture, homeopathy, pytotherapy
i, in case of recurrent nasal polyps
j, in patients with allergic rhinitis
k, allergen avoidance, hand washing, quit smoking, nasal saline
l, allergen avoidance
m, these three guidelines provide additional recommendations for medical therapy post-surgery, results are not reflected in this article

DISCUSSION

Synopsis of key findings

We performed an extensive literature search and selected 10 (inter)national CPGs on CRS. We assessed their quality using the AGREE II instrument.[3,5] Rosenfeld, DEGAM and CBO scored highest, with good to sufficient quality, whereas EPOS and Desrosiers showerd sufficient quality.[7-11] The remaining CPGs often did not meet the AGREE II criteria, with insufficient scores especially in the domain "applicability".[12-16] We were able to harmonize all recommendations for comparison and found much variation between CPGs; in entry question (diagnostic test or type of treatment), in direction of evidence (advised to use/ not to use) and GoR. Only five CPGs provided recommendations on diagnosis, all of them recommended to perform nasal endoscopy, CT scan and allergy testing (expect for allergy testing in patients with nasal polyps), although with varying GoR's.[7-9,11, 13] All 10 CPGs provided recommendations on treatment of CRS, however there was only one treatment, i.e. the use of intranasal steroids, that was recommended by all CPGs (again with varying GoR).[7-16]

Comparison with previous studies

In 2010, Aarts et al. searched for CPGs on obstructive sleep apnea and concluded that 3 out of 7 were of good quality.[19] With AGREE II scores of 82 or more, quality was higher than for CRS.[19] Likewise, outside the field of otolaryngology, multiple CPG comparisons have been performed, for example for diabetes, glaucoma and juvenile arthritis.[20-22] These also show varying quality, with CPGs on similar topics varying between high and low quality. Typically, domain 2 and domain 4 score highest, and domain 5 (applicability) and 6 (editorial independence) score lowest, which is comparable to our results.[20-22]

We found that 37% of included studies in CRS CPGs were classified as high LoE (Table 3). This amount is high compared to a previous study in cardiology CPGs, where the amount of high-quality evidence studies ranged between 10 to 15%.[23]

When comparing recommendations, it is striking that there is much variation in entry questions which makes it difficult to compare CPGs. This has also been described as a major problem in previous studies.[19,22] Contradicting recommendations and variation in levels of evidence have also been previously reported.[19] On the other hand, for adult acute rhinosinusitis there seems to be more agreement, since a CPG comparison in 2018 for diagnosis and treatment found many similarities between recommendations, although CPG quality was not assessed in this study.[24]

Strengths & Limitations

We performed an extensive literature search and CPGs were retrieved and assessed by two independent assessors. We compared all recommendations for diagnosis and treatment for the 10 available guidelines.[7-16] However, some aspects of our study need further consideration.

First, although we performed an extensive search, we might have missed a CPG.

Second, we assessed AGREE II based on two independent assessors. It is advised to a minimum of two, but preferably four assessors, to increase reliability of the instrument.[3,5]

Third, we compared CPGs from different countries (Table 1) with different intended users which can lead to differences between guidelines. It is known that recommendations might differ per intended user, doctor's habits, patient expectations and healthcare structures.[25-27] This could partially explain differences in CPG entry questions.

Fourth, there are some limitations that can be addressed for the AGREE II quality assessment.[3,5] The instrument does not evaluate the clinical appropriateness or validity of the recommendations themselves. Even though rigorous methodology is important, this does not guarantee optimal and acceptable recommendations or improved health outcomes. For example, Rosenfeld scored highest according to AGREE II, but only provides 7 recommendations for diagnosis and management of CRS, and does not report on important aspects of treatment like FESS or use of antibiotics or steroids.[7] In addition, our results show that for assessing CPG quality one cannot rely on AGREE II alone, since CPGs with sufficient to good quality according to AGREE II, still show varying GoR and even contradicting recommendations.[7-10] On the other hand, our study shows that AGREE II does cover the most important aspects of CPG development, i.e. the transparency in the process of evaluating and explicitly describing considerations made before grading a recommendation.

Fifth, the overall quality of most of the selected CPGs is low.[11-16] This might have caused the variation of entry questions, contradicting recommendations and variation in levels of evidence. In contrast, these aspects were also reported in CPGs with higher quality.[7-10]

Sixth, it can be debated whether the differences between "strong" and moderate" on the one hand, and "moderate" and "weak" on the other hand, are large enough to influence CPG users. In general, it is advised to use the GRADE system, which uses a 2-point system for grading recommendations, for differentiating between either a strong or a conditional (weak) recommendation.[4,6]

Implications

The general public and especially patients with CRS can be reassured by the fact that there are five CPGs with sufficient to good quality for CRS.[7-11] However, it is obvious that future CPGs need to improve. Patient involvement through patient organizations may be an important step in achieving this. For CPG users, this study is important to raise awareness of the fact that CPGs show varying quality and sometimes contradicting recommendations. Therefore, they should be assessed critically before they are applied to patient care. Also, our results show that CPGs will not always provide answers to important clinical questions of otolaryngologists, like for example whether to perform diagnostic strategies or FESS.

For authors and board members involved in CPG development on CRS these results are important to keep in mind when updating or developing new CPGs. First, there should be uniformity in the definition for CRS, use of VAS score and distinction between with/without nasal polyps. Second, it is extremely important to follow AGREE II, since this is the international recommended tool for CPG development.[3,5] Especially in terms of facilitation of applicability improvement is needed. Third, for grading of evidence and recommendations it is advised to use GRADE.[4,6] Fourth, since for CRS so many CPGs already exist, it might be worthwhile to use existing CPGs in the process of updating or developing guidelines, like the ADAPTE CPG adaptation approach.[28] With this methodology CPGs are developed based on existing recommendations, that are either adopted or adapted to form a new CPG. Also, methodology for systematic reviews of CPGs has been suggested.[29] These methods can improve quality and reduce variation between CPGs in the future.

Our results can promote understanding of healthcare workers, help health care insurers and policy makers of the importance for defining standards for CPG development and quality. Thereby, they could improve CPG development and reduce variation between CPG.

For researchers, this study could be used to find knowledge gaps, or diagnostic tests or treatments with contradicting recommendations. For these topics, like for example the effectiveness of FESS or long-term antibiotics on CRS, studies can be set up and the results can be incorporated into updated or future CPGs. Also, our results show the need for development of rigorous methods to keep CPGs up to date.

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APPENDICES

Appendix 1. Search Strategy

Database	Search	Hits
Pubmed	((((((((((guideline[Title/Abstract]) OR guidelines[Title/Abstract]) OR guidance[Title/Abstract]) OR guidances[Title/Abstract]) OR protocol[Title/Abstract]) OR protocols[Title/Abstract]) OR standard[Title/Abstract]) OR standards[Title/Abstract]) OR "position paper"[Title/Abstract])) AND ((((((((sinusitis[Title/Abstract]) OR sinusitides[Title/Abstract]) OR rhinosinusitis[Title/Abstract]) OR rhinosinusitides[Title/Abstract]) OR nasosinusitis[Title/Abstract]) OR nasosinusitides[Title/Abstract])) OR (((((inflammatory[Title/Abstract]) OR inflammation[Title/Abstract]) OR infection[Title/Abstract]) OR disease[Title/Abstract]) AND ((((sinus[Title/Abstract]) OR sinal[Title/Abstract]) OR sinuses[Title/Abstract]) OR paranasal[Title/Abstract])))) AND ("1900/01/01"[Date - Publication] : "2018/11/16"[Date - Publication])	3626
Embase	(guideline:ab,ti OR guidelines:ab,ti OR guidance:ab,ti OR guidances:ab,ti OR protocol:ab,ti OR protocols:ab,ti OR standard:ab,ti OR standards:ab,ti OR 'position paper':ab,ti) AND (sinusitis:ab,ti OR sinusitides:ab,ti OR rhinosinusitis:ab,ti OR rhinosinusitides:ab,ti OR nasosinusitis:ab,ti OR nasosinusitides:ab,ti OR ((inflammatory:ab,ti OR inflammation:ab,ti OR infection:ab,ti OR disease:ab,ti) AND (sinus:ab,ti OR sinal:ab,ti OR sinuses:ab,ti OR paranasal:ab,ti))) AND [1-1-1900]/sd NOT [17-11-2018]/sd	6231

