

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Cohort profile of COpenhagen ROsacea COhort (COROCO) and COpenhagen MIgraine COhort (COMICO)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039445
Article Type:	Cohort profile
Date Submitted by the Author:	15-Apr-2020
Complete List of Authors:	Wienholtz, Nita; Rigshospitalet Glostrup, Danish Headache Center; Gentofte Hospital, Dermatology and Allergy Christensen, Casper; Rigshospitalet Glostrup, Danish Headache Center Haugaard, Jeanette; Gentofte Hospital, Dermatology and Allergy Zhang, Ditte; Rigshospitalet Glostrup, Danish Headache Center Ashina, Messsoud; University of Copenhagen, Denmark, Danish Headache Centre and Department of Neurology Thyssen, JP; Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen Egeberg, A; Gentofte Hospital, Department of Dermatology and Allergy
Keywords:	Migraine < NEUROLOGY, DERMATOLOGY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 Cohort profile of Copenhagen ROsacea COhort (COROCO) and Copenhagen MIgraine
5
6
7 COhort (COMICO)
8
9
10
11

12 Nita Wienholtz, MD^{1,2,3}, Casper Emil Christensen, MD, PhD¹, Jeanette Halskou Haugaard, MD^{2,3}, Ditte
13
14 Georgina Zhang¹, Messoud Ashina, MD, PhD, DMSc¹, Jacob P. Thyssen, MD, PhD, DMSc^{2,3},
15
16
17 Alexander Egeberg, MD, PhD^{2,3}
18
19
20
21
22

23 ¹ Danish Headache Center, Department of Neurology, Rigshospitalet Glostrup, Glostrup,
24
25 Denmark
26
27

28 ² Copenhagen Research Group for Inflammatory Skin (CORGIS), Hellerup, Denmark
29
30

31 ³ Department of Dermatology and Allergy, Herlev and Gentofte Hospital, Hellerup,
32
33 Denmark
34
35
36
37
38

39 **Correspondence:**
40

41 Alexander Egeberg
42
43

44 Department of Dermatology and Allergy
45
46

47 Herlev and Gentofte Hospital
48
49

50 Kildegaardsvej 28
51

52 DK-2900 Hellerup
53

54 Telephone: (+45) 38 67 41 52
55
56

57 E-mail: alexander.egeberg@gmail.com
58
59
60

1
2
3
4
5
6
7 **Word count: 3332**

8
9
10 **Number of tables: 1**

11
12 **Number of figures: 2**

13
14
15 **Number of appendices: 3**

16
17
18 **Number of references: 78**

19
20
21
22
23 **Key words:** cohort study, migraine, prospective, rosacea

24
25
26
27
28 **Conflicts of interest**

29
30
31 None declared

32
33
34
35
36
37
38
39 **Funding sources**

40
41 The study was supported by grants from Novo Nordisk Foundation (NNF170C0029698)

42
43
44 and Augustinus Foundation (17-2523).

45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Purpose

Migraine has consistently been connected to rosacea. Commonalities in epidemiology, trigger factors and associated neuropeptides support shared etiology and pathophysiological pathways, though underlying mechanisms remain unclear. We established two cohorts of patients diagnosed with either migraine and/or rosacea. All patients were phenotyped in regard to migraine and rosacea. In this article, we describe baseline parameters of the cohorts. In the future we expect that these cohorts will help uncover potential disease overlaps and allow for prolonged follow up through national Danish health registries.

Participants

Copenhagen Rosacea Cohort (COROCO) and Copenhagen Migraine Cohort (COMICO) are prospective cohorts based in the Capital region of Denmark. Participants for COROCO were recruited primarily through two tertiary dermatology clinics in Copenhagen, Denmark and patients for COMICO were recruited through a tertiary neurology clinic in Copenhagen, Denmark.

Findings to date

COROCO consists of 300 adults with rosacea and COMICO consists of 304 adults with migraine. All participants have been phenotyped through face-to-face semi-structured

1
2
3
4 interviews. Additionally, blood and skin samples as well as pictures taken with normal and
5
6 thermal cameras were collected. In this article we describe baseline data of the cohorts
7
8 along with family history of migraine and rosacea, smoking, alcohol, body mass index
9
10 (BMI) and dermatology life quality index (DLQI). Cohorts were not age- and sex-matched
11
12 as they will not undergo direct comparison.
13
14
15
16
17
18
19

20 **Future plans**

21
22 COROCO and COMICO offer the possibility of studying epidemiology, risk factors, natural
23
24 history and comorbidities in both disorders. We plan for longitudinal follow up through
25
26 national Danish registries and to invite participants for a follow-up in 5-10 years. Unveiling
27
28 a possible disease overlap between migraine and rosacea may also help in determining
29
30 mechanisms behind both of these widespread and debilitating disorders.
31
32
33
34
35
36
37
38

39 **Registration**

40
41 This observational cohort is registered with clinicaltrials.gov (NCT03872050).
42
43
44
45
46

47 **Keywords**

48
49 migraine, phenotype, rosacea
50
51
52
53
54

55 **Strengths and limitations of this study**

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- Copenhagen Rosacea Cohort (COROCO) and Copenhagen Migraine Cohort (COMICO) are large cohorts of adults with either physician-diagnosed migraine or rosacea that were phenotyped through face-to-face interview by trained professionals.
 - Diagnoses are validated through pictures evaluated by three physicians.
 - Collected information includes pictures with normal and thermal cameras, blood samples, inflammatory markers and DNA for thorough description of each participant.
 - Future linkage to Danish national health registries enables us to follow patients for a prolonged period of time.
 - Limitations include risk of selection bias as participants are recruited from specialty units, and risk of recall bias as the cohort is based on interviews.

INTRODUCTION

Migraine has repeatedly been associated with rosacea.[1] Both are chronic inflammatory conditions with relapsing episodes of headache for migraine, and redness/flushing and/or papules/pustules for rosacea. Relapses may be triggered by various endogenous and/or exogenous factors such as different foods and drinks, exercise, sun/UV exposure, heat and stress.[2,3] Migraine is common with a prevalence of 12%[4] and up to 18.3% for women.[4–6] Migraine seems to be underdiagnosed and undertreated[6,7] and the actual prevalence is probably higher. Rosacea has an overall prevalence of 5.5%[8] and usually affects individuals over the age of 30 years.[8,9] Both disorders are primarily seen in individuals of Caucasian descent.[4,8] Etiology for both is largely unknown, but seems to involve a mix of genetic and environmental factors.[10,11] Other commonalities between migraine and rosacea include neuroinflammation and upregulation of signaling neuropeptides, such as pituitary adenylate cyclase-activating polypeptide-38 (PACAP38)[2,12] and calcitonin gene-related peptide (CGRP),[13,14] though there are other suggested signaling pathways for both migraine and rosacea.[10] Common demography, triggers and associated neuropeptides suggest a shared pathophysiological pathway.[1]

Despite overwhelming evidence of a connection between migraine and rosacea,[15–20] underdiagnosis in both disorders must be considered as a confounder in previous research, and a systematic approach is therefore needed to confirm this connection and

1
2
3
4 better characterize exact overlap of these diseases. Establishment of prospective patient
5
6
7 cohorts with a physician-diagnosis of either migraine or rosacea will help confirm this
8
9
10 connection and uncover possible risk factors and comorbidities in both.
11
12
13
14

15 COHORT DESCRIPTION

16 17 **Study approval, registry and data availability**

18
19
20 The study was approved by the Ethical Committee of the Capital Region of Denmark (H-
21
22 17023750) and was registered at www.clinicaltrials.gov (NCT03872050). All participants
23
24 provided written informed consent in accordance with the declaration of Helsinki anno
25
26 1964 with adjustments until 64th WMA General Assembly, Fortaleza, Brazil, October 2013.
27
28 All data are under the supervision of the corresponding author and can be made available
29
30 upon reasonable request.
31
32
33
34
35
36
37
38

39 **Study population and setting**

40
41 Two cohorts were established; Copenhagen Rosacea Cohort (COROCO) and Copenhagen
42
43 Migraine Cohort (COMICO). Willing participants had to be aged 18 years or above. A
44
45 physician-diagnosis of rosacea was needed to be included in COROCO, and a physician-
46
47 diagnosis of migraine was needed to be included in COMICO. There were no exclusion
48
49 criteria. All participants signed an informed consent upon enrollment.
50
51
52
53
54
55
56

57 Recruitment

1
2
3
4 *Copenhagen Rosacea Cohort (COROCO)*
5

6
7 Electronic Medical Records (EMR) were searched for adults who consulted a doctor for a
8
9 diagnosis of rosacea at either *Department of Dermatology and Allergy at Gentofte Hospital*
10
11 (between September 3rd, 2013 – May 5th, 2019) or *Department of Dermatology and Wound*
12
13 *Healing Centre at Bispebjerg Hospital* (between January 1st, 2014 – November 21st, 2018).
14
15

16
17 Diagnosis of rosacea was defined as one of the following ICD-10 codes: DL71, DL718A,
18
19 DL719, DL718.[21]
20
21

22
23 A total of 790 patients were identified through EMR and invited to participate in the
24
25 rosacea cohort. Five letters were not delivered due to wrong address, and invitations were
26
27 thus delivered to 785 patients. Patients could respond through one of three routes: mailing
28
29 the 'return envelope' (free of charge), sending an e-mail, or calling/texting a dedicated
30
31 phone. The response rate was 46.8% (367 patients). Nine patients informed us that they
32
33 did not want to participate due to illness, lack of time or because they did not believe to
34
35 have rosacea. Of the 358 patients who responded positively to the invitation, we
36
37 interviewed 274 patients before reaching the pre-specified inclusion number (see Figure 1
38
39 for details). An additional 35 patients with a prior diagnosis of rosacea were included via
40
41 the Danish Headache Center at Rigshospitalet Glostrup or via online recruitment
42
43 (www.forsøgsperson.dk). Interviews were performed in 309 patients, and after reviewing
44
45 pictures, nine patients were excluded from analysis, as their symptoms could not clearly be
46
47 attributed to rosacea. COROCO thus included a total of 300 patients. Interviews were
48
49 performed between September 17th to 2018 to October 14th, 2019.
50
51
52
53
54
55
56
57
58
59
60

Copenhagen Migraine Cohort (COMICO)

Patients for COMICO were recruited through the Danish Headache Center, department of Neurology at Rigshospitalet Glostrup, Copenhagen, Denmark. The Danish Headache Center is a tertiary care facility for patients with persistent or difficult-to-treat headaches who have been referred by either a general practitioner or from a specialist neurology clinic. Patients were asked to participate when they came for an outpatient visit at the Headache Center. A physician-diagnosis of migraine (with or without aura) was necessary for inclusion. In all, 281 patients were recruited from the Danish Headache Center. An additional 23 patients were recruited online (www.forsogsperson.dk) (see Figure 2 for details). A total of 304 patients were included in COMICO. Interviews were performed between September 14th, 2018 – October 29th, 2019.

Study visit

Patients were seen once during the study period. The visit took place in one of three locations of the patient's choice: Danish Headache Center (Rigshospitalet Glostrup), Department of Dermatology (Gentofte hospital), or by home visit at the patient's home/work.

The visit lasted approximately 60 minutes and included interview, blood sample, pictures with digital and thermal cameras, superficial stratum corneum sampling of the forearm and

1
2
3
4 cheek, and mouth swab for DNA sampling. Procedures are described below. Patients only
5
6
7 had to agree to the semi-structured interview to be eligible for the study.
8
9
10

11 **INTERVIEW**

12
13
14
15 A semi-structured interview was performed at the beginning of the visit. The interview was
16
17 performed either by a medical doctor (author NW) or by trained senior medical students.
18
19
20 All patients were asked questions based on two questionnaires.
21
22
23
24
25

26 Questionnaire – rosacea

27
28 Demographic information, comorbidities, family history, dermatology life quality index
29
30 (DLQI) and presence of symptoms and manifestations of rosacea. If patients had a prior
31
32 diagnosis of rosacea, first presenting symptom of rosacea, diagnostic delay and previous
33
34 treatments were also collected (appendix 1). Patients were also evaluated with the National
35
36 Rosacea Society Rosacea Clinical Scorecard.[22]
37
38
39
40
41
42
43

44 Questionnaire – migraine

45
46
47 A validated semi-structured questionnaire on diagnosis and subtyping of migraine[23] was
48
49 adapted by author NW for the purpose of interviewing patients with no known migraine or
50
51 headache (appendix 2). Questions included family history, headache/migraine and aura
52
53 symptoms along with risk factors for headache/migraine. If patients had a diagnosis of
54
55 migraine, migraine onset and headache frequency were collected.
56
57
58
59
60

CLINICAL EXAMINATION

Standardized photography

A standardized picture was taken with a digital Canon PowerShot G12 camera at a distance of approximately 70 cm, with a flash and zoom when needed. Pictures were rated according to phenotype and the newly developed rosacea scoring tool 'Rosacea Area and Severity Index' (RASI) (manuscript in development), to ensure correct diagnosis and classification of rosacea.

All pictures were evaluated by three authors (JT, AE, NW). Disagreements were resolved by discussion. In cases of doubt, patients were rated as 'not rosacea' or 'non-classifiable'.

These ratings will be compared with interview data in a future publication, to evaluate the validity of both.

Thermography

Thermographic pictures were recorded after patients had been placed in a room with a stable temperature for at least 15 minutes. Pictures were recorded on FLIRA655sc with a 25° lens. The camera has a range of -40°C to +150°C and temperature accuracy of +/- 1°C. Pictures were recorded at a distance of approximately 50 centimeters from the subject. For each subject, a total of three pictures were recorded - one picture from the front and one from each side. The FLIR program *ResearchIR* was used to record pictures. Analyses were performed in the program *FLIR TOOLS*. Temperature was measured at each side of the face

1
2
3
4 corresponding to the facial area of the three branches of the trigeminus (forehead, cheeks,
5
6
7 chin). An additional temperature measurement was performed on the tip of the nose
8
9
10 (appendix 3). The measure point was matched to the size of the iris to adjust for
11
12 differences in distances from which the pictures were taken.
13
14
15
16
17

18 Facial skin temperature has previously been investigated in both migraine and rosacea
19
20 with unclear results.[24] We therefore offer baseline temperatures in a large group of
21
22 patients with both disorders to determine whether previous findings reflect true
23
24 differences or simply interindividual differences within patient groups.
25
26
27
28
29
30

31 **Superficial stratum corneum sampling**

32
33 A sample of stratum corneum was collected using the tape stripping method. Samples were
34
35 collected from two sites (one forearm and one cheek), Seven consecutive tape stripping discs
36
37 (22 mm) (D-squame, CuDerm, Dallas, Texas) were collected at each site. Discs were applied
38
39 with tweezers followed by a standardized pressure with a D-squame pressure application
40
41 pen for 5 seconds. The first 3 discs from each site were discarded, and the following 4 discs
42
43 were stored at -80°C immediately after sampling. The discs will be examined for cytokines
44
45 and skin microbiome.
46
47
48
49
50

51
52 Rosacea is characterized by local inflammation of the face, however, recent evidence
53
54 suggests that the inflammation may be systemic.[25] Migraine has also been suggested to
55
56
57
58
59
60

1
2
3
4 involve inflammation, especially neuroinflammation, but possibly also systemic
5
6
7 inflammation.[26]
8

9
10 Measurement of inflammatory markers from the skin will allow us to compare facial
11
12 inflammation (cheek) to systemic inflammation (forearm) and to compare patients with
13
14 migraine and rosacea to uncover a possible subclinical inflammation in both disorders.
15
16
17 Furthermore, we hope to investigate whether there is a correlation between local/systemic
18
19 inflammation, subtypes of rosacea and disease activity.
20
21
22
23
24

25 **Genetics**

26
27
28 Patients were not allowed to eat, drink, smoke, chew gum or clean teeth one hour before
29
30 collection. All patients were instructed to rinse their mouth with water immediately before
31
32 collection. For the analyses, one SK-1S DNA buccal swab (Isohelix, Harrietsham, U.K) was
33
34 rubbed against cheek mucosa for 60 seconds before returning the swab to the supplied
35
36 tube without touching the head of the swab. The shaft was broken on the edge of the tube
37
38 which left the head of the swab in the tube. The tube was stored at -80° C until analysis.
39
40
41
42
43
44
45
46

47 The purpose of DNA collection was to perform a genome-wide association-study (GWAS)
48
49 for the most common gene mutations in rosacea and migraine. GWAS has only been done
50
51 a few times in rosacea and only on populations selected from the '23andMe' customer
52
53 base.[27,28] Analysis will not include genes listed on the ACMG Recommendations for
54
55 Reporting of Incidental Findings in Clinical Exome and Genome Sequencing.[29]
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Blood sample

A blood sample was collected from a cubital vein (Vacuette® Safety Blood Collection Set) into three 9 ml EDTA tubes (Vacuette® K2EDTA) which were each inverted 10 times immediately after collection to let blood mix with the separator gel. Samples were kept at room temperature (between 20-24 degrees Celsius) and within 30 minutes of sampling, full blood was transferred with a pipette (Alpha Laboratories pipette standard micro sterile pastette) from one EDTA tube into 2 – 4 sterile 2,0ml cryo vials (IVUS). The two remaining EDTA tubes were centrifuged (Hettich Zentrifugen EBA 20) at 2500 rpm for 5 minutes to separate plasma. Plasma was then transferred (Alpha Laboratories pipette standard micro sterile pastette) into 2 – 4 sterile 2,0ml cryo vials (IVUS) and 2 – 4 sterile 2,0ml cryo vials (IVUS) with Thermo scientific protease inhibitor (10 µl per ml of plasma). All samples were stored at -80 degrees Celsius until analysis.

The purpose of this blood sample was to analyze samples for CGRP. CGRP is a signaling neuropeptide which has previously been related to both migraine[30] and rosacea[31] and has been suggested to be related to disease pathology. CGRP has been relatively well-described in migraine, and CRGP-antibodies have recently proven beneficial in preventive treatment of migraine.[32]

By stratifying CGRP measurements in this project we hope to be able to uncover the relationship between CGRP, subtypes and disease activity for especially rosacea.

Findings to date

Age and sex

Median age in the migraine cohort was 41 years (interquartile range (IQR) 29.5 – 51.0) and 51 years (IQR 43.0 – 61.0) in the rosacea cohort. There were 88.5% females in the migraine cohort and 67.7% females in the rosacea cohort. Cohorts were not age- and sex-matched. Onset of migraine differs with age and sex, mostly affecting individuals above age 14 with a peak incidence between ages 25 – 34 years.[4] Rosacea usually affects individuals above age 30 years[9] with a peak onset between 45 – 60 years.[8] For migraine patients there is a strong female predominance with almost twice as many women being affected,[4,33] whereas rosacea is more evenly distributed with only a tendency towards female predominance.[8] Our cohorts thus resemble previous findings in studies on migraine and rosacea, respectively. Cohorts are not intended for direct comparison and differences in age and sex between cohorts will therefore not be a problem.

Family history of migraine

Family history of migraine was found in 73.4% in the migraine cohort and 44.3% in the rosacea cohort. In patients with migraine, family history has previously been reported between 54-77%, [34,35] however, family history of migraine in the general population is usually underreported, [36,37] which may contribute to the low prevalence of family history of migraine in our rosacea cohort.

Family history of rosacea

Family history of rosacea was more common in the rosacea cohort (45.0%) than in the migraine cohort (18.4%).

Previous studies find reports on family history up to 55% in rosacea patients and between 12 - 17% in controls.[38,39] Rosacea is largely underestimated and often goes undiagnosed,[17,40,41] which may contribute the low reports of rosacea family history in both cohorts. Some patients stated that they suspected family members of having rosacea, but only certain diagnoses were included in our analysis, possibly underestimating family history of rosacea in our cohorts.

Smoking

Current smoking was slightly more prevalent in the migraine cohort (17.1%) compared with the rosacea cohort (13.0%). When looking at pack-years for the two cohorts, patients in the migraine cohort had a lower number of pack-years with a median of 12.0 years (IQR 5.0 – 21.0) compared to a median of 24.6 years (IQR 13.3-26.0) in the rosacea cohort. There were fewer former smokers in the migraine cohort (26.0%) compared to the rosacea cohort (36.6%).

Smoking in migraine is debated. A study from 1976 reports that smoking is unlikely to be related to migraine[42] whereas more recent research finds found an increased risk of migraine in past and current smokers.[43] Another study found that patients with migraine

1
2
3
4 were more frequent and heavy smokers than their peers,[44] and smoking has been
5
6 suggested as a precipitating factor for migraine attacks.[45] Furthermore, a higher
7
8 prevalence of non-migraine-specific headache has been found among current
9
10 smokers.[46]
11
12
13
14
15
16
17

18 Smoking in rosacea is also debated. Some studies find a lower prevalence of smoking in
19
20 patients with rosacea[47,48] and that smoking is protective against incident rosacea[49]
21
22 whereas others find a higher prevalence of smoking.[50,51]. Past smoking has been
23
24 associated with a higher risk of incident rosacea compared to never smokers,[38,49]
25
26 perhaps due to an autoimmune response, but this needs further investigation. Smoking
27
28 constricts the peripheral blood vessels, possibly masking rosacea which could be a reason
29
30 for why we see a lower prevalence of current smoking in the rosacea group.
31
32
33
34
35
36
37
38

39 *Alcohol*

40
41 Regular intake of alcohol was less common in the migraine cohort (62.3%) than in the
42
43 rosacea cohort (79.3%). In those with regular intake of alcohol, median average weekly
44
45 intake for those in the migraine cohort was 2 items/week (IQR 1.0 – 3.0) and 4 items/week
46
47 (IQR 1.0 – 9.0) for rosacea.
48
49
50

51
52 Alcohol is a common trigger of migraine attacks,[3,52–55] which was also one of the most
53
54 commonly reported anecdotal reasons for alcohol abstinence in the migraine cohort.
55
56
57
58
59
60

1
2
3
4 Alcohol is a commonly acknowledged trigger of rosacea flushing,[56–58] and intake of
5
6 alcohol seems to be associated with a higher risk of incident rosacea,[47,59,60] though
7
8 some studies failed to find significant associations between rosacea and alcohol
9
10
11
12 intake.[38,61,62]
13
14
15
16

17 *Body mass index*

18
19
20 Median body mass index (BMI) was 24.6 (IQR 21.5 – 28.2) for the migraine cohort and 25.7
21
22 (23.1 – 29.0) for the rosacea cohort. Stratified into groups, underweight (BMI < 18.5) was
23
24 seen in 3.3% (10 patients) of the migraine cohort and 1.3% (4 patients) of the rosacea
25
26 cohort. Normal weight (BMI between 18.5 – 25) was found in 50.7% (154 patients) in the
27
28 migraine cohort and 39.7% (119 patients) in the rosacea cohort. Overweight (BMI between
29
30 25 – 30) was found in 28.6% (87 patients) of the migraine cohort and 40.7% (122 patients)
31
32 of the rosacea cohort. Obesity (BMI > 30) was found in 15.6% (53 patients) in the migraine
33
34 cohort and 18.3% (55 patients) in the rosacea cohort.
35
36
37
38
39
40
41
42
43

44 Obesity is debated in migraine. Some studies suggest that obesity might be a risk factor
45
46 for migraine,[63–66] however, it seems more certain that obesity and weight gain can
47
48 contribute to worsening migraine, potentially turning episodic migraine into chronic
49
50 migraine.[67–71] Our migraine cohort mainly consists of patients that were recruited
51
52 through the Danish Headache Center, which is a highly specialized unit that will contain
53
54 many patients with chronic migraine, which could be a confounder for BMI in this group.
55
56
57
58
59
60

1
2
3
4
5
6
7 BMI may be a risk factor for incident rosacea.[72,73] It has been suggested that metabolic
8
9
10 disease[72] and cardiovascular comorbidities are more common in rosacea, though this is
11
12
13 debated.[50,74–76] We do find more patients in the overweight group in our rosacea
14
15
16 cohort compared to the migraine cohort, however, patients with both disorders may be
17
18
19 present in both groups. Furthermore, as patients were not age- and sex-matched, more
20
21
22 analyses are needed after proper phenotyping to rule out potential confounders in both
23
24
25
26
27
28
29 groups.

DLQI

30
31 Median DLQI is 1 (IQR 0 – 2) for the migraine cohort and 2 (IQR 1 - 5) for the rosacea
32
33
34 cohort. Stratified into groups, DLQI of 0-1 (no effect on quality of life) was present in 65.1%
35
36
37 (198 patients) in the migraine cohort and 42.7% (128 patients) in the rosacea cohorts. DLQI
38
39
40 between 2-5 (mild effect on quality of life) was present in 27.3% (83 patients) in the
41
42
43 migraine cohort and 35.0% (105 patients) in the rosacea cohort. DLQI between 6-10
44
45
46 (moderate effect on quality of life) was found in 5.6% (17 patients) in the migraine cohort
47
48
49 and 12.0% (26 patients) in the rosacea cohort. DLQI 11-20 (large effect on quality of life)
50
51
52 was found in 2.0% (6 patients) in the migraine cohort and 10.0% (30 patients) in the
53
54
55 rosacea cohort. DLQI 20 (extreme effect on quality of life) was not found in any of the
56
57
58
59
60 patients in the migraine cohort, and in 0.3% (1 patient) in the rosacea cohort.

The effect on DLQI in the migraine cohort could be attributed comorbid rosacea or other skin disorders, however, recent data suggests that DLQI in a control population is comparable to minimal disease level in patients with atopic dermatitis or psoriasis.[77]

Table 1: Baseline data for COROCO and COMICO.

	N	COROCO (Rosacea)	N	COMICO (Migraine)
Age, median (IQR)	300	51.0 (43.0-61.0)	304	41.0 (29.5-51.0)
Sex, n(%)	300		304	
Men		97 (32.3)		35 (11.5)
Women		203 (67.7)		269 (88.5)
Family history of migraine, n(%)				
Any family member	300	133 (44.3)	304	223 (73.4)
First degree relative	133	117 (39.0)	223	193 (63.5)
Second degree relative	133	32 (10.7)	223	119 (39.1)
Third degree relative	133	5 (1.7)	223	3 (1.0)
Family history of rosacea, n(%)				
Any family member	300	135 (45.0)	304	56 (18.4)
First degree relative		124 (41.3)		45 (14.8)
Second degree relative		27 (9.0)		21 (6.9)
Third degree relative		3 (1.0)		0 (0)
Smoking, n(%)	300		304	
Never		151 (49.8)		173 (56.9)
Former smoker		111 (36.6)		79 (26.0)

Current smoker		39 (13.0)		52 (17.1)
Cigarettes per day	39		52	
< 5/day		15 (38.5)		21(40.4)
6-10/day		7 (18.0)		15 (28.9)
11-20/day		15 (38.5)		12 (23.0)
21-30/day		1 (2.6)		3 (5.8)
<30/day		1 (2.6)		1 (1.9)
Pack-years*, median (IQR)	31	24.6 (13.3-36.0)	40	12 (5-21)
Alcohol, current use	300	238 (79.3)	304	189 (62.2)
Alcohol, n (%)				
< 7/week	244	170 (71.4)	189	173 (91.5)
8-14/week	244	34 (14.3)	189	11 (5.8)
15-21/week	244	18 (7.6)	189	5 (2.7)
>21/week	244	16 (6.7)	189	0
Items per week, median (IQR)	244	4 (1.0-9.0)	189	2 (1.0-3.0)
BMI, n(%)	300		304	
< 18.5		4 (1.3)		10 (3.3)
18.5-25		119 (39.7)		154 (50.7)
>25-30		122 (40.7)		87 (28.6)
>30-35		35 (11.7)		32 (10.5)
>35		20 (6.7)		21 (6.9)
BMI, median (IQR)		25.7 (23.1-29.0)		24.6 (21.5-28.2)
DLQI, n(%)	309		304	
0-1		128 (42.7)		198 (65.1)
2-5		105 (35.0)		83 (27.3)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

6-10	36 (12.0)	17 (5.6)
11-20	30 (10.0)	6 (2.0)
21-30	1 (0.3)	0
DLQI, median	2 (1-5)	1 (0-2)

BMI, body mass index; DLQI, dermatology life quality index; N, number of subjects; SD, standard deviation; IQR, Inter Quartile Range

* Pack years are defined as years of smoking 20 cigarettes per day.

Strengths and limitations

The COROCO and COMICO have several strengths. First, the cohorts offer phenotyping through face-to-face interview by trained personnel, which has been shown to be the most valid way to ensure correct diagnosis of migraine,[78] and for rosacea phenotyping, pictures are subsequently validated by three authors. Questions on rosacea onset and timely relationship to migraine diagnosis may prove valuable in further explaining the connection between the two. Furthermore, the comprehensive reports on rosacea symptoms, first presenting symptoms and later onset of other rosacea symptoms may also prove valuable in determining the natural history of rosacea. Additional collected data will help in further characterizing patients and possibly explaining the mechanisms behind both disorders. A major strength is the possibility of linking cohorts to the national health registries in Denmark for additional info and follow-up.

