PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile of COpenhagen ROsacea COhort (COROCO) and COpenhagen MIgraine COhort (COMICO)
AUTHORS	Wienholtz, Nita; Christensen, Casper; Haugaard, Jeanette; Zhang, Ditte; Ashina, Messsoud; Thyssen, JP; Egeberg, A

VERSION 1 – REVIEW

REVIEWER	Jerry Tan Western University, Canada Advisor, consultant, speaker and/or trialist for Allergan, Almirall, Bausch, Botanix, Galderma, Promius, Sun
REVIEW RETURNED	07-May-2020

GENERAL COMMENTS	p8, line 52: Current NRS diagnostic and major criteria for rosacea are signs with only 1 symptom (flushing). Pls clarify if you mean symptoms, signs or both? p11, line 46: symptoms is used here (and throughout) again with a sense of ambiguity. What do you mean by symptoms and manifestations? do you mean features ie signs and symptoms? p 11, line 26: Who completed the survey and interrogated signs/symptoms and used the score card? Same question for Questionnaire- migraine p12, line 42: did you limit activity, beverage ingestion? p20, line 31 - the low DLQI for the rosacea cohort is surprising and concerning. Was this a very mildly affected group with minimal features or severity thereof? or under treatment where positive effect reflected in low DLQI. This issue needs clarification. p21, line 46 - to is missing between atrributed and comorbide p23, line 25 - While you declare that phenotypes were determined, I don't see a frequency distribution of the features of rosacea cohort

REVIEWER	Angeliki Vgontzas Brigham and Women's Hospital, Department of Neurology, Harvard Medical School, Boston, MA, USA
REVIEW RETURNED	08-May-2020

GENERAL COMMENTS	The authors present an interesting and novel descriptive paper of two different cohorts of diseases with shared comorbidity within the same population. The manuscript is well written, but the structure

	requires revision. My general recommendation is this: The authors state the two clinical cohorts will not undergo direct comparison. However, the manuscript is structured such that it is amenable to direct comparison. If this is meant to be purely descriptive, then I would recommend that the results be framed separately for each cohort. The discussion would then include separate paragraphs for each cohort and perhaps a final paragraph noting any potential mechanistic insights or interesting questions from your first look at the descriptive data. The current structure is a bit atypical. Specifics: Methods: Regarding the migraine semi-structured interview, please provide more detail on how a diagnosis of migraine was defined. Based on my review, it appears that a patient-reported diagnosis of migraine would meet the criteria of migraine and if there was no diagnosis, then the interview criteria would have to be met? Is this correct? Were the criteria consistent with ICHD-3? I would also explicitly state if the interviews done by trained medical students were reviewed by the headache specialist. With respect to the migraine cohort, were these patients with episodic or chronic migraine. Given they came from a headache center, there is a high likelihood that most of these patients were chronic migraine. This is relevant as it may not be generalizable to episodic migraine. Also, patients with chronic migraine tend to have more comorbitidies. It makes sense to first look at a chronic migraine population when studying comorbidity in order to maximize insights into disease pathophysiology, so the methodology is sound. However, the % of episodic vs chronic migraine patients will likely affect your results going forward, so it is important to include. With respect to GWAS, are you looking at SNPs reported in both rosacea and migraine GWAS? Your methods only reference rosacea studies. If also looking at migraine associated SNPs, the most comprehensive migraine one to date is by Gormley at al, 2016 which is a meta-analysis which included several GWAS (not only 23 and me). It is likely a newer GWAS with a greater number of migraine-associated SNPs is forthcoming. Again, I would recommend including the Gormley paper as a reference if you are looking at migraine associated SNPs. You mention PACAP in the introduction, but this was not measured. One consideration is to look at PACAP and CGRP genes in addition to the direct measurement you noted. (You don't need need to necessarily include this here, but that is an idea). The average age of your cohorts is quite different (as is expected for the known age of onset of these different disorders). Given this is a longitudinal study, is it possible that the follow up for the migraine cohort may need to be longer (on the order of 20 years or so? You may want to allude to this age difference in your discussion and also how that may affect the types of analyses you do. Please reference rates of smoking for those in Denmark. Given marked variability in smoking prevalence from country to country, this may be relevant. Regarding smoking, I don't think that non-migraine headache associated with smoking is relevant here. I don't agree that "obesity is debated in migraine". The epidemiologic data is clear that there is an association with chronification of migraine. The mechanisms are unclear and this is perhaps what you are referring to. A major limitation of family history is that if the patient recognizes he/she has the disorder, they are more likely to identify if a family

	member has had it. I would include this in your discussion.

