PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Regional differences in endoscopic sinus surgery in Finland: a nationwide register based study
AUTHORS	Toppila-Salmi, Sanna; Rihkanen, Heikki; Arffman, Martti; Manderbacka, Kristiina; Keskimaki, Ilmo; Hytönen, Maija

VERSION 1 – REVIEW

REVIEWER	Orlando Guntinas-Lichius Jena University Hospital, Germany
REVIEW RETURNED	30-Mar-2018

GENERAL COMMENTS	Title: "nationwide" - the readers should know the country you talk about Title. should make clear the methodology: population-based? register-based? ... Abstract: "Setting: Hospital discharge data ..." - i.e. all ESS patients are treated as inpatients in hospitals in Finland? Abstract: "Patients aged under 15 years ... were excluded" - I miss a rationale for this decision Abstract: "and at a younger age" - what is "younger age"? Abstract: "There is a fourfold difference between the districts with the highest and lowest rates" - and this was statistically different? I miss hard data Abstract: "Compared with males, females undergo ESS significantly more frequently (57% of the procedures), more often due to CRS without nasal polyps, and at a younger age"- Same, I miss hard statistical data Abstract: "Multilevel analyses showed that lower age and availability of medical services were independently associated with higher ESS rates" - same, what is "lower age"? and what means "availablility" - is this distance to ESS surgeon/hospital? Results: Main indications? CRS with/without polyps? Allergy background of the patients? Conclusions: are conclusions for Finland, make this clear. Conclusions: an important factor is of course, also the quality of medical treatment of CRS, and the criteria to indicate ESS Strength/limitation bullets: "the actual need for sinus surgery"- what do you mean with "actual"? What this paper adds: "survey" - would not use this term, the readers could think of interviews/questionnaires What this paper adds": "in availability of medical services" - see above, it should be clearer what is meant by "availability"? Introduction: Fine but too long. Get more to the heart of your topic. Methods: I do not find any definition or clear model for "hospital availability"? What do it really mean when a patient is operated

	outside his home district? For me actually nothing without knowing the reasons. Methods: "Most patients use the closest public hospital in their home hospital district" - I miss a reference for this statement Methods: "Diagnosis was determined as CRS with nasal polyps (CRSwNP) if any of the main or secondary diagnosis codes were J33. "- This is imprecise. J33 is focused on polyps in the nasal cavity and there is no security that J33 is coded in all patients with CRSwNP Table 1: redundant Results/Table 1: why is hypertrophy or air cells of the turbinates an indication for ESS? Results: I do not see it clearly: Was there a different surgery rate in private hospitals or not? Discussion: Actually the authors did not know much about the patients: age, gender, public/private hospital, without/with polyps (although the quality of this parameter was poor). Due to major limitations, partly addressed, especially not knowing anything about the pre-treatment, discussion on the variability is predominantly pure speculation. 5 1/2 pages for that is much too long. Discussion should not be longer than 3 pages

REVIEWER	Shahzada Ahmed University Hospital Birmingham Mindelsohn Way Edgbaston Birmingham B15 2TH
REVIEW RETURNED	27-May-2018

GENERAL COMMENTS	Excellent paper which adds to the literature on this topic.

REVIEWER	Carl Philpott University of East Anglia, UK
REVIEW RETURNED	28-May-2018

GENERAL COMMENTS	This paper has the potential to be informative but unfortunately is lost in the current presentation of the study. Major concerns: 1. The authors have adopted the use of the SQUIRE guidelines but as i will elucidate below there is a lack of structure and they would be better adopting the STROBE guidelines to help clarify the message. 2. The section headed "patients" includes details of ethical approvals 3. The inclusion and exclusion criteria are completely unclear as there are mixed messages evident through various parts of the paper as to exactly what patients' data was included: Page 11, Line 28 suggests specific surgical steps were part of the inclusion criteria If the focus of the study was ESS for CRS then why include other diagnoses? if there is a justification to include these cases, then they need carefully defining in the inclusion criteria. Page 23, line 3 - suggests cases of recurrent ARS were included in the study 4. The reporting and analysis appears to be overly focused around sex and phenotype, neither of which are modifiable factors in the patients - this leaves the reader feeling as though the paper has not really elucidated anything that adheres to the aims of the study. 5. Page 20, line 47 - the last sentence of this paragraph is not consistent in this study!!!