Limitations include risk of recall bias as interviews are based on the patient reports with rosacea diagnosis or first presenting symptom sometimes many years prior to interview.

1
2
3
4 There is also a risk of selection bias, as patients were recruited primarily through specialist
5
6 clinics where only the most severely affected patients are seen. As patients were not
7
8 excluded from one of the cohorts if they had both diagnoses, comparison between groups
9
10 is also problematic as differences and similarities may be attributed to both patient groups
11
12 being present in both cohorts. Furthermore, it might be speculated that patients who
13
14 identified with the investigated disorders, e.g. migraine patients who also identified with
15
16 rosacea symptoms, or who had family members with the disease, were more prone to
17
18 accept the invitation to participate. However, we believe that the fairly short one-time
19
20 study-visit that could be combined with their outpatient visit was enough motivation in
21
22 most cases. For rosacea, the disorder is relatively un-investigated, and patients seemed
23
24 motivated to participate simply due to this fact.
25
26
27
28
29
30
31
32
33
34
35

36 **Patient and public involvement**

37
38 Patients and public were not involved in the design of this study. On completion of the
39
40 study, all patients who wish to will receive a concluding letter with study findings and
41
42 information of future perspectives of the research.
43
44
45
46
47
48
49

50 **Acknowledgements**

51
52 We thank all participants for their contribution to the cohorts. We thank all staff members
53
54 at Rigshospitalet Glostrup and Gentofte Hospital who have contributed, and the
55
56
57
58
59
60

1
2
3
4 department of Dermatology and Wound Healing at Bispebjerg hospital for contributing to
5
6
7 this study.
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

References

1. Christensen CE, Andersen FS, Wienholtz N, Egeberg A, Thyssen JP, Ashina M. The relationship between migraine and rosacea: Systematic review and meta-analysis. *Cephalalgia*. 2017;0(0).
2. Steinhoff M, Schaubert J, Leyden JJ. New insights into rosacea pathophysiology: A review of recent findings. *J Am Acad Dermatol*. 2013;69(6 SUPPL.1):15–26.
3. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia*. 2007;27(5):394–402.
4. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. *Neurol Clin*. 2019;37(4):631–49.
5. Steiner T, Scher A, Stewart W, Kolodner K, Liberman J, Lipton R. The Prevalence and Disability Burden of Adult Migraine in England and their Relationships to Age, Gender and Ethnicity. *Cephalalgia*. 2003 Sep;23(7):519–27.
6. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343–9.
7. Brandes JL. Global trends in migraine care: Results from the MAZE survey. *CNS Drugs*. 2002;16(SUPPL. 1):13–8.
8. Gether L, Overgaard L, Egeberg A, Thyssen J. Incidence and prevalence of rosacea: a systematic review and meta-analysis. *Br J Dermatol*. 2018;179:282–9.
9. Tan J, Berg M. Rosacea: Current state of epidemiology. *J Am Acad Dermatol*.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2013;69(6 SUPPL.1):S27–35.

10. Gallo RL, Granstein RD, Kang S, Mannis M, Steinhoff M, Tan J, et al. Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol*. 2018;78(1):148–55.
11. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol*. 2018;17(2):174–82.
12. Vollesen ALH, Ashina M. PACAP38: Emerging Drug Target in Migraine and Cluster Headache. *Headache*. 2017;57(Phase 3):56–63.
13. Khan S, Olesen A, Ashina M. CGRP, a target for preventive therapy in migraine and cluster headache: Systematic review of clinical data. *Cephalalgia*. 2019;39(3):374–89.
14. Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. *Exp Dermatol*. 2017;26(8):659–67.
15. Egeberg A, Ashina M, Gaist D, Gislason GH, Thyssen JP. Prevalence and risk of migraine in patients with rosacea: A population-based cohort study. *J Am Acad Dermatol*. 2017;76(3):454–8.
16. Tan SG, Cunliffe WJ. Rosacea and migraine. *Br Med J*. 1976;1(6000):21.
17. Berg M, Lidén S. An epidemiological study of rosacea. *Acta Derm Venereol*. 1989;69(5):419–23.
18. Spoenclin J, Voegel JJ, Jick SS, Meier CR. Migraine, triptans, and the risk of developing rosacea: A population-based study within the United Kingdom. *J Am Acad Dermatol*. 2013;69(3):399–406.

- 1
2
3
4 19. Ramelet A. Rosacea: A Reaction Pattern Associated With Ocular Lesions and
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
20. Berg M, Lidén S. Postmenopausal Female Rosacea Patients Are More Disposed to React with Migraine. *Dermatology*. 1996;193:73–4.
21. WHO. ICD-10 [Internet]. 2019. Available from: <https://icd.who.int/browse10/2019/en>
22. Rosacea Clinical Scorecard [Internet]. [cited 2019 Jun 29]. Available from: <https://www.rosacea.org/physicians/rosacea-clinical-scorecard>
23. Gervil M, Ulrich V, Olesen J, Russell MB. Screening for migraine in the general population: Validation of a simple questionnaire. *Cephalalgia*. 1998;18(6):342–8.
24. Wienholtz N, Christensen CE, Egeberg A, Thyssen JP, Ashina M. Vasomotor reactions in the face and head of patients with migraine. *Cephalalgia Reports*. 2018;1.
25. Sinikumpu SP, Huilaja L, Auvinen J, Jokelainen J, Puukka K, Ruokonen A, et al. The association between low grade systemic inflammation and skin diseases: A cross-sectional survey in the Northern Finland Birth Cohort 1966. *Acta Derm Venereol*. 2018;98(1):65–9.
26. Edvinsson L, Haanes KA, Warfvinge K. Does inflammation have a role in migraine? *Nat Rev Neurol*. 2019;15(8):483–90.
27. Chang A, Raber I, Xu J, Li R, Spitale R, Chen J, et al. Assessment of the genetic basis of rosacea by genome-wide association study. *J Invest Dermatol*. 2015;135:1548–55.
28. Aponte JL, Chiano MN, Yerges-Armstrong LM, Hinds DA, Tian C, Gupta A, et al. Assessment of rosacea symptom severity by genome-wide association study and

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

expression analysis highlights immuno-inflammatory and skin pigmentation genes.

Hum Mol Genet. 2018;27(15):2762–72.

29. Green RC, Berg JS, Grody WW, Kalia S, Kort B, Martin C, et al. ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing. Genet Med Author Manuscr. 2013;15(7):565–74.
30. Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. Nat Rev Neurol. 2010;6(10):573–82.
31. Woo YR, Lim JH, Cho DH, Park HJ. Rosacea: Molecular mechanisms and management of a chronic cutaneous inflammatory condition. Int J Mol Sci. 2016;17(9):1–23.
32. Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: A Phase 3 Randomized Trial of Erenumab for Episodic Migraine. Cephalalgia. 2018;38(6):1026–37.
33. Russell MB, Rasmussen BK, Thorvaldsen P, Olesen J. Prevalence and sex-ratio of the subtypes of migraine. Int J Epidemiol. 1995;24(3):612–8.
34. Hernandez-Latorre M, Roig M. Natural history of migraine in childhood. Cephalalgia. 2000;20(6):573–9.
35. Dzoljic E, Vlajinac H, Sipetic S, Marinkovic J, Grbatinic I, Kostic V. A survey of female students with migraine: What is the influence of family history and lifestyle? Int J Neurosci. 2014;124(2):82–7.
36. Russell M, Fenger K, Olesen J. The family history of migraine. Direct versus indirect information. Cephalalgia. 1996;16:156–60.

- 1
2
3
4 37. Lateef T, Cui L, Nakamura E, Dozier J, Merikangas K. Accuracy of Family History
5
6 Reports of Migraine in a Community-Based Family Study of Migraine. *Headache*.
7
8 2017;66(3):407–12.
9
- 10
11
12 38. Abram K, Silm H, Maaros H, Oona M. Risk factors associated with rosacea. *J Eur*
13
14 *Acad Dermatol Venereol*. 2010;24:565–71.
15
- 16
17 39. Rainer BM, Fischer AH, Luz Felipe Da Silva D, Kang S, Chien AL. Rosacea is associated
18
19 with chronic systemic diseases in a skin severity-dependent manner: Results of a
20
21 case-control study. *J Am Acad Dermatol*. 2015;73(4):604–8.
22
23
- 24
25 40. Tan J, Schöfer H, Araviiskaia E, Audibert F, Kerrouche N, Berg M. Prevalence of
26
27 rosacea in the general population of Germany and Russia - The RISE study. *J Eur*
28
29 *Acad Dermatology Venereol*. 2016;30(3):428–34.
30
31
- 32
33 41. Tizek L, Schielein MC, Seifert F, Biedermann T, Böhner A, Zink A. Skin diseases are
34
35 more common than we think: screening results of an unreferred population at the
36
37 Munich Oktoberfest. *J Eur Acad Dermatology Venereol*. 2019;33(7):1421–8.
38
39
- 40
41 42. Baharuddin NA, Al-Bayaty FH. The relationship between smoking and migraine.
42
43 *Postgrad Med J*. 1976;52:80–2.
44
45
- 46
47 43. Hagen K, Åsberg AN, Stovner L, Linde M, Zwart JA, Winsvold BS, et al. Lifestyle
48
49 factors and risk of migraine and tension-type headache. Follow-up data from the
50
51 Nord-Trøndelag Health Surveys 1995–1997 and 2006–2008. *Cephalalgia*.
52
53 2018;38(13):1919–26.
54
55
- 56
57 44. Chen TC, Leviton A, Edelstein S, Ellenberg JH. Migraine and Other Diseases in
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Women of Reproductive Age: The Influence of Smoking on Observed Associations.

Arch Neurol. 1987;44(10):1024–8.

45. López-Mesonero L, Márquez S, Parra P, Gámez-Leyva G, Muñoz P, Pascual J. Smoking as a precipitating factor for migraine: A survey in medical students. *J Headache Pain*. 2009;10(2):101–3.
46. Qi Gan W, Estus S, Smith JH. Association between Overall and Mentholated Cigarette Smoking with Headache in a Nationally Representative Sample. *Headache*. 2016;56(3):511–8.
47. Spoenclin J, Voegel JJ, Jick SS, Meier CR. A study on the epidemiology of rosacea in the U.K. *Br J Dermatol*. 2012;167(3):598–605.
48. Li WQ, Zhang M, Danby FW, Han J, Qureshi AA. Personal history of rosacea and risk of incident cancer among women in the US. *Br J Cancer*. 2015;113(3):520–3.
49. Li S, Cho E, Drucker AM, Qureshi AA, Li WQ. Cigarette Smoking and Risk of Incident Rosacea in Women. *Am J Epidemiol*. 2017;186(1):38–45.
50. Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: A case control study. *J Eur Acad Dermatology Venereol*. 2014;28(9):1165–9.
51. Kucukunal A, Altunay I, Arici JE, Cerman AA. Is the effect of smoking on rosacea still somewhat of a mystery? *Cutan Ocul Toxicol*. 2016;35(2):110–4.
52. Hauge AW, Kirchmann M, Olesen J. Trigger factors in migraine with aura. *Cephalalgia*. 2010;30(3):346–53.
53. Panconesi A, Bartolozzi ML, Guidi L. Alcohol and migraine: What should we tell

- 1
2
3
4 patients? *Curr Pain Headache Rep.* 2011;15(3):177–84.
5
6
7 54. Panconesi A. Alcohol and migraine: Trigger factor, consumption, mechanisms. A
8
9 review. *J Headache Pain.* 2008;9(1):19–27.
10
11
12 55. Davis-Martin RE, Polk AN, Smitherman TA. Alcohol Use as a Comorbidity and
13
14 Precipitant of Primary Headache: Review and Meta-analysis. *Curr Pain Headache Rep.*
15
16 2017;21(10).
17
18
19 56. Weiss E, Katta R. Diet and rosacea: the role of dietary change in the management of
20
21 rosacea. *Dermatol Pract Concept.* 2017;7(4):31–7.
22
23
24 57. Bae YI, Yun SJ, Lee JB, Kim SJ, Won YH, Lee SC. Clinical evaluation of 168 Korean
25
26 patients with rosacea: The sun exposure correlates with the erythematotelangiectatic
27
28 subtype. *Ann Dermatol.* 2009;21(3):243–9.
29
30
31
32 58. Elewski BE, Draelos Z, Dréno B, Jansen T, Layton A, Picardo M. Rosacea - Global
33
34 diversity and optimized outcome: Proposed international consensus from the
35
36 Rosacea international expert group. *J Eur Acad Dermatology Venereol.*
37
38 2011;25(2):188–200.
39
40
41
42 59. Li S, Cho E, Drucker A, Qureshi A, Li W. Alcohol intake and risk of incident rosacea in
43
44 US women. *J Am Acad Dermatol.* 2017;76(6):1061–7.
45
46
47
48 60. Aldrich N, Gerstenblith M, Fu P, Tuttle MS, Varma P, Gotow E, et al. Genetic vs
49
50 environmental factors that correlate with rosacea: A cohort-based survey of twins.
51
52 *JAMA Dermatology.* 2015;151(11):1213–9.
53
54
55
56 61. Alinia H, Tuchayi SM, Patel NU, Patel N, Awosika O, Bahrami N, et al. Rosacea
57
58
59
60

- 1
2
3
4 Triggers: Alcohol and Smoking. *Dermatol Clin*. 2018;36(2):123–6.
5
6
7 62. Curnier A, Choudhary S. Rhinophyma: Dispelling the myths. *Plast Reconstr Surg*.
8
9 2004;114(2):351–4.
10
11
12 63. Ford ES, Li C, Pearson WS, Zhao G, Strine TW, Mokdad AH. Body mass index and
13
14 headaches: Findings from a national sample of US adults. *Cephalalgia*.
15
16 2008;28(12):1270–6.
17
18
19 64. Peterlin BL, Rapoport AM, Kurth T. Migraine and obesity: Epidemiology, mechanisms,
20
21 and implications. *Headache*. 2010;50(4):631–48.
22
23
24 65. Vo M, Ainalem A, Qiu C, Peterlin BL, Aurora SK, Williams MA. Body mass index and
25
26 adult weight gain among reproductive age women with migraine. *Headache*.
27
28 2011;51(4):559–69.
29
30
31
32 66. Yu S, Liu R, Yang X, Zhao G, Qiao X, Feng J, et al. Body mass index and migraine: A
33
34 survey of the Chinese adult population. *J Headache Pain*. 2012;13(7):531–6.
35
36
37
38 67. Bigal ME, Lipton RB. Obesity is a risk factor for transformed migraine but not chronic
39
40 tension-type headache. *Neurology*. 2006;67(2):252–7.
41
42
43
44 68. Bigal ME. Body Mass Index and Episodic Headaches. *Arch Intern Med*.
45
46 2007;167(18):1964–70.
47
48
49 69. Keith SW, Wang C, Fontaine KR, Cowan CD, Allison DB. BMI and headache among
50
51 women: Results from 11 epidemiologic datasets. *Obesity*. 2008;16(2):377–83.
52
53
54
55 70. Winter AC, Berger K, Buring JE, Kurth T. Body mass index, migraine, migraine
56
57 frequency and migraine features in women. *Cephalalgia*. 2009;29(2):269–78.
58
59
60

- 1
2
3
4 71. Giraud P, Chauvet S, Tessy M. Migraine and obesity, is there a link ? Rev Neurol
5
6 (Paris). 2013;169(5):413–8.
7
8
9
10 72. Akin Belli A, Ozbas Gok S, Akbaba G, Etku F, Dogan G. The relationship between
11
12 rosacea and insulin resistance and metabolic syndrome. Eur J Dermatol.
13
14 2016;26(3):260–4.
15
16
17 73. Li S, Cho E, Drucker AM, Qureshi AA, Li W-Q. Obesity and Risk for Incident Rosacea
18
19 in US Women. J Am Acad Dermatol. 2017;77(6):1083–7.
20
21
22
23 74. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Assessment of the risk of
24
25 cardiovascular disease in patients with rosacea. J Am Acad Dermatol. 2016;75(2):336–
26
27 9.
28
29
30
31 75. Hua TC, Chung PI, Chen YJ, Wu LC, Chen Y Da, Hwang CY, et al. Cardiovascular
32
33 comorbidities in patients with rosacea: A nationwide case-control study from Taiwan.
34
35 J Am Acad Dermatol. 2015;73(2):249–54.
36
37
38
39 76. Dosal J, Keri J. Rosacea and cardiovascular disease: Is there an association? J Am
40
41 Acad Dermatol. 2015;73(2):308–9.
42
43
44 77. Egeberg A, Griffiths CEM, Williams HC, Andersen YMF, Thyssen JP. Clinical
45
46 characteristics, symptoms, and burden of psoriasis and atopic dermatitis in adults
47
48 (epub ahead of print). Br J Dermatol. 2019;0(0):0.
49
50
51
52 78. Rasmussen B, Jensen R, Olesen J. Questionnaire Versus Clinical Interview in the
53
54 Diagnosis of Headache. Headache. 31(5):290–5.
55
56
57
58
59
60

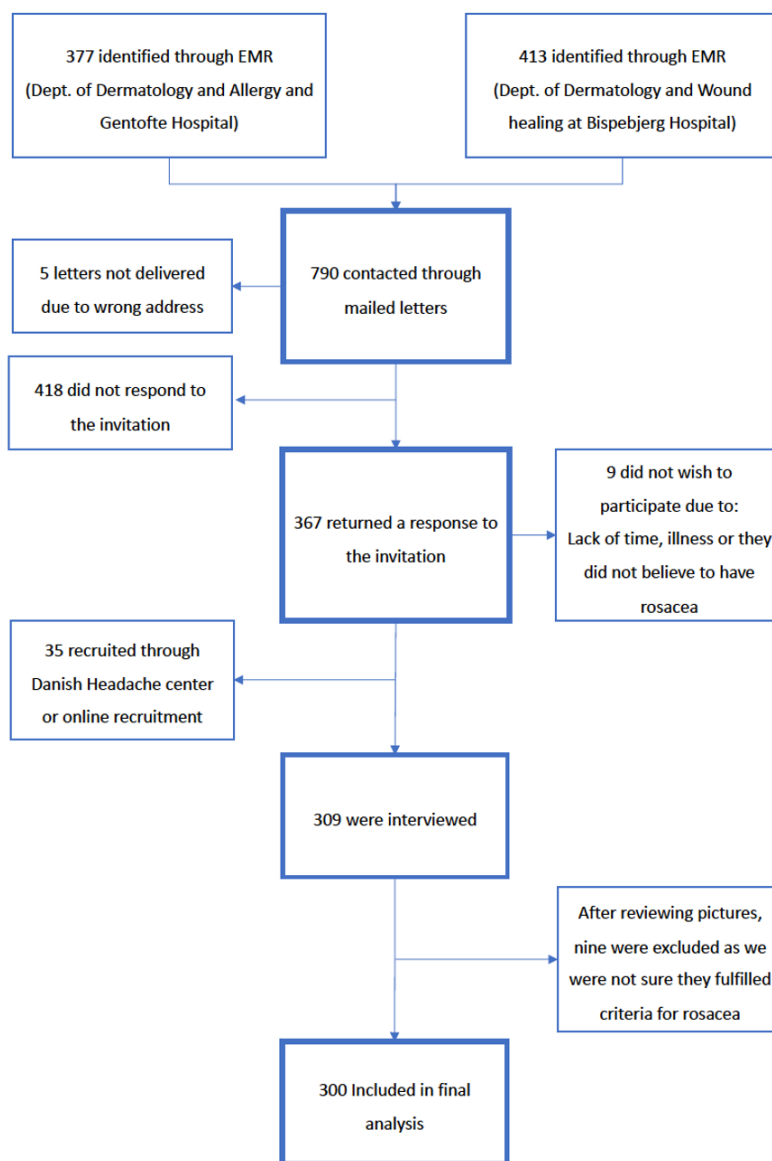


Figure 1. Flow chart detailing enrolment in COROCO. EMR = Electronic Medical Records.

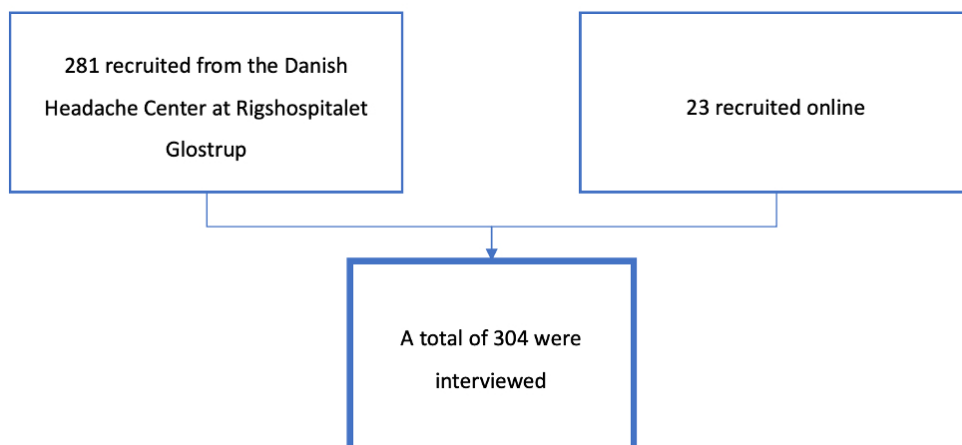


Figure 2: Flow chart detailing enrolment in COMICO.

Appendix 1:

Semi-structured rosacea questionnaire made by authors NW, JT and AE at the department of Dermatology in Gentofte to uncover symptoms and diagnosis of rosacea, previous treatments and known diseases in patient and/or 1st or 2nd degree relatives. The questionnaire also includes sleeping habits, smoking, alcohol, BMI, dermatology quality of life index and severity rating of rosacea according to the National Rosacea Society.

1. Rosacea

1.1 Has a doctor ever told you that you have rosacea? (one answer)

- No – and I do not have rosacea
- Yes, I am certain I have rosacea, but a doctor has never told me.
- Yes – a doctor who is not a dermatologist (e.g. GP)
- Yes – a dermatologist

If yes to one of the above, go to question. 1.2. If no, move on to question 3

1.2 Which symptom(s) of rosacea did you first notice? (multiple answers)

- Redness of particularly cheeks and/or the chest, which did not want to go away
- Flushing attacks (sudden warmth/burning sensations and redness which lasts a few minutes – half an hour)
- Persistent (> 1 hour) attacks of flushing
- Telangiectasias in the face (cheeks, nose, chin or eyelids)
- Symptoms from the eyes
- Recurrent formation of pimples in the face
- Change of the nose's look or size
- Other? _____

1.2.1 At what age did you experience the first symptom(s) of rosacea? Age years

1.2.2 How much time passed from your first symptom(s) of rosacea until a doctor diagnosed you with rosacea?

Year Months

1.3 Has any of the following symptoms appeared since you noticed the first symptom(s) of rosacea? (multiple answers)

- Redness of particularly cheeks and/or the chest, which did not want to go away
- Flushing attacks (sudden warmth/burning sensations and redness which lasts a few minutes – half an hour)
- Persistent (> 1 hour) attacks of flushing
- Telangiectasias in the face (cheeks, nose, chin or eyelids)
- Symptoms from the eyes
- Recurrent formation of pimples in the face
- Change of the nose's look or size
- Other? _____

1.4 Do you still have symptoms of Rosacea? (one answer)

- No
- Improvement
- Worsening
- Unchanged symptoms

Describe:

2. ROSACEA TREATMENTS

2.1 Have you ever been treatment for rosacea? (one answer)

- No, never (move on to question 3)
- Yes, but I am no longer in treatment
- Yes, I still receive treatment

2.2 How long did/have you receive(d) treatment for rosacea? (cumulated time)

- Less than 3 months
- 3 months – 1 year
- More than 1 year – how long (years) _____

2.3 If no longer in treatment for rosacea – why did you stop treatment? (one answer)

- My symptoms improved / disappeared after treatment
- There was no effect of the treatment on my symptoms
- My symptoms worsened due to treatment
- I got side effects from the treatment
- I do not wish to be on daily medication

2.4 Which type of treatment(s) have you received? (multiple answers)

- Creme/gel/ointment
- Pills
- Laser treatment

2.5 Which drug(s) have you tried, and did it/they have any effect? (multiple answers)

Yes No Do not know

- | | | | |
|--|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> Mirvaso (brimonidine tartrate) creme/gel | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Finacea (azelaic acid) creme/gel | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Metronidazole / metrocrem / rozex / robaz creme/gel | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Oracea (doxycycline) tablet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Soolantra (ivermectin) creme | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Tetracycline | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Erythromycin (macrolide) tablet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Accutin / Isotretinoin tablet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other: _____ | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

2.6 Which symptom(s) did the treatment influence? (multiple answers)

- Papules and pustules (impurities/pimples)
- Unwanted redness of the face
- Telangiectasias in the face
- Eye symptoms
- Nose Changes
- Other: _____

Other comments to treatment:

3. FLUSHING + OTHER SYMPTOMS

REDNESS/ SENSITIVE SKIN

- 3.1 Are any areas of your face often pink or red? No Yes
- 3.2 Is your face often pink or red compared with other people? No Yes
- 3.3 Is your face often pink or red compared to other body areas (e.g. abdomen, upper arms) No Yes
- 3.4 Have others previously mentioned that your face was pink or red? No Yes
- 3.5 Do you experience that coldness, heat or direct sunlight can provoke a facial burning/stinging sensation after only short exposure?
 No Rarely In periods (e.g. winter) Monthly Weekly Daily
- 3.6 Do you experience dry/scaly skin in central areas of your face, e.g. where you usually experience redness?
 No Rarely In periods (e.g. winter) Monthly Weekly Daily
- 3.7 Is your skin sensitive, i.e. blushes easily and/or gets tight/dry easily?
 No Rarely In periods (e.g. winter) Monthly Weekly Daily

TELANGIECTASIAS

- 3.8 Do you have telangiectasias in the face (e.g. around the nose or center of the cheeks)? No Yes
- 3.8.1 If yes, where are the telangiectasias located?
 on top of the nose sides of the nose cheeks chin eyelids other: _____

FLUSHING

- 3.9 Have you experienced flushing in the *past year*?
 No, not at all Yes, a few times (less than 12 times) Yes, periodically Monthly Weekly Daily
- 3.9.1 In your experience, was the start of flushing related to something?
 no menopause (hot flushes) high/low metabolism medication other _____
- 3.9.2 If yes to flushing, in which areas of the skin do you experience flushing?
 forehead center of the cheeks nose ears chin neck chest
- 3.9.3 How long does a (severe) flushing last? (describe any other symptoms)

- 3.10 As a *child or teenager*, did you experience that your face would easily become red (e.g. when you were nervous/shy or exercised)
 No, never
 Yes, I have experienced it a couple of times (few times a year or less)
 It happened occasionally/frequently
 I would always blush when I got embarrassed
 I experienced it daily and sometimes without a trigger
- 3.10.1 How old were you the first time you experienced flushing? Age years

3.11 Can any of the following give you a sudden sensation of warmth (flushing) (multiple answers)

No Yes

- Alcohol
 Hot food or drinks
 Spicy food
 Sunlight
 Hot and humid surrounds e.g. sauna or hot bath etc.
 Physical activity (e.g. sport)
 Psychological stress or emotional revolt (e.g. holding a speech in front of a large audience)
 Other: _____
 None of the above

3.12 **Do you experience having thickened skin on your nose** Yes No

4. ACNE

4.1 Have you experienced frequently having impure skin/pimples in the face after becoming an adult (above 25 years of age)

- No (Go to question 5)
 No, but I had acne when I was younger
 Yes, I have previously experienced pimples, which occurred after I became an adult, but I do not anymore
 Yes, and I still frequently experience having pimples

4.2 If yes, do they occur in relation to anything special?

- No Periods Alcohol Other _____

4.3 Where are these impurities/pimples typically located when you have them? (multiple answers)

- Forehead Cheeks Nose Chin Chest Back Shoulders Other _____

5. EYE SYMPTOMS

5.1 Do you **frequently** experience

No Yes

- red/bloodshot eyes
 watery/runny eyes
 foreign body sensation of the eyes
 stinging sensation in eye/eyes
 itching sensation in eye/eyes
 small, fine scales around eyelid margins
 thickened sensation of eyelid(s), which can be sore or red
 feeling the need to close eyes in the evening, in air-conditioned spaces, during flights etc.