537940-L-sub01-bw-Kaper
Processed on: 20-12-2019

Appendix 1. Continued

Database	Search	Hits
Internet search	NIHR https://www.nihr.ac.uk/ NICE: http://www.nice.org.uk ICSI: http://www.icsi.org CADTH : http://www.cadth.ca/ DACEHTA : http://www.sst.dk/English/DACEHTA.aspx GIN : http://www.g-i-n.net AHRQ: https://www.ahrq.gov/ INAHTA: http://www.inahta.net/ https://richtlijnendatabase.nl/ NHMRC https://nhmrc.gov.au/ NZGG: https://www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group SIGN: http://www.sign.ac.uk/ USPSTF: http://www.USPreventiveServicesTaskForce.org CEP: https://effectivepractice.org/ SCHIN: https://clarity.co.uk/prodigy/ Clinical guidelines: www.clinicalguidelines.gov.au CMA: https://www.cma.ca/en/pages/cma_default.aspx ACP: http://www.acponline.org/clinical_information/guidelines/guidelines/ CPFC: http://cfpc.ca/ClinicalPracticeGuidelines/ Open Clinical: www.openclinical.org/guidelines.html American Academy of Otolaryngology–Head and Neck Surgery: https://www.entnet.org/ GIN: https://www.g-i-n.net/library	No new guidelines (all accessed November 21, 2018)
Google	"Guideline" OR "guidance" OR "position paper" OR "protocol" OR "standard" AND ("sinusitis" OR "sinusitis" OR "rhinosinusitis" OR "nasosinusitis" OR "inflammatory sinus disease" OR "sinus infection" OR "sinal inflammation" OR "sinal infection" OR "sinal inflammation" OR "paranasal infection" OR "paranasal inflammation")	Hits: 25.800.000 on November 21, 2018 First 150 hits; no new guidelines

Appendix 2. Excluded based on full-text screening

Authors name	Reason of exclusion
Alberta CPG	acute
Gruppo Bologna	children
American Academy of paediatrics	Children (up to 21 yrs)
Blomgren	acute
Benninger	Primary care
Brink	acute
Esposito	Acute/children
Fokkens 2005	Old version (replaced by 2012)
Gwaltney	acute
Hickner	acute
Huntzinger	Primary care
Hytonen	Primary care
ICSI	Primary care
IDSA	acute
Lim	Primary care
Cordero	acute
Medical Associates	acute
Thomas	Primary care (EPOS)
NHG	Primary care
NICE	Primary care
Orlandi	Not a clinical practice guideline*
Meltzer	Not a clinical practice guideline**
Sierra Health Care	Primary care
Sinus and Allergy Health Partnership	acute
Siow (singapore)	Primary care
Skye	Primary care
Snow	acute
Stuck	old version (replaced by DEGAM)
Tremolieres	acute
Washington Sate Department	acute
Wong	acute
Zhongua	Chinese

Legend:
*, in the introduction it is stated that the document should not be seen as a clinical practice guideline
**; guideline for setting up further research in CRS

Appendix 3. Harmonization of level of evidence (LoE) and grade of recommendation (GoR)

		Rosenfeld	CBO	Degam, Desrosiers	EPOS, Scadding[b], Slavin, Brazilian, Bachert[c]	Dibildox
LoE	High	A/B	A/B	Strong	Ia/Ib	1++/1+
	Moderate	B/C	B/C	Moderate	II	2
	Low/very low	C, D	C, D	Option, weak[a]	III+IV	3, 4
GoR	Strong	Strong	1	Strong	A	A
	Recommendation	Recommendation	2	Moderate	B	B
	Weak	Option	3,4	Weak	C, D	C, D

Legend:
Systems of grading: CBO; CBO. Rosenfeld; AAP[17]. Degam; GRADE[4], Desrosiers GRADE[4], AAP[17]. EPOS/Scadding/Slavin; Shekelle[18]. Brazilian/Bachert/Dibildox; grading system not described
a, low/very low for Degam
b, adapted from EPOS 2012
c, adapted from EPOS 2007

Appendix 4. Upgrading and downgrading of recommendations (7 CPGs[a])

LoE	GoR	Rosenfeld n (%)	CBO n (%)	EPOS n (%)	Desrosiers n (%)	Bachert n (%)	Dibildox n (%)	Brazil n (%)
high	strong	0	1 (4)	24 (41)	0	7 (50)	16 (44)	3 (20)
high	moderate	3 (38)	4 (15)	0	0	0	0	0
high	weak	0	0	7 (12)	0	0	0	0
moderate	strong	1 (13)	0	0	1 (6)	0	0	0
moderate	moderate	1 (13)	4 (15)	4 (7)	4 (25)	0	0	0
moderate	weak	0	2 (8)	3 (5)	0	0	0	0
Low/very low[b]	strong	0	0	1 (2)	3 (19)	0	0	0
Low/very low[b]	moderate	1 (13)	0	0	4 (25)	0	0	0
Low/very low[b]	weak	1 (13)	15 (58)	20 (34)	4 (25)	0	20 (66)	12 (80)
No recommendation		1 (13)	0	0	0	7 (50)	0	0
Total (up or downgrading)		4 (50)	10 (38)	26 (44)	12 (75)	0	0	0
Explanation for up/down grading		yes	yes	yes	yes	NA	NA	NA
Total		8	26	59	16	14	36	15

Legend:
LoE, Level of evidence
GoR, Grade of recommendation
In the black box, CPGs with sufficient to good AGREE II scores are displayed
a, excluded because no LoE was provided: DEGAM, Scadding and Slavin
n, number of recommendations
%, percentage
b, low level of evidence or no data
□, downgrading of evidence
■, upgrading of evidence
NA, not applicable

Appendix 5. Definition of Chronic Rhinosinusitis

Chronic Rhinosinusitis (with or without nasal polyps) in adults is defined as:

Presence of two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

± Facial pain/pressure;

± reduction or loss of smell;

for ≥12 weeks;

and either

• endoscopic signs of:

- nasal polyps, and/or

- mucopurulent discharge primarily from middle meatus

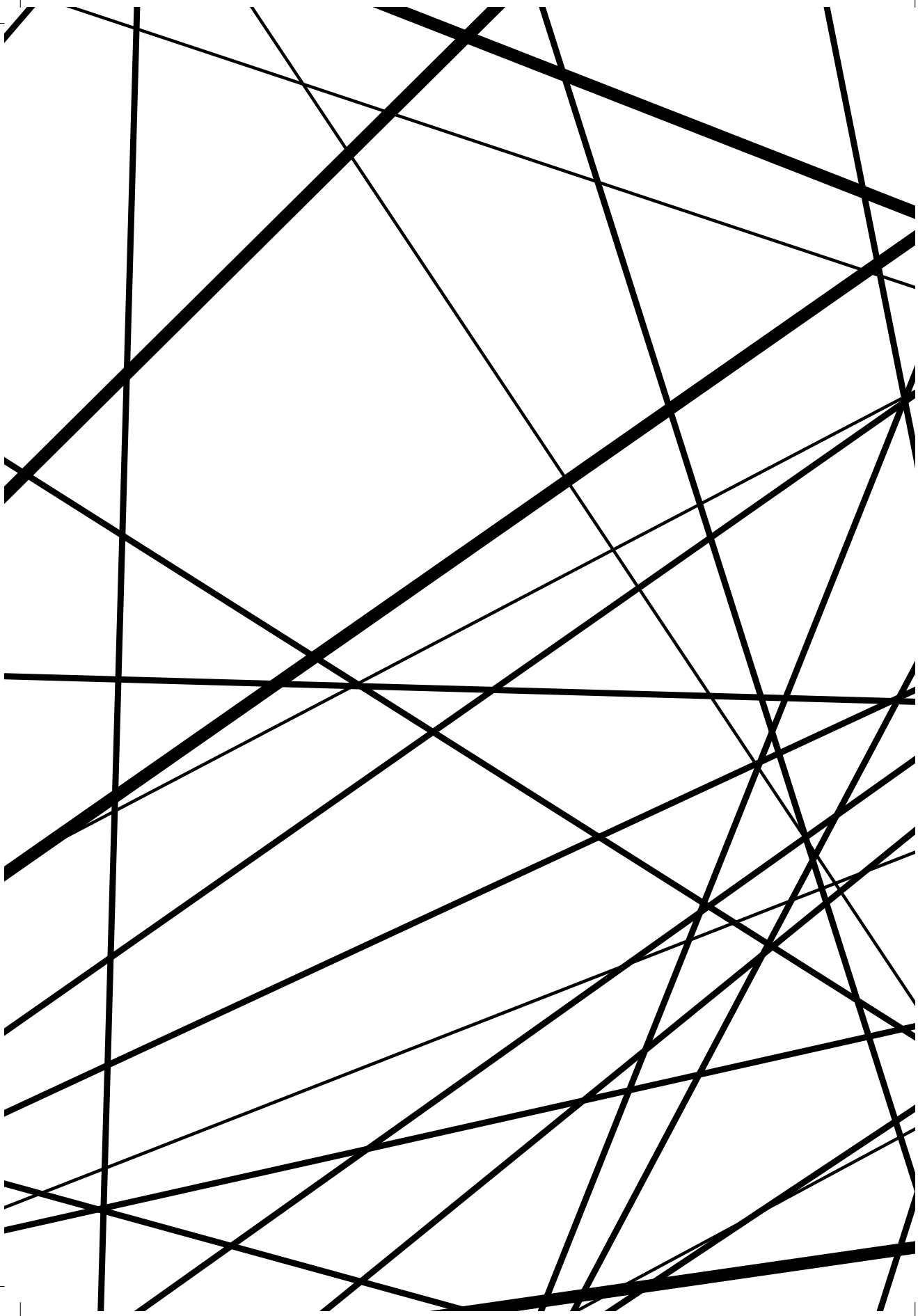
and/or

-edema/mucosal obstruction primarily in middle meatus

and/or

• CT changes:

- mucosal changes within the osteomeatal complex and/or sinuses



CHAPTER 9

Summary of main results and general discussion

SUMMARY

In part one, behavior around evidence in otolaryngology practice is further assessed. In **Chapter 2** the development and validation of an inventory to measure barriers and facilitators for evidence-based practice behavior (EBP) are described. This EBP Inventory is a framework for future studies and is ultimately intended for health care teams and organizations to assess local conditions for EBP, to aim efforts at improving or maximizing EBP. The inventory was developed with the support of international EBP experts and consists of items in five dimensions; attitude, subjective norm, perceived behavioral control, decision making, intention and behavior. It shows adequate face and content validity, discriminative power, internal consistency and test-retest reliability. In Chapters 3 and 4 guideline compliance for chronic rhinosinusitis (CRS) among Dutch otolaryngologists is assessed using different methods. In **Chapter 3**, clinical practice guideline (CPG) adherence for CRS is measured with a nationwide survey, conducted in 2017. In the Netherlands, both the Dutch guideline (CBO 2010) and EPOS 2012 are in use. Dutch otolaryngologists show high self-reported adherence and sufficient to good guideline adherence measured with questions about clinical scenarios based on guideline recommendations.

In **Chapter 4**, healthcare reimbursement claims data for the diagnostic code “sinusitis” of 2016 are presented. Data on >99% of healthcare providers in the Netherlands were included. 61% of patients underwent nasal endoscopy, 51% CT scanning and 16% were operated (mostly functional endoscopic sinus surgery) Except for nasal endoscopy, health care utilization patterns were in line with guideline recommendations., which is corroborated by limited regional practice variation.

In part two, the quality of the evidence base for otolaryngology in general is assessed. In **Chapter 5**, the different publication types from major otolaryngology journals and high impact factor medical journals in the year 2010 are presented. 2% of publications in high impact factor medical journals, were studies conducted in the field of otolaryngology. In the context of EBP, systematic reviews and original publications concerning patient care are found to be most relevant, especially with research questions related to therapy, diagnosis, prognosis and etiology. Overall, we found a low proportion of systematic reviews (2%) and just under 50% of otolaryngology publications that were publications related to patient care. In **Chapter 6** the risk of bias (RoB) of the therapeutic publications identified in Chapter 5 was critically assessed. 9% of publications had a low or moderate RoB, 91% had a high RoB. Results were better (24% vs 76%) for high impact factor medical journals, compared to otolaryngology journals (5% vs 95%).

In part three the quality of the evidence base for CRS is further assessed. **Chapter 7** displays three Evidence-Based Case Reports (EBCRs), that are based on clinical questions for CRS, with a corresponding systematic search for evidence, critical appraisal and formulating of a recommendation. (7.1) Diagnosis: nasal endoscopy is recommended to confirm the diagnosis of CRS. In case of negative findings at endoscopy, a CT is recommended. (7.2) Prognosis: there were no studies or inconclusive evidence for age as a predictor for a prolonged or chronic course of ARS. Therefore, older patients should not be managed in a separate way. (7.3) Therapy: nasal saline irrigation (compared to nasal saline spray) as an adjunct to co-medication, showed limited symptom improvement against little risk of side effects. The EBCRs have been used in two CPG updates (USA and Germany), which shows their potential use for (modular) updating of CPGs.

Chapter 8 shows a quality assessment and comparison of the 10 international CPGs for CRS that currently exist. Five guidelines were of good or sufficient quality according to AGREE II. Overall, there was much variation between guidelines in recommended diagnostic test or intervention, direction of evidence and grade of recommendation. We found consensus for nasal endoscopy, CT scan, allergy testing and intranasal steroids. CPGs should be systematically updated and developed using standardized methodology, in order to improve quality and comparability.

GENERAL DISCUSSION

Main findings

Otolaryngologists seem to have adopted CRS guidelines and adhere to them in their daily practice. However, the quality of a large part of the underlying evidence and guidelines is insufficient and needs to be improved. According to the EBP principle, patient outcomes are optimal when the best available evidence is followed and medical practice is provided according to existing CPGs. The evidence pipeline model merely assumes that the challenge of EBP is the integration of evidence in daily practice. However, our results show that, at least in otolaryngology practice, this integration has already taken place, despite multiple barriers that have been previously described. Our findings suggest that the biggest concern is no longer the integration of evidence into practice, but the characteristics of the evidence itself and the role of CPG's. Despite a substantial evidence base in otolaryngology, some important limitations can be addressed.

In otolaryngology journals, there is limited availability of publications based on clinical research topics relevant for patient care (therapy, diagnosis and prognosis), while these publications types are most important for otolaryngologists when answering clinical questions.

Most of these clinical research publications are of low quality, e.g. over 90% of therapeutic publications suffer from a high risk of bias. These findings are supported by previous research in different health care settings.[1-3]

CPG recommendations are often based on insufficient quality evidence. For CRS, we found that almost 50% of the evidence underlying recommendations of 10 major guidelines were of high (37%) or moderate (12%) quality. For 37% quality was low and for 14% there was no evidence available.

The quality of CPGs is varying. Ten CPGs for CRS currently exist, with quality varying from low (five guidelines) to satisfactory/good (five guidelines). Guidelines with sufficient to good quality still showed remarkable differences.

The findings of this thesis raise some important concerns regarding the role and place of research evidence, CPGs and clinical practice variation in otolaryngology.

PART ONE: EVIDENCE-BASED PRACTICE BEHAVIOR

Distinction between warranted and unwarranted variation

One of the main benefits of working according to EBP, is that it has the potential to reduce unwarranted practice variation, i.e. variation that is not explained by patient needs or patient factors and thus raises issues about efficiency and effectiveness of health care.[4]

Clinical care can be grouped into three main categories; effective care, preference-sensitive care and supply-sensitive care, each with a different risk for the occurrence of unwarranted variation.[4]

Effective care is healthcare that has proven to be effective, there is evidence or a CPG recommendation that benefits outweigh the risk. Virtually all patients with medical needs should receive this care. When variation is found in this category, it is most likely to be unwarranted. Nonetheless, warranted variation remains possible when patients might not accept the offered care.