	6. Page 21, line 34 - this is an example of where the explanation of the data is confusing/lacking - do the authors mean to imply that tertiary referrals have a higher operative rate as they are more likely to be revision cases? 7. Page 23 - lines 3-5 contradicts line 11-14 which suggests the need for ESS is not known - usually in cases of CRS it is where medical therapy alone has failed. 8. Line 54 in the conclusion makes a statement that is not qualified by any data captured in the study. 9. Over the page there is a mention of cost-effectiveness - this appears to be a missed opportunity within this study to not have looked at the tariffs for ESS in Finland and how that plays out with the varying rates. Minor concerns: 1.The list of strengths and limitations of the study on page 6 lists 3 results not strengths or limitations - please modify accordingly 2. Likewise, the section headed "what this paper adds" is just a summary of the paper and not an outline of the potential contribution to the literature. 3. It is not clear how prevalence data is derived from reference 3. 4. CRS is a clinical disorder encompassing a heterogeneous group of endotypes and two main phenotypes. 5. There is mention of predisposing factors being genetic and anatomical but these should be specifically referenced. 6. Comparing with other studies - ref 3 has a rate of 0.71/1000 - exactly the same so i would add this 7. Page 21, page 41 - what do you mean by "those with medical faculties"? 8. Page 22, line 15 - what do you mean by "ESS is usually a preference-sensitive care" 9. The word "thus" is over-repeated in this paragraph 10. The first sentence of the conclusion uses the word "also" but this appears misplaced as it is not clear what or where the also is additional to. In summary, this paper needs a major reworking to make it acceptable for publication by clarifying the message and reporting or what factors do indeed lead to variations.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Title: "nationwide" - the readers should know the country you talk about Title. should make clear the methodology: population-based? register-based? ...

Response. We have now revised the title as indicated.

Abstract: "Setting: Hospital discharge data ..." - i.e. all ESS patients are treated as inpatients in hospitals in Finland?

Response. We have now reformulated the setting part of the abstract as suggested and clarified this in the Methods section.

Abstract: "Patients aged under 15 years ... were excluded" - I miss a rationale for this decision
Abstract: "and at a younger age" - what is "younger age"?

Response. We appreciate the opportunity to clarify these points. Pediatric CRS patients under 15 years of age were not included due to potential differences in their disease etiopathogenesis and treatment (1). Future studies should address potential variation in ESS in pediatric population. We have clarified these points in the Methods and Discussion sections.
We have clarified the sentence “at a younger age” in the Abstract section.

Abstract: "There is a fourfold difference between the districts with the highest and lowest rates" - and this was statistically different? I miss hard data

Response. We have now added rates and their 95% CIs for the highest and lowest hospital district rates in the Results and Abstract sections.
Abstract: "Compared with males, females undergo ESS significantly more frequently (57% of the procedures), more often due to CRS without nasal polyps, and at a younger age"- Same, I miss hard statistical data

Response. We have clarified the sentence in the Abstract section.

Abstract: "Multilevel analyses showed that lower age and availability of medical services were independently associated with higher ESS rates" - same, what is "lower age"? and what means "availability" - is this distance to ESS surgeon/hospital?

Response. We appreciate the opportunity to clarify these points. Lower age mean 24-45 years of age and availability means any kind of ease to get the medical service including distance, queuing time, easiness to get appointment, etc. These aspects have now been clarified in the Abstract and Discussion sections.

Results: Main indications? CRS with/without polyps? Allergy background of the patients?
Conclusions: are conclusions for Finland, make this clear.

Response. This nationwide study aimed to examine ESS performed due to inflammatory sinonasal diseases including CRS with/without polyps. We agree that allergy background would have been important, yet atopy data was not available. Conclusions are for Finland. We have now added these to Abstract, Introduction, Discussion and Conclusion sections.

Conclusions: an important factor is of course, also the quality of medical treatment of CRS, and the criteria to indicate ESS Strength/limitation bullets: "the actual need for sinus surgery"- what do you mean with "actual"?

Response. Thank you for the excellent comment. We have now reformulated the sentence to better convey the message that disease prevalence data are not available in this study.