5.2 If yes to any of the above, have you ever visited an ophthalmologist due to these symptoms? No Yes

5.3 Have you had the need to use viscous/watery eyedrops (artificial tears) for longer/shorter periods of time? No Yes

6. TREATMENT WITH CORTICOSTEROIDS/ADRENOCORTICAL HORMONE

6.1 Have you ever been treated with corticosteroids (also called adrenocortical hormone or prednisolone)?

- No, never (move on to question 7) Yes – creme/ointment Yes – pills Yes – syringe

6.2 Have you ever been treated with corticosteroids/adrenocortical hormone?

- No, never Yes, a short period of time (less than 1 month cumulated) Yes, a longer period (1-12 months cumulated)

- Yes, a long period (>12 months cumulated)

6.2.1 If yes, at what age were you when you were first treated with corticosteroids in the face? Age years

7. OTHER DISEASES AND TREATMENT

7.1 Has a doctor ever told you or someone in your family that you/they had any of the following diseases? (Only biologically related family members, i.e. not stepsister or stepparents)

SKIN

Rosacea

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Acne

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Seborrheic dermatitis

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Psoriasis

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Atopic dermatitis

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Non-melanoma skin cancer

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Malignant melanoma

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Urticaria (hives)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Any other skin disorder

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Please describe: _____

PSYCHIATRIC

Anxiety

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

If 'me', have you ever been treated for anxiety? No, never Yes, and I am still in treatment Yes, but I am no longer in treatment

Depression

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

If 'me', have you ever been treated for depression? No, never Yes, and I am still in treatment Yes, but I am no longer in treatment

Any other psychiatric disorder

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Please describe: _____

STOMACH AND GUT

Heartburn/reflux

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Inflammatory bowel disease (Crohn's disease/Ulcerative colitis)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Gluten intolerance/coeliac disease

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Do you frequently experience discomfort/bloating and changing bowel habits? (Irritated bowel syndrome)

No Rarely (few times a year) Monthly Weekly Daily

OTHER DISEASES

Type 1 diabetes

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Type 2 diabetes

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Sjogren's syndrome

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Metabolic disease

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

High cholesterol

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Hypertension (high blood pressure)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

If 'me', are you taking any treatment for hypertension? No Yes, pills, If yes, describe: _____

Raynaud's phenomenon

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

AIRWAYS

COPD (chronic obstructive pulmonary disease)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Asthma

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Hay fever

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

NEUROLOGICAL

Parkinson's disease

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Alzheimer's disease

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

7.2 Do you often experience having cold nose and/or hands? No Yes, nose Yes, hands

7.3 Have you been diagnosed with/treated for any other diseases? No Yes, please describe: _____

8. SLEEP

8.1 How often do you find it difficult to fall asleep?

Once a month or less (never) 2-4 times a month one to several times a week daily

8.2 How often do you wake up earlier than what you intended (without being woken by an alarm or other noise)?

Once a month or less (never). 2-4 times a month one to several times a week daily

9. SMOKING

9.1 Do you smoke? (one answer)

No, I have never smoked No, but I have previously smoked Yes, occasionally (less than 1 cigarette per day). Yes, daily

ANSWERS FROM DAILY SMOKERS

9.2 How many cigarettes do you smoke on average? (daily number of cigarettes)

Number of cigarettes Other, describe: _____

ANSWERS FROM OCCASIONAL SMOKERS

9.3 How many cigarettes do you smoke on average a week? (weekly number of cigarettes)

Number of cigarettes Other, describe: _____

ANSWERS FROM OCCASIONAL AND FORMER SMOKERS

9.4 Have you previously smoked every day? yes no

9.5 If yes, how much did you smoke on average a day?

Number of cigarettes Other, describe: _____

9.6 When did you stop smoking daily? (which year)

ANSWER FROM ALL SMOKERS

9.7 How old were you when you started smoking? (age in years) years

10. ALCOHOL

10.1 Have you been drinking alcohol in the past year? No Yes

10.2 How much was your average weekly intake during the past 12 months? (Write '0' if none) drinks per week

11. HEIGHT AND WEIGHT

11.1 What is your current height (without shoes)? _____ cm

11.2 What is your current weight without clothes and shoes? _____ kg

12. DERMATOLOGY LIFE QUALITY INDEX (DLQI)

12.1 Within the past week to what extent has your skin been itching, sore, hurting or stinging?

Extremely Very A bit Not at all

12.2 Within the past week to what extent have you been embarrassed or shy because of your skin?

Extremely Very A bit Not at all

12.3 Within the past week to what extent has your skin bothered you in terms of shopping or taking care of your house or back yard?

Extremely Very A bit Not at all Not relevant

12.4 Within the past week to what extent has your skin affected the way you dress?

Extremely Very A bit Not at all Not relevant

12.5 Within the past week to what extent has your skin affected your social activities or leisure activities?

Extremely Very A bit Not at all Not relevant

12.6 Within the past week to what extent has your skin complicated your opportunities of exercise?

Extremely Very A bit Not at all Not relevant

12.7 Within the past week has your skin prevented you from working or studying?

Yes No Not relevant

If "No", within the past week has your skin been a problem for you at work or during studies?

Extremely Very A bit Not at all

12.8 Within the past week to what extent has your skin caused problems in relation to your partner, close friends or relatives?

Extremely Very A bit Not at all Not relevant

12.9 Within the past week to what extent has your skin caused sexual problems?

Extremely Very A bit Not at all Not relevant

12.10 Within the past week, has treatment of your skin caused problems, e.g. by making your home messy or dirty, or by being time consuming?

Extremely Very A bit Not at all Not relevant

Appendix 2:

Semi-structured headache and migraine questionnaire adapted from the validated questionnaire from the Danish Headache Center (last updated November 18th, 2012) adapted for the purpose of interviewing patients without headache by NW.

Semi-Structured Migraine and Headache Interview

0. Headache

0.1 Have you been diagnosed with migraine

Yes No

0.1.1 If yes, did anything happen in relation to debut of migraine?

Yes No

0.1.1.1 If yes – what happened

- Menarche
- Head trauma / Concussion
- Other _____

0.1.2 If NO:

0.1.2.1 Do you experience regular headaches?

0.1.2.1.1 If yes, how often (days per month) ____

0.1.2.1.2 Is the headache related to anything in particular

Yes No

0.1.2.1.3 If yes, what? _____

For all patients:

Do you ever experience headaches that are:

	Yes	No
a. Unilateral	<input type="checkbox"/> 1 <input type="checkbox"/> 2	<input type="checkbox"/> 1 <input type="checkbox"/> 2
b. Pulsating	<input type="checkbox"/> 1 <input type="checkbox"/> 2	<input type="checkbox"/> 1 <input type="checkbox"/> 2
c. Moderate/severe intensity	<input type="checkbox"/> 1 <input type="checkbox"/> 2	<input type="checkbox"/> 1 <input type="checkbox"/> 2
d. Aggravation by physical activity	<input type="checkbox"/> 1 <input type="checkbox"/> 2	<input type="checkbox"/> 1 <input type="checkbox"/> 2
e. Nausea	<input type="checkbox"/> 1 <input type="checkbox"/> 2	<input type="checkbox"/> 1 <input type="checkbox"/> 2
f. Vomiting	<input type="checkbox"/> 1 <input type="checkbox"/> 2	<input type="checkbox"/> 1 <input type="checkbox"/> 2
g. Photophobia	<input type="checkbox"/> 1 <input type="checkbox"/> 2	<input type="checkbox"/> 1 <input type="checkbox"/> 2
h. Phonophobia	<input type="checkbox"/> 1 <input type="checkbox"/> 2	<input type="checkbox"/> 1 <input type="checkbox"/> 2
i. Osmophobia	<input type="checkbox"/> 1 <input type="checkbox"/> 2	<input type="checkbox"/> 1 <input type="checkbox"/> 2

Duration of the headache without medication:

- < ½ h 1
- ½ - 4 h 2
- 5 h – 23 h 3
- 1 - 3 days 4
- 4 – 7 days 5
- >7 days 6

1. MIGRAINE WITH AURA (MA)

a. Do you have migraine with aura?

1 2

1.1 Visual aura

Yes No

- a. Are there visual disturbances? 1 2
- b. Unilateral 1 2
- c. Gradually progressing 1 2
- d. Scotoma 1 2
- e. Zig-zag lines (fortification) 1 2
- f. Flickering 1 2
- g. Preserved central vision 1 2
- h. Duration of gradual development _____min
- j. Duration of visual aura _____min

1.2 Sensory aura

Yes No

- a. Are there sensory disturbances? 1 2
- b. Unilateral 1 2
- c. Gradually progressing 1 2

Do the sensory disturbances involve:

- d. The face 1 2
- e. The tongue 1 2
- f. The hand 1 2
- g. The arm 1 2
- h. The foot 1 2
- i. The leg 1 2
- j. The body 1 2
- k. Duration of gradual development _____min
- l. Duration of visual aura _____min

1.3 Motor aura

Yes No

- a. Are there motor disturbances? 1 2
- b. Unilateral 1 2
- c. Gradually progressing 1 2

Do the motor disturbances involve:

- d. The face 1 2
- e. The tongue 1 2
- f. The hand 1 2
- g. The arm 1 2
- h. The foot 1 2
- i. The leg 1 2
- j. The body 1 2
- k. Duration of gradual development _____min
- l. Duration of visual aura _____min

1.4 Aphasia/

Speech disturbances

Yes No

- a. Are there speech disturbances? 1 2

Are the speech impairments due to:

- b. Problems articulating speech 1 2
- c. Problems finding the right words 1 2
- d. Problems understanding what people say 1 2
- e. Problematic for other people to understand your speech 1 2
- f. Duration of speech/aphasic disturbances _____min

- 1 **1.5 Basilar-type aura** Yes No
- 2 a. Are there basilar/occipital
- 3 symptoms? 1 2
- 4 Are there:
- 5 b. Bilateral pareses/parestesias 1 2
- 6 c. Bilateral visual symptoms 1 2
- 7 d. Dysarthria 1 2
- 8 e. Vertigo 1 2
- 9 f. Diplopia 1 2
- 10 g. Tinnitus 1 2
- 11 h. Hypacusia 1 2
- 12 i. Decreased level of consciousness 1 2
- 13 j. Ataxia 1 2

- 15 **1.6 Succession of aura symptoms**
- 16 a. If more than 1 aura type, is the succession of the auras:
- 17 Successive 1
- 18 Simultaneously 2
- 19 Not applicable (NA) 3

- 21 **1.7 Aura with headache** Yes No
- 22 a. Do you have aura with headache 1 2
- 23 b. Does the onset of the headache typically come:
- 24 Before the aura 1
- 25 After the aura 2
- 26 Simultaneously with the
- 27 aura 3
- 28 c. How long time before/after the aura _____min

- 30 **1.8 Aura without headache** Yes No
- 31 a. Do you have aura without
- 32 headache 1 2

- 35 **1.9 Migraine with aura over time**
- 36 a. Age at onset _____years
- 37 b. Age at last attack _____years
- 38 c. No. of attacks within last year:
- 39 0 1
- 40 1-5 2
- 41 6-12 3
- 42 13-24 4
- 43 25-36 5
- 44 >36 6
- 45 d. No. of lifetime attacks:
- 46 1 1
- 47 2-4 2
- 48 5-9 3
- 49 10-49 4
- 50 50-100 5
- 51 >100 6

2. MIGRAINE WITHOUT AURA (MO)

- a. Do you have migraine without aura? Yes No
- 1 2

2.1 Migraine without aura over time

- a. Age at onset _____years
- b. Age at last attack _____years
- c. No. of attacks within last year:
- 0 1
- 1-5 2
- 6-12 3
- 13-24 4
- 25-36 5
- >36 6
- d. No. of lifetime attacks:
- 1 1
- 2-4 2
- 5-9 3
- 10-49 4
- 50-100 5
- >100 6

3. Migraine triggers

- a. Are there factors that can trigger a migraine attack? Yes No NA
- 1 2 3
- b. What type of migraine? MO MA MA+MO
- 1 2 3
- 3.1. Can these factors trigger a migraine attack:
- Yes No
- a. Physical activity 1 2
- b. Light 1 2
- c. Stress 1 2
- d. Menstruation 1 2
- e. Alcohol 1 2
- f. Strong smells 1 2
- g. Lack of/too much sleep 1 2
- h. Other factors: _____

4. Chronic migraine (MA+MO)

During the past 3 successive months, have you had:

- a. Headache at least 15 days a month Yes No
- 1 2
- b. Migraine at least 8 days a month 1 2

5. Tension-type headache

- Yes No
- Do you have tension-type headaches 1 2

- 5.1 Headache characteristics Yes No
- a. Bilateral 1 2
- b. Pressing 1 2
- c. Mild/moderate intensity 1 2
- d. Aggravation by physical activity 1 2
- e. Nausea 1 2
- f. Vomiting 1 2
- g. Photophobia 1 2
- h. Phonophobia 1 2

5.2 Duration of headache

- < ½ h 1
- ½ - 4 h 2
- 5 h – 23 h 3
- 1 - 3 days 4
- 4 – 7 days 5
- >7 days 6

5.3 Tension-type headache over time

a. Headache days within last year:

- 0 1
- 1-7 2
- 8-14 3
- 15-30 4
- 31-179 5
- ≥180 6

b. No. of tension-type headache days during the three last months: _____ days

c. If ≥45 headache days, are the days evenly spaced out Yes No
 1 2

6. MIGRAINE TREATMENT (MA+ MO)

6.1 Treatment of migraine attacks

- | | Yes | No | NA |
|--|----------------------------|----------------------------|----------------------------|
| a. Triptans are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| b. Regular painkillers (NSAID, Paracetamol etc.) are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| c. Ergotamine drugs are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| d. Other drug(s) _____ | | | |

6.2 Use of medication

- a. No. of days of triptan-use per month _____
- b. No. of days of regular painkiller-use per month _____

6.3 Prophylactic treatment of migraine

- | | Yes | No | NA |
|---|----------------------------|----------------------------|----------------------------|
| a. Beta-blockers are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| b. Ca ²⁺ -antagonists are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| c. Angiotensin II receptor blockers are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| d. ACE-inhibitors are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| e. Anti-epilepsy drugs are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| f. Antidepressive medication (mirtazapine) is efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| g. Hormone treatment is efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| h. Other drug(s) _____ | | | |

g. Are you currently receiving prophylactic treatment(s) for migraine Yes No
 1 2

8. SECONDARY HEADACHES? Yes 1 No 2

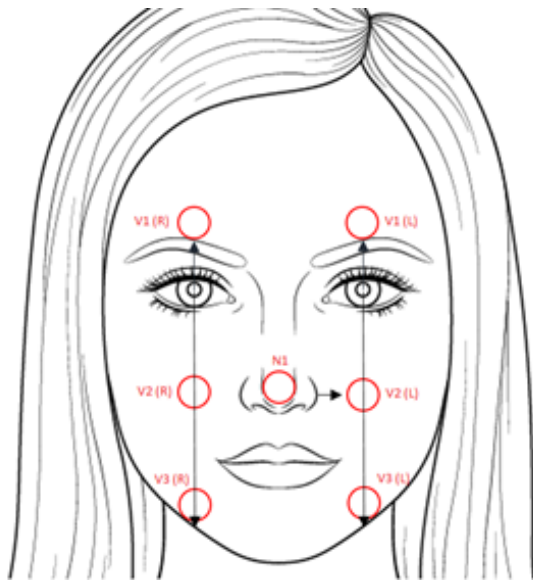
If yes, specify: _____

11. Migraine within the family

- | | Yes | No |
|-------------------------------|----------------------------|----------------------------|
| a. Mother has/had migraine | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| b. Father has/had migraine | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| d. Siblings have/had migraine | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| e. Children have/had migraine | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |

Interview conducted by: _____

1
2
3
4 **Appendix 3:** Guide for standardized measure of the three branches of the trigeminus on both sides
5
6 of the face (forehead, cheeks, chin) and the tip of the nose. The circles were adjusted to be the same
7
8 size as the pupil and iris to adjust for possible differences in sizes of the pictures. Guide was made
9
10 by authors CC, DGZ and NW.
11
12
13
14
15



BMJ Open

Cohort profile of COpenhagen ROsacea COhort (COROCO) and COpenhagen MIgraine COhort (COMICO)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039445.R1
Article Type:	Cohort profile
Date Submitted by the Author:	29-Jun-2020
Complete List of Authors:	Wienholtz, Nita; Rigshospitalet Glostrup, Danish Headache Center; Gentofte Hospital, Dermatology and Allergy Christensen, Casper; Rigshospitalet Glostrup, Danish Headache Center Haugaard, Jeanette; Gentofte Hospital, Dermatology and Allergy Zhang, Ditte; Rigshospitalet Glostrup, Danish Headache Center Ashina, Messoud; University of Copenhagen, Denmark, Danish Headache Centre and Department of Neurology Thyssen, JP; Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen Egeberg, A; Gentofte Hospital, Department of Dermatology and Allergy
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Neurology
Keywords:	Migraine < NEUROLOGY, DERMATOLOGY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1 Cohort profile of Copenhagen ROsacea COhort (COROCO) and Copenhagen MIgraine
5
6
7 2 COhort (COMICO)
8
9

10 3
11
12 4 Nita Wienholtz, MD^{1,2,3}, Casper Emil Christensen, MD, PhD¹, Jeanette Halskou Haugaard, MD^{2,3}, Ditte
13
14
15 5 Georgina Zhang¹, Messoud Ashina, MD, PhD, DMSc¹, Jacob P. Thyssen, MD, PhD, DMSc^{2,3},
16
17
18 6 Alexander Egeberg, MD, PhD^{2,3}
19

20 7
21
22
23 8 ¹ Danish Headache Center, Department of Neurology, Rigshospitalet Glostrup, Glostrup,
24
25
26 9 Denmark
27

28 10 ² Copenhagen Research Group for Inflammatory Skin (CORGIS), Hellerup, Denmark
29

30
31 11 ³ Department of Dermatology and Allergy, Herlev and Gentofte Hospital, Hellerup,
32
33
34 12 Denmark
35

36 13
37
38
39 14 **Correspondence:**

40
41 15 Alexander Egeberg

42
43 16 Department of Dermatology and Allergy

44
45 17 Herlev and Gentofte Hospital

46
47 18 Kildegaardsvej 28

48
49 19 DK-2900 Hellerup

50
51 20 Telephone: (+45) 38 67 41 52

52
53 21 E-mail: alexander.egeberg@gmail.com
54
55
56
57 22
58
59
60

1
2
3
4 1 **Word count: 3827**

5
6
7 2 **Number of tables: 2**

8
9
10 3 **Number of figures: 2**

11
12 4 **Number of appendices: 3**

13
14
15 5 **Number of references: 79**

16
17 6 **Key words:** cohort study, epidemiology, migraine, prospective, rosacea

18
19
20 7
21
22
23 8 **Conflicts of interest**

24
25 9 NW has received personal fees from Novartis and the Kgl Hofbundtmager Aage Bang Foundation.

26
27 10 CEC received personal fees from Teva and acts as consultant for Teva. JHH and DGZ declare no

28
29 11 conflicts relevant to the manuscript. AE has received research funding from Pfizer, Eli Lilly, the

30
31 12 Danish National Psoriasis Foundation and the Kgl Hofbundtmager Aage Bang Foundation, and

32
33 13 honoraria as consultant and/or speaker from Almirall, Leo Pharma, Samsung Bioepis Co., Ltd.

34
35 14 Pfizer, Eli Lilly & Co, Novartis, Galderma, Dermavant, Bristol-Myers Squibb, and Janssen

36
37 15 Pharmaceuticals. JPT has attended advisory boards for Sanofi-Genzyme, Eli Lilly & Co, Pfizer,

38
39 16 Abbvie, and Union Therapeutics, and received honoraria as a speaker from LEO Pharma,

40
41 17 Regeneron, Abbvie, and Sanofi-Genzyme, and has been an investigator for Sanofi-Genzyme, Eli

42
43 18 Lilly & Co, LEO Pharma, Pfizer, and Abbvie.

44
45 19 MA is a consultant, speaker or scientific advisor for Alder, Allergan, Amgen, Eli Lilly, Lundbeck,

46
47 20 Novartis, and Teva, primary investigator for Alder, Allergan, Amgen, Eli Lilly, Novartis and Teva

48
49 21 trials. MA has no ownership interest and does not own stocks of any pharmaceutical company. MA

50
51 22 serves as associate editor of Cephalalgia, associate editor of Headache, associate editor of the

52
53 23 Journal of Headache and Pain. MA is President of the International Headache Society.

1
2
3
4 1
5
6

7 2 **Funding sources**
8

9
10 3 The study was supported by grants from Novo Nordisk Foundation (NNF170C0029698)
11
12 4 and Augustinus Foundation (17-2523).
13
14

15 5
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **ABSTRACT**

2 **Purpose**

3 Migraine has consistently been connected to rosacea. Commonalities in epidemiology,
4 trigger factors and associated neuropeptides support shared etiology and
5 pathophysiological pathways, though underlying mechanisms remain unclear. We
6 established two cohorts of patients diagnosed with either migraine and/or rosacea. All
7 patients were phenotyped in regard to migraine and rosacea. In this article, we describe
8 baseline parameters of the cohorts. In the future we expect that these cohorts will help
9 uncover potential disease overlaps and allow for prolonged follow up through national
10 Danish health registries.

12 **Participants**

13 Copenhagen Rosacea Cohort (COROCO) and Copenhagen Migraine Cohort (COMICO) are
14 prospective cohorts based in the Capital region of Denmark. Participants for COROCO
15 were recruited primarily through two tertiary dermatology clinics in Copenhagen, Denmark
16 and patients for COMICO were recruited through a tertiary neurology clinic in
17 Copenhagen, Denmark.

19 **Findings to date**

20 COROCO consists of 300 adults with rosacea and COMICO consists of 304 adults with
21 migraine. All participants have been phenotyped through face-to-face semi-structured

1
2
3
4 1 interviews. Additionally, blood and skin samples as well as pictures taken with normal and
5
6
7 2 thermal cameras were collected. In this article we describe baseline data of the cohorts
8
9
10 3 along with family history of migraine and rosacea, smoking, alcohol, body mass index
11
12 4 (BMI) and dermatology life quality index (DLQI). Cohorts were not age- and sex-matched
13
14
15 5 as they will not undergo direct comparison.
16
17
18 6

7 **Future plans**

8 COROCO and COMICO serve as strong data sources that will be used for future studies on
9
10 9 rosacea and migraine with focus on risk factors, occurrence, treatment, natural history,
11
12 10 complications, comorbidities and prognosis.
13
14
15 11

12 **Registration**

13 This observational cohort is registered with clinicaltrials.gov (NCT03872050).
14
15 14

15 **Strengths and limitations of this study**

- 16 • Copenhagen Rosacea Cohort (COROCO) and Copenhagen Migraine Cohort
17 (COMICO) are large cohorts of adults with either physician-diagnosed migraine or
18 rosacea that were phenotyped through face-to-face interview by trained
19 professionals.
- 20 • Rosacea diagnoses are validated through pictures evaluated by three physicians and
21 migraine diagnoses validated through semi-structured interviews.

- 1
2
3
4 1 • Collected information includes pictures with normal and thermal cameras, blood
5
6
7 2 samples, inflammatory markers and DNA for thorough description of each
8
9
10 3 participant.
11
12 4 • Future linkage to Danish national health registries enables us to follow patients for a
13
14
15 5 prolonged period of time.
16
17
18 6 • Limitations include risk of selection bias as participants are recruited from specialty
19
20 7 units, and risk of recall bias as the cohort is based on interviews.
21
22
23 8

1 INTRODUCTION

2 Migraine has repeatedly been associated with rosacea.[1] Both are chronic
3 inflammatory conditions with relapsing episodes of headache for migraine, and
4 redness/flushing and/or papules/pustules for rosacea. Relapses may be triggered by
5 various endogenous and/or exogenous factors such as different foods and drinks,
6 exercise, sun/UV exposure, heat and stress.[2,3] Migraine is common with a prevalence
7 of 12%[4] and up to 18.3% for women.[4–6] Migraine seems to be underdiagnosed and
8 undertreated[6,7] and the actual prevalence is probably higher. Rosacea has an overall
9 prevalence of 5.5%[8] and usually affects individuals over the age of 30 years.[8,9] Both
10 disorders are primarily seen in individuals of Caucasian descent.[4,8] Etiology for both is
11 largely unknown, but seems to involve a mix of genetic and environmental
12 factors.[10,11] Other commonalities between migraine and rosacea include
13 neuroinflammation and upregulation of signaling neuropeptides, such as pituitary
14 adenylate cyclase-activating polypeptide-38 (PACAP38)[2,12] and calcitonin gene-
15 related peptide (CGRP),[13,14] though there are other suggested signaling pathways
16 for both migraine and rosacea.[10] Common demography, triggers and associated
17 neuropeptides suggest a shared pathophysiological pathway.[1]

18
19 Despite overwhelming evidence of a connection between migraine and rosacea,[15–20]
20 underdiagnosis in both disorders must be considered as a confounder in previous
21 research, and a systematic approach is therefore needed to confirm this connection and

1
2
3
4 1 better characterize exact overlap of these diseases. Establishment of prospective patient
5
6
7 2 cohorts with a physician-diagnosis of either migraine or rosacea will help confirm this
8
9
10 3 connection and uncover possible risk factors and comorbidities in both.
11
12
13 4

15 5 COHORT DESCRIPTION

18 6 **Study approval, registry and data availability**

19
20 7 The study was approved by the Ethical Committee of the Capital Region of Denmark (H-
21
22
23 8 17023750) and was registered at www.clinicaltrials.gov (NCT03872050). All participants
24
25
26 9 provided written informed consent in accordance with the declaration of Helsinki anno
27
28 10 1964 with adjustments until 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

29
30
31 11 All data are under the supervision of the corresponding author and can be made available
32
33
34 12 upon reasonable request.
35
36
37 13

39 14 **Study population and setting**

40
41
42 15 Two cohorts were established; Copenhagen Rosacea Cohort (COROCO) and Copenhagen
43
44 16 Migraine Cohort (COMICO). Willing participants had to be aged 18 years or above. A
45
46
47 17 physician-diagnosis of rosacea was needed to be included in COROCO, and a physician-
48
49
50 18 diagnosis of migraine was needed to be included in COMICO. There were no exclusion
51
52 19 criteria. All participants signed an informed consent upon enrollment.
53
54
55 20

57 21 Recruitment

1
2
3
4 1 *Copenhagen Rosacea Cohort (COROCO)*

5
6
7 2 Electronic Medical Records (EMR) were searched for adults who consulted a doctor for a
8
9
10 3 diagnosis of rosacea at either *Department of Dermatology and Allergy at Gentofte Hospital*
11
12 4 (between September 3rd, 2013 – May 5th, 2019) or *Department of Dermatology and Wound*
13
14
15 5 *Healing Centre at Bispebjerg Hospital* (between January 1st, 2014 – November 21st, 2018).

16
17
18 6 Diagnosis of rosacea was defined as one of the following ICD-10 codes: DL71, DL718A,
19
20 7 DL719, DL718.[21]

21
22
23 8 A total of 790 patients were identified through EMR and invited to participate in the
24
25
26 9 rosacea cohort. Five letters were not delivered due to wrong address, and invitations were
27
28
29 10 thus delivered to 785 patients. Patients could respond through one of three routes: mailing
30
31 11 the 'return envelope' (free of charge), sending an e-mail, or calling/texting a dedicated
32
33
34 12 phone. The response rate was 46.8% (367 patients). Nine patients informed us that they
35
36
37 13 did not want to participate due to illness, lack of time or because they did not believe to
38
39 14 have rosacea. Of the 358 patients who responded positively to the invitation, we
40
41
42 15 interviewed 274 patients before reaching the pre-specified inclusion number (see Figure 1
43
44
45 16 for details). An additional 35 patients with a prior diagnosis of rosacea were included via
46
47 17 the Danish Headache Center at Rigshospitalet Glostrup or via online recruitment
48
49
50 18 (www.forsogsperson.dk). Interviews were performed in 309 patients, and after reviewing
51
52
53 19 pictures, nine patients were excluded from analysis, as their signs could not clearly be
54
55 20 attributed to rosacea. COROCO thus included a total of 300 patients. Interviews were
56
57
58 21 performed between September 17th to 2018 to October 14th, 2019.

1
2
3
4 15
6
7 2 *Copenhagen Migraine Cohort (COMICO)*

8
9
10 3 Patients for COMICO were recruited through the Danish Headache Center, department of
11
12 4 Neurology at Rigshospitalet Glostrup, Copenhagen, Denmark. The Danish Headache
13
14
15 5 Center is a tertiary care facility for patients with persistent or difficult-to-treat headaches
16
17
18 6 who have been referred by either a general practitioner or from a specialist neurology
19
20
21 7 clinic. Patients were asked to participate when they came for an outpatient visit at the
22
23 8 Headache Center. A physician-diagnosis of migraine (with or without aura) was necessary
24
25
26 9 for inclusion. In all, 281 patients were recruited from the Danish Headache Center. An
27
28
29 10 additional 23 patients were recruited online (www.forsøgsperson.dk) (see Figure 2 for
30
31 11 details). A total of 304 patients were included in COMICO. Interviews were performed
32
33
34 12 between September 14th, 2018 – October 29th, 2019.