Preference-sensitive care involves care where several generally accepted interventions of equivocal effectiveness are available (e.g. elective surgery). For this category, variation is acceptable if based on informed patient choice by shared decision making and not on differences in professional opinion. FESS is considered elective surgery and most CRS related health care falls into the category of preference-sensitive care, making it likely for

variation to occur. The fact that we found limited practice variation, therefore, shows that non-patient-centered decision making for CRS probably doesn't take place on a regular basis in the Netherlands.

Supply-sensitive care comprises clinical activities (doctor visits, diagnostic tests, hospital admissions), that are related to the capacity of the local healthcare system. Increases in use often don't lead to improved health outcomes but they do increase costs. For CRS data, we found that hospital visits and diagnostic testing showed limited variation, therefore, we have little reason to believe that this is care dictated by the healthcare system.

The role of mindlines

Decision making in clinicians is not only based on the stepwise integration of research evidence, which is assumed by the evidence pipeline model. We found during the development of the EBP inventory that EBP behavior consists of at least 5 different dimensions in a formative model (attitude, subjective norm, perceived behavioral control, decision making, intention and behavior), which is integrated by clinicians in their decision-making process. In 2004 this process was studied in further detail in general practitioners.[5] It was shown that clinicians predominantly base their decisions on "mindlines"; internalized and collectively reinforced tacit guidelines and they rarely used explicit evidence or research directly.[5] In **Chapter 4**, to support this, the majority of respondents (61%) indicated that, although they adhered to evidence-based CPGs, they read publications on CRS less than once a month. This has important implications for the dissemination of research findings in clinical practice.[5] Although tacit knowledge is described in the original definition of EBP, the focus in strategies for implementing EBP has mostly been on explicit knowledge and the aspect of mindlines has not been explored much.[6]

PART TWO & THREE: QUALITY OF THE EVIDENCE IN OTOLARYNGOLOGY AND CRS

Reducing research waste

Our findings suggest that research quality needs improvement. These findings are supported by previous research calling for a transformation of EBP and refocusing it on usable evidence.[1-3] Despite the increasing number of scientists, the accumulation of scientific publications and growth of research investments, research quality has not improved.[2,3] This calls for prioritizing of high-quality research and establishing research agendas involving research funders, research ethics committees and investigators.[2,3]

Several measures to achieve this can be addressed: Clinical trials should focus on clinical significance rather than statistical significance.[7] There should be more regulation of adequate, systematically developed reporting and quality protocols and methodologists should be involved at a greater extent.[3] Increased transparency should be achieved by protocol and data-sharing.[2,3]

Scientists should be rewarded based on good research and documentation quality and reproducibility of study outcomes, rather than on statistical significance and "bean counting" (counting publications and height of impact factor).[2,8] The pharmaceutical industry should not influence research agendas.[3,8]

The role of experience

Even though there is an extensive and expanding evidence base, there are still many clinical questions that cannot be answered using EBP. It is estimated that for about 50% of questions concerning medical practice there is some evidence available.[9] Besides, a substantial amount of established medical treatments remains that have never been validated or challenged.[10]

So, despite existing protocols and standards for care, the rest of medicine is not based on evidence from systematic clinical empirical research. Medicine is shaped by conventional craftsmanship, relies on see-one, do-one, teach-one principle and therefore will continue to rest on traditions and routines.

Additionally, it might even be stated that recommendations based on low quality and indirect evidence might pose the same level of uncertainty about patient outcomes, as recommendations formed in the absence of evidence. Also, the fact that evidence for a certain diagnosis or treatment is absent or not statistically significant, does not automatically mean it is ineffective or it should not be used in daily practice (absence of evidence does not mean evidence of absence).[11]

Limitations of clinical practice guidelines

Our results showed a varying quality of CPGs, with even sufficient to high-quality CPGs providing a wide range of different and even contradicting recommendations. The recommendations from the CPGs we identified are often based on research evidence of low or moderate quality. It is debatable whether follow up of low-quality evidence or a weak grade of recommendation will have a positive impact on patient outcomes. On the other hand, physicians should be cautious to deviate from strong recommendations based on undisputed low risk of bias and high applicability, so-called "effective care".[4] There the principles of shared decision making may warrant to deviate from the evidence only when after careful deliberation the perspective, conditions and circumstances of a patient may trump such evidence.

During CPG development, the formulation of recommendations by the guideline panel relies on consensus for the interpretation of evidence. In this way, professional opinion and local practice of key figures can still strongly influence CPG development, which might lead to recommendations that are not consistent with underlying evidence.[12] This may cause considerable differences between CPGs and again lead to unwarranted practice variation. Guideline panels should focus on the systematic approach consisting of searching and appraising evidence and translating this into transparent recommendations rather than formulating of consensus-based recommendations when the strength of the evidence is low.

Since medical science is evolving at a fast rate, guidelines might be outdated as soon as they are developed.[13] In addition, quality standards not only for medical research but also for guidelines development are constantly evolving. As a result, clinicians that follow outdated or insufficient CPGs might disadvantage or even harm their patients. In contrast, clinicians that act according to the latest medical research evidence might act in contradiction with outdated or insufficient CPGs.

In the past, the use of CPGs was considered to be supportive of clinical practice. In recent years, this has evolved towards CPGs being leading in clinical practice, and in some instances even dictating practice. CPG recommendations are increasingly being used by external parties, such as health care insurers, medical boards, and the Department of Health and have become mandatory measurements to measure and compare quality.[14] On the one hand, this may provide an excellent route for improving guideline adherence and limit practice variation, in particular for so-called “effective care”.[4] On the other hand, considering their limitations, even if CPGs are fully implemented a large uncertainty about the direction and precision of patient outcomes remains. The current quality level of the evidence and CPGs in otolaryngology has been demonstrated to be not convincing enough to conclude that all clinical practice should be based on it. As a result, only after careful consideration and with great caution, CPG recommendations can be used as a healthcare quality benchmark or can be considered as legally binding. Recommendations based on low-quality evidence, recommendations from outdated CPGs or CPGs with insufficient quality, should certainly not be used for this purpose. It should be kept in mind that many longstanding medical traditions, for which the benefit-harm ratio or the cost-effectiveness ratio has not been proven, have later been abandoned.[15] As such, only strong recommendations, based on low risk of bias, with a large direction of evidence should be considered eligible to serve for normative quality benchmarking. Even for this so-called “effective care”, it should be kept in mind that limited (warranted) variation due to patient’s preferences might still exist.[4]

IMPLICATIONS

Overall, it can be concluded that the best available evidence and clinical practice guidelines, should not define healthcare decisions, although they have become "standard of care". Due to patient factors and preferences, based on shared decision making, warranted variation will continue to have a place in clinical practice.[1,4] Based on this conclusion, we formulated multiple action points in relation to the future improvement of medical care.

Reducing unwarranted practice variation

The responsibility to make healthcare more transparent for patients lies primarily with healthcare providers, not just in the consultation room, but also at a population level. Medical professional organizations for different professions, together with patient and government organizations must set standards for quality of healthcare in order to self-regulate. If they fail to do so, patients could lose trust in the healthcare system and third parties (health care insurance companies) might step in to dictate practice.

Quality benchmarks are a method to increase transparency, assess and possibly even reduce unwarranted variation. In the Netherlands, all hospitals annually provide a limited amount of benchmarks to the Department of Health, usually based on CPG recommendations. This helps hospitals with optimizing quality standards and indicates where there might be variation that cannot be explained by patient factors. Every 5 years, a more extensive quality audit, including peer review, for each medical profession is performed. CRS has been subject of this quality audit for the last couple of years, which might have contributed to the observed limited practice variation. Although the registration burden is high, increased comparison of performances, with both national and international peers, is key in improving healthcare.