What this paper adds: "survey" - would not use this term, the readers could think of interviews/questionnaires What this paper adds": "in availability of medical services" - see above, it should be clearer what is meant by "availability"?

Response. We have removed the word “survey”. The paragraph “What this paper adds” has now been removed as indicated by the Editor. The word “availability” has now been explained in the Discussion section.

Introduction: Fine but too long. Get more to the heart of your topic.

Response. We have shortened the Introduction section as indicated. Thank you for this remark.

Methods: I do not find any definition or clear model for "hospital availability"? What do it really mean when a patient is operated outside his home district? For me actually nothing without knowing the reasons.

Response. We agree with the Reviewer that ”hospital availability” lacks a clear definition. We have used the term availability of medical services. We acknowledge that this term also requires more clarification, which we have now added in the Discussion section.

Methods: "Most patients use the closest public hospital in their home hospital district" - I miss a reference for this statement

Response. We have now added the reference in the Methods section as indicated by the Reviewer.

Methods: "Diagnosis was determined as CRS with nasal polyps (CRSwNP) if any of the main or secondary diagnosis codes were J33. "- This is imprecise. J33 is focused on polyps in the nasal cavity and there is no security that J33 is coded in all patients with CRSwNP Table 1: redundant Results/Table 1: why is hypertrophy or air cells of the turbinates an indication for ESS?

Response. We agree that there exists different definitions of solitary NPs in the nasal cavity. In this study we used EPOS definition of CRSwNP, in which any nasal polyps are considered as belonging to the phenotype of CRSwNP (1). We have added a reference to the Methods section. We agree that the information of Table 1 is redundant and have removed it.
We agree that hypertrophy or air cells of the turbinates does not normally fulfil criteria for ESS and could in part be related to wrong or incomplete insertion of diagnosis code. We have added this in the Discussion section.

Results: I do not see it clearly: Was there a different surgery rate in private hospitals or not?

Response. This is a very important question. Private hospitals, in which 13 % of all ESS procedures were performed, lack precise catchment areas in Finland and thereby population at risk. Yet, the risk ratios of the current study suggest that the proportion of private hospitals in the hospital district did have an effect on ESS operations. We have added discussion concerning this in the Discussion section.

Discussion: Actually the authors did not know much about the patients: age, gender, public/private hospital, without/with polyps (although the quality of this parameter was poor). Due to major limitations, partly addressed, especially not knowing anything about the pre-treatment, discussion on the variability is predominantly pure speculation. 5 1/2 pages for that is much too long. Discussion should not be longer than 3 pages

Response. Thank you for the excellent remark. We agree that our register-based data has limited information on background factors. We have now added this information in the Limitations chapter and have shortened the Discussion section as indicated.

Reviewer: 2

Reviewer Name: Shahzada Ahmed
Institution and Country: University Hospital Birmingham, Mindelsohn Way Edgbaston, Birmingham, B15 2TH, UK Competing Interests: None Declared

Excellent paper which adds to the literature on this topic.

Response. We would like to thank the reviewer for this positive assesment of our manuscript.

Reviewer: 3

This paper has the potential to be informative but unfortunately is lost in the current presentation of the study.

Major concerns:
1. The authors have adopted the use of the SQUIRE guidelines but as i will elucidate below there is a lack of structure and they would be better adopting the STROBE guidelines to help clarify the message.

Response. Indeed, this is not a quality improvement study. We have now removed The SQUIRE checklist and have provided the STROBE checklist instead.

2. The section headed "patients" includes details of ethical approvals

Response. The section concerning ethics approval and permission to use the data has now been moved.
3. The inclusion and exclusion criteria are completely unclear as there are mixed messages evident through various parts of the paper as to exactly what patients' data was included:
Page 11, Line 28 suggests specific surgical steps were part of the inclusion criteria If the focus of the study was ESS for CRS then why include other diagnoses? if there is a justification to include these cases, then they need carefully defining in the inclusion criteria.

Response. This study aimed to examine the number and rates of ESS performed due to inflammatory sinonasal diseases. We have now corrected this in the Introduction section as indicated.

Page 23, line 3 - suggests cases of recurrent ARS were included in the study

Response. Cases of recurrent acute rhinosinusitis without NPs were included in the study and were regarded here as being a subgroup of CRSsNP (with recurrent exacerbations). This has now been clarified in the Methods section.