35
36 13

37 14

38 15

39 16

40 17

41 18

42 19

43 20

44 21

45 22

46 23

47 24

48 25

49 26

50 27

51 28

52 29

53 30

54 31

55 32

56 33

57 34

58 35

59 36

60 37

Study visit

44 18 Patients were seen once during the study period. The visit took place at one of three
45
46
47 19 locations of the patient's choice: Danish Headache Center (Rigshospitalet Glostrup),
48
49
50 20 Department of Dermatology (Gentofte hospital), or by home visit at the patient's
51
52 21 home/work.

1
2
3
4 1 The entire visit; both interviews and clinical examination, was performed by either a
5
6
7 2 medical doctor (author NW) or by senior medical students who were specifically trained to
8
9
10 3 perform both.

11
12 4 Each visit lasted approximately 60 minutes and included interview, blood sample, pictures
13
14
15 5 with digital and thermal cameras, superficial stratum corneum sampling of the forearm and
16
17
18 6 cheek, and mouth swab for DNA sampling. Procedures are described below. Patients only
19
20
21 7 had to agree to the semi-structured interview to be eligible for the study, as this was the
22
23 8 essential part of the investigation; however, most patients agreed to all investigations.
24
25
26 9

27 28 10 **INTERVIEW**

29
30
31 11 A semi-structured interview was performed at the beginning of the visit based on two
32
33
34 12 questionnaires. All participants were asked questions on both rosacea and migraine to
35
36
37 13 confirm diagnosis and phenotype. All questionnaires were reviewed by author NW. In case
38
39 14 of doubt about rosacea diagnosis, authors AE and JPT were consulted, and in case of
40
41
42 15 doubt about migraine diagnosis, author MA was consulted.
43
44
45 16

46 47 17 Questionnaire – rosacea

48
49
50 18 Demographic information, comorbidities, family history, dermatology life quality index
51
52
53 19 (DLQI) and presence of rosacea features. If patients had a prior diagnosis of rosacea, first
54
55 20 presenting sign or symptom of rosacea, diagnostic delay and previous treatments were
56
57
58
59
60

1
2
3
4 1 also collected (appendix 1). Patients were also evaluated with the National Rosacea Society
5
6
7 2 Rosacea Clinical Scorecard.[22]

8
9
10 3 Questionnaire – migraine

11
12 4 A validated semi-structured questionnaire on diagnosis and subtyping of migraine[23] was
13
14
15 5 adapted by author NW for the purpose of interviewing patients with no known migraine or
16
17
18 6 headache (appendix 2). Questions included family history, headache/migraine and aura
19
20
21 7 symptoms along with risk factors for headache/migraine. All patients; also those who
22
23
24 8 claimed to have a previous diagnosis of migraine, were asked about headache
25
26
27 9 characteristics to validate migraine diagnosis. If patients had a diagnosis of migraine,
28
29 10 migraine onset and headache frequency were collected.
30

31 11
32
33
34 12 **CLINICAL EXAMINATION**

35
36 13 The following examinations were performed after the interview, and patients had therefore
37
38
39 14 been sitting calmly for at least 30 minutes and drinking nothing but water, prior to
40
41
42 15 examinations.
43

44 16 All examinations were performed on patients included in both COROCO and COMICO.
45
46
47 17

48
49
50 18 **Standardized photography**

51
52 19 A standardized picture was taken with a digital Canon PowerShot G12 camera at a distance
53
54
55 20 of approximately 70 cm, with a flash and zoom when needed. Pictures were rated
56
57
58 21 according to phenotype and the newly developed rosacea scoring tool 'Rosacea Area and
59
60

1
2
3
4 1 Severity Index' (RASI) (manuscript in development), to ensure correct diagnosis and
5
6
7 2 classification of rosacea.
8
9

10 3 All pictures were evaluated by three authors (JT, AE, NW). Disagreements were resolved by
11
12 4 discussion. In cases of doubt, patients were rated as 'not rosacea' or 'non-classifiable'.
13
14

15 5 These ratings will be compared with interview data in a future publication, to evaluate the
16
17 6 validity of both.
18
19

20 7 21 22 23 8 24 25 26 9 27 28 10 **Thermography**

29
30
31 11 Thermographic pictures were recorded after patients had been placed in a room with a
32
33 12 stable temperature for at least 15 minutes. Pictures were recorded on FLIRA655sc with a
34
35 13 25° lens. The camera has a range of -40°C to +150°C and temperature accuracy of +/- 1°C.
36
37
38
39 14 Pictures were recorded at a distance of approximately 50 centimeters from the subject. For
40
41 15 each subject, a total of three pictures were recorded - one picture from the front and one
42
43 16 from each side. The FLIR program *ResearchIR* was used to record pictures. Analyses were
44
45 17 performed in the program *FLIR TOOLS*. Temperature was measured at each side of the face
46
47 18 corresponding to the facial area of the three branches of the trigeminus (forehead, cheeks,
48
49 19 chin). An additional temperature measurement was performed on the tip of the nose
50
51 20 (appendix 3). The measure point was matched to the size of the iris to adjust for
52
53 21 differences in distances from which the pictures were taken.
54
55
56
57
58
59
60

1
2
3
4
5 1
6

7 2 Facial skin temperature has previously been investigated in both migraine and rosacea
8
9
10 3 with unclear results.[24] We therefore offer baseline temperatures in a large group of
11
12 4 patients with both disorders to determine whether previous findings reflect true
13
14
15 5 differences or simply interindividual differences within patient groups.
16
17

18 6
19

20 7 **Superficial stratum corneum sampling**

21
22
23 8 A sample of stratum corneum was collected using the tape stripping method. Samples were
24
25
26 9 collected from two sites (one forearm and one cheek), Seven consecutive tape stripping discs
27
28 10 (22 mm) (D-squame, CuDerm, Dallas, Texas) were collected at each site. Discs were applied
29
30
31 11 with tweezers followed by a standardized pressure with a D-squame pressure application
32
33
34 12 pen for 5 seconds. The first 3 discs from each site were discarded, and the following 4 discs
35
36 13 were stored at -80°C immediately after sampling. The discs will be examined for cytokines
37
38
39 14 and skin microbiome.

40
41
42 15 Rosacea is characterized by local inflammation of the face, however, recent evidence
43
44 16 suggests that the inflammation may be systemic.[25] Migraine has also been suggested to
45
46
47 17 involve inflammation, especially neuroinflammation, but possibly also systemic
48
49
50 18 inflammation.[26]

51
52 19 Measurement of inflammatory markers from the skin will allow us to compare facial
53
54
55 20 inflammation (cheek) to systemic inflammation (forearm) and to compare patients with
56
57
58 21 migraine and rosacea to uncover a possible subclinical inflammation in both disorders.
59
60

1
2
3
4 1 Furthermore, we hope to investigate whether there is a correlation between local/systemic
5
6
7 2 inflammation, subtypes of rosacea and disease activity.
8
9
10 3

11 12 4 **Genetics**

13
14
15 5 Patients were not allowed to eat, drink, smoke, chew gum or clean teeth one hour before
16
17
18 6 collection. All patients were instructed to rinse their mouth with water immediately before
19
20
21 7 collection. For the analyses, one SK-1S DNA buccal swab (Isohelix, Harrietsham, U.K) was
22
23 8 rubbed against cheek mucosa for 60 seconds before returning the swab to the supplied
24
25
26 9 tube without touching the head of the swab. The shaft was broken on the edge of the tube
27
28
29 10 which left the head of the swab in the tube. The tube was stored at -80° C until analysis.
30
31
32 11

33
34 12 The purpose of DNA collection was to perform a genome-wide association-study (GWAS)
35
36
37 13 for the most common gene mutations in rosacea and migraine. A large meta-analysis of
38
39 14 375,000 individuals has located 38 loci relevant for migraine[27], whereas GWAS has only
40
41
42 15 been done a few times in rosacea and only on populations selected from the '23andMe'
43
44
45 16 customer base.[28,29] We will look at loci relevant to both migraine and rosacea in both
46
47 17 patients groups to discover any potential overlaps. Analysis will not include genes listed on
48
49
50 18 the ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and
51
52
53 19 Genome Sequencing.[30]

54 55 20 **Blood sample**

56
57
58
59
60

1
2
3
4 1 A blood sample was collected from a cubital vein (Vacuette® Safety Blood Collection Set)
5
6
7 2 into three 9 ml EDTA tubes (Vacuette® K2EDTA) which were each inverted 10 times
8
9
10 3 immediately after collection to let blood mix with the separator gel. Samples were kept at
11
12
13 4 room temperature (between 20-24 degrees Celsius) and within 30 minutes of sampling, full
14
15 5 blood was transferred with a pipette (Alpha Laboratories pipette standard micro sterile
16
17
18 6 pastette) from one EDTA tube into 2 – 4 sterile 2,0ml cryo vials (IVUS). The two remaining
19
20
21 7 EDTA tubes were centrifuged (Hettich Zentrifugen EBA 20) at 2500 rpm for 5 minutes to
22
23
24 8 separate plasma. Plasma was then transferred (Alpha Laboratories pipette standard micro
25
26
27 9 sterile pastette) into 2 – 4 sterile 2,0ml cryo vials (IVUS) and 2 – 4 sterile 2,0ml cryo vials
28
29 10 (IVUS) with Thermo scientific protease inhibitor (10 µl per ml of plasma). All samples were
30
31 11 stored at -80 degrees Celsius until analysis.
32
33
34 12

35
36 13 The purpose of this blood sample was to analyze samples for CGRP. CGRP is a signaling
37
38
39 14 neuropeptide which has previously been related to both migraine[31] and rosacea[32] and
40
41
42 15 has been suggested to be related to disease pathology. CGRP has been relatively well-
43
44
45 16 described in migraine, and CRGP-antibodies have recently proven beneficial in preventive
46
47 17 treatment of migraine.[33]

48
49
50 18 By stratifying CGRP measurements in this project we hope to be able to uncover the
51
52
53 19 relationship between CGRP, subtypes and disease activity for especially rosacea.
54
55 20

57 21 **Findings to date**

58
59
60

1
2
3
4 1 Findings are summarized in table 1 for COROCO and table 2 for COMICO.
5
6
7 2
8
9

10 3 *Age and sex*

11
12 4 *COROCO*

13
14
15 5 Median age was 51 years (interquartile range (IQR) 43.0 – 61.0) and there were 67.7%
16
17 6 females in the cohort.

18
19
20 7 Rosacea usually affects individuals above age 30 years[9] with a peak onset between 45 –
21
22 8 60 years.[8] The sex distribution is more or less even, with only a tendency towards a
23
24 9 female predominance.[8] COROCO thus resembles previous studies in rosacea.
25
26
27

28 10
29
30
31 11 *COMICO*

32
33 12 Median age was 41 years (IQR 29.5 – 51.0) and 88.5% were females.

34
35
36 13 Onset of migraine differs with age and sex, mostly affecting individuals above age 14 with
37
38 14 a peak incidence between ages 25 – 34 years.[4] There is a strong female predominance
39
40 15 with almost twice as many women as men being affected.[4,34] COMICO therefore
41
42 16 resembles previous findings in migraine.
43
44
45
46

47 17
48
49 18 Cohorts are not intended for direct comparison and differences in age and sex between
50
51 19 cohorts will therefore not be a problem.
52
53
54

55 20
56
57 21 *Family history of migraine*
58
59
60

1
2
3
4 1 *COROCO*

5
6
7 2 Family history of migraine was present in 44.3% of the rosacea cohort.
8

9
10 3 Family history of migraine in the general population is usually underreported, [35,36] which
11
12 4 may contribute to the low prevalence of family history of migraine in our rosacea cohort.
13
14

15 5

16
17 6 *COMICO*

18
19
20 7 Family history of migraine was found in 73.4% of those in the migraine cohort. Previous
21

22
23 8 studies have found family history reports between 54-77%,[37,38] and we expect that
24

25
26 9 patients with migraine are more aware of their family history and believe that this might be
27

28
29 10 more or less the true prevalence of family history.
30
31
32
33
34
35

36 13 *Family history of rosacea*

37
38
39 14 *COROCO*

40
41
42 15 Family history of rosacea was 45% in the rosacea cohort. Family history in rosacea has
43

44
45 16 previously been reported up to 55% compared to 12 - 17% in controls.[39,40] Rosacea is
46

47
48 17 largely underestimated and often goes undiagnosed,[17,41,42] contributing to the low
49

50
51 18 family history reports of rosacea. In our cohort, some patients stated that they suspected
52

53
54 19 family members of having rosacea, but only definite diagnoses were included in our
55

56
57 20 analysis, probably underestimating family history of rosacea in our cohorts.
58
59
60

1
2
3
4 1 *COMICO*

5
6
7 2 Family history of rosacea was 18.4% in the migraine cohort, corresponding to previous
8
9
10 3 findings of 12 - 17% in controls.[39,40] As stated above, underdiagnosing of rosacea
11
12 4 probably contributes to low family history reports in the migraine cohort as well.[17,41,42]
13
14

15 5

16
17 6 *Smoking*

18
19
20 7 *COROCO*

21
22
23 8 There were 13.0% current smokers in COROCO. The median pack-years for smokers were
24
25 9 24.6 years (IQR 13.3-26.0). A total of 36.6% were former smokers.

26
27
28 10 Smoking in rosacea is debated. Some studies find a lower prevalence of smoking in
29
30
31 11 patients with rosacea,[43,44] and find smoking to be protective against incident
32
33
34 12 rosacea,[45] whereas others find a higher prevalence of smoking.[46,47]. Past smoking has
35
36 13 been associated with a higher risk of incident rosacea compared to never smokers,[39,45]
37
38
39 14 perhaps due to an autoimmune response, but this needs further investigation. Smoking
40
41
42 15 constricts the peripheral blood vessels, possibly masking rosacea which could be a reason
43
44 16 for why we see a lower prevalence of current smoking in the rosacea group.
45
46

47 17

48
49
50 18 *COMICO*

51
52 19 There were 17% current smokers in COMICO. Median pack-years were 12.0 years (IQR 5.0 –
53
54
55 20 21.0). There were 26.0% who were former smokers.
56
57
58
59
60

1
2
3
4 1 Smoking in migraine is debated. A study from 1976 reports that smoking is unlikely to be
5
6
7 2 related to migraine[48] whereas more recent research finds found an increased risk of
8
9
10 3 migraine in past and current smokers.[49] Another study found that patients with migraine
11
12
13 4 were more frequent and heavy smokers than their peers,[50] and smoking has been
14
15 5 suggested as a precipitating factor for migraine attacks.[51]
16
17

18 6
19
20 7 Smoking in the general population in Denmark was 23% in 2018 (22% in women and 24%
21
22
23 8 in men)[52], and it thus looks like we have a lower prevalence of smoking in our cohorts
24
25
26 9 than in the background population. This could be because smoking cessation may trigger
27
28
29 10 either rosacea or migraine, although there is no clear evidence of this, as stated above.
30
31

32 11 33 12 *Alcohol*

34 13 *COROCO*

35
36 14 Regular intake of alcohol was seen in 79.3% of COROCO with a median average intake of
37
38
39 15 4 items/week (IQR 1.0 – 9.0).
40
41

42 16 Alcohol is a common trigger of flushing in rosacea,[53–55] alcohol intake seems to be
43
44
45 17 associated with a higher risk of incident rosacea,[43,56,57] though some studies have failed
46
47
48
49 18 to confirm this association.[39,58,59]
50
51

52 19 53 54 20 *COMICO*

55
56
57
58
59
60

1
2
3
4 1 In COMICO, 62.3% regularly drank alcohol, with a median average intake of 2 items/week
5
6
7 2 (IQR 1.0 – 3.0).
8

9
10 3 Alcohol is a common trigger of migraine attacks,[3,60–63] which was also one of the most
11
12 4 commonly anecdotally reported reasons for alcohol abstinence in this cohort.
13
14

15 5

16
17
18 6 *Body mass index*

19
20 7 *COROCO*

21
22
23 8 Median body mass index (BMI) was 25.7 (23.1 – 29.0). Stratified into groups, underweight
24
25 9 (BMI < 18.5) was seen in 1.3% (4 patients), normal weight (BMI between 18.5 – 25) was
26
27 10 found in 39.7% (119 patients) , overweight (BMI between 25 – 30) was present in 40.7%
28
29 11 (122 patients), and obesity (BMI > 30) was found in 18.3% (55 patients).
30
31
32

33 12

34
35
36 13 High BMI may be a risk factor for incident rosacea.[64,65] Metabolic disease[64] and
37
38 14 cardiovascular comorbidities are more common in rosacea, though the causal relationship
39
40 15 is debated.[46,66–68]
41
42
43

44 16

45
46
47 17 *COMICO*

48
49 18 Median BMI was 24.6 (IQR 21.5 – 28.2). Stratified into groups, underweight was seen in
50
51 19 3.3% (10 patients), normal weight was found in 50.7% (154 patients), overweight was seen
52
53 20 in 28.6% (87 patients), and obesity was found in 15.6% (53 patients).
54
55
56

57 21

1
2
3
4 1 Obesity seems to be a risk factor for migraine,[69–72] and obesity and weight gain
5
6
7 2 contributes to worsening of migraine, with the potential of turning episodic migraine into
8
9
10 3 chronic migraine.[73–77] Patients for COMICO were primarily recruited through the Danish
11
12 4 Headache Center, which is a highly specialized unit and 38.2% turned out to have chronic
13
14
15 5 migraine, which may have contributed to a higher BMI in this group.
16
17

18 6
19
20 7 *DLQI*

21
22
23 8 *COROCO*

24
25 9 Median DLQI was 2 (IQR 1 - 5). Stratified into groups, DLQI of 0-1 (no effect on quality of
26
27
28 10 life) was present in 42.7% (128 patients). DLQI between 2-5 (mild effect on quality of life)
29
30
31 11 was present in 35.0% (105 patients). DLQI between 6-10 (moderate effect on quality of life)
32
33
34 12 was found in 12.0% (26 patients), and DLQI between 11-20 (large effect on quality of life)
35
36
37 13 was found in 10.0% (30 patients). DLQI 20 (extreme effect on quality of life) was found in
38
39 14 0.3% (1 patient).
40
41

42 15
43
44 16 Interestingly, we find a very low impact of rosacea on daily quality of life. There may be a
45
46
47 17 number of reasons for this. One, DLQI is an immediate view on quality of life during the
48
49
50 18 past week. Rosacea is fluctuating and patients may not have had a lot of symptoms at the
51
52
53 19 time of the interview, and thus a low DLQI. Second, many patients reported to have
54
55 20 previously been very affected by their rosacea, but they were now less affected, either due
56
57
58 21 to acceptance of their symptoms, or because they had been effectively treated. Thirdly,
59
60

DLQI may not be the best instrument for evaluating rosacea, as the questions are not rosacea-specific, but rather concern the whole skin, which may be why these patients have a low DLQI score, i.e. questions 3, 4 and 7-10 are often not relevant in rosacea.

COMICO

Median DLQI was 1 (IQR 0 – 2). Stratified into groups, DLQI of 0-1 was present in 65.1% (198 patients), DLQI between 2-5 was present in 27.3% (83 patients), DLQI between 6-10 was found in 5.6% (17 patients), DLQI between 11-20 was found in 2.0% (6 patients) and no patients had DLQI 20.

The effect on DLQI in the migraine cohort could be attributed to comorbid rosacea or other skin disorders, however, recent data suggests that DLQI in a control population is comparable to minimal disease level in patients with atopic dermatitis or psoriasis.[78]

Table 1. Baseline data for COROCO

	N	COROCO (Rosacea)
Age, median (IQR)	300	51.0 (43.0-61.0)
Sex, n(%)	300	
Men		97 (32.3)
Women		203 (67.7)
Family history of rosacea, n(%)		
Any family member	300	135 (45.0)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

First degree relative	124 (41.3)
Second degree relative	27 (9.0)
Third degree relative	3 (1.0)
Family history of migraine,	
n(%)	
Any family member	300 133 (44.3)
First degree relative	133 117 (39.0)
Second degree relative	133 32 (10.7)
Third degree relative	133 5 (1.7)
Smoking, n(%)	
300	
Never	151 (49.8)
Former smoker	111 (36.6)
Current smoker	39 (13.0)
Cigarettes per day	
39	
< 5/day	15 (38.5)
6-10/day	7 (18.0)
11-20/day	15 (38.5)
21-30/day	1 (2.6)
<30/day	1 (2.6)
Pack-years*, median (IQR)	31 24.6 (13.3-36.0)
Alcohol, current use	
300 238 (79.3)	
Alcohol, n (%)	
< 7/week	244 170 (71.4)
8-14/week	244 34 (14.3)
15-21/week	244 18 (7.6)

>21/week	244	16 (6.7)
Items per week, median (IQR)	244	4 (1.0-9.0)
BMI, n(%)	300	
< 18.5		4 (1.3)
18.5-25		119 (39.7)
>25-30		122 (40.7)
>30-35		35 (11.7)
>35		20 (6.7)
BMI, median (IQR)		25.7 (23.1-29.0)
DLQI, n(%)	309	
0-1		128 (42.7)
2-5		105 (35.0)
6-10		36 (12.0)
11-20		30 (10.0)
21-30		1 (0.3)
DLQI, median		2 (1-5)

BMI, body mass index; DLQI, dermatology life quality index; N, number of subjects; SD, standard deviation; IQR, Inter Quartile Range

* Pack years are defined as years of smoking 20 cigarettes per day.

1

2 **Table 2.** Baseline data for COMICO

	N	COMICO (Migraine)
Age , median (IQR)	304	41.0 (29.5-51.0)
Sex , n(%)	304	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Men	35 (11.5)
Women	269 (88.5)
Chronic migraine, n(%)	304 116 (38.2)
Migraine with aura, n(%)	304 116 (38.2)
Migraine without aura, n(%)	304 188 (61.8)
Family history of migraine,	
n(%)	
Any family member	304 223 (73.4)
First degree relative	223 193 (63.5)
Second degree relative	223 119 (39.1)
Third degree relative	223 3 (1.0)
Family history of rosacea, n(%)	
Any family member	304 56 (18.4)
First degree relative	45 (14.8)
Second degree relative	21 (6.9)
Third degree relative	0 (0)
Smoking, n(%)	304
Never	173 (56.9)
Former smoker	79 (26.0)
Current smoker	52 (17.1)
Cigarettes per day	52
< 5/day	21(40.4)
6-10/day	15 (28.9)
11-20/day	12 (23.0)
21-30/day	3 (5.8)

<30/day	1 (1.9)
Pack-years*, median (IQR)	40 12 (5-21)
Alcohol, current use	304 189 (62.2)
Alcohol, n (%)	
< 7/week	189 173 (91.5)
8-14/week	189 11 (5.8)
15-21/week	189 5 (2.7)
>21/week	189 0
Items per week, median (IQR)	189 2 (1.0-3.0)
BMI, n(%)	304
< 18.5	10 (3.3)
18.5-25	154 (50.7)
>25-30	87 (28.6)
>30-35	32 (10.5)
>35	21 (6.9)
BMI, median (IQR)	24.6 (21.5-28.2)
DLQI, n(%)	304
0-1	198 (65.1)
2-5	83 (27.3)
6-10	17 (5.6)
11-20	6 (2.0)
21-30	0
DLQI, median	1 (0-2)

BMI, body mass index; DLQI, dermatology life quality index; N, number of subjects; SD, standard deviation; IQR, Inter Quartile Range

* Pack years are defined as years of smoking 20 cigarettes per day.

1

2 **Future plans**

3 We plan for longitudinal follow up through national Danish registries studying risk factors,
4 occurrence, natural history, treatment, complications, comorbidities and prognosis. We
5 also plan to invite participants for a follow-up in 10-20 years,

6

7 **Strengths and limitations**

8 The COROCO and COMICO have several strengths. First, the cohorts offer phenotyping
9 through face-to-face interview by trained personnel, which has been shown to be the most
10 valid way to ensure correct diagnosis of migraine,[79] and for rosacea phenotyping,
11 pictures are subsequently validated by three authors. Questions on rosacea onset and
12 timely relationship to migraine diagnosis may prove valuable in further explaining the
13 connection between the two. Furthermore, the comprehensive reports on rosacea features,
14 first presenting sign/symptom and later onset of other rosacea features may also prove
15 valuable in determining the natural history of rosacea. Additional collected data will help in
16 further characterizing patients and possibly explaining the mechanisms behind both
17 disorders. A major strength is the possibility of linking cohorts to the national health
18 registries in Denmark for additional info and follow-up.

19 Limitations include risk of recall bias as interviews are based on the patient reports with
20 rosacea diagnosis or first presenting rosacea feature sometimes many years prior to

1
2
3
4 1 interview. In those with either rosacea or migraine, there is a higher chance that they will
5
6
7 2 be aware of their family history of that specific disorder, whereas they might neglect the
8
9
10 3 other disorder, and a major limitation is that we will see lower family histories in those who
11
12
13 4 do not have the disorder, i.e. family history of rosacea in patients with migraine. There is
14
15 5 also a risk of selection bias, as patients were recruited primarily through specialist clinics
16
17
18 6 where only the most severely affected patients are seen, however, in COROCO, we invited
19
20
21 7 patients who had been seen with rosacea in the past 5 years, and their disease may have
22
23 8 been less severe than when they came for their first visit; possibly underestimating
24
25
26 9 symptoms and effect on quality of life. As patients were not excluded from one of the
27
28
29 10 cohorts if they had both diagnoses, comparison between groups is also problematic as
30
31
32 11 differences and similarities may be attributed to both patient groups being present in both
33
34 12 cohorts. Furthermore, it might be speculated that patients who identified with the
35
36
37 13 investigated disorders, e.g. migraine patients who also identified with rosacea features, or
38
39 14 who had family members with the disease, were more prone to accept the invitation to
40
41
42 15 participate. However, we believe that the fairly short one-time study-visit that could be
43
44
45 16 combined with their outpatient visit was enough motivation in most cases. For rosacea, the
46
47 17 disorder is relatively un-investigated, and patients seemed motivated to participate simply
48
49
50 18 due to this fact.

51
52 19

53 54 55 20 **Patient and public involvement**

1
2
3
4 1 Patients and public were not involved in the design of this study. On completion of the
5
6
7 2 study, all patients who wish to will receive a concluding letter with study findings and
8
9
10 3 information of future perspectives of the research.
11
12
13 4

15 5 **Contributors**

16
17
18 6 NW, CC, MA, AE and JT designed the study. NW and DGZ collected data for the study. NW
19
20 7 and JHH performed the analysis under supervision of AE. NW drafted the manuscript. All
21
22
23 8 authors reviewed and edited the manuscript. All authors approved the final manuscript.
24
25
26 9

28 10 **Acknowledgements**

29
30
31 11 We thank all participants for their contribution to the cohorts. We thank all staff members
32
33
34 12 at Rigshospitalet Glostrup and Gentofte Hospital who have contributed, and the
35
36 13 department of Dermatology and Wound Healing at Bispebjerg hospital for contributing to
37
38
39 14 this study.
40
41
42 15

References

1. Christensen CE, Andersen FS, Wienholtz N, Egeberg A, Thyssen JP, Ashina M. The relationship between migraine and rosacea: Systematic review and meta-analysis. *Cephalalgia*. 2017;0(0).
2. Steinhoff M, Schaubert J, Leyden JJ. New insights into rosacea pathophysiology: A review of recent findings. *J Am Acad Dermatol*. 2013;69(6 SUPPL.1):15–26.
3. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia*. 2007;27(5):394–402.
4. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. *Neurol Clin*. 2019;37(4):631–49.
5. Steiner T, Scher A, Stewart W, Kolodner K, Liberman J, Lipton R. The Prevalence and Disability Burden of Adult Migraine in England and their Relationships to Age, Gender and Ethnicity. *Cephalalgia*. 2003 Sep;23(7):519–27.
6. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343–9.
7. Brandes JL. Global trends in migraine care: Results from the MAZE survey. *CNS Drugs*. 2002;16(SUPPL. 1):13–8.
8. Gether L, Overgaard L, Egeberg A, Thyssen J. Incidence and prevalence of rosacea: a systematic review and meta-analysis. *Br J Dermatol*. 2018;179:282–9.
9. Tan J, Berg M. Rosacea: Current state of epidemiology. *J Am Acad Dermatol*.