REVIEWER	Julia Spoendlin Basel Pharmacoepidemiology Unit, University Hospital Basel and University of Basel, Switzerland
REVIEW RETURNED	13-May-2020

GENERAL COMMENTS	The authors describe 2 prospective cohorts: 1) the COROCO, which includes some 300 patients with rosacea recruited at a tertiary dermatology center in Copenhagen, Denmark and 2) the COMICO, which includes some 300 patients with migraine, recruited at a tertiary neurology center in Copenhagen, Denmark. Both cohorts were characterized in terms of demographics and lifestyle factors and the different examinations performed are described. Overall, I think having two prospective cohorts evaluating the association between migraine and rosacea is desirable and interesting and the described cohorts have been carefully selected. I have a few points that may need clarification. Strengths and Limitations (bullet points): • Roseacea diagnoses were validated through pictures. I am assuming this was not the case for migraine. How were migraine diagnoses validated? Methods: • Some 35 rosacea patients were recruited from a headache center…. What was the rationale for this? None of the COMICO patients were recruited at the rosacea center…… • It is not always clear which tests were performed in which cohort. I would assume photography, thermography, and stratum corneum sample were only performed among rosacea patients? This should be stated clearly in the methods section. • The authors state that patients only had to agree to being interviewed in order to be eligible. However, the two cohorts aim to evaluate the association between rosacea and migraine, which will mainly be done by blood and DNA anayses…..How many patients denied DNA and/or blood sampling? Will patients who only conducted the interview be informative for future studies? Results: • Page 17 line 55: the word ‘find’ is doubled Strengths and Limitations: • How many patients were recorded into both cohorts? • It is not entirely clear to me, how these two cohorts will be used in the future to evaluate an association between rosacea and migraine. I think an additional ‘outlook’ paragraph discussing planned projects based on these cohorts would be interesting. Will the overlap of the two diseases mainly be evaluated through GWAS? • The authors also mention linkage to national patient registers as a key strength of the cohorts. What studies could be of interest there: discussing this may be informative to the reader.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Jerry Tan

Institution and Country: Western University, Canada

Please state any competing interests or state 'None declared': Advisor, consultant, speaker and/or trialist for Allergan, Almirall, Bausch, Botanix, Galderma, Promius, Sun

p8, line 52: Current NRS diagnostic and major criteria for rosacea are signs with only 1 symptom (flushing). Pls clarify if you mean symptoms, signs or both?

Response: Thank you for your comment – we mean signs. It has been corrected.

p11, line 46: symptoms is used here (and throughout) again with a sense of ambiguity. What do you mean by symptoms and manifestations? do you mean features ie signs and symptoms?

Response: We mean features, i.e. signs and symptoms. We have gone through the manuscript to ensure correct use of signs and symptoms.

p 11, line 26: Who completed the survey and interrogated signs/symptoms and used the score card? Same question for Questionnaire- migraine

Response: Survey/Interviews; including signs/symptoms and score card, were completed by either NW (MD, PhD-fellow), or one of the senior medical students who had been specifically trained for interviews. Both interviews on rosacea and migraine were performed in the same session by the same person. All interviews were reviewed by author NW, and in cases of doubt, also by authors JPT (Professor, MD, PhD, DMSc) and AE (MD, PhD) for rosacea questions, and headache specialist author MA (MD, PhD, DMSc) for migraine questions. We have elaborated on this to clarify on page 12, lines 13-17.

p12, line 42: did you limit activity, beverage ingestion?

Response: We would have liked to do this, as we realize that it might be important for the quality of

the data, but unfortunately it wasn't feasible as patients were recruited directly from the outpatient clinic, and we therefore couldn't limit these measures.

Patients were sat for at least 30 minutes (during the interviews), drinking only water, before performing additional investigations. We have clarified this on page 13, lines 15-18.

p20, line 31 - the low DLQI for the rosacea cohort is surprising and concerning. Was this a very mildly affected group with minimal features or severity thereof? or under treatment where positive effect reflected in low DLQI. This issue needs clarification.