Although we found that healthcare claims data are not suitable to measure patient outcomes, they are widely used to search for regional practice variation. In the United Kingdom, the NHS Atlas of Variation in Healthcare shows geographic variation or routinely available data, aiming to serve as a stimulus for the search of unwarranted variation and as a guidance tool for areas where health and health care could be improved.[16] The Australian Atlas of Healthcare Variation and Dartmouth Atlas project (USA) are other examples.[17,18] In the Netherland, such an atlas is not yet published, but the availability of these routinely gathered data could increase transparency of healthcare for patients and healthcare providers. Our results show that these data could be generated through our national healthcare claims registration system, without the burden of additional registration. This could serve as a first step towards identifying unwarranted variation or possible guidelines deviations.

For the future, strategies should be developed to use data from the growing amount of information in electronic patient files to generate a better understanding of the clinical decision-making process. This could ultimately lead to more insight into practice variation and even has the potential to distinguish between warranted and unwarranted health care variation.

Improvement of science

Research agendas should be reprioritized based on patient-centered knowledge gaps. For example, they could be based on knowledge gaps that arise during guideline development, or that are formulated by medical professional associations and patients organizations.

Data science and artificial intelligence could greatly improve information and evidence management, which remains to be extremely time-consuming. The main goals could be to automate search and selection of articles and the development of updates on the availability of new research on specific topics.

Improvement of CPGs

Vigorous effort and great work has already been put into CPG development, resulting in numerous guidelines on a variety of topics, with for CRS alone ten available CPGs. In general, all CPG's should be developed and updated using current standardized methodology, preferably AGREE II and GRADE.[19,20]

For CRS in particular, our results call for an extensive update of the available evidence and alteration of the CPGs to current quality standards, since we found that all CPGs except one was published more than three years ago and that five CPGs for CRS met quality standards according to AGREE II.[19] Also GRADE methodology has not been implemented for most guidelines.[20] Besides, more consideration should be given to diagnostic guideline entry questions and prognostic entry questions should be formulated.

Updating of CPGs has been proven to be extremely challenging, not only for CRS but in various medical fields.[13] Central regulation of guideline updating should be set up by government authorities and/or medical professional associations to achieve improvement. For example, in the Netherlands, recently a government-funded project to update 4 outdated otolaryngology guidelines has been approved.

New strategies and research methods should focus on the process and methodology of updating CPGs. Since the process of updating is recourse intensive and time-consuming, it has been proposed that recommendations should be prioritized, to identify recommendations in the greatest need for revision.[21] Modular improvement of CPG's

could assist this selective updating approach. EBCRs could be applied to answer guideline entry questions that have been selected for updating like we showed in **Chapter 7** for CRS. These EBCRs were used to update both the American and German guidelines.

Other approaches could be the extended use of existing CPGs, in the form of systematic reviews of CPG's or the application of the ADAPTE approach to existing guidelines.[22,23] This allows for specific evidence to be updated, with the possibility of adapting the guideline to local settings. Since in the Netherland two guidelines for CRS are in use, these methods could be applied to bring more agreement between the Dutch guideline and EPOS.

International collaborations, like EPOS for CRS, produce guidelines that are intended to be used across multiple countries and have the potential to be more efficient in the use of resources and efforts for updating. Since other Western countries, i.e. Germany, USA and Canada also produce high-quality CPGs, collaboration with them might be the next step to further increase efficiency in guideline updating and possibly even limit practice variation at an international level.

CPGs should combine recommendations with context in a more individualized approach, to assist shared decision making. Research evidence should be introduced to inform the dialogue between patient and physician.[1] An example of this is patients decision aids and patient summaries of CPGs that are produced by some guideline groups.[1,24] Also, research findings should be expressed in ways that patients will understand (number needed to treat, absolute risk reduction).[1,25] For some diseases in otolaryngology decision aids have been developed (e.g. sudden deafness, pediatric tonsillectomy), though not yet for CRS.

More studies should focus on underlying mechanisms as to how medical research is used in daily practice and whether and how this contributes to the improvement of quality of the care provided. Implementation of research evidence and CPGs should continuously be further assessed, measured and improved, for instance, using the concept of "mindlines".[5]

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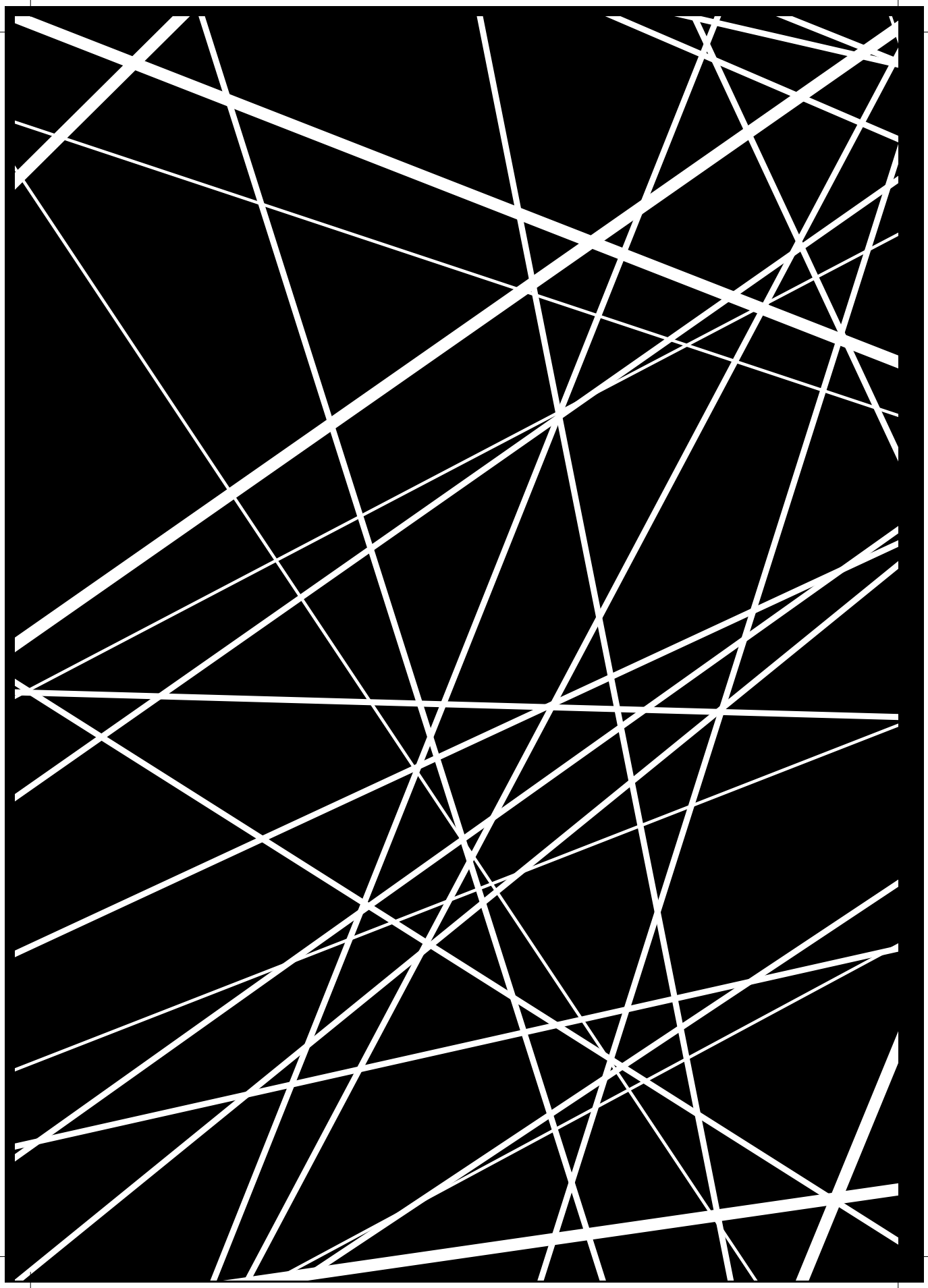
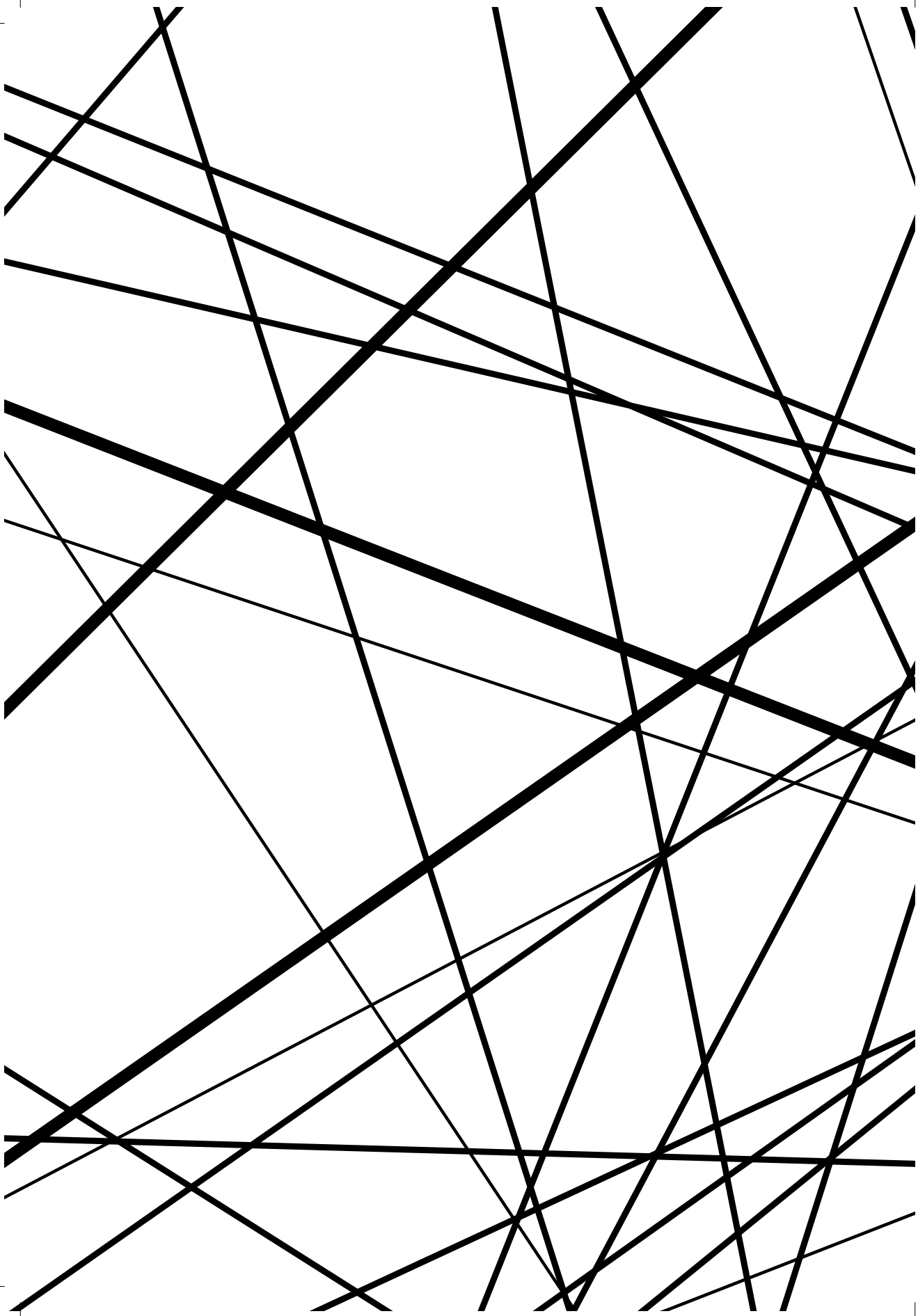