4. The reporting and analysis appears to be overly focused around sex and phenotype, neither of which are modifiable factors in the patients - this leaves the reader feeling as though the paper has not really elucidated anything that adheres to the aims of the study.

Response. The reviewer makes a very important point. We have now rewritten the results section to focus more specifically to regional differences as it is the main study question.

5. Page 20, line 47 - the last sentence of this paragraph is not consistent in this study!!!

Response. As suggested by the reviewer we have removed the sentence.

6. Page 21, line 34 - this is an example of where the explanation of the data is confusing/lacking - do the authors mean to imply that tertiary referrals have a higher operative rate as they are more likely to be revision cases?

Response. We agree that this explanation of data has limited information value and we have thus removed it. Thank you.

7. Page 23 - lines 3-5 contradicts line 11-14 which suggests the need for ESS is not known - usually in cases of CRS it is where medical therapy alone has failed.

Response. We fully agree with the Reviewer that candidates for ESS can be defined precisely, however, no register data exist concerning the total population eligible for the operation but only for the population undergoing ESS. We have now reformulated this.

8. Line 54 in the conclusion makes a statement that is not qualified by any data captured in the study.

Response. We agree and have removed this sentence.

9. Over the page there is a mention of cost-effectiveness - this appears to be a missed opportunity within this study to not have looked at the tariffs for ESS in Finland and how that plays out with the varying rates.

Response. The reviewer pointed out a very important research question. Unfortunately register based data in our disposal lacks data on exact costs of ESS in Finland. Exact costs might differ in some parts from the billed costs of ESS in Finland. Thus we were not able to collect or include cost-effectiveness analyses in this study. We have now removed the word “cost-effectiveness” from the manuscript. We have added this information in the Limitations chapter.

Minor concerns:
1.The list of strengths and limitations of the study on page 6 lists 3 results not strengths or limitations - please modify accordingly

Response. We have now amended the strengths and limitations of the study section as indicated.

2. Likewise, the section headed "what this paper adds" is just a summary of the paper and not an outline of the potential contribution to the literature.

Response. Amended as indicated.

3. It is not clear how prevalence data is derived from reference 3.

Response. We have now corrected this.

4. CRS is a clinical disorder encompassing a heterogeneous group of endotypes and two main phenotypes.

Response. We have added this information in the Introduction section. Thank you.

5. There is mention of predisposing factors being genetic and anatomical but these should be specifically referenced.

Response. We have modified this sentence and add reference.

6. Comparing with other studies - ref 3 has a rate of 0.71/1000 - exactly the same so i would add this

Response. We have added this comparison as indicated by the Reviewer.

7. Page 21, page 41 - what do you mean by "those with medical faculties"?

Response. Higher ESS rates were detected in hospital districts with a high density of ENT specialists as well as in hospital districts having a University Hospital with medical faculty. We have now clarified this in the Results section.

8. Page 22, line 15 - what do you mean by "ESS is usually a preference-sensitive care"

Response. We agree with the Reviewer that this is not clear and have removed the sentence.

9. The word "thus" is over-repeated in this paragraph 10. The first sentence of the conclusion uses the word "also" but this appears misplaced as it is not clear what or where the also is additional to.

Response. We have now modified this paragraph.

In summary, this paper needs a major reworking to make it acceptable for publication by clarifying the message and reporting or what factors do indeed lead to variations.

Response. We thank for this comment which helped us to reformulate the text and to clarify the message of our manuscript. We hope that it is now more suitable for consideration of publication.

FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:
- We have implemented an additional requirement to all articles to include 'Patient and Public Involvement statement' within the main text of your main document. Please refer below for more information regarding this new instruction:

Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'.

Response. This has been done as indicated.

This should provide a brief response to the following questions:

How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?

Response. Not applicable

How did you involve patients in the design of this study?

Response. Not involved.

Were patients involved in the recruitment to and conduct of the study?

Response. No.

How will the results be disseminated to study participants?

Response. Not applicable.

For randomised controlled trials, was the burden of the intervention assessed by patients themselves?

Response. Not applicable.

Patient advisers should also be thanked in the contributorship statement/acknowledgements.
If patients were not involved please state this.

Response. Not applicable.

References

(1) Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012 Mar;(23)(23):3 p preceding table of contents, 1-298.