Response: Thank you for this interesting point. We were also surprised by this finding and will be looking into DLQI according to severity of rosacea, but we have not looked at those data yet. However, DLQI isn't ideal for evaluation of rosacea, as questions 3, 4, and 7-10 are rarely relevant for patients with rosacea, which may be one of the reasons for a low DLQI.
Anecdotally (not part of our questionnaire), many patients reported to have previously been very affected by their rosacea; however, at the time of the interview, they were less affected as they'd had rosacea for many years, or because they were now less severely affected than they had been; either due to effective treatment, or simply due to the natural course of the disease. Our data may thus have been different if we only interviewed patients who were newly diagnosed or had a flare-up of rosacea at the time of investigation, and that is a limitation of our study. We have added a comment about this on page 25, lines 16-21, page 26, lines 1-7 and to limitations on page 32, lines 12-15.

p21, line 46 - to is missing between atrributed and comorbide

Response: Thank you, this has been added.

p23, line 25 - While you declare that phenotypes were determined, I don't see a frequency distribution of the features of rosacea cohort

Response: Thank you for your comment. We have not yet finished the phenotyping part and will present those data in another paper.

Reviewer: 2

Reviewer Name: Angeliki Vgontzas

Institution and Country: Brigham and Women's Hospital, Department of Neurology, Harvard Medical School, Boston, MA, USA

Please state any competing interests or state ‘None declared’: None declared

The authors present an interesting and novel descriptive paper of two different cohorts of diseases with shared comorbidity within the same population. The manuscript is well written, but the structure requires revision. My general recommendation is this:

The authors state the two clinical cohorts will not undergo direct comparison. However, the manuscript is structured such that it is amenable to direct comparison. If this is meant to be purely descriptive, then I would recommend that the results be framed separately for each cohort. The discussion would then include separate paragraphs for each cohort and perhaps a final paragraph noting any potential mechanistic insights or interesting questions from your first look at the descriptive data. The current structure is a bit atypical.

Response: Thank you for your comment – we understand that this might be confusing. We have split the table into two tables and have made subheadings in the discussion, discussing rosacea and migraine separately.

Specifics:

Methods:

Regarding the migraine semi-structured interview, please provide more detail on how a diagnosis of migraine was defined. Based on my review, it appears that a patient-reported diagnosis of migraine would meet the criteria of migraine and if there was no diagnosis, then the interview criteria would have to be met? Is this correct? Were the criteria consistent with ICHD-3? I would also explicitly state if the interviews done by trained medical students were reviewed by the headache specialist.

Response: To be included in the migraine cohort, patients had to have a physician-diagnosis of migraine. For those included in the rosacea cohort, we also asked if they believed to have a diagnosis of migraine.

All patients (both those with and without a previous diagnosis of migraine) were asked additional questions to determine whether they actually fulfilled criteria for migraine according to ICHD-3 criteria. All interviews were reviewed by author NW, and in cases of doubt, also by headache specialist MA. We have elaborated on this on age 12, lines 13-17.

With respect to the migraine cohort, were these patients with episodic or chronic migraine. Given they came from a headache center, there is a high likelihood that most of these patients were chronic migraine. This is relevant as it may not be generalizable to episodic migraine. Also, patients with chronic migraine tend to have more comorbidities. It makes sense to first look at a chronic migraine population when studying comorbidity in order to maximize insights into disease pathophysiology, so the methodology is sound. However, the % of episodic vs chronic migraine patients will likely affect your results going forward, so it is important to include.

Response: Thank you for this comment. As you correctly note, a high number of our patients had chronic migraine (38.2%), and we will adjust for this when making further analyses. We have added the % of chronic migraine in our migraine cohort to table 2 on page 29.

With respect to GWAS, are you looking at SNPs reported in both rosacea and migraine GWAS? Your methods only reference rosacea studies. If also looking at migraine associated SNPs, the most comprehensive migraine one to date is by Gormley at al, 2016 which is a meta-analysis which included several GWAS (not only 23 and me). It is likely a newer GWAS with a greater number of migraine-associated SNPs is forthcoming. Again, I would recommend including the Gormley paper as a reference if you are looking at migraine associated SNPs.

Response: Thank you, we have added a comment and the reference on page 16, lines 16-17.

You mention PACAP in the introduction, but this was not measured. One consideration is to look at PACAP and CGRP genes in addition to the direct measurement you noted. (You don't need to necessarily include this here, but that is an idea).

Response: Thank you for this interesting point. We will definitely consider this when analyzing the DNA samples.