Dutch Summary
List of publications
Dankwoord



Dutch Summary
(Nederlandse samenvatting)

DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

In **hoofdstuk 1**, de inleiding, wordt beschreven wat Evidence Based Practice (EBP) inhoudt, namelijk het uitvoeren van een handeling volgens de huidige zorgstandaard. Deze werkwijze gaat uit van het best beschikbare bewijs uit medisch wetenschappelijk onderzoek gecombineerd met de eigen ervaring van de beroepsbeoefenaar en voorkeuren van de patiënt.

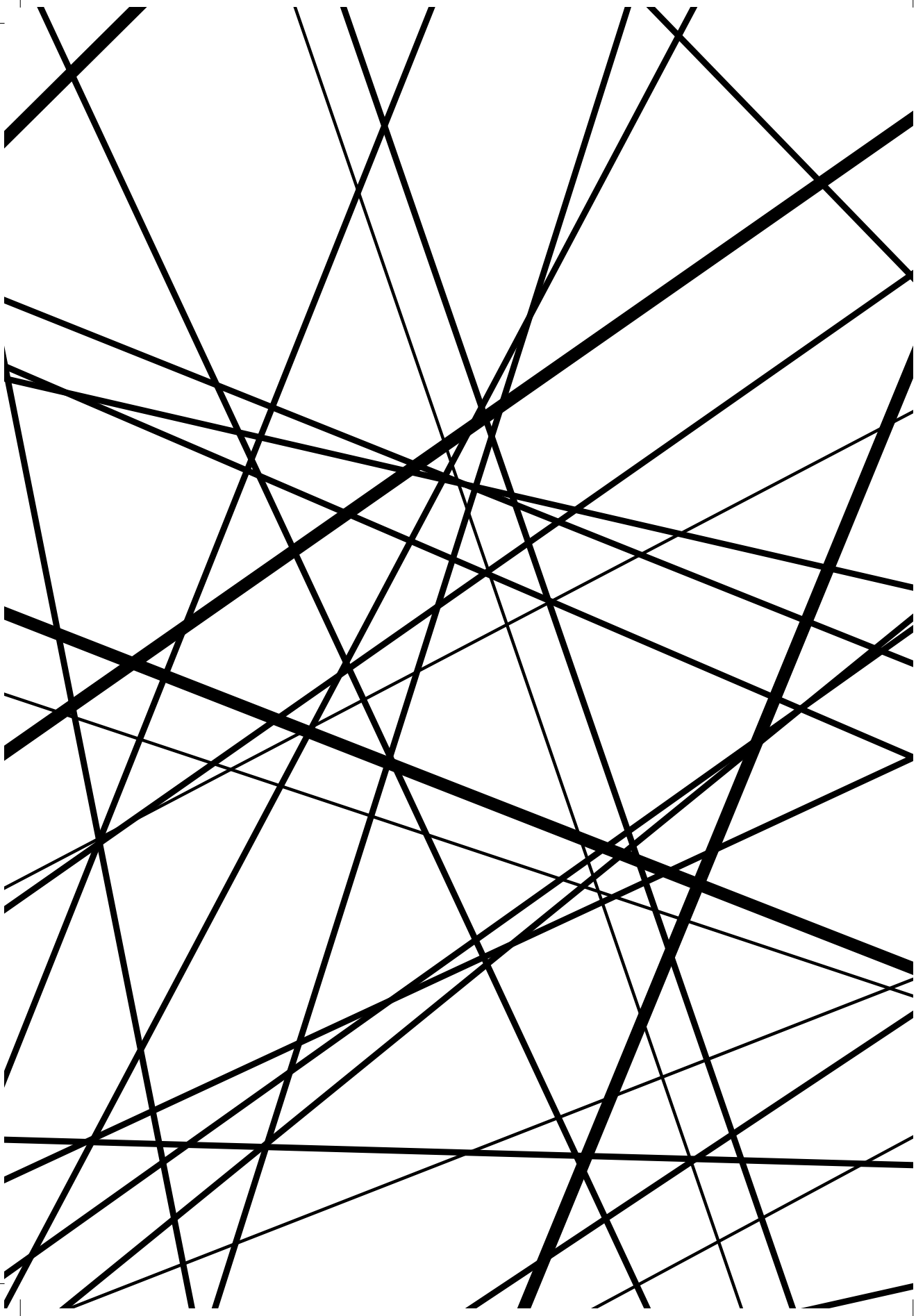
In het eerste deel van het proefschrift, wordt het EBP-gedrag van (kno-)artsen nader onderzocht. **Hoofdstuk 2** behelst de ontwikkeling van een vragenlijst met de hulp van internationale experts om barrières en facilitatoren van EBP te meten, gevolgd door validering van de vragenlijst. **Hoofdstuk 3** beschrijft de implementatie van de richtlijnen CBO en EPOS over chronische rhinosinusitis (CRS) en neuspoliepen naar aanleiding van een landelijke enquête onder Nederlandse kno-artsen. Uit deze samen met de Nederlandse KNO-vereniging uitgevoerde enquête blijkt dat aanbevelingen uit de richtlijnen voldoende tot goed worden opgevolgd in de dagelijkse praktijk. In **hoofdstuk 4** wordt op basis van via Vektis verkregen verzekeringsdata, het zorggebruik rond rhinosinusitis (DOT 36) in kaart gebracht. Hierbij wordt beperkte praktijkvariatie gezien en lijkt er niet structureel afgeweken te worden van het merendeel van de aanbevelingen uit de CBO richtlijn.