- 1
2
3
4 1 2013;69(6 SUPPL.1):S27–35.
5
6
7 2 10. Gallo RL, Granstein RD, Kang S, Mannis M, Steinhoff M, Tan J, et al. Standard
8
9
10 3 classification and pathophysiology of rosacea: The 2017 update by the National
11
12 4 Rosacea Society Expert Committee. *J Am Acad Dermatol*. 2018;78(1):148–55.
13
14
15 5 11. Charles A. The pathophysiology of migraine: implications for clinical management.
16
17 6 *Lancet Neurol*. 2018;17(2):174–82.
18
19
20 7 12. Vollesen ALH, Ashina M. PACAP38: Emerging Drug Target in Migraine and Cluster
21
22 8 Headache. *Headache*. 2017;57(Phase 3):56–63.
23
24
25 9 13. Khan S, Olesen A, Ashina M. CGRP, a target for preventive therapy in migraine and
26
27 10 cluster headache: Systematic review of clinical data. *Cephalalgia*. 2019;39(3):374–89.
28
29
30 11 14. Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical
31
32 12 presentation and new therapeutics. *Exp Dermatol*. 2017;26(8):659–67.
33
34
35 13 15. Egeberg A, Ashina M, Gaist D, Gislason GH, Thyssen JP. Prevalence and risk of
36
37 14 migraine in patients with rosacea: A population-based cohort study. *J Am Acad*
38
39 15 *Dermatol*. 2017;76(3):454–8.
40
41
42 16 16. Tan SG, Cunliffe WJ. Rosacea and migraine. *Br Med J*. 1976;1(6000):21.
43
44
45 17 17. Berg M, Lidén S. An epidemiological study of rosacea. *Acta Derm Venereol*.
46
47 18 1989;69(5):419–23.
48
49
50 19 18. Spoendlin J, Voegel JJ, Jick SS, Meier CR. Migraine, triptans, and the risk of
51
52 20 developing rosacea: A population-based study within the United Kingdom. *J Am*
53
54 21 *Acad Dermatol*. 2013;69(3):399–406.
55
56
57
58
59
60

- 1
2
3
4 1 19. Ramelet A. Rosacea: A Reaction Pattern Associated With Ocular Lesions and
5
6
7 2 Migraine? *Arch Dermatol*. 1994;130:1448.
8
9
10 3 20. Berg M, Lidén S. Postmenopausal Female Rosacea Patients Are More Disposed to
11
12 4 React with Migraine. *Dermatology*. 1996;193:73–4.
13
14
15 5 21. WHO. ICD-10 [Internet]. 2019. Available from: <https://icd.who.int/browse10/2019/en>
16
17
18 6 22. Rosacea Clinical Scorecard [Internet]. [cited 2019 Jun 29]. Available from:
19
20 7 <https://www.rosacea.org/physicians/rosacea-clinical-scorecard>
21
22
23 8 23. Gervil M, Ulrich V, Olesen J, Russell MB. Screening for migraine in the general
24
25 9 population: Validation of a simple questionnaire. *Cephalalgia*. 1998;18(6):342–8.
26
27
28 10 24. Wienholtz N, Christensen CE, Egeberg A, Thyssen JP, Ashina M. Vasomotor reactions
29
30 11 in the face and head of patients with migraine. *Cephalalgia Reports*. 2018;1.
31
32
33 12 25. Sinikumpu SP, Huilaja L, Auvinen J, Jokelainen J, Puukka K, Ruokonen A, et al. The
34
35 13 association between low grade systemic inflammation and skin diseases: A cross-
36
37 14 sectional survey in the Northern Finland Birth Cohort 1966. *Acta Derm Venereol*.
38
39 15 2018;98(1):65–9.
40
41
42 16 26. Edvinsson L, Haanes KA, Warfvinge K. Does inflammation have a role in migraine?
43
44 17 *Nat Rev Neurol*. 2019;15(8):483–90.
45
46
47 18 27. Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers T, et al. Meta-analysis of
48
49 19 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat Genet*.
50
51
52 20 2016;48(8):856–66.
53
54
55 21 28. Chang A, Raber I, Xu J, Li R, Spitale R, Chen J, et al. Assessment of the genetic basis
56
57
58
59
60

- 1
2
3
4 1 of rosacea by genome-wide association study. *J Invest Dermatol.* 2015;135:1548–55.
5
6
7 2 29. Aponte JL, Chiano MN, Yerges-Armstrong LM, Hinds DA, Tian C, Gupta A, et al.
8
9
10 3 Assessment of rosacea symptom severity by genome-wide association study and
11
12 4 expression analysis highlights immuno-inflammatory and skin pigmentation genes.
13
14
15 5 *Hum Mol Genet.* 2018;27(15):2762–72.
16
17
18 6 30. Green RC, Berg JS, Grody WW, Kalia S, Kort B, Martin C, et al. ACMG
19
20 7 Recommendations for Reporting of Incidental Findings in Clinical Exome and
21
22
23 8 Genome Sequencing. *Genet Med Author Manuscr.* 2013;15(7):565–74.
24
25
26 9 31. Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into
27
28 10 migraine pathophysiology. *Nat Rev Neurol.* 2010;6(10):573–82.
29
30
31 11 32. Woo YR, Lim JH, Cho DH, Park HJ. Rosacea: Molecular mechanisms and management
32
33
34 12 of a chronic cutaneous inflammatory condition. *Int J Mol Sci.* 2016;17(9):1–23.
35
36
37 13 33. Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al.
38
39 14 ARISE: A Phase 3 Randomized Trial of Erenumab for Episodic Migraine. *Cephalalgia.*
40
41
42 15 2018;38(6):1026–37.
43
44
45 16 34. Russell MB, Rasmussen BK, Thorvaldsen P, Olesen J. Prevalence and sex-ratio of the
46
47 17 subtypes of migraine. *Int J Epidemiol.* 1995;24(3):612–8.
48
49
50 18 35. Russell M, Fenger K, Olesen J. The family history of migraine. Direct versus indirect
51
52 19 information. *Cephalalgia.* 1996;16:156–60.
53
54
55 20 36. Lateef T, Cui L, Nakamura E, Dozier J, Merikangas K. Accuracy of Family History
56
57 21 Reports of Migraine in a Community-Based Family Study of Migraine. *Headache.*
58
59
60

- 1
2
3
4 1 2017;66(3):407–12.
5
6
7 2 37. Hernandez-Latorre M, Roig M. Natural history of migraine in childhood. *Cephalalgia*.
8
9
10 3 2000;20(6):573–9.
11
12 4 38. Dzoljic E, Vlajinac H, Sipetic S, Marinkovic J, Grbatinic I, Kostic V. A survey of female
13
14
15 5 students with migraine: What is the influence of family history and lifestyle? *Int J*
16
17
18 6 *Neurosci*. 2014;124(2):82–7.
19
20 7 39. Abram K, Silm H, Maarros H, Oona M. Risk factors associated with rosacea. *J Eur*
21
22
23 8 *Acad Dermatol Venereol*. 2010;24:565–71.
24
25
26 9 40. Rainer BM, Fischer AH, Luz Felipe Da Silva D, Kang S, Chien AL. Rosacea is associated
27
28
29 10 with chronic systemic diseases in a skin severity-dependent manner: Results of a
30
31
32 11 case-control study. *J Am Acad Dermatol*. 2015;73(4):604–8.
33
34 12 41. Tan J, Schöfer H, Araviiskaia E, Audibert F, Kerrouche N, Berg M. Prevalence of
35
36
37 13 rosacea in the general population of Germany and Russia - The RISE study. *J Eur*
38
39 14 *Acad Dermatology Venereol*. 2016;30(3):428–34.
40
41
42 15 42. Tizek L, Schielein MC, Seifert F, Biedermann T, Böhner A, Zink A. Skin diseases are
43
44
45 16 more common than we think: screening results of an unreferral population at the
46
47 17 Munich Oktoberfest. *J Eur Acad Dermatology Venereol*. 2019;33(7):1421–8.
48
49
50 18 43. Spöndlin J, Voegel JJ, Jick SS, Meier CR. A study on the epidemiology of rosacea in
51
52
53 19 the U.K. *Br J Dermatol*. 2012;167(3):598–605.
54
55 20 44. Li WQ, Zhang M, Danby FW, Han J, Qureshi AA. Personal history of rosacea and risk
56
57
58 21 of incident cancer among women in the US. *Br J Cancer*. 2015;113(3):520–3.
59
60

- 1
2
3
4 1 45. Li S, Cho E, Drucker AM, Qureshi AA, Li WQ. Cigarette Smoking and Risk of Incident
5
6 Rosacea in Women. *Am J Epidemiol*. 2017;186(1):38–45.
7 2
8
9 3 46. Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: A case
10
11 control study. *J Eur Acad Dermatology Venereol*. 2014;28(9):1165–9.
12 4
13
14 5 47. Kucukunal A, Altunay I, Arici JE, Cerman AA. Is the effect of smoking on rosacea still
15
16 somewhat of a mystery? *Cutan Ocul Toxicol*. 2016;35(2):110–4.
17 6
18
19 7 48. Baharuddin NA, Al-Bayaty FH. The relationship between smoking and migraine.
20
21 *Postgrad Med J*. 1976;52:80–2.
22 8
23
24 9 49. Hagen K, Åsberg AN, Stovner L, Linde M, Zwart JA, Winsvold BS, et al. Lifestyle
25
26 factors and risk of migraine and tension-type headache. Follow-up data from the
27
28 Nord-Trøndelag Health Surveys 1995–1997 and 2006–2008. *Cephalalgia*.
29 10
30
31 11 2018;38(13):1919–26.
32
33
34 12
35
36 13 50. Chen TC, Leviton A, Edelstein S, Ellenberg JH. Migraine and Other Diseases in
37
38 Women of Reproductive Age: The Influence of Smoking on Observed Associations.
39 14
40
41 *Arch Neurol*. 1987;44(10):1024–8.
42 15
43
44 16 51. López-Mesonero L, Márquez S, Parra P, Gámez-Leyva G, Muñoz P, Pascual J.
45
46 Smoking as a precipitating factor for migraine: A survey in medical students. *J*
47 17
48 *Headache Pain*. 2009;10(2):101–3.
49 18
50
51 19 52. Sunhedsstyrelsen, Kræftens_Bekæmpelse, Hjerteforeningen_og_Lungeforeningen.
52
53 Danskernes rygevaner 2018 - nøgletal [Danish] [Internet]. Available from:
54 20
55
56 <https://www.sst.dk/-/media/Udgivelser/2019/Danskernes-rygevaner->
57 21
58
59
60

- 1
2
3
4 1 2018/Danskernes-rygevaner-
5
6
7 2 2018_nøgletal.ashx?la=da&hash=55335DED0545970499485950C4E375CEC5A465AF
8
9
10 3 53. Weiss E, Katta R. Diet and rosacea: the role of dietary change in the management of
11
12 4 rosacea. *Dermatol Pract Concept*. 2017;7(4):31–7.
13
14
15 5 54. Bae YI, Yun SJ, Lee JB, Kim SJ, Won YH, Lee SC. Clinical evaluation of 168 Korean
16
17 6 patients with rosacea: The sun exposure correlates with the erythematotelangiectatic
18
19 7 subtype. *Ann Dermatol*. 2009;21(3):243–9.
20
21
22
23 8 55. Elewski BE, Draelos Z, Dréno B, Jansen T, Layton A, Picardo M. Rosacea - Global
24
25 9 diversity and optimized outcome: Proposed international consensus from the
26
27 10 Rosacea international expert group. *J Eur Acad Dermatology Venereol*.
28
29 11 2011;25(2):188–200.
30
31
32
33 12 56. Li S, Cho E, Drucker A, Qureshi A, Li W. Alcohol intake and risk of incident rosacea in
34
35 13 US women. *J Am Acad Dermatol*. 2017;76(6):1061–7.
36
37
38
39 14 57. Aldrich N, Gerstenblith M, Fu P, Tuttle MS, Varma P, Gotow E, et al. Genetic vs
40
41 15 environmental factors that correlate with rosacea: A cohort-based survey of twins.
42
43 16 *JAMA Dermatology*. 2015;151(11):1213–9.
44
45
46
47 17 58. Alinia H, Tuchayi SM, Patel NU, Patel N, Awosika O, Bahrami N, et al. Rosacea
48
49 18 Triggers: Alcohol and Smoking. *Dermatol Clin*. 2018;36(2):123–6.
50
51
52 19 59. Curnier A, Choudhary S. Rhinophyma: Dispelling the myths. *Plast Reconstr Surg*.
53
54 20 2004;114(2):351–4.
55
56
57 21 60. Hauge AW, Kirchmann M, Olesen J. Trigger factors in migraine with aura.
58
59
60

- 1
2
3
4 1 Cephalalgia. 2010;30(3):346–53.
5
6
7 2 61. Panconesi A, Bartolozzi ML, Guidi L. Alcohol and migraine: What should we tell
8
9
10 3 patients? Curr Pain Headache Rep. 2011;15(3):177–84.
11
12 4 62. Panconesi A. Alcohol and migraine: Trigger factor, consumption, mechanisms. A
13
14
15 5 review. J Headache Pain. 2008;9(1):19–27.
16
17 6 63. Davis-Martin RE, Polk AN, Smitherman TA. Alcohol Use as a Comorbidity and
18
19
20 7 Precipitant of Primary Headache: Review and Meta-analysis. Curr Pain Headache Rep.
21
22
23 8 2017;21(10).
24
25 9 64. Akin Belli A, Ozbas Gok S, Akbaba G, Etku F, Dogan G. The relationship between
26
27
28 10 rosacea and insulin resistance and metabolic syndrome. Eur J Dermatol.
29
30
31 11 2016;26(3):260–4.
32
33 12 65. Li S, Cho E, Drucker AM, Qureshi AA, Li W-Q. Obesity and Risk for Incident Rosacea
34
35
36 13 in US Women. J Am Acad Dermatol. 2017;77(6):1083–7.
37
38
39 14 66. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Assessment of the risk of
40
41
42 15 cardiovascular disease in patients with rosacea. J Am Acad Dermatol. 2016;75(2):336–
43
44 16 9.
45
46
47 17 67. Hua TC, Chung PI, Chen YJ, Wu LC, Chen Y Da, Hwang CY, et al. Cardiovascular
48
49
50 18 comorbidities in patients with rosacea: A nationwide case-control study from Taiwan.
51
52
53 19 J Am Acad Dermatol. 2015;73(2):249–54.
54
55 20 68. Dosal J, Keri J. Rosacea and cardiovascular disease: Is there an association? J Am
56
57
58 21 Acad Dermatol. 2015;73(2):308–9.
59
60

- 1
2
3
4 1 69. Ford ES, Li C, Pearson WS, Zhao G, Strine TW, Mokdad AH. Body mass index and
5
6
7 2 headaches: Findings from a national sample of US adults. *Cephalalgia*.
8
9
10 3 2008;28(12):1270–6.
11
12 4 70. Peterlin BL, Rapoport AM, Kurth T. Migraine and obesity: Epidemiology, mechanisms,
13
14
15 5 and implications. *Headache*. 2010;50(4):631–48.
16
17
18 6 71. Vo M, Ainalem A, Qiu C, Peterlin BL, Aurora SK, Williams MA. Body mass index and
19
20
21 7 adult weight gain among reproductive age women with migraine. *Headache*.
22
23 8 2011;51(4):559–69.
24
25
26 9 72. Yu S, Liu R, Yang X, Zhao G, Qiao X, Feng J, et al. Body mass index and migraine: A
27
28
29 10 survey of the Chinese adult population. *J Headache Pain*. 2012;13(7):531–6.
30
31
32 11 73. Bigal ME, Lipton RB. Obesity is a risk factor for transformed migraine but not chronic
33
34 12 tension-type headache. *Neurology*. 2006;67(2):252–7.
35
36
37 13 74. Bigal ME. Body Mass Index and Episodic Headaches. *Arch Intern Med*.
38
39 14 2007;167(18):1964–70.
40
41
42 15 75. Keith SW, Wang C, Fontaine KR, Cowan CD, Allison DB. BMI and headache among
43
44 16 women: Results from 11 epidemiologic datasets. *Obesity*. 2008;16(2):377–83.
45
46
47 17 76. Winter AC, Berger K, Buring JE, Kurth T. Body mass index, migraine, migraine
48
49 18 frequency and migraine features in women. *Cephalalgia*. 2009;29(2):269–78.
50
51
52 19 77. Giraud P, Chauvet S, Tessy M. Migraine and obesity, is there a link ? *Rev Neurol*
53
54 20 (Paris). 2013;169(5):413–8.
55
56
57 21 78. Egeberg A, Griffiths CEM, Williams HC, Andersen YMF, Thyssen JP. Clinical
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 characteristics, symptoms, and burden of psoriasis and atopic dermatitis in adults
2 (epub ahead of print). Br J Dermatol. 2019;0(0):0.
3 79. Rasmussen B, Jensen R, Olesen J. Questionnaire Versus Clinical Interview in the
4 Diagnosis of Headache. Headache. 31(5):290–5.

For peer review only

1 **Figure captions**

2 **Figure 1.** Flow chart detailing enrollment in Copenhagen Rosacea Cohort (COROCO). EMR,
3 Electronic Medical Records.

4
5 **Figure 2.** Flow chart detailing enrollment in Copenhagen Migraine Cohort (COMICO).

6 **Appendices**

7 **Appendix 1.** Semi-structured interview developed at the department of Dermatology in
8 Gentofte, Denmark by authors NW, JT and AE. The purpose of the interviews is to
9 uncover rosacea features, previous treatments for rosacea, and comorbidities in the
10 patient and in 1st and 2nd degree relatives. The interview also includes sleeping
11 habits, smoking, alcohol, BMI, dermatology life quality index (DLQI) and rosacea
12 clinical scorecard.
13

14
15 **Appendix 2.** Semi-structured interview for diagnosing headache and migraine. Adapted
16 from a validated interview from the Danish Headache Center (last updated
17 November 18, 2012) for the purpose of interviewing patients without a diagnosis of
18 migraine.
19

20 **Appendix 3.** Reference for evaluating thermal pictures. Each side of the face will be
21 evaluated at areas corresponding to the three branches of the trigeminal nerve
22

1
2
3
4 1 (forehead, cheeks, chin) and on the tip of the nose. Measurements will be performed
5
6
7 2 on small areas (circles) rather than single points, to obtain an average from each
8
9
10 3 area. To ensure correct ratio, circles were adjusted to match the pupil and iris of each
11
12 4 picture. V1, ophthalmic nerve; V2, maxillary nerve; V3, mandibular nerve; R, right; L,
13
14
15 5 left.
16
17
18 6

For peer review only

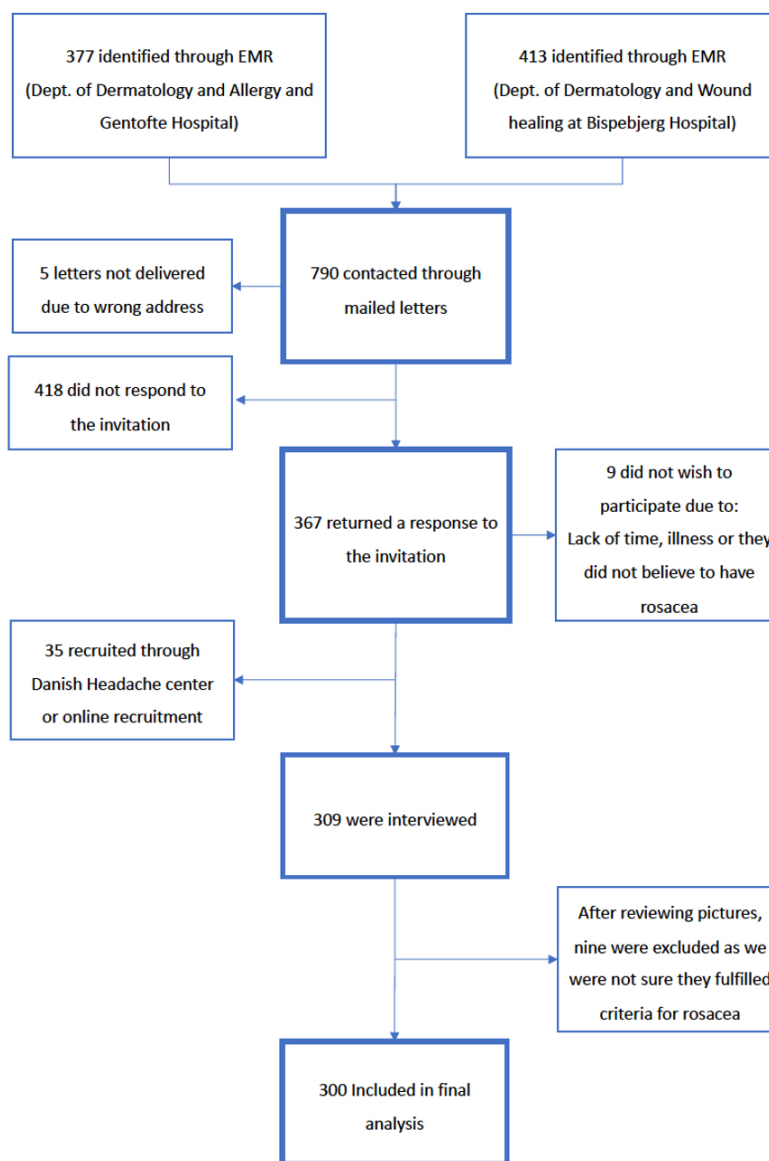


Figure 1. Flow chart detailing enrollment in Copenhagen Rosacea Cohort (COROCO). EMR, Electronic Medical Records.

150x225mm (150 x 150 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

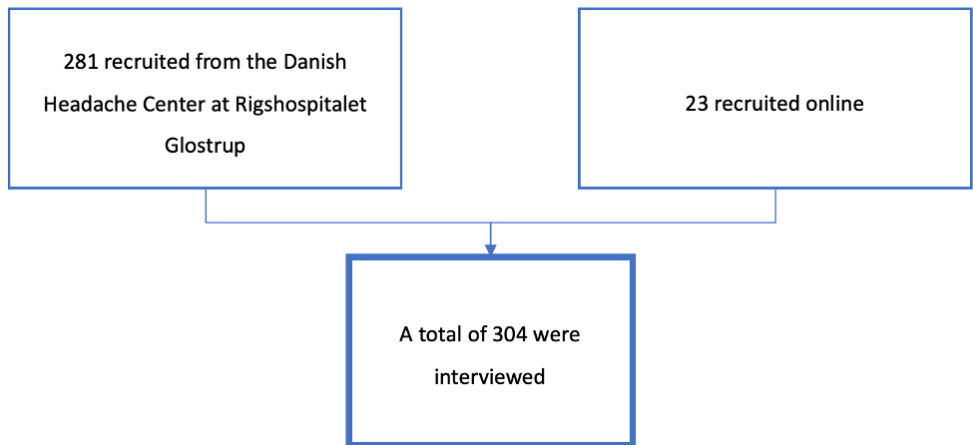


Figure 2. Flow chart detailing enrollment in Copenhagen Migraine Cohort (COMICO).
169x79mm (150 x 150 DPI)

Appendix 1. Semi-structured interview developed at the department of Dermatology in Gentofte, Denmark by authors NW, JT and AE. The purpose of the interviews is to uncover rosacea features, previous treatments for rosacea, and comorbidities in the patient and in 1st and 2nd degree relatives. The interview also includes sleeping habits, smoking, alcohol, BMI, dermatology life quality index (DLQI) and rosacea clinical scorecard.

1. Rosacea

1.1 Has a doctor ever told you that you have rosacea? (one answer)

- No – and I do not have rosacea
- Yes, I am certain I have rosacea, but a doctor has never told me.
- Yes – a doctor who is not a dermatologist (e.g. GP)
- Yes – a dermatologist

If yes to one of the above, go to question. 1.2. If no, move on to question 3

1.2 Which symptom(s) of rosacea did you first notice? (multiple answers)

- Redness of particularly cheeks and/or the chest, which did not want to go away
- Flushing attacks (sudden warmth/burning sensations and redness which lasts a few minutes – half an hour)
- Persistent (> 1 hour) attacks of flushing
- Telangiectasias in the face (cheeks, nose, chin or eyelids)
- Symptoms from the eyes
- Recurrent formation of pimples in the face
- Change of the nose's look or size
- Other? _____

1.2.1 At what age did you experience the first symptom(s) of rosacea? Age years

1.2.2 How much time passed from your first symptom(s) of rosacea until a doctor diagnosed you with rosacea?

Year Months

1.3 Has any of the following symptoms appeared since you noticed the first symptom(s) of rosacea? (multiple answers)

- Redness of particularly cheeks and/or the chest, which did not want to go away
- Flushing attacks (sudden warmth/burning sensations and redness which lasts a few minutes – half an hour)
- Persistent (> 1 hour) attacks of flushing
- Telangiectasias in the face (cheeks, nose, chin or eyelids)
- Symptoms from the eyes
- Recurrent formation of pimples in the face
- Change of the nose's look or size
- Other? _____

1.4 Do you still have symptoms of Rosacea? (one answer)

- No
- Improvement
- Worsening
- Unchanged symptoms

Describe:

2. ROSACEA TREATMENTS

2.1 Have you ever been treatment for rosacea? (one answer)

- No, never (move on to question 3)
- Yes, but I am no longer in treatment
- Yes, I still receive treatment

2.2 How long did/have you receive(d) treatment for rosacea? (cumulated time)

- Less than 3 months
- 3 months – 1 year
- More than 1 year – how long (years) _____

2.3 If no longer in treatment for rosacea – why did you stop treatment? (one answer)

- My symptoms improved / disappeared after treatment
- There was no effect of the treatment on my symptoms
- My symptoms worsened due to treatment
- I got side effects from the treatment
- I do not wish to be on daily medication

2.4 Which type of treatment(s) have you received? (multiple answers)

- Creme/gel/ointment
- Pills
- Laser treatment

2.5 Which drug(s) have you tried, and did it/they have any effect? (multiple answers)

Yes No Do not know

- | | | | |
|--|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> Mirvaso (brimonidine tartrate) creme/gel | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Finacea (azelaic acid) creme/gel | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Metronidazole / metrocrem / rozex / robaz creme/gel | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Oracea (doxycycline) tablet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Soolantra (ivermectin) creme | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Tetracycline | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Erythromycin (macrolide) tablet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Accutin / Isotretinoin tablet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other: _____ | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

2.6 Which symptom(s) did the treatment influence? (multiple answers)

- Papules and pustules (impurities/pimples)
- Unwanted redness of the face
- Telangiectasias in the face
- Eye symptoms
- Nose Changes
- Other: _____

Other comments to treatment:

3. FLUSHING + OTHER SYMPTOMS

REDNESS/ SENSITIVE SKIN

- 3.1 Are any areas of your face often pink or red? No Yes
- 3.2 Is your face often pink or red compared with other people? No Yes
- 3.3 Is your face often pink or red compared to other body areas (e.g. abdomen, upper arms) No Yes
- 3.4 Have others previously mentioned that your face was pink or red? No Yes
- 3.5 Do you experience that coldness, heat or direct sunlight can provoke a facial burning/stinging sensation after only short exposure?
 No Rarely In periods (e.g. winter) Monthly Weekly Daily
- 3.6 Do you experience dry/scaly skin in central areas of your face, e.g. where you usually experience redness?
 No Rarely In periods (e.g. winter) Monthly Weekly Daily
- 3.7 Is your skin sensitive, i.e. blushes easily and/or gets tight/dry easily?
 No Rarely In periods (e.g. winter) Monthly Weekly Daily

TELANGIECTASIAS

- 3.8 Do you have telangiectasias in the face (e.g. around the nose or center of the cheeks)? No Yes
- 3.8.1 If yes, where are the telangiectasias located?
 on top of the nose sides of the nose cheeks chin eyelids other: _____

FLUSHING

- 3.9 Have you experienced flushing in the *past year*?
 No, not at all Yes, a few times (less than 12 times) Yes, periodically Monthly Weekly Daily
- 3.9.1 In your experience, was the start of flushing related to something?
 no menopause (hot flushes) high/low metabolism medication other _____
- 3.9.2 If yes to flushing, in which areas of the skin do you experience flushing?
 forehead center of the cheeks nose ears chin neck chest
- 3.9.3 How long does a (severe) flushing last? (describe any other symptoms)

- 3.10 As a *child or teenager*, did you experience that your face would easily become red (e.g. when you were nervous/shy or exercised)
 No, never
 Yes, I have experienced it a couple of times (few times a year or less)
 It happened occasionally/frequently
 I would always blush when I got embarrassed
 I experienced it daily and sometimes without a trigger
- 3.10.1 How old were you the first time you experienced flushing? Age years

3.11 Can any of the following give you a sudden sensation of warmth (flushing) (multiple answers)

No Yes

- Alcohol
- Hot food or drinks
- Spicy food
- Sunlight
- Hot and humid surrounds e.g. sauna or hot bath etc.
- Physical activity (e.g. sport)
- Psychological stress or emotional revolt (e.g. holding a speech in front of a large audience)
- Other: _____
- None of the above

3.12 **Do you experience having thickened skin on your nose** Yes No

4. ACNE

4.1 Have you experienced frequently having impure skin/pimples in the face after becoming an adult (above 25 years of age)

- No (Go to question 5)
- No, but I had acne when I was younger
- Yes, I have previously experienced pimples, which occurred after I became an adult, but I do not anymore
- Yes, and I still frequently experience having pimples

4.2 If yes, do they occur in relation to anything special?

- No Periods Alcohol Other _____

4.3 Where are these impurities/pimples typically located when you have them? (multiple answers)

- Forehead Cheeks Nose Chin Chest Back Shoulders Other _____

5. EYE SYMPTOMS

5.1 Do you **frequently** experience

No Yes

- red/bloodshot eyes
- watery/runny eyes
- foreign body sensation of the eyes
- stinging sensation in eye/eyes
- itching sensation in eye/eyes
- small, fine scales around eyelid margins
- thickened sensation of eyelid(s), which can be sore or red
- feeling the need to close eyes in the evening, in air-conditioned spaces, during flights etc.