The average age of your cohorts is quite different (as is expected for the known age of onset of these different disorders). Given this is a longitudinal study, is it possible that the follow up for the migraine cohort may need to be longer (on the order of 20 years or so? You may want to allude to this age difference in your discussion and also how that may affect the types of analyses you do.

Response: That is a good point. We have altered the expected follow up to 10-20 years, which is probably more likely to be the actual time of follow up, on page 31, line 3-5.

Please reference rates of smoking for those in Denmark. Given marked variability in smoking prevalence from country to country, this may be relevant.

Response: Thank you, that is a good point. We have added the reference below on page 23, lines 1-4. The reference is an update on the Danish Smoking habits in 2018 (article in Danish).

Sunhedsstyrelsen, Kræftens_Bekæmpelse, Hjerteforeningen_og_Lungeforeningen. Danskernes rygevaner 2018 - nøgletal [Danish] [Internet]. Available from: https://www.sst.dk/-/media/Udgivelser/2019/Danskernes-rygevaner-2018/Danskernes-rygevaner-2018_nøgletal.ashx?la=da&hash=55335DED0545970499485950C4E375CEC5A465AF

Regarding smoking, I don't think that non-migraine headache associated with smoking is relevant here.

Response: We agree. We have deleted the comment about non-migraine headache in smoking.

I don't agree that "obesity is debated in migraine". The epidemiologic data is clear that there is an association with chronification of migraine. The mechanisms are unclear and this is perhaps what you are referring to.

Response: Thank you, we agree. We have clarified this on page 25, line 1.

A major limitation of family history is that if the patient recognizes he/she has the disorder, they are more likely to identify if a family member has had it. I would include this in your discussion.

Response: Yes, as with all studies of patient-reported family history, recall bias is a potential issue. We have included a comment about this on page 32, lines 7-10.

Reviewer: 3

Reviewer Name: Julia Spoendlin

Institution and Country: Basel Pharmacoepidemiology Unit, University Hospital Basel and University of Basel, Switzerland

Please state any competing interests or state 'None declared': None declared

The authors describe 2 prospective cohorts: 1) the COROCO, which includes some 300 patients with rosacea recruited at a tertiary dermatology center in Copenhagen, Denmark and 2) the COMICO, which includes some 300 patents with migraine, recruited at a tertiary neurology center in Copenhagen, Denmark. Both cohorts were characterized in terms of demographics and lifestyle factors and the different examinations performed are described. Overall, I think having two prospective cohorts evaluating the association between migraine and rosacea is desirable and interesting and the described cohorts have been carefully selected. I have a few points that may need clarification.

Strengths and Limitations (bullet points):

- Roseacea diagnoses were validated through pictures. I am assuming this was not the case for migraine. How were migraine diagnoses validated?

Response: Thank you for this question. Migraine diagnoses were validated through the semi-structed interview on migraine which ensured that patients fulfilled migraine criteria according to ICHD-3 criteria. All interviews were reviewed by author NW, and in cases of doubt, headache specialist MA (MD, PhD, DMSc). We adjusted the bullet points on page 6, lines 8-9 and have clarified on page 12, lines 14-17 and page 13, lines 9-11.

Methods:

- Some 35 rosacea patients were recruited from a headache center…. What was the rationale for this? None of the COMICO patients were recruited at the rosacea center……

Response: The reason for this was practical. Some doctors at the headache center were very good at referring patients as soon as they noticed a diagnosis of rosacea. These patients may have also had a diagnosis of migraine, but we included them as the diagnosis they were referred to us with.

It is not always clear which tests were performed in which cohort. I would assume photography, thermography, and stratum corneum sample were only performed among rosacea patients? This should be stated clearly in the methods section.

Response: All tests were performed in all patients of both cohorts. The purpose is to investigate whether there is a difference between patients with one/both diseases and between phenotypes. We have clarified this on page 13 line 18.

- The authors state that patients only had to agree to being interviewed in order to be eligible. However, the two cohorts aim to evaluate the association between rosacea and migraine, which will mainly be done by blood and DNA anayses…..How many patients denied DNA and/or blood sampling? Will patients who only conducted the interview be informative for future studies?

Response: In general, patients were willing to participate in all analyses, and usually only denied one of the analyses; either DNA, blood sampling or pictures. Less than 50 patients denied either of the three.