Het tweede deel van het proefschrift gaat over de kwaliteit van publicaties in een aantal belangrijke kno-tijdschriften en algemene medische tijdschriften met een hoge “impact factor”. In de context van EBP zijn systematische reviews en publicaties die direct betrekking hebben op patiëntenzorg, het meest relevant. Het betreft dan de onderwerpen diagnose, prognose, therapie en etiologie. Uit **hoofdstuk 5** blijkt dat 2% van de publicaties in kno-tijdschriften systematische reviews zijn en dat minder dan 50% van de publicaties de patiëntenzorg als onderwerp hadden. In **hoofdstuk 6** worden de therapeutische studies uit hoofdstuk 5 beoordeeld op hun methodologische kwaliteit door middel van een “risk of bias” (RoB) assessment. 9% van de publicaties had een lage tot gemiddelde RoB, 91% een hoge RoB. In algemene medische tijdschriften waren de resultaten beter (24% versus 76%) dan in de kno-tijdschriften, (5% versus 95%). Vergeleken met de algemene tijdschriften hadden de KNO tijdschriften een lagere impact factor.

In het derde deel van het proefschrift wordt de kwaliteit van wetenschappelijk onderzoek naar en richtlijnen over CRS beschreven. **Hoofdstuk 7** bestaat uit drie korte systematische reviews over diagnose (er wordt aangeraden een nasendoscopie te verrichten bij patiënten met CRS), prognose (geen andere behandeling van oudere patiënten met acute rhinosinusitis) en therapie (neusspoelen wordt aangeraden als toevoeging aan medicamenteuze therapie bij patiënten met CRS). In **hoofdstuk 8** worden de huidige 10

beschikbare richtlijnen voor CRS met elkaar vergeleken. Volgens AGREE II, een instrument om richtlijnen te beoordelen, waren er vijf van voldoende tot goede kwaliteit. Met betrekking tot ingangsvragen, richting van effect en sterkte van de aanbeveling bleken de richtlijnen aanzienlijk te verschillen. Alleen over het uitvoeren van nasendoscopie, CT-scan, allergietest en de toediening van intranasale corticosteroïden bestond consensus.

In **hoofdstuk 9** wordt geconcludeerd dat de Nederlands KNO-artsen in het algemeen bekend zijn met de inhoud van de beschikbare richtlijnen en deze ook toepassen in hun praktijk. De kwaliteit van de richtlijnen en het onderliggende bewijs laat echter nog vaak te wensen over. Verschillende strategieën die mogelijk voor verbetering zouden kunnen zorgen, zoals systematische richtlijnvernieuwing, gebruik makend van gestandaardiseerde methodologie, worden besproken.



List of publications

LIST OF PUBLICATIONS

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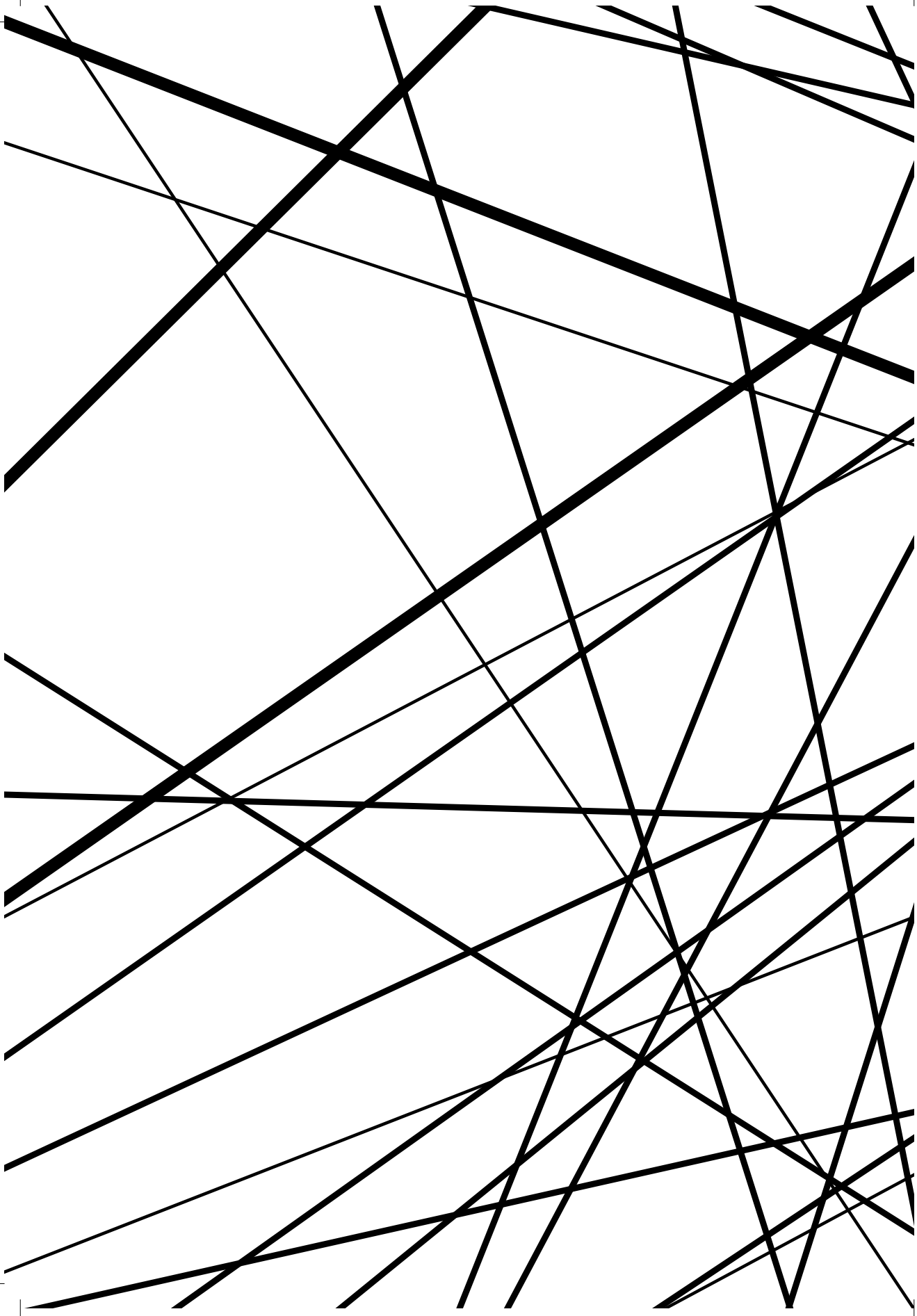

Dankwoord

DANKWOORD

Promotor, professor van der Heijden, beste Geert, we kennen elkaar inmiddels al weer bijna 10 jaar, vanaf de tijd dat ik als wetenschapsstudent in Utrecht bij jou begon. Jouw begeleiding motiveerde mij enorm, en ik was dan ook ontzettend blij dat ik in 2012 als arts-onderzoeker onder jouw hoede kon starten. Jij maakte al snel de prachtige overstap naar ACTA als professor in de Sociale Tandheelkunde en ik was net begonnen aan een roerige opleiding tot KNO-arts, met als gevolg dat het onderzoek een aantal jaren op een laag pitje kwam te staan. In 2017 wilden we het weer oppakken en met de toetreding tot het promotieteam van Mark en later ook Robert konden we de zaken vlottrekken. Nu kunnen we eindelijk de vruchten plukken van ons harde werken. Ik wil je ontzettend bedanken voor je geduld, je inzet, je tijd en je niet aflatende enthousiasme. Zonder jou was dit proefschrift nooit tot stand gekomen! Je bent altijd ontspannen, met evenzeer brede interesse in zaken binnen als buiten de wetenschap, een echte familieman en je raakt nooit uitgepraat, waardoor ik me altijd op mijn gemak voelde in jouw aanwezigheid. Wat het onderzoek betreft was je steeds snel met reacties en wedervragen, en elk overleg eindigde in een brainstormsessie waar ik weer nieuwe inspiratie uit putte.