5.2 If yes to any of the above, have you ever visited an ophthalmologist due to these symptoms? No Yes

5.3 Have you had the need to use viscous/watery eyedrops (artificial tears) for longer/shorter periods of time? No Yes

6. TREATMENT WITH CORTICOSTEROIDS/ADRENOCORTICAL HORMONE

6.1 Have you ever been treated with corticosteroids (also called adrenocortical hormone or prednisolone)?

- No, never (move on to question 7) Yes – creme/ointment Yes – pills Yes – syringe

6.2 Have you ever been treated with corticosteroids/adrenocortical hormone?

- No, never Yes, a short period of time (less than 1 month cumulated) Yes, a longer period (1-12 months cumulated)
- Yes, a long period (>12 months cumulated)

6.2.1 If yes, at what age were you when you were first treated with corticosteroids in the face? Age years

7. OTHER DISEASES AND TREATMENT

7.1 Has a doctor ever told you or someone in your family that you/they had any of the following diseases? (Only biologically related family members, i.e. not stepsister or stepparents)

SKIN

Rosacea

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Acne

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Seborrheic dermatitis

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Psoriasis

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Atopic dermatitis

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Non-melanoma skin cancer

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Malignant melanoma

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Urticaria (hives)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Any other skin disorder

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Please describe: _____

PSYCHIATRIC

Anxiety

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

If 'me', have you ever been treated for anxiety? No, never Yes, and I am still in treatment Yes, but I am no longer in treatment

Depression

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

If 'me', have you ever been treated for depression? No, never Yes, and I am still in treatment Yes, but I am no longer in treatment

Any other psychiatric disorder

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Please describe: _____

STOMACH AND GUT

Heartburn/reflux

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Inflammatory bowel disease (Crohn's disease/Ulcerative colitis)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Gluten intolerance/coeliac disease

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Do you frequently experience discomfort/bloating and changing bowel habits? (Irritated bowel syndrome)

No Rarely (few times a year) Monthly Weekly Daily

OTHER DISEASES

Type 1 diabetes

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Type 2 diabetes

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Sjogren's syndrome

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Metabolic disease

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

High cholesterol

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Hypertension (high blood pressure)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

If 'me', are you taking any treatment for hypertension? No Yes, pills, If yes, describe: _____

Raynaud's phenomenon

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60**AIRWAYS**

COPD (chronic obstructive pulmonary disease)

 no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Asthma

 no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Hay fever

 no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)**NEUROLOGICAL**

Parkinson's disease

 no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Alzheimer's disease

 no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)7.2 Do you often experience having cold nose and/or hands? No Yes, nose Yes, hands7.3 Have you been diagnosed with/treated for any other diseases? No Yes, please describe: _____**8. SLEEP**

8.1 How often do you find it difficult to fall asleep?

 Once a month or less (never) 2-4 times a month one to several times a week daily

8.2 How often do you wake up earlier than what you intended (without being woken by an alarm or other noise)?

 Once a month or less (never). 2-4 times a month one to several times a week daily**9. SMOKING**

9.1 Do you smoke? (one answer)

 No, I have never smoked No, but I have previously smoked Yes, occasionally (less than 1 cigarette per day). Yes, daily**ANSWERS FROM DAILY SMOKERS**

9.2 How many cigarettes do you smoke on average? (daily number of cigarettes)

Number of cigarettes Other, describe: _____**ANSWERS FROM OCCASIONAL SMOKERS**

9.3 How many cigarettes do you smoke on average a week? (weekly number of cigarettes)

Number of cigarettes Other, describe: _____**ANSWERS FROM OCCASIONAL AND FORMER SMOKERS**9.4 Have you previously smoked every day? yes no

9.5 If yes, how much did you smoke on average a day?

Number of cigarettes Other, describe: _____9.6 When did you stop smoking daily? (which year) **ANSWER FROM ALL SMOKERS**9.7 How old were you when you started smoking? (age in years) years

1
2
3
4 10. ALCOHOL
5

6 10.1 Have you been drinking alcohol in the past year? No Yes

7
8 10.2 How much was you average weekly intake during the past 12 months? (Write '0' if none) drinks per week
9

10
11 11. HEIGHT AND WEIGHT
12

13 11.1 What is your current height (without shoes)? _____ cm

14 11.2 What is your current weight without clothes and shoes? _____ kg

15
16 12. DERMATOLOGY LIFE QUALITY INDEX (DLQI)
17

18 12.1 Within the past week to what extent has your skin been itching, sore, hurting or stinging?

19 Extremely Very A bit Not at all

20
21 12.2 Within the past week to what extent have you been embarrassed or shy because of your skin?

22 Extremely Very A bit Not at all

23
24 12.3 Within the past week to what extent has your skin bothered you in terms of shopping or taking care of your house or back yard?

25 Extremely Very A bit Not at all Not relevant

26
27 12.4 Within the past week to what extent has your skin affected the way you dress?

28 Extremely Very A bit Not at all Not relevant

29
30 12.5 Within the past week to what extent has you skin affected your social activities or leisure activities?

31 Extremely Very A bit Not at all Not relevant

32
33 12.6 Within the past week to what extent has you skin complicated your opportunities of exercise?

34 Extremely Very A bit Not at all Not relevant

35
36 12.7 Within the past week has your skin prevented you from working or studying?

37 Yes No Not relevant

38 If "No", within the past week has your skin been a problem for you at work or during studies?

39 Extremely Very A bit Not at all

40
41 12.8 Within the past week to what extent has your skin caused problems in relation to your partner, close friends or relatives?

42 Extremely Very A bit Not at all Not relevant

43
44 12.9 Within the past week to what extent has your skin caused sexual problems?

45 Extremely Very A bit Not at all Not relevant

46
47 12.10 Within the past week, has treatment of your skin caused problems, e.g. by making your home messy or dirty, or by being time consuming?

48 Extremely Very A bit Not at all Not relevant
49
50
51
52
53
54
55
56
57
58
59
60

Appendix 2:

Semi-structured interview for diagnosing headache and migraine. Adapted from a validated interview from the Danish Headache Center (last updated November 18, 2012) for the purpose of interviewing patients without a diagnosis of migraine.

Semi-Structured Migraine and Headache Interview**0. Headache****0.1 Have you been diagnosed with migraine**

Yes No

0.1.1 If yes, did anything happen in relation to debut of migraine?

Yes No

0.1.1.1 If yes – what happened

- Menarche
 Head trauma / Concussion
 Other _____

0.1.2 If NO:**0.1.2.1 Do you experience regular headaches?****0.1.2.1.1 If yes, how often (days per month) ____****0.1.2.1.2 Is the headache related to anything in particular**

Yes No

0.1.2.1.3 If yes, what? _____**For all patients:****Do you ever experience headaches that are:**

	Yes	No
a. Unilateral	<input type="checkbox"/> 1	<input type="checkbox"/> 2
b. Pulsating	<input type="checkbox"/> 1	<input type="checkbox"/> 2
c. Moderate/severe intensity	<input type="checkbox"/> 1	<input type="checkbox"/> 2
d. Aggravation by physical activity	<input type="checkbox"/> 1	<input type="checkbox"/> 2
e. Nausea	<input type="checkbox"/> 1	<input type="checkbox"/> 2
f. Vomiting	<input type="checkbox"/> 1	<input type="checkbox"/> 2
g. Photophobia	<input type="checkbox"/> 1	<input type="checkbox"/> 2
h. Phonophobia	<input type="checkbox"/> 1	<input type="checkbox"/> 2
i. Osmophobia	<input type="checkbox"/> 1	<input type="checkbox"/> 2

Duration of the headache without medication:

< ½ h 1

½ - 4 h 2

5 h – 23 h 3

1 - 3 days 4

4 – 7 days 5

>7 days 6

1. MIGRAINE WITH AURA (MA)**a. Do you have migraine with aura?**

1 2

1.1 Visual aura

Yes No

a. Are there visual disturbances? 1 2

b. Unilateral 1 2

c. Gradually progressing 1 2

d. Scotoma 1 2

e. Zig-zag lines (fortification) 1 2

f. Flickering 1 2

g. Preserved central vision 1 2

h. Duration of gradual development _____min

j. Duration of visual aura _____min

1.2 Sensory aura

Yes No

a. Are there sensory disturbances? 1 2

b. Unilateral 1 2

c. Gradually progressing 1 2

Do the sensory disturbances involve:

d. The face 1 2

e. The tongue 1 2

f. The hand 1 2

g. The arm 1 2

h. The foot 1 2

i. The leg 1 2

j. The body 1 2

k. Duration of gradual development _____min

l. Duration of visual aura _____min

1.3 Motor aura

Yes No

a. Are there motor disturbances? 1 2

b. Unilateral 1 2

c. Gradually progressing 1 2

Do the motor disturbances involve:

d. The face 1 2

e. The tongue 1 2

f. The hand 1 2

g. The arm 1 2

h. The foot 1 2

i. The leg 1 2

j. The body 1 2

k. Duration of gradual development _____min

l. Duration of visual aura _____min

1.4 Aphasia/**Speech disturbances**

Yes No

a. Are there speech disturbances? 1 2

Are the speech impairments due to:

b. Problems articulating speech 1 2

c. Problems finding the right words 1 2

d. Problems understanding what

people say 1 2

e. Problematic for other people to

understand your speech 1 2

f. Duration of speech/aphasic

disturbances _____min

- 1.5 Basilar-type aura** Yes No
- a. Are there basilar/occipital symptoms? 1 2
- Are there:
- b. Bilateral pareses/paresthesias 1 2
- c. Bilateral visual symptoms 1 2
- d. Dysarthria 1 2
- e. Vertigo 1 2
- f. Diplopia 1 2
- g. Tinnitus 1 2
- h. Hypacusia 1 2
- i. Decreased level of consciousness 1 2
- j. Ataxia 1 2

1.6 Succession of aura symptoms

- a. If more than 1 aura type, is the succession of the auras:
- Successive 1
- Simultaneously 2
- Not applicable (NA) 3

1.7 Aura with headache

- Yes No
- a. Do you have aura with headache 1 2
- b. Does the onset of the headache typically come:
- Before the aura 1
- After the aura 2
- Simultaneously with the aura 3
- c. How long time before/after the aura _____ min

1.8 Aura without headache

- Yes No
- a. Do you have aura without headache 1 2

1.9 Migraine with aura over time

- a. Age at onset _____ years
- b. Date of last attack _____
- c. No. of attacks within last year:
- 0 1
- 1-5 2
- 6-12 3
- 13-24 4
- 25-36 5
- >36 6
- d. No. of lifetime attacks:
- 1 1
- 2-4 2
- 5-9 3
- 10-49 4
- 50-100 5
- >100 6

2. MIGRAINE WITHOUT AURA (MO)

- a. Do you have migraine without aura? Yes No
- 1 2

2.1 Migraine without aura over time

- a. Age at onset _____ years
- b. Date of last attack _____
- c. No. of attacks within last year:
- 0 1
- 1-5 2
- 6-12 3
- 13-24 4
- 25-36 5
- >36 6
- d. No. of lifetime attacks:
- 1 1
- 2-4 2
- 5-9 3
- 10-49 4
- 50-100 5
- >100 6

3. Migraine triggers

- a. Are there factors that can trigger a migraine attack? Yes No NA
- 1 2 3
- b. What type of migraine? MO MA MA+MO
- 1 2 3
- 3.1. Can these factors trigger a migraine attack:**
- Yes No
- a. Physical activity 1 2
- b. Light 1 2
- c. Stress 1 2
- d. Menstruation 1 2
- e. Alcohol 1 2
- f. Strong smells 1 2
- g. Lack of/too much sleep 1 2
- h. Other factors: _____

4. Chronic migraine (MA+MO)

During the past 3 successive months, have you had:

- a. Headache at least 15 days a month Yes No
- 1 2
- b. Migraine at least 8 days a month 1 2

5. Tension-type headache

Yes No

Do you have tension-type headaches 1 2**5.1 Headache characteristics**

Yes No

- a. Bilateral 1 2
- b. Pressing 1 2
- c. Mild/moderate intensity 1 2
- d. Aggravation by physical activity 1 2
- e. Nausea 1 2
- f. Vomiting 1 2
- g. Photophobia 1 2
- h. Phonophobia 1 2

5.2 Duration of headache

- < ½ h 1
- ½ - 4 h 2
- 5 h - 23 h 3
- 1 - 3 days 4
- 4 - 7 days 5
- >7 days 6

5.3 Tension-type headache over time

a. Headache days within last year:

- 0 1
- 1-7 2
- 8-14 3
- 15-30 4
- 31-179 5
- ≥180 6

b. No. of tension-type headache days during the three last months: _____ days

c. If ≥45 headache days, are the days evenly spaced out

Yes No
 1 2**6. MIGRAINE TREATMENT (MA+ MO)****6.1 Treatment of migraine attacks**

Yes No NA

- a. Triptans are efficient 1 2 3
- b. Regular painkillers (NSAID, Paracetamol etc.) are efficient 1 2 3
- c. Ergotamine drugs are efficient 1 2 3
- d. Other drug(s) _____

6.2 Use of medication

- a. No. of days of triptan-use per month _____
- b. No. of days of regular painkiller-use per month _____

6.3 Prophylactic treatment of migraine

Yes No NA

- a. Beta-blockers are efficient 1 2 3
- b. Ca²⁺-antagonists are efficient 1 2 3
- c. Angiotensin II receptor blockers are efficient 1 2 3
- d. ACE-inhibitors are efficient 1 2 3
- e. Anti-epilepsy drugs are efficient 1 2 3
- f. Antidepressive medication (mirtazapine) is efficient 1 2 3
- g. Hormone treatment is efficient 1 2 3
- h. Other drug(s) _____

g. Are you currently receiving prophylactic treatment(s) for migraine

Yes No
 1 2**8. SECONDARY HEADACHES?** Yes No
 1 2

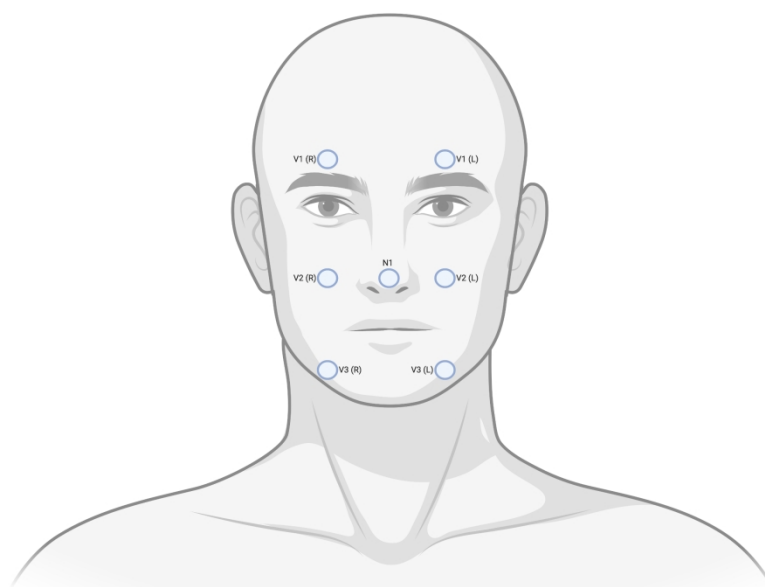
If yes, specify: _____

11. Migraine within the family

Yes No

- a. Mother has/had migraine 1 2
- b. Father has/had migraine 1 2
- d. Siblings have/had migraine 1 2
- e. Children have/had migraine 1 2

Interview conducted by: _____



Appendix 3. Reference for evaluating thermal pictures. Each side of the face will be evaluated at areas corresponding to the three branches of the trigeminal nerve (forehead, cheeks, chin) and on the tip of the nose. Measurements will be performed on small areas (circles) rather than single points, to obtain an average from each area. To ensure correct ratio, circles were adjusted to match the pupil and iris of each picture. V1, ophthalmic nerve; V2, maxillary nerve; V3, mandibular nerve; R = right; L = left.

254x177mm (300 x 300 DPI)

BMJ Open

Cohort profile of COpenhagen ROsacea COhort (COROCO) and COpenhagen MIgraine COhort (COMICO)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039445.R2
Article Type:	Cohort profile
Date Submitted by the Author:	14-Jul-2020
Complete List of Authors:	Wienholtz, Nita; Rigshospitalet Glostrup, Danish Headache Center; Gentofte Hospital, Dermatology and Allergy Christensen, Casper; Rigshospitalet Glostrup, Danish Headache Center Haugaard, Jeanette; Gentofte Hospital, Dermatology and Allergy Zhang, Ditte; Rigshospitalet Glostrup, Danish Headache Center Ashina, Messoud; University of Copenhagen, Denmark, Danish Headache Centre and Department of Neurology Thyssen, JP; Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen Egeberg, A; Gentofte Hospital, Department of Dermatology and Allergy
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Neurology
Keywords:	Migraine < NEUROLOGY, DERMATOLOGY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1 Cohort profile of Copenhagen ROsacea Cohort (COROCO) and Copenhagen MIgraine
5
6
7 2 Cohort (COMICO)
8
9
10 3

11
12 4 Nita Katarina Frifelt Wienholtz, MD^{1,2,3}, Casper Emil Christensen, MD, PhD¹, Jeanette Halskou

13
14
15 5 Haugaard, MD^{2,3}, Ditte Georgina Zhang¹, Messoud Ashina, MD, PhD, DMSc¹, Jacob Pontoppidan

16
17
18 6 Thyssen, MD, PhD, DMSc^{2,3}, Alexander Egeberg, MD, PhD^{2,3}
19

20
21
22
23 8 ¹ Danish Headache Center, Department of Neurology, Rigshospitalet Glostrup, Glostrup, Denmark

24
25 9 ² Copenhagen Research Group for Inflammatory Skin (CORGIS), Hellerup, Denmark

26
27 10 ³ Department of Dermatology and Allergy, Herlev and Gentofte Hospital, Hellerup, Denmark
28
29
30 11

31
32 12 **Correspondence:**

33
34
35 13 Alexander Egeberg

36
37 14 Department of Dermatology and Allergy

38
39 15 Herlev and Gentofte Hospital

40
41 16 Kildegaardsvej 28

42
43 17 DK-2900 Hellerup

44
45 18 Telephone: (+45) 38 67 41 52

46
47 19 E-mail: alexander.egeberg@gmail.com
48
49
50
51 20

52
53 21 **Word count: 3931**

54
55 22 **Number of tables: 2**

56
57 23 **Number of figures: 2**
58
59
60

1
2
3
4 1 **Number of appendices: 3**

5
6
7 2 **Number of references: 79**

8
9
10 3 **Key words:** cohort study, epidemiology, migraine, prospective, rosacea

11
12
13
14
15 5 **Conflicts of interest**

16
17 6 NW has received personal fees from Novartis and the Kgl Hofbundtmager Aage Bang Foundation.
18
19
20 7 CC received personal fees from Teva and acts as consultant for Teva. JH and DZ declare no
21
22 8 conflicts relevant to the manuscript. MA is a consultant, speaker or scientific advisor for Alder,
23
24 9 Allergan, Amgen, Eli Lilly, Lundbeck, Novartis, and Teva, primary investigator for Alder,
25
26
27 10 Allergan, Amgen, Eli Lilly, Novartis and Teva trials. MA has no ownership interest and does not
28
29 11 own stocks of any pharmaceutical company. MA serves as associate editor of Cephalalgia, associate
30
31 12 editor of Headache, associate editor of the Journal of Headache and Pain. MA is President of the
32
33
34 13 International Headache Society. JT has attended advisory boards for Sanofi-Genzyme, Eli Lilly &
35
36 14 Co, Pfizer, Abbvie, and Union Therapeutics, and received honoraria as a speaker from LEO
37
38 15 Pharma, Regeneron, Abbvie, and Sanofi-Genzyme, and has been an investigator for Sanofi-
39
40
41 16 Genzyme, Eli Lilly & Co, LEO Pharma, Pfizer, and Abbvie. AE has received research funding from
42
43 17 Pfizer, Eli Lilly, the Danish National Psoriasis Foundation and the Kgl Hofbundtmager Aage Bang
44
45 18 Foundation, and honoraria as consultant and/or speaker from Almirall, Leo Pharma, Samsung
46
47 19 Bioepis Co., Ltd. Pfizer, Eli Lilly & Co, Novartis, Galderma, Dermavant, Bristol-Myers Squibb,
48
49
50 20 and Janssen Pharmaceuticals.

51
52 21
53
54 22
55
56
57 23 **Funding sources**

1
2
3
4 1 The study was supported by grants from Novo Nordisk Foundation (NNF170C0029698)
5
6
7 2 and Augustinus Foundation (17-2523).
8
9
10 3
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **ABSTRACT**

2 **Purpose**

3 Migraine has consistently been connected to rosacea. Commonalities in epidemiology,
4 trigger factors and associated neuropeptides support shared etiology and
5 pathophysiological pathways, though underlying mechanisms remain unclear. We
6 established two cohorts of patients diagnosed with either migraine and/or rosacea. All
7 patients were phenotyped in regard to migraine and rosacea. In this article, we describe
8 baseline parameters of the cohorts. In the future we expect that these cohorts will help
9 uncover potential disease overlaps and allow for prolonged follow up through national
10 Danish health registries.

12 **Participants**

13 Copenhagen Rosacea Cohort (COROCO) and Copenhagen Migraine Cohort (COMICO) are
14 prospective cohorts based in the Capital region of Denmark. Participants for COROCO
15 were recruited primarily through two tertiary dermatology clinics in Copenhagen, Denmark
16 and patients for COMICO were recruited through a tertiary neurology clinic in
17 Copenhagen, Denmark.

19 **Findings to date**

20 COROCO: 67.7% women (median age 51 years (interquartile range (IQR) 43.0 – 61.0)).
21 Family history of migraine: 44.3%. Family history of rosacea: 45%. There were 13% who

1
2
3
4 1 currently smoked and 36.6% were former smokers. Regular intake of alcohol was present in
5
6
7 2 79.3% (median 4 items/week (IQR 1.0 – 9.0)). Median body mass index (BMI): 25.7 (IQR 23.1
8
9
10 3 – 29.0). Median DLQI: 2 (IQR 1 - 5).
11
12 4 COMICO: 88.5% women (median age 41 years (IQR 29.5 – 51.0)). Family history of
13
14
15 5 migraine: 73.4%. Family history of rosacea: 18.4%. There were 17% who currently smoked
16
17
18 6 and 26.0% former smokers. Regular intake of alcohol was present in 62.3% (median intake:
19
20 7 2 item/week (IQR 1.0 – 3.0)). Median BMI was 24.6 (IQR 21.5 – 28.2). Median DLQI was 1
21
22
23 8 (IQR 0 – 2).
24
25
26 9

10 **Future plans**

11 COROCO and COMICO serve as strong data sources that will be used for future studies on
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34 12 rosacea and migraine with focus on risk factors, occurrence, treatment, natural history,
35
36
37 13 complications, comorbidities and prognosis.
38
39
40
41
42
43
44
45
46
47
48
49
50
51

15 **Registration**

16 This observational cohort is registered with clinicaltrials.gov (NCT03872050).
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51

18 **Strengths and limitations of this study**

- 52 19 • Copenhagen Rosacea Cohort (COROCO) and Copenhagen Migraine Cohort
53
54
55 20 (COMICO) are large cohorts of adults with either physician-diagnosed migraine or
56
57
58
59
60

- 1
2
3
4 1 rosacea that are phenotyped through face-to-face interview by trained
5
6
7 2 professionals.
8
9
10 3 • Rosacea diagnoses are validated through pictures evaluated by three physicians and
11
12 4 migraine diagnoses validated through semi-structured interviews.
13
14
15 5 • Collected information includes pictures with normal and thermal cameras, blood
16
17 6 samples, inflammatory markers and DNA for thorough description of each
18
19 7 participant.
20
21
22
23 8 • Future linkage to Danish national health registries enables us to follow patients for a
24
25 9 prolonged period of time.
26
27
28 10 • Limitations include risk of selection bias as participants are recruited from specialty
29
30 11 units, and risk of recall bias as the cohort is based on interviews.
31
32
33
34 12

1 INTRODUCTION

2 Migraine has repeatedly been associated with rosacea.[1] Both are chronic
3 inflammatory conditions with relapsing episodes of headache for migraine, and
4 redness/flushing and/or papules/pustules for rosacea. Relapses may be triggered by
5 various endogenous and/or exogenous factors such as different foods and drinks,
6 exercise, sun/UV exposure, heat and stress.[2,3] Migraine is common with a prevalence
7 of 12%,[4] and up to 18.3% for women.[4–6] Migraine seems to be underdiagnosed and
8 undertreated[6,7] and the actual prevalence is probably higher. Rosacea has an overall
9 prevalence of 5.5%[8] and usually affects individuals above the age of 30 years.[8,9]
10 The disorders are primarily seen in individuals of Caucasian descent.[4,8] Etiology for
11 both is largely unknown, but seems to involve a mix of genetic and environmental
12 factors.[10,11] Other commonalities between migraine and rosacea include
13 neuroinflammation and upregulation of signaling neuropeptides, such as pituitary
14 adenylate cyclase-activating polypeptide-38 (PACAP38)[2,12] and calcitonin gene-
15 related peptide (CGRP),[13,14] though there are other suggested signaling pathways
16 for both disorders.[10] Common demography, triggers and associated neuropeptides
17 suggest a shared pathophysiological pathway.[1]

18
19 Despite overwhelming evidence of a connection between migraine and rosacea,[15–20]
20 underdiagnosis in both disorders must be considered as a confounder in previous
21 research, and a systematic approach is therefore needed to confirm this connection and

1
2
3
4 1 better characterize exact overlap of these diseases. Establishment of prospective patient
5
6
7 2 cohorts with a physician-diagnosis of either migraine or rosacea will help confirm this
8
9
10 3 connection and uncover possible risk factors and comorbidities in both.
11
12
13 4

15 5 COHORT DESCRIPTION

18 6 **Study approval, registry and data availability**

19
20 7 The study was approved by the Ethical Committee of the Capital Region of Denmark (H-
21
22
23 8 17023750) and was registered at www.clinicaltrials.gov (NCT03872050). All participants
24
25
26 9 provided written informed consent in accordance with the declaration of Helsinki anno
27
28 10 1964 with adjustments until 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

30
31 11 All data are under the supervision of the corresponding author and can be made available
32
33
34 12 upon reasonable request.
35
36
37 13

39 14 **Study population and setting**

40
41
42 15 Two cohorts were established; Copenhagen Rosacea Cohort (COROCO) and Copenhagen
43
44 16 Migraine Cohort (COMICO). Willing participants had to be aged 18 years or above. A
45
46
47 17 physician-diagnosis of rosacea was needed to be included in COROCO, and a physician-
48
49
50 18 diagnosis of migraine was needed to be included in COMICO. There were no exclusion
51
52 19 criteria. All participants signed an informed consent upon enrollment.
53
54
55 20

57 21 **Recruitment**

58
59
60

1
2
3
4 1 *Copenhagen Rosacea Cohort (COROCO)*

5
6
7 2 Electronic Medical Records (EMR) were searched for adults who consulted a doctor for a
8
9
10 3 diagnosis of rosacea at either *Department of Dermatology and Allergy at Gentofte Hospital*
11
12 4 (between September 3rd, 2013 – May 5th, 2019) or *Department of Dermatology and Wound*
13
14
15 5 *Healing Centre at Bispebjerg Hospital* (between January 1st, 2014 – November 21st, 2018).

16
17
18 6 Diagnosis of rosacea was defined as one of the following ICD-10 codes: DL71, DL718A,
19
20 7 DL719, DL718.[21]

21
22
23 8 A total of 790 patients were identified through EMR and invited to participate in the
24
25
26 9 rosacea cohort. Five letters were not delivered due to wrong address, and invitations were
27
28
29 10 thus delivered to 785 patients. Patients could respond through one of three routes: mailing
30
31 11 the 'return envelope' (free of charge), sending an e-mail, or calling/texting a dedicated
32
33
34 12 phone. The response rate was 46.8% (367 patients). Nine patients informed us that they
35
36
37 13 did not want to participate due to illness, lack of time or because they did not believe to
38
39 14 have rosacea. Of the 358 patients who responded positively to the invitation, we
40
41
42 15 interviewed 274 patients before reaching the pre-specified inclusion number (see Figure 1
43
44
45 16 for details). An additional 35 patients with a prior diagnosis of rosacea were included via
46
47 17 the Danish Headache Center at Rigshospitalet Glostrup or via online recruitment
48
49
50 18 (www.forsogsperson.dk). Interviews were performed in 309 patients, and after reviewing
51
52
53 19 pictures, nine patients were excluded from analysis, as their signs could not clearly be
54
55 20 attributed to rosacea. COROCO thus included a total of 300 patients. Interviews were
56
57
58 21 performed between September 17th, 2018 – October 14th, 2019.