Future studies will primarily be based on the phenotyping, done via interviews, whereas DNA and blood samples are only meant for further support, but are not essential to analysis.

In the future, we hope to study occurrence, risk factors, natural history, treatment, complications, comorbidities and prognosis for both disorders, mainly via national Danish registries. We also plan to invite participants for a follow-up in 10-20 years. We have elaborated on this on page 12, lines 6-8 and in '*Future plans'* on page 31, lines 2-5.

Results:

- Page 17 line 55: the word ‘find’ is doubled

Response: Thank you. This has been deleted.

Strengths and Limitations:

- How many patients were recorded into both cohorts?

Response: No patients were recorded in both cohorts; however, some of the patients that were included in e.g. the migraine cohort, also turned out to have a diagnosis of rosacea; both previously diagnosed, and also confirmed through interviews.

- It is not entirely clear to me, how these two cohorts will be used in the future to evaluate an association between rosacea and migraine. I think an additional ‘outlook’ paragraph discussing planned projects based on these cohorts would be interesting. Will the overlap of the two diseases mainly be evaluated through GWAS?

Response: GWAS is only a minor part of the project. As both diseases are clinically diagnosed, the overlap will be evaluated by the phenotyping interviews. We have added a ‘*future plans’* paragraph to clarify our plans for future studies on page 31, lines 2-5.

- The authors also mention linkage to national patient registers as a key strength of the cohorts. What studies could be of interest there: discussing this may be informative to the reader.

Response: Thank you. We have added this to *‘future plans’* paragraph on page 31, lines 2-5

VERSION 2 – REVIEW

REVIEWER	Jerry Tan Western University, Canada
REVIEW RETURNED	05-Jul-2020

GENERAL COMMENTS	Update manuscript has incorporated recommendations.

REVIEWER	Angeliki Vgontzas Brigham and Women's Hospital, Harvard Medical school
REVIEW RETURNED	09-Jul-2020

GENERAL COMMENTS	The authors have resubmitted the descriptive paper of these two

	interesting cohorts which will hopefully shed some light on these comorbid conditions. The manuscript is overall improved and they have addressed my initial concerns. They may want to consider collapsing some of the subcategories in the tables (for example, 2nd and 3rd degree relatives, some of the smoking categories, etc) and also considering formatting some of the subcategories with indentation as this would be easier on the eyes. I would recommend describing each cohort separately in the results (ie, Including all the descriptive information for Cohort 1 and then a paragraph with all the descriptive information for Cohort 2). However, this is a stylistic preference.

REVIEWER	Julia Spoendlin Basel Pharmacoepidemiology Unit, University of Basel and University Hospital Basel, Switzerland
REVIEW RETURNED	01-Jul-2020

GENERAL COMMENTS	No further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Jerry Tan

Institution and Country: Western University, Canada

Please state any competing interests or state ‘None declared’: Author of ROSCO and NRS papers

Update manuscript has incorporated recommendations.

Response: Thank you.

Reviewer: 2

Reviewer Name: Angeliki Vgontzas

Institution and Country: Brigham and Women's Hospital, Harvard Medical school

Please state any competing interests or state ‘None declared’: None declared

The authors have resubmitted the descriptive paper of these two interesting cohorts which will hopefully shed some light on these comorbid conditions. The manuscript is overall improved and they have addressed my initial concerns. They may want to consider collapsing some of the subcategories

in the tables (for example, 2nd and 3rd degree relatives, some of the smoking categories, etc) and also considering formatting some of the subcategories with indentation as this would be easier on the eyes. I would recommend describing each cohort separately in the results (ie, Including all the descriptive information for Cohort 1 and then a paragraph with all the descriptive information for Cohort 2). However, this is a stylistic preference.

Response: Thank you, we agree that this would ease reading of the paper.

Tables: We have collapsed 2nd and 3rd degree relatives along with some of the smoking and alcohol categories, and indented subheadings. Changes have not been marked with track changes as this became too messy. We hope that is OK.

Results: As you suggested, we have split results to include first all data for COROCO and then all data for COMICO. The cutting/ inserting has not been marked with track changes as all sections are with original wording. Any changes in wording have been marked with track changes.

Reviewer: 3

Reviewer Name: Julia Spoendlin

Institution and Country: Basel Pharmacoepidemiology Unit, University of Basel and University Hospital Basel, Switzerland

Please state any competing interests or state ‘None declared’: none

No further comments

Response: Thank you.