Promotor, professor Stokroos, beste Robert, dank voor de stabiliteit en rust die je hebt gebracht in het UMC Utrecht en de steun die je bood aan mijn laatste projecten. Hiermee heb jij mij in staat gesteld om mijn proefschrift af te ronden. Je pragmatische instelling heb ik enorm gewaardeerd.

Copromotor, dr. Aarts, beste Mark, mijn proefschrift was geïnspireerd op jouw proefschrift en ik heb dan ook heel erg veel gehad aan jouw begeleiding. Toen Geert jou toevoegde aan het promotieteam, werkte dat als een katalysator en ik ben heel blij met de bijdrage die je hebt geleverd aan de verschillende projecten. Je was nauw betrokken, had altijd nuttig commentaar en bracht een goede balans tussen wetenschap en praktijk. Onze Skype-meetings waarbij jij vanaf de poli in Den Bosch inbelde en Geert vanuit ACTA waren altijd constructief en bovendien gezellig. Dank voor je no-nonsense manier van aanpakken en het altijd prettige overleg.

Ook wil ik mijn hartelijke dank uitspreken aan de geachte leden van de lees- en promotiecommissie voor het beoordelen van dit proefschrift en het deelnemen aan de zitting.

Beste medeauteurs, dank voor jullie inzet en bijdrage aan dit proefschrift.

Beste stafleden en opleiders van het UMC Utrecht, Meander en St. Antonius, dank voor de uitstekende opleiding die ik van jullie heb gehad.

Beste Maarten, Remco, Wilbert, Jan-Willem en Hubert, dank voor het vertrouwen dat jullie in mij stelden, eerst als arts-assistent en nu als KNO-arts. Jullie enthousiasme voor het vak werkt aanstekelijk. Ik leer nog steeds ontzettend veel van jullie en werk elke dag met veel plezier in de Gelderse Vallei.

Lieve arts-assistenten en oud-assistenten van het UMC Utrecht, jullie hebben het leven naast de opleiding en promotie een stuk draaglijker gemaakt! Samen carpoolen met de A'dammers, het koffiekwartiertje, gezelligheid op de H20-gang en later op de D5-gang, samen steppen, skiën en borrelen. Heel erg bedankt voor de leuke tijd en altijd fijn om jullie weer te zien bij KNO-dagen, borrels en andere KNO-evenementen. Met speciale dank aan van Bemmel van wie ik ongelooflijk veel heb geleerd!

Mijn liefste vrienden en vriendinnen, bedankt voor het lachen! Door jullie kon ik het ziekenhuis even vergeten, maar bovendien boden jullie altijd een luisterend oor. Jullie zijn me allemaal heel dierbaar.

Lieve Poepjes, al sinds onze studententijd in Utrecht waren we regelmatig samen in het Foxy Hole of in het Pakhuis, o.d.z. 'Ben je op pad met het Griekse leger?' Later naar Amsterdam voor veel festivals, onze fijne traditie om voor elke verjaardag lekker samen uit eten te gaan en natuurlijk Noordwijk. Helaas bleek een aantal Portugese campers niet tegen ons opgewassen. Inmiddels zijn we volwassen(er) geworden maar als we samen zijn is het nog steeds een oorverdovend kippenhok. Laat dat alsjeblieft nog heel lang duren.

Lieve Conyo's, we kwamen bij elkaar uit liefde voor feestjes en dat hebben we dan ook veel gedaan. Samen hebben we niet alleen heel Amsterdam afgestruind, maar ook Frankfurt, Ibiza en de Tiroolse Alpen. En ook voor de keerzijde van de medaille konden we bij elkaar terecht. Dank voor al deze momenten en de vele mooie die zeker nog gaan komen in de toekomst!

Lieve Apeldoorn-vriendinnetjes, Isabelle, Kirsten, Els en Gelein, zo bijzonder hoe lang ik jullie al ken en wat hebben we samen een heerlijke basisschool, middelbareschooltijd en studententijd gehad, inclusief vele gênante momenten die nog steeds graag worden opgerakeld. Altijd als we elkaar zien is het alsof die tijd nog gisteren was.

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Lieve Liet, ‘Stokstaartje’, wat is het altijd gezellig met jou en je tomeloze energie, brede interesse en gemak in de omgang. Je bent altijd van de partij en hebt verhalen voor tien. Hiermee wist je me in zware tijden weer op te peppen en af te leiden.

Lieve Noor, op veel vlakken zijn we elkaars tegenpool maar op de een of andere manier pakt het goed uit. We kunnen elkaar adviseren en soms bekritiseren zonder strijd en dat levert altijd weer interessante gesprekken op. We zijn meerdere malen huisgenoten geweest, hebben regelmatig gefungeerd als elkaars vangnet en daarmee ben je inmiddels bijna familie geworden.

Lieve Al, we zijn al sinds het begin van onze onderzoekstijd onafscheidelijk. Ik kwam zelfs al snel bij jou in de straat wonen en we deelden een autootje. Behalve dat ik ontzettend veel steun aan je heb gehad, hebben we het vooral ook heel erg leuk! Eindeloos veel verre reizen, tripjes, lunches, festivals, feestjes, etentjes, yoga en kitesessies. Je bent een bijzondere combi: rap van tong, met een groot hart en een luisterend oor, altijd gehuld in een stylish outfit.

Lieve familie Nijpjes, Fred, Marian, Thijs, Karin, Lukas en Anne, jullie zijn een geweldige en gezellige schoonfamilie die me vanaf dag één op mijn gemak stelde en bij wie ik me helemaal thuis voel.

Lieve Jan en Chris, mijn liefste oudertjes, wat heb ik allemaal aan jullie te danken. Een heerlijke jeugd, een onbezorgde studententijd en een niet aflatend vertrouwen in mijn kunnen, ook als ik er zelf niet van overtuigd was. Dank voor jullie oneindige steun, liefde en vertrouwen, die zich onder andere uitte in een eindeloze stroom peptalks, bakjes met eten in de ijskast, uitgeknipte krantenartikelen die ik niet mocht missen, onderhoudsbeurten voor de auto, en regelmatig informeren of ik wel genoeg vitamines binnenkreeg. Ik durf nu ook toe te geven dat dit proefschrift niet tot stand had kunnen komen zonder Jans uitstekende Excel skills...

Lieve Joost, ik weet dat je dit vreselijk vindt maar je moet er nu toch echt aan geloven. Heel veel dank voor alle liefde en rust die ik bij je heb gevonden. Met jou zijn de alledaagse dingen bijzonder geworden en je maakt me altijd aan het lachen. We lijken op elkaar in meerdere opzichten en dat maakt alles makkelijk; in nuchterheid, zelfspot, relativeringsvermogen en ongevoeligheid voor een niet-opgeruimd huis. Daarnaast kunnen we samen ook genieten van de goede dingen des levens, van eten in een sterrentent tot op pad gaan in een klein campertje volgepropt met kitespullen. Je maakt me heel gelukkig en ik kijk uit naar de komende jaren. We hebben we heel wat mooie avonturen in het verschiet, om te beginnen in Nieuw-Zeeland.