1
2
3
4 15
6
7 2 *Copenhagen Migraine Cohort (COMICO)*

8
9
10 3 Patients for COMICO were recruited through the Danish Headache Center, department of
11
12 4 Neurology at Rigshospitalet Glostrup, Copenhagen, Denmark. The Danish Headache
13
14
15 5 Center is a tertiary care facility for patients with persistent or difficult-to-treat headaches
16
17
18 6 who have been referred by either a general practitioner or from a specialist neurology
19
20
21 7 clinic. Patients were asked to participate when they came for an outpatient visit at the
22
23 8 Headache Center. A physician-diagnosis of migraine (with or without aura) was necessary
24
25
26 9 for inclusion. In all, 281 patients were recruited from the Danish Headache Center. An
27
28
29 10 additional 23 patients were recruited online (www.forsøgsperson.dk) (see Figure 2 for
30
31 11 details). A total of 304 patients were included in COMICO. Interviews were performed
32
33
34 12 between September 14th, 2018 – October 29th, 2019.

35
36 13

37 14

38 15

39 16

40 17

41 18

42 19

43 20

44 21

45 22

46 23

47 24

48 25

49 26

50 27

51 28

52 29

53 30

54 31

55 32

56 33

57 34

58 35

59 36

60 37

Study visit

44 18 Patients were seen once during the study period. The visit took place at one of three
45
46
47 19 locations of the patient's choice: Danish Headache Center (Rigshospitalet Glostrup),
48
49
50 20 Department of Dermatology (Gentofte hospital), or by home visit at the patient's
51
52 21 home/work.

1
2
3
4 1 The entire visit; both interviews and clinical examination, was performed by either a
5
6
7 2 medical doctor (author NW) or by senior medical students who were specifically trained to
8
9
10 3 perform both.

11
12 4 Each visit lasted approximately 60 minutes and included interview, blood sample, pictures
13
14
15 5 with digital and thermal cameras, superficial stratum corneum sampling of the forearm and
16
17
18 6 cheek, and mouth swab for DNA sampling. Procedures are described below. Patients only
19
20
21 7 had to agree to the semi-structured interview to be eligible for the study, as this was the
22
23 8 essential part of the investigation; however, most patients agreed to all investigations.
24
25
26 9

27 28 10 **INTERVIEW**

29
30
31 11 A semi-structured interview was performed at the beginning of the visit based on two
32
33
34 12 questionnaires. All participants were asked questions on both rosacea and migraine to
35
36
37 13 confirm diagnosis and phenotype. All questionnaires were reviewed by author NW. In case
38
39 14 of doubt about rosacea diagnosis, authors AE and JPT were consulted, and in case of
40
41
42 15 doubt about migraine diagnosis, author MA was consulted.
43
44
45 16

46 47 17 Questionnaire – rosacea

48
49
50 18 Demographic information, comorbidities, family history, dermatology life quality index
51
52
53 19 (DLQI) and presence of rosacea features. If patients had a prior diagnosis of rosacea, first
54
55 20 presenting sign or symptom of rosacea, diagnostic delay and previous treatments were
56
57
58
59
60

1
2
3
4 1 also collected (appendix 1). Patients were also evaluated with the National Rosacea Society
5
6
7 2 Rosacea Clinical Scorecard.[22]
8
9

10 3 11 12 4 Questionnaire – migraine 13 14

15 5 A validated semi-structured questionnaire on diagnosis and subtyping of migraine[23] was
16
17
18 6 adapted by author NW for the purpose of interviewing patients with no known migraine or
19
20
21 7 headache (appendix 2). Questions included family history, headache/migraine and aura
22
23
24 8 symptoms along with risk factors for headache/migraine. All patients; also those who
25
26
27 9 claimed to have a previous diagnosis of migraine, were asked about headache
28
29
30 10 characteristics to validate migraine diagnosis. If patients fulfilled criteria for a diagnosis of
31
32
33 11 migraine, migraine onset and headache frequency were collected.
34
35

36 13 CLINICAL EXAMINATION 37 38

39 14 The following examinations were performed after the interview, and patients had therefore
40
41
42 15 been sitting calmly for at least 30 minutes and drinking nothing but water, prior to
43
44
45 16 examinations.
46

47 17 All examinations were performed on patients included in both COROCO and COMICO.
48
49
50 18

51 52 19 **Standardized photography** 53 54

55 20 A standardized picture was taken with a digital Canon PowerShot G12 camera at a distance
56
57
58 21 of approximately 70 cm, with a flash and zoom when needed. Pictures were rated
59
60

1
2
3
4 1 according to phenotype and the newly developed rosacea scoring tool 'Rosacea Area and
5
6
7 2 Severity Index' (RASI) (manuscript in development), to ensure correct diagnosis and
8
9
10 3 classification of rosacea.

11
12 4 All pictures were evaluated by three authors (JT, AE, NW). Disagreements were resolved by
13
14
15 5 discussion. In cases of doubt, patients were rated as 'not rosacea' or 'non-classifiable'.

16
17
18 6 These ratings will be compared with interview data in a future publication, to evaluate the
19
20
21 7 validity of both.
22
23
24
25
26
27

28 10 **Thermography**

29
30
31 11 Thermographic pictures were recorded after patients had been placed in a room with a
32
33
34 12 stable temperature for at least 15 minutes. Pictures were recorded on FLIRA655sc with a
35
36
37 13 25° lens. The camera has a range of -40°C to +150°C and temperature accuracy of +/- 1°C.
38
39 14 Pictures were recorded at a distance of approximately 50 centimeters from the subject. For
40
41
42 15 each subject, a total of three pictures were recorded - one picture from the front and one
43
44
45 16 from each side. The FLIR program *ResearchIR* was used to record pictures. Analyses were
46
47 17 performed in the program *FLIR TOOLS*. Temperature was measured at each side of the face
48
49
50 18 corresponding to the facial area of the three branches of the trigeminus (forehead, cheeks
51
52
53 19 and chin). An additional temperature measurement was performed on the tip of the nose
54
55 20 (appendix 3). The measure point was matched to the size of the iris to adjust for
56
57
58 21 differences in distances from which the pictures were taken.
59
60

1
2
3
4 1
5
6
7 2 Facial skin temperature has previously been investigated in both migraine and rosacea
8
9
10 3 with unclear results.[24] We therefore offer baseline temperatures in a large group of
11
12 4 patients with both disorders to determine whether previous findings reflect true
13
14
15 5 differences or simply interindividual differences within patient groups.
16
17
18 6

7 **Superficial stratum corneum sampling**

8 A sample of stratum corneum was collected using the tape stripping method. Samples were
9 collected from two sites (one forearm and one cheek), Seven consecutive tape stripping discs
10 (22 mm) (D-squame, CuDerm, Dallas, Texas) were collected at each site. Discs were applied
11 with tweezers followed by a standardized pressure with a D-squame pressure application
12 pen for 5 seconds. The first 3 discs from each site were discarded, and the following 4 discs
13 were stored at -80°C immediately after sampling. The discs will be examined for cytokines
14 and skin microbiome.

15 Rosacea is characterized by local inflammation of the face, however, recent evidence
16 suggests that the inflammation may be systemic.[25] Migraine has also been suggested to
17 involve inflammation, especially neuroinflammation, but possibly also systemic
18 inflammation.[26]

19 Measurement of inflammatory markers from the skin will allow us to compare facial
20 inflammation (cheek) to systemic inflammation (forearm) and to compare patients with
21 migraine and rosacea to uncover a possible subclinical inflammation in both disorders.

1
2
3
4 1 Furthermore, we hope to investigate whether there is a correlation between local/systemic
5
6
7 2 inflammation, subtypes of rosacea and disease activity.
8
9
10 3

11 12 4 **Genetics**

13
14
15 5 Patients were not allowed to eat, drink, smoke, chew gum or clean teeth one hour before
16
17
18 6 collection. All patients were instructed to rinse their mouth with water immediately prior to
19
20
21 7 collection. For the analyses, one SK-1S DNA buccal swab (Isohelix, Harrietsham, U.K) was
22
23 8 rubbed against cheek mucosa for 60 seconds before returning the swab to the supplied
24
25
26 9 tube without touching the head of the swab. The shaft was broken on the edge of the tube
27
28
29 10 which left the head of the swab in the tube. The tube was stored at -80° C until analysis.
30
31
32 11

33
34 12 The purpose of DNA collection was to perform a genome-wide association-study (GWAS)
35
36
37 13 for the most common gene mutations in rosacea and migraine. A large meta-analysis of
38
39 14 375,000 individuals has located 38 loci relevant for migraine[27], whereas GWAS has only
40
41
42 15 been done a few times in rosacea and only on populations selected from the '23andMe'
43
44
45 16 customer base.[28,29] We will look at loci relevant to both migraine and rosacea in both
46
47 17 patients groups to discover any potential overlaps. Analysis will not include genes listed on
48
49
50 18 the ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and
51
52 19 Genome Sequencing.[30]
53
54
55 20

56 57 58 21 **Blood sample** 59 60

1
2
3
4 1 A blood sample was collected from a cubital vein (Vacuette® Safety Blood Collection Set)
5
6
7 2 into three 9 ml EDTA tubes (Vacuette® K2EDTA) which were each inverted 10 times
8
9
10 3 immediately after collection to let blood mix with the separator gel. Samples were kept at
11
12
13 4 room temperature (between 20-24 degrees Celsius) and within 30 minutes of sampling, full
14
15 5 blood was transferred with a pipette (Alpha Laboratories pipette standard micro sterile
16
17
18 6 pastette) from one EDTA tube into 2 – 4 sterile 2,0ml cryo vials (IVUS). The two remaining
19
20
21 7 EDTA tubes were centrifuged (Hettich Zentrifugen EBA 20) at 2500 rpm for 5 minutes to
22
23
24 8 separate plasma. Plasma was then transferred (Alpha Laboratories pipette standard micro
25
26
27 9 sterile pastette) into 2 – 4 sterile 2,0ml cryo vials (IVUS) and 2 – 4 sterile 2,0ml cryo vials
28
29 10 (IVUS) with Thermo scientific protease inhibitor (10 µl per ml of plasma). All samples were
30
31 11 stored at -80 degrees Celsius until analysis.
32
33
34 12

35
36 13 The purpose of this blood sample was to analyze samples for CGRP. CGRP is a signaling
37
38
39 14 neuropeptide which has previously been linked to both migraine[31] and rosacea[32] and
40
41
42 15 has been suggested to be related to disease pathology. CGRP is relatively well-described in
43
44
45 16 migraine, and CRGP-antibodies have recently proven beneficial in preventive treatment of
46
47 17 migraine.[33]

48
49
50 18 By stratifying CGRP measurements in this project we hope to be able to uncover a possible
51
52
53 19 relationship between CGRP, subtypes and disease activity in especially rosacea.
54
55 20

57 21 **Findings to date**

58
59
60

1
2
3
4 1 Findings are summarized in table 1 for COROCO and table 2 for COMICO.
5
6
7 2
8
9

10 3 **COROCO**

13 4 *Age and sex*

15
16 5 Median age was 51 years (interquartile range (IQR) 43.0 – 61.0) and there were 67.7%
17
18 6 females in the cohort.

21 7 Rosacea usually affects individuals above age 30 years[9] with a peak onset between 45 –
22
23 8 60 years.[8] The sex distribution is more or less even, with only a tendency towards a
24
25 9 female predominance.[8] COROCO thus resembles previous studies in rosacea.
26
27
28
29 10

31 11 *Family history of migraine*

32 12 Family history of migraine was present in 44.3% of the rosacea cohort.

34 13 Family history of migraine in the general population is usually underreported, [34,35] which
35
36 14 may contribute to the low prevalence of family history of migraine in our rosacea cohort.
37
38
39
40
41
42 15

43 16 *Family history of rosacea*

44
45 17 Family history of rosacea was 45% in the rosacea cohort. Family history of rosacea in
46
47 18 patients with rosacea has previously been reported in up to 55%, compared to 12 - 17% in
48
49 19 controls.[36,37] Rosacea is largely underestimated and often goes undiagnosed,[17,38,39]
50
51 20 contributing to low family history reports of rosacea. In our cohort, some patients stated
52
53
54
55
56
57
58
59
60

1
2
3
4 1 that they suspected family members of having rosacea, but only definite diagnoses were
5
6
7 2 included in our analysis, probably underestimating family history of rosacea.
8
9

10 3 11 12 4 *Smoking*

13
14
15 5 There were 13.0% current smokers in COROCO. The median pack-years for smokers were
16
17 6 24.6 years (IQR 13.3-26.0). A total of 36.6% were former smokers.

18
19
20 7 Smoking in rosacea is debated. Some studies find a lower prevalence of smoking in
21
22
23 8 patients with rosacea,[40,41] and find current smoking to be protective against incident
24
25
26 9 rosacea,[42] whereas others find a higher prevalence of smoking.[43,44]. Smoking
27
28
29 10 constricts the peripheral blood vessels, possibly masking rosacea which could be a reason
30
31 11 for why we see a lower prevalence of current smoking in the rosacea group. Interestingly,
32
33
34 12 past smoking has been associated with a higher risk of incident rosacea compared to never
35
36
37 13 smokers,[36,42] perhaps due to an autoimmune response, but this needs further
38
39 14 investigation.
40

41 42 15 43 44 16 *Alcohol*

45
46
47 17 Regular intake of alcohol was seen in 79.3% of COROCO with a median average intake of 4
48
49 18 items/week (IQR 1.0 – 9.0).

50
51
52 19 Alcohol is a common trigger of flushing in patients who already have rosacea.[45–47]
53
54
55 20 Intake of alcohol seems to be associated with a higher risk of incident rosacea in some
56
57
58 21 studies,[40,48,49] though other studies have failed to confirm this association.[36,50,51]
59
60

1
2
3
4
5 16
7 2 *Body mass index*

8
9
10 3 Median body mass index (BMI) was 25.7 (23.1 – 29.0). Stratified into groups, underweight
11
12 4 (BMI < 18.5) was seen in 1.3% (4 patients), normal weight (BMI between 18.5 – 25) was
13
14
15 5 found in 39.7% (119 patients), overweight (BMI between 25 – 30) was present in 40.7%
16
17
18 6 (122 patients), and obesity (BMI > 30) was found in 18.3% (55 patients).

19
20 7

21
22
23 8 High BMI may be a risk factor for incident rosacea.[52,53] Metabolic disease[52] and
24
25
26 9 cardiovascular comorbidities are more common in rosacea, though the causal relationship
27
28
29 10 is debated.[43,54–56]

30
31 1132
33
34 12 *Dermatology Life Quality Index (DLQI)*

35
36 13 Median DLQI was 2 (IQR 1 - 5). Stratified into groups, DLQI of 0-1 (no effect on quality of
37
38
39 14 life) was present in 42.7% (128 patients). DLQI between 2-5 (mild effect on quality of life)
40
41
42 15 was present in 35.0% (105 patients). DLQI between 6-10 (moderate effect on quality of life)
43
44
45 16 was found in 12.0% (26 patients), and DLQI between 11-20 (large effect on quality of life)
46
47 17 was found in 10.0% (30 patients). DLQI 20 (extreme effect on quality of life) was found in
48
49
50 18 0.3% (1 patient).

51
52 19

53
54
55 20 Interestingly, we find a very low impact of rosacea on daily quality of life. There may be a
56
57
58 21 number of reasons for this. One, DLQI is an immediate view on quality of life during the
59
60

1 past week. Rosacea is fluctuating and patients may not have had a lot of symptoms at the
 2 time of the interview, and thus a low DLQI. Second, many patients reported to have
 3 previously been very affected by their rosacea, but they were now less affected, either due
 4 to acceptance of their symptoms, or because they had been effectively treated. Thirdly,
 5 DLQI may not be the best instrument for evaluating rosacea, as the questions are not
 6 rosacea-specific, but rather concern the whole skin, which may be why these patients have
 7 a low DLQI score, i.e. questions 3, 4 and 7-10 are often not relevant in rosacea.

9 **Table 1.** Baseline data for COROCO

	N	COROCO (Rosacea)
Age, median (IQR)	300	51.0 (43.0-61.0)
Sex, n(%)	300	
Men		97 (32.3)
Women		203 (67.7)
Family history of rosacea, n(%)		
Any family member	300	135 (45.0)
First degree relative		124 (41.3)
Second and third degree relative		30 (10.0)
Family history of migraine, n(%)		
Any family member	300	133 (44.3)
First degree relative	300	117 (39.0)
Second and third degree relative	300	37 (12.3)
Smoking, n(%)	300	
Never		151 (49.8)

Former smoker	111 (36.6)
Current smoker	39 (13.0)
Cigarettes per day	39
0 - 10/day	22 (56.4)
>10/day	17 (43.6)
Pack-years*, median (IQR)	31 24.6 (13.3-36.0)
Alcohol, current use	300 238 (79.3)
Alcohol, n (%)	238
0 - 14/week	204 (85.7)
>14/week	34 (14.3)
Items per week, median (IQR)	244 4 (1.0-9.0)
BMI, n(%)	300
< 18.5	4 (1.3)
18.5-25	119 (39.7)
>25-30	122 (40.7)
>30-35	35 (11.7)
>35	20 (6.7)
BMI, median (IQR)	25.7 (23.1-29.0)
DLQI, n(%)	309
0-1	128 (42.7)
2-5	105 (35.0)
6-10	36 (12.0)
11-20	30 (10.0)
21-30	1 (0.3)
DLQI, median	2 (1-5)

1

BMI, body mass index; DLQI, dermatology life quality index; N, number of subjects; SD, standard deviation; IQR, Inter Quartile Range

* Pack years are defined as years of smoking 20 cigarettes per day.

1

2 **COMICO**

3 *Age and sex*

4 Median age was 41 years (IQR 29.5 – 51.0) and 88.5% were females.

5 Onset of migraine differs with age and sex, mostly affecting individuals above age 14 with
6 a peak incidence between ages 25 – 34 years.[4] There is a strong female predominance
7 with almost twice as many women as men being affected.[4,57] COMICO therefore
8 resembles previous findings in migraine.

9
10 COMICO and COROCO are not intended for direct comparison and differences in age and
11 sex between cohorts will therefore not be a problem.

12 13 *Family history of migraine*

14 Family history of migraine was found in 73.4% of those in the migraine cohort. Previous
15 studies have found family history reports between 54-77%,[58,59] and we expect that
16 patients with migraine are more aware of their family history and believe that this might be
17 more or less the true prevalence of family history.

18

1 *Family history of rosacea*

2 Family history of rosacea was 18.4% in the migraine cohort, corresponding to previous
3 findings of 12 - 17% in controls.[36,37] As stated above, underdiagnosing of rosacea
4 probably contributes to low family history reports in the migraine cohort as well.[17,38,39]

6 *Smoking*

7 There were 17% current smokers in COMICO. Median pack-years were 12.0 years (IQR 5.0 –
8 21.0). There were 26.0% who were former smokers.

9 Smoking in migraine is debated. A study from 1976 reports that smoking is unlikely to be
10 related to migraine[60] whereas more recent research finds found an increased risk of
11 migraine in past and current smokers.[61] Another study found that patients with migraine
12 were more frequent and heavy smokers than their peers,[62] and smoking has been
13 suggested as a precipitating factor for migraine attacks.[63]

15 Smoking in the general population in Denmark was 23% in 2018 (22% in women and 24%
16 in men)[64], and it thus looks like we have a lower prevalence of smoking in our cohorts
17 than in the background population. This could be because smoking cessation may trigger
18 either rosacea or migraine, although there is no clear evidence of this, as stated above.

20 *Alcohol*

1
2
3
4 1 In COMICO, 62.3% regularly drank alcohol, with a median average intake of 2 items/week
5
6
7 2 (IQR 1.0 – 3.0).
8

9
10 3 Alcohol is a common trigger of migraine attacks,[3,65–68] which was also one of the most
11
12 4 commonly anecdotally reported reasons for alcohol abstinence in this cohort.
13
14

15 5

16 17 6 *Body Mass Index*

18
19
20 7 Median BMI was 24.6 (IQR 21.5 – 28.2). Stratified into groups, underweight was seen in
21
22
23 8 3.3% (10 patients), normal weight was found in 50.7% (154 patients), overweight was seen
24
25
26 9 in 28.6% (87 patients), and obesity was found in 15.6% (53 patients).
27

28 10

29
30
31 11 Obesity seems to be a risk factor for migraine,[69–72] and obesity and weight gain
32
33 12 contributes to worsening of migraine, with the potential of turning episodic migraine into
34
35
36 13 chronic migraine.[73–77] Patients for COMICO were primarily recruited through the Danish
37
38
39 14 Headache Center, which is a highly specialized unit and 38.2% turned out to have chronic
40
41
42 15 migraine, which may have contributed to a higher BMI in this group.
43

44 16

45 46 47 17 *Dermatology Life Quality Index (DLQI)*

48
49
50 18 Median DLQI was 1 (IQR 0 – 2). Stratified into groups, DLQI of 0-1 was present in 65.1%
51
52
53 19 (198 patients), DLQI between 2-5 was present in 27.3% (83 patients), DLQI between 6-10
54
55 20 was found in 5.6% (17 patients), DLQI between 11-20 was found in 2.0% (6 patients) and
56
57
58 21 no patients had DLQI 20.
59
60

1
2
3
4
5 1
6
7 2 The effect on DLQI in the migraine cohort could be attributed to comorbid rosacea or
8
9
10 3 other skin disorders, however, recent data suggests that DLQI in a control population is
11
12 4 comparable to minimal disease level in patients with atopic dermatitis or psoriasis.[78]
13
14
15 5
16
17
18 6

Table 2. Baseline data for COMICO

	N	COMICO (Migraine)
Age, median (IQR)	304	41.0 (29.5-51.0)
Sex, n(%)	304	
Men		35 (11.5)
Women		269 (88.5)
Migraine characteristics		
Migraine with aura, n(%)	304	116 (38.2)
Migraine without aura, n(%)	304	188 (61.8)
Chronic migraine, n(%)	304	116 (38.2)
Family history of migraine, n(%)		
Any family member	304	223 (73.4)
First degree relative	223	193 (63.5)
Second and third degree relative	223	122 (40.1)
Family history of rosacea, n(%)		
Any family member	304	56 (18.4)
First degree relative		45 (14.8)
Second and third degree relative		21 (6.9)
Smoking, n(%)	304	
Never		173 (56.9)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Former smoker	79 (26.0)
Current smoker	52 (17.1)
Cigarettes per day	52
0 - 10 /day	36 (69.2)
> 10/day	16 (30.8)
Pack-years*, median (IQR)	40 12 (5-21)
Alcohol , current use	304 189 (62.2)
Alcohol, n (%)	189
0 - 14/week	184 (97.3)
>14/week	5 (2.7)
Items per week, median (IQR)	189 2 (1.0-3.0)
BMI , n(%)	304
< 18.5	10 (3.3)
18.5-25	154 (50.7)
>25-30	87 (28.6)
>30-35	32 (10.5)
>35	21 (6.9)
BMI, median (IQR)	24.6 (21.5-28.2)
DLQI , n(%)	304
0-1	198 (65.1)
2-5	83 (27.3)
6-10	17 (5.6)
11-20	6 (2.0)
21-30	0
DLQI, median	1 (0-2)

BMI, body mass index; DLQI, dermatology life quality index; N, number of subjects; SD, standard deviation; IQR, Inter Quartile Range

* Pack years are defined as years of smoking 20 cigarettes per day.

1
2
3
4
5 1
67 2 **Future plans**
8

9
10 3 We plan for longitudinal follow up through national Danish registries studying risk factors,
11
12 4 occurrence, natural history, treatment, complications, comorbidities and prognosis. We
13
14
15 5 also plan to invite participants for a follow-up in 10-20 years,
16
17

18 6
1920 7 **Strengths and limitations**
21

22
23 8 The COROCO and COMICO have several strengths. First, the cohorts offer phenotyping
24
25
26 9 through face-to-face interview by trained personnel, which has been shown to be the most
27
28
29 10 valid way to ensure correct diagnosis of migraine,[79] and for rosacea phenotyping,
30
31 11 pictures are subsequently validated by three authors. Questions on rosacea onset and
32
33
34 12 timely relationship to migraine diagnosis may prove valuable in further explaining the
35
36
37 13 connection between the two. Furthermore, the comprehensive reports on rosacea features,
38
39 14 first presenting sign/symptom and later onset of other rosacea features may also prove
40
41
42 15 valuable in determining the natural history of rosacea. Additional collected data will help in
43
44
45 16 further characterizing patients and possibly explaining the mechanisms behind both
46
47
48 17 disorders. A major strength is the possibility of linking cohorts to the national health
49
50 18 registries in Denmark for additional info and follow-up.

51
52 19 Limitations include risk of recall bias as interviews are based on the patient reports with
53
54
55 20 rosacea diagnosis or first presenting rosacea feature sometimes many years prior to
56
57
58 21 interview. In those with either rosacea or migraine, there is a higher chance that they will
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 be aware of their family history of that specific disorder, whereas they might neglect the
2 other disorder, and a major limitation is that we will see lower family histories in those who
3 do not have the disorder, i.e. family history of rosacea in patients with migraine. There is
4 also a risk of selection bias, as patients were recruited primarily through specialist clinics
5 where only the most severely affected patients are seen; however, in COROCO, we invited
6 patients who had been seen with rosacea in the past 5 years, and their disease may have
7 been less severe than when they came for their first visit; possibly underestimating
8 symptoms and effect on quality of life. As patients were not excluded from one of the
9 cohorts if they had both diagnoses, comparison between groups is also problematic as
10 differences and similarities may be attributed to both patient groups being present in both
11 cohorts. Furthermore, it might be speculated that patients who identified with the
12 investigated disorders, e.g. migraine patients who also identified with rosacea features, or
13 who had family members with the disease, were more prone to accept the invitation to
14 participate. However, we believe that the fairly short one-time study-visit that could be
15 combined with their outpatient visit was enough motivation in most cases. For rosacea, the
16 disorder is relatively un-investigated, and patients seemed motivated to participate simply
17 due to this fact.

18

19 **Collaboration**

20 For future potential collaborations and secondary use of the data, the corresponding
21 author can be contacted after the appropriate legal approvals have been obtained.

Data availability statement

Data are available upon reasonable request.

Patient and public involvement

Patients and public were not involved in the design of this study. On completion of the study, all patients who wish to will receive a concluding letter with study findings and information of future perspectives of the research.

Contributors

NW, CC, MA, AE and JT designed the study. NW and DZ collected data for the study. NW and JH performed the analysis under supervision of AE. NW drafted the manuscript. All authors reviewed and edited the manuscript. All authors approved the final manuscript.

Acknowledgements

We thank all participants for their contribution to the cohorts. We thank all staff members at Rigshospitalet Glostrup and Gentofte Hospital who have contributed, and the department of Dermatology and Wound Healing at Bispebjerg hospital for contributing to this study.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **References**

- 2 1. Christensen CE, Andersen FS, Wienholtz N, Egeberg A, Thyssen JP, Ashina M. The
3 relationship between migraine and rosacea: Systematic review and meta-analysis.
4 *Cephalalgia*. 2017;0(0).
- 5 2. Steinhoff M, Schaubert J, Leyden JJ. New insights into rosacea pathophysiology: A
6 review of recent findings. *J Am Acad Dermatol*. 2013;69(6 SUPPL.1):15–26.
- 7 3. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia*.
8 2007;27(5):394–402.
- 9 4. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity.
10 *Neurol Clin*. 2019;37(4):631–49.
- 11 5. Steiner T, Scher A, Stewart W, Kolodner K, Liberman J, Lipton R. The Prevalence and
12 Disability Burden of Adult Migraine in England and their Relationships to Age,
13 Gender and Ethnicity. *Cephalalgia*. 2003 Sep;23(7):519–27.
- 14 6. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine
15 prevalence, disease burden, and the need for preventive therapy. *Neurology*.
16 2007;68(5):343–9.
- 17 7. Brandes JL. Global trends in migraine care: Results from the MAZE survey. *CNS*
18 *Drugs*. 2002;16(SUPPL. 1):13–8.
- 19 8. Gether L, Overgaard L, Egeberg A, Thyssen J. Incidence and prevalence of rosacea: a
20 systematic review and meta-analysis. *Br J Dermatol*. 2018;179:282–9.
- 21 9. Tan J, Berg M. Rosacea: Current state of epidemiology. *J Am Acad Dermatol*.

- 1
2
3
4 1 2013;69(6 SUPPL.1):S27–35.
5
6
7 2 10. Gallo RL, Granstein RD, Kang S, Mannis M, Steinhoff M, Tan J, et al. Standard
8
9
10 3 classification and pathophysiology of rosacea: The 2017 update by the National
11
12 4 Rosacea Society Expert Committee. *J Am Acad Dermatol*. 2018;78(1):148–55.
13
14
15 5 11. Charles A. The pathophysiology of migraine: implications for clinical management.
16
17 6 *Lancet Neurol*. 2018;17(2):174–82.
18
19
20 7 12. Vollesen ALH, Ashina M. PACAP38: Emerging Drug Target in Migraine and Cluster
21
22 8 Headache. *Headache*. 2017;57(Phase 3):56–63.
23
24
25 9 13. Khan S, Olesen A, Ashina M. CGRP, a target for preventive therapy in migraine and
26
27 10 cluster headache: Systematic review of clinical data. *Cephalalgia*. 2019;39(3):374–89.
28
29
30 11 14. Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical
31
32 12 presentation and new therapeutics. *Exp Dermatol*. 2017;26(8):659–67.
33
34
35 13 15. Egeberg A, Ashina M, Gaist D, Gislason GH, Thyssen JP. Prevalence and risk of
36
37 14 migraine in patients with rosacea: A population-based cohort study. *J Am Acad*
38
39 15 *Dermatol*. 2017;76(3):454–8.
40
41
42 16 16. Tan SG, Cunliffe WJ. Rosacea and migraine. *Br Med J*. 1976;1(6000):21.
43
44
45 17 17. Berg M, Lidén S. An epidemiological study of rosacea. *Acta Derm Venereol*.
46
47 18 1989;69(5):419–23.
48
49
50 19 18. Spoendlin J, Voegel JJ, Jick SS, Meier CR. Migraine, triptans, and the risk of
51
52 20 developing rosacea: A population-based study within the United Kingdom. *J Am*
53
54 21 *Acad Dermatol*. 2013;69(3):399–406.
55
56
57
58
59
60

- 1
2
3
4 1 19. Ramelet A. Rosacea: A Reaction Pattern Associated With Ocular Lesions and
5
6
7 2 Migraine? *Arch Dermatol*. 1994;130:1448.
8
9
10 3 20. Berg M, Lidén S. Postmenopausal Female Rosacea Patients Are More Disposed to
11
12 4 React with Migraine. *Dermatology*. 1996;193:73–4.
13
14
15 5 21. WHO. ICD-10 [Internet]. 2019. Available from: <https://icd.who.int/browse10/2019/en>
16
17
18 6 22. Rosacea Clinical Scorecard [Internet]. [cited 2019 Jun 29]. Available from:
19
20 7 <https://www.rosacea.org/physicians/rosacea-clinical-scorecard>
21
22
23 8 23. Gervil M, Ulrich V, Olesen J, Russell MB. Screening for migraine in the general
24
25 9 population: Validation of a simple questionnaire. *Cephalalgia*. 1998;18(6):342–8.
26
27
28 10 24. Wienholtz N, Christensen CE, Egeberg A, Thyssen JP, Ashina M. Vasomotor reactions
29
30 11 in the face and head of patients with migraine. *Cephalalgia Reports*. 2018;1.
31
32
33 12 25. Sinikumpu SP, Huilaja L, Auvinen J, Jokelainen J, Puukka K, Ruokonen A, et al. The
34
35 13 association between low grade systemic inflammation and skin diseases: A cross-
36
37 14 sectional survey in the Northern Finland Birth Cohort 1966. *Acta Derm Venereol*.
38
39 15 2018;98(1):65–9.
40
41
42 16 26. Edvinsson L, Haanes KA, Warfvinge K. Does inflammation have a role in migraine?
43
44 17 *Nat Rev Neurol*. 2019;15(8):483–90.
45
46
47 18 27. Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers T, et al. Meta-analysis of
48
49 19 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat Genet*.
50
51
52 20 2016;48(8):856–66.
53
54
55 21 28. Chang A, Raber I, Xu J, Li R, Spitale R, Chen J, et al. Assessment of the genetic basis
56
57
58
59
60

- 1
2
3
4 1 of rosacea by genome-wide association study. *J Invest Dermatol.* 2015;135:1548–55.
5
6
7 2 29. Aponte JL, Chiano MN, Yerges-Armstrong LM, Hinds DA, Tian C, Gupta A, et al.
8
9
10 3 Assessment of rosacea symptom severity by genome-wide association study and
11
12 4 expression analysis highlights immuno-inflammatory and skin pigmentation genes.
13
14
15 5 *Hum Mol Genet.* 2018;27(15):2762–72.
16
17
18 6 30. Green RC, Berg JS, Grody WW, Kalia S, Kort B, Martin C, et al. ACMG
19
20 7 Recommendations for Reporting of Incidental Findings in Clinical Exome and
21
22
23 8 Genome Sequencing. *Genet Med Author Manuscr.* 2013;15(7):565–74.
24
25
26 9 31. Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into
27
28 10 migraine pathophysiology. *Nat Rev Neurol.* 2010;6(10):573–82.
29
30
31 11 32. Woo YR, Lim JH, Cho DH, Park HJ. Rosacea: Molecular mechanisms and management
32
33
34 12 of a chronic cutaneous inflammatory condition. *Int J Mol Sci.* 2016;17(9):1–23.
35
36
37 13 33. Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al.
38
39 14 ARISE: A Phase 3 Randomized Trial of Erenumab for Episodic Migraine. *Cephalalgia.*
40
41
42 15 2018;38(6):1026–37.
43
44
45 16 34. Russell M, Fenger K, Olesen J. The family history of migraine. Direct versus indirect
46
47 17 information. *Cephalalgia.* 1996;16:156–60.
48
49
50 18 35. Lateef T, Cui L, Nakamura E, Dozier J, Merikangas K. Accuracy of Family History
51
52 19 Reports of Migraine in a Community-Based Family Study of Migraine. *Headache.*
53
54
55 20 2017;66(3):407–12.
56
57
58 21 36. Abram K, Silm H, Maaros H, Oona M. Risk factors associated with rosacea. *J Eur*
59
60

- 1
2
3
4 1 Acad Dermatol Venereol. 2010;24:565–71.
5
6
7 2 37. Rainer BM, Fischer AH, Luz Felipe Da Silva D, Kang S, Chien AL. Rosacea is associated
8
9
10 3 with chronic systemic diseases in a skin severity-dependent manner: Results of a
11
12 4 case-control study. *J Am Acad Dermatol*. 2015;73(4):604–8.
13
14
15 5 38. Tan J, Schöfer H, Araviiskaia E, Audibert F, Kerrouche N, Berg M. Prevalence of
16
17 6 rosacea in the general population of Germany and Russia - The RISE study. *J Eur*
18
19
20 7 *Acad Dermatology Venereol*. 2016;30(3):428–34.
21
22
23 8 39. Tizek L, Schielein MC, Seifert F, Biedermann T, Böhner A, Zink A. Skin diseases are
24
25 9 more common than we think: screening results of an unreferral population at the
26
27
28 10 Munich Oktoberfest. *J Eur Acad Dermatology Venereol*. 2019;33(7):1421–8.
29
30
31 11 40. Spöndlin J, Voegel JJ, Jick SS, Meier CR. A study on the epidemiology of rosacea in
32
33 12 the U.K. *Br J Dermatol*. 2012;167(3):598–605.
34
35
36 13 41. Li WQ, Zhang M, Danby FW, Han J, Qureshi AA. Personal history of rosacea and risk
37
38 14 of incident cancer among women in the US. *Br J Cancer*. 2015;113(3):520–3.
39
40
41 15 42. Li S, Cho E, Drucker AM, Qureshi AA, Li WQ. Cigarette Smoking and Risk of Incident
42
43 16 Rosacea in Women. *Am J Epidemiol*. 2017;186(1):38–45.
44
45
46
47 17 43. Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: A case
48
49 18 control study. *J Eur Acad Dermatology Venereol*. 2014;28(9):1165–9.
50
51
52 19 44. Kucukunal A, Altunay I, Arici JE, Cerman AA. Is the effect of smoking on rosacea still
53
54 20 somewhat of a mystery? *Cutan Ocul Toxicol*. 2016;35(2):110–4.
55
56
57 21 45. Weiss E, Katta R. Diet and rosacea: the role of dietary change in the management of
58
59
60

- 1
2
3
4 1 rosacea. *Dermatol Pract Concept*. 2017;7(4):31–7.
5
6
7 2 46. Bae YI, Yun SJ, Lee JB, Kim SJ, Won YH, Lee SC. Clinical evaluation of 168 Korean
8
9
10 3 patients with rosacea: The sun exposure correlates with the erythematotelangiectatic
11
12 4 subtype. *Ann Dermatol*. 2009;21(3):243–9.
13
14
15 5 47. Elewski BE, Draelos Z, Dréno B, Jansen T, Layton A, Picardo M. Rosacea - Global
16
17 6 diversity and optimized outcome: Proposed international consensus from the
18
19 7 Rosacea international expert group. *J Eur Acad Dermatology Venereol*.
20
21 8 2011;25(2):188–200.
22
23
24
25 9 48. Li S, Cho E, Drucker A, Qureshi A, Li W. Alcohol intake and risk of incident rosacea in
26
27 10 US women. *J Am Acad Dermatol*. 2017;76(6):1061–7.
28
29
30
31 11 49. Aldrich N, Gerstenblith M, Fu P, Tuttle MS, Varma P, Gotow E, et al. Genetic vs
32
33 12 environmental factors that correlate with rosacea: A cohort-based survey of twins.
34
35 13 *JAMA Dermatology*. 2015;151(11):1213–9.
36
37
38
39 14 50. Alinia H, Tuchayi SM, Patel NU, Patel N, Awosika O, Bahrami N, et al. Rosacea
40
41 15 Triggers: Alcohol and Smoking. *Dermatol Clin*. 2018;36(2):123–6.
42
43
44 16 51. Curnier A, Choudhary S. Rhinophyma: Dispelling the myths. *Plast Reconstr Surg*.
45
46 17 2004;114(2):351–4.
47
48
49 18 52. Akin Belli A, Ozbas Gok S, Akbaba G, Etgu F, Dogan G. The relationship between
50
51 19 rosacea and insulin resistance and metabolic syndrome. *Eur J Dermatol*.
52
53 20 2016;26(3):260–4.
54
55
56
57 21 53. Li S, Cho E, Drucker AM, Qureshi AA, Li W-Q. Obesity and Risk for Incident Rosacea
58
59
60

- 1
2
3
4 1 in US Women. *J Am Acad Dermatol.* 2017;77(6):1083–7.
5
6
7 2 54. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Assessment of the risk of
8
9
10 3 cardiovascular disease in patients with rosacea. *J Am Acad Dermatol.* 2016;75(2):336–
11
12 4 9.
13
14
15 5 55. Hua TC, Chung PI, Chen YJ, Wu LC, Chen Y Da, Hwang CY, et al. Cardiovascular
16
17
18 6 comorbidities in patients with rosacea: A nationwide case-control study from Taiwan.
19
20 7 *J Am Acad Dermatol.* 2015;73(2):249–54.
21
22
23 8 56. Dosal J, Keri J. Rosacea and cardiovascular disease: Is there an association? *J Am*
24
25
26 9 *Acad Dermatol.* 2015;73(2):308–9.
27
28
29 10 57. Russell MB, Rasmussen BK, Thorvaldsen P, Olesen J. Prevalence and sex-ratio of the
30
31 11 subtypes of migraine. *Int J Epidemiol.* 1995;24(3):612–8.
32
33
34 12 58. Hernandez-Latorre M, Roig M. Natural history of migraine in childhood. *Cephalalgia.*
35
36 13 2000;20(6):573–9.
37
38
39 14 59. Dzoljic E, Vlajinac H, Sipetic S, Marinkovic J, Grbatinic I, Kostic V. A survey of female
40
41
42 15 students with migraine: What is the influence of family history and lifestyle? *Int J*
43
44 16 *Neurosci.* 2014;124(2):82–7.
45
46
47 17 60. Baharuddin NA, Al-Bayaty FH. The relationship between smoking and migraine.
48
49
50 18 *Postgrad Med J.* 1976;52:80–2.
51
52
53 19 61. Hagen K, Åsberg AN, Stovner L, Linde M, Zwart JA, Winsvold BS, et al. Lifestyle
54
55 20 factors and risk of migraine and tension-type headache. Follow-up data from the
56
57
58 21 Nord-Trøndelag Health Surveys 1995–1997 and 2006–2008. *Cephalalgia.*
59
60

- 1
2
3
4 1 2018;38(13):1919–26.
5
6
7 2 62. Chen TC, Leviton A, Edelman S, Ellenberg JH. Migraine and Other Diseases in
8
9
10 3 Women of Reproductive Age: The Influence of Smoking on Observed Associations.
11
12 4 Arch Neurol. 1987;44(10):1024–8.
13
14
15 5 63. López-Mesonero L, Márquez S, Parra P, Gámez-Leyva G, Muñoz P, Pascual J.
16
17 6 Smoking as a precipitating factor for migraine: A survey in medical students. J
18
19
20 7 Headache Pain. 2009;10(2):101–3.
21
22
23 8 64. Sundhedsstyrelsen, Kræftens_Bekæmpelse, Hjerteforeningen_og_Lungeforeningen.
24
25 9 Danskernes rygevaner 2018 - nøgletal [Danish] [Internet]. Available from:
26
27
28 10 [https://www.sst.dk/-/media/Udgivelser/2019/Danskernes-rygevaner-](https://www.sst.dk/-/media/Udgivelser/2019/Danskernes-rygevaner-2018/Danskernes-rygevaner-2018_nøgletal.ashx?la=da&hash=55335DED0545970499485950C4E375CEC5A465AF)
29
30
31 11 [2018/Danskernes-rygevaner-](https://www.sst.dk/-/media/Udgivelser/2019/Danskernes-rygevaner-2018_nøgletal.ashx?la=da&hash=55335DED0545970499485950C4E375CEC5A465AF)
32
33
34 12 [2018_nøgletal.ashx?la=da&hash=55335DED0545970499485950C4E375CEC5A465AF](https://www.sst.dk/-/media/Udgivelser/2019/Danskernes-rygevaner-2018_nøgletal.ashx?la=da&hash=55335DED0545970499485950C4E375CEC5A465AF)
35
36
37 13 65. Hauge AW, Kirchmann M, Olesen J. Trigger factors in migraine with aura.
38
39 14 Cephalalgia. 2010;30(3):346–53.
40
41
42 15 66. Panconesi A, Bartolozzi ML, Guidi L. Alcohol and migraine: What should we tell
43
44 16 patients? Curr Pain Headache Rep. 2011;15(3):177–84.
45
46
47 17 67. Panconesi A. Alcohol and migraine: Trigger factor, consumption, mechanisms. A
48
49 18 review. J Headache Pain. 2008;9(1):19–27.
50
51
52 19 68. Davis-Martin RE, Polk AN, Smitherman TA. Alcohol Use as a Comorbidity and
53
54
55 20 Precipitant of Primary Headache: Review and Meta-analysis. Curr Pain Headache Rep.
56
57
58 21 2017;21(10).
59
60

- 1
2
3
4 1 69. Ford ES, Li C, Pearson WS, Zhao G, Strine TW, Mokdad AH. Body mass index and
5
6
7 2 headaches: Findings from a national sample of US adults. *Cephalalgia*.
8
9
10 3 2008;28(12):1270–6.
11
12 4 70. Peterlin BL, Rapoport AM, Kurth T. Migraine and obesity: Epidemiology, mechanisms,
13
14
15 5 and implications. *Headache*. 2010;50(4):631–48.
16
17
18 6 71. Vo M, Ainalem A, Qiu C, Peterlin BL, Aurora SK, Williams MA. Body mass index and
19
20
21 7 adult weight gain among reproductive age women with migraine. *Headache*.
22
23 8 2011;51(4):559–69.
24
25
26 9 72. Yu S, Liu R, Yang X, Zhao G, Qiao X, Feng J, et al. Body mass index and migraine: A
27
28
29 10 survey of the Chinese adult population. *J Headache Pain*. 2012;13(7):531–6.
30
31
32 11 73. Bigal ME, Lipton RB. Obesity is a risk factor for transformed migraine but not chronic
33
34 12 tension-type headache. *Neurology*. 2006;67(2):252–7.
35
36
37 13 74. Bigal ME. Body Mass Index and Episodic Headaches. *Arch Intern Med*.
38
39 14 2007;167(18):1964–70.
40
41
42 15 75. Keith SW, Wang C, Fontaine KR, Cowan CD, Allison DB. BMI and headache among
43
44
45 16 women: Results from 11 epidemiologic datasets. *Obesity*. 2008;16(2):377–83.
46
47
48 17 76. Winter AC, Berger K, Buring JE, Kurth T. Body mass index, migraine, migraine
49
50 18 frequency and migraine features in women. *Cephalalgia*. 2009;29(2):269–78.
51
52
53 19 77. Giraud P, Chauvet S, Tessy M. Migraine and obesity, is there a link ? *Rev Neurol*
54
55 20 (Paris). 2013;169(5):413–8.
56
57
58 21 78. Egeberg A, Griffiths CEM, Williams HC, Andersen YMF, Thyssen JP. Clinical
59
60

- 1
2
3
4 1 characteristics, symptoms, and burden of psoriasis and atopic dermatitis in adults
5
6
7 2 (epub ahead of print). Br J Dermatol. 2019;0(0):0.
8
9
10 3 79. Rasmussen B, Jensen R, Olesen J. Questionnaire Versus Clinical Interview in the
11
12 4 Diagnosis of Headache. Headache. 31(5):290–5.
13
14
15 5
16
17
18 6
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Figure captions**

2 **Figure 1.** Flow chart detailing enrollment in Copenhagen Rosacea Cohort (COROCO). EMR,
3 Electronic Medical Records.

4
5 **Figure 2.** Flow chart detailing enrollment in Copenhagen Migraine Cohort (COMICO).

6 7 **Appendices**

8 **Appendix 1.** Semi-structured interview developed at the department of Dermatology in
9 Gentofte, Denmark by authors NW, JT and AE. The purpose of the interviews is to
10 uncover rosacea features, previous treatments for rosacea, and comorbidities in the
11 patient and in 1st and 2nd degree relatives. The interview also includes sleeping
12 habits, smoking, alcohol, BMI, dermatology life quality index (DLQI) and rosacea
13 clinical scorecard.

14
15 **Appendix 2.** Semi-structured interview for diagnosing headache and migraine. Adapted
16 from a validated interview from the Danish Headache Center (last updated
17 November 18, 2012) for the purpose of interviewing patients without a diagnosis of
18 migraine.

19
20 **Appendix 3.** Reference for evaluating thermal pictures. Each side of the face will be
21 evaluated at areas corresponding to the three branches of the trigeminal nerve

1
2
3
4 1 (forehead, cheeks, chin) and on the tip of the nose. Measurements will be performed
5
6
7 2 on small areas (circles) rather than single points, to obtain an average from each
8
9
10 3 area. To ensure correct ratio, circles were adjusted to match the pupil and iris of each
11
12 4 picture. V1, ophthalmic nerve; V2, maxillary nerve; V3, mandibular nerve; R, right; L,
13
14
15 5 left.
16
17
18 6

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

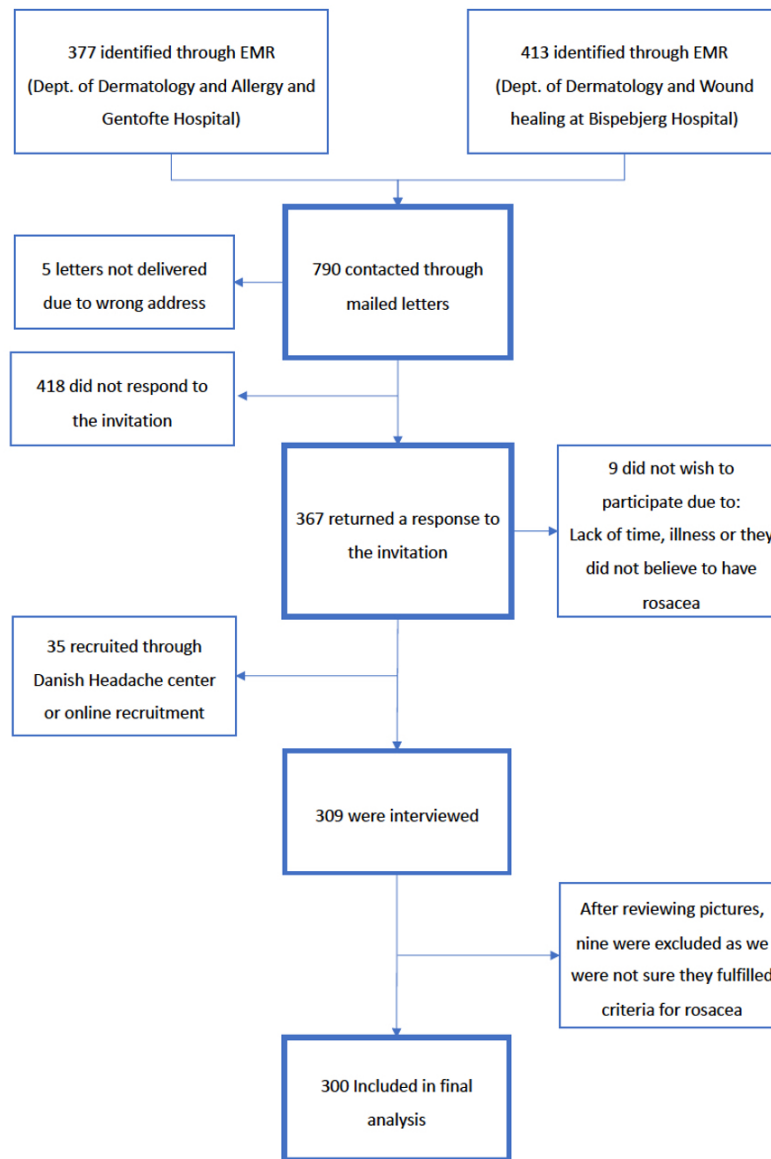


Figure 1. Flow chart detailing enrollment in Copenhagen Rosacea Cohort (COROCO). EMR, Electronic Medical Records.

150x225mm (150 x 150 DPI)

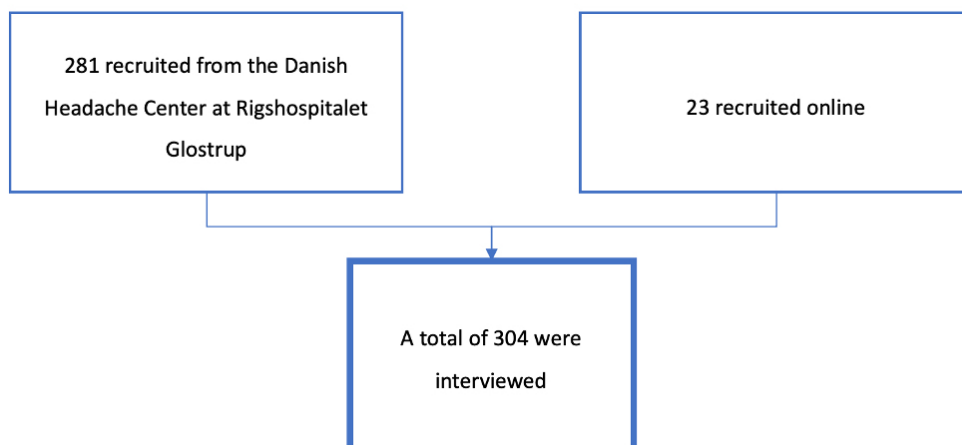


Figure 2. Flow chart detailing enrollment in Copenhagen Migraine Cohort (COMICO).

169x79mm (150 x 150 DPI)

Appendix 1. Semi-structured interview developed at the department of Dermatology in Gentofte, Denmark by authors NW, JT and AE. The purpose of the interviews is to uncover rosacea features, previous treatments for rosacea, and comorbidities in the patient and in 1st and 2nd degree relatives. The interview also includes sleeping habits, smoking, alcohol, BMI, dermatology life quality index (DLQI) and rosacea clinical scorecard.

1. Rosacea

1.1 Has a doctor ever told you that you have rosacea? (one answer)

- No – and I do not have rosacea
- Yes, I am certain I have rosacea, but a doctor has never told me.
- Yes – a doctor who is not a dermatologist (e.g. GP)
- Yes – a dermatologist

If yes to one of the above, go to question. 1.2. If no, move on to question 3

1.2 Which symptom(s) of rosacea did you first notice? (multiple answers)

- Redness of particularly cheeks and/or the chest, which did not want to go away
- Flushing attacks (sudden warmth/burning sensations and redness which lasts a few minutes – half an hour)
- Persistent (> 1 hour) attacks of flushing
- Telangiectasias in the face (cheeks, nose, chin or eyelids)
- Symptoms from the eyes
- Recurrent formation of pimples in the face
- Change of the nose's look or size
- Other? _____

1.2.1 At what age did you experience the first symptom(s) of rosacea? Age years

1.2.2 How much time passed from your first symptom(s) of rosacea until a doctor diagnosed you with rosacea?

Year Months

1.3 Has any of the following symptoms appeared started appearing since you noticed the first symptom(s) of rosacea? (multiple answers)

- Redness of particularly cheeks and/or the chest, which did not want to go away
- Flushing attacks (sudden warmth/burning sensations and redness which lasts a few minutes – half an hour)
- Persistent (> 1 hour) attacks of flushing
- Telangiectasias in the face (cheeks, nose, chin or eyelids)
- Symptoms from the eyes
- Recurrent formation of pimples in the face
- Change of the nose's look or size
- Other? _____

1.4 Do you still have symptoms of Rosacea? (one answer)

- No
- Improvement
- Worsening
- Unchanged symptoms

Describe:

2. ROSACEA TREATMENTS

2.1 Have you ever been treatment for rosacea? (one answer)

- No, never (move on to question 3)
- Yes, but I am no longer in treatment
- Yes, I still receive treatment

2.2 How long did/have you receive(d) treatment for rosacea? (cumulated time)

- Less than 3 months
- 3 months – 1 year
- More than 1 year – how long (years) _____

2.3 If no longer in treatment for rosacea – why did you stop treatment? (one answer)

- My symptoms improved / disappeared after treatment
- There was no effect of the treatment on my symptoms
- My symptoms worsened due to treatment
- I got side effects from the treatment
- I do not wish to be on daily medication

2.4 Which type of treatment(s) have you received? (multiple answers)

- Creme/gel/ointment
- Pills
- Laser treatment

2.5 Which drug(s) have you tried, and did it/they have any effect? (multiple answers)

Yes No Do not know

- | | | | |
|--|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> Mirvaso (brimonidine tartrate) creme/gel | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Finacea (azelaic acid) creme/gel | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Metronidazole / metrocrem / rozex / robaz creme/gel | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Oracea (doxycycline) tablet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Soolantra (ivermectin) creme | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Tetracycline | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Erythromycin (macrolide) tablet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Accutin / Isotretinoin tablet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other: _____ | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

2.6 Which symptom(s) did the treatment influence? (multiple answers)

- Papules and pustules (impurities/pimples)
- Unwanted redness of the face
- Telangiectasias in the face
- Eye symptoms
- Nose Changes
- Other: _____

Other comments to treatment:

3. FLUSHING + OTHER SYMPTOMS

REDNESS/ SENSITIVE SKIN

- 3.1 Are any areas of your face often pink or red? No Yes
- 3.2 Is your face often pink or red compared with other people? No Yes
- 3.3 Is your face often pink or red compared to other body areas (e.g. abdomen, upper arms) No Yes
- 3.4 Have others previously mentioned that your face was pink or red? No Yes
- 3.5 Do you experience that coldness, heat or direct sunlight can provoke a facial burning/stinging sensation after only short exposure?
 No Rarely In periods (e.g. winter) Monthly Weekly Daily
- 3.6 Do you experience dry/scaly skin in central areas of your face, e.g. where you usually experience redness?
 No Rarely In periods (e.g. winter) Monthly Weekly Daily
- 3.7 Is your skin sensitive, i.e. blushes easily and/or gets tight/dry easily?
 No Rarely In periods (e.g. winter) Monthly Weekly Daily

TELANGIECTASIAS

- 3.8 Do you have telangiectasias in the face (e.g. around the nose or center of the cheeks)? No Yes
- 3.8.1 If yes, where are the telangiectasias located?
 on top of the nose sides of the nose cheeks chin eyelids other: _____

FLUSHING

- 3.9 Have you experienced flushing in the *past year*?
 No, not at all Yes, a few times (less than 12 times) Yes, periodically Monthly Weekly Daily
- 3.9.1 In your experience, was the start of flushing related to something?
 no menopause (hot flushes) high/low metabolism medication other _____
- 3.9.2 If yes to flushing, in which areas of the skin do you experience flushing?
 forehead center of the cheeks nose ears chin neck chest
- 3.9.3 How long does a (severe) flushing last? (describe any other symptoms)

- 3.10 As a *child or teenager*, did you experience that your face would easily become red (e.g. when you were nervous/shy or exercised)
 No, never
 Yes, I have experienced it a couple of times (few times a year or less)
 It happened occasionally/frequently
 I would always blush when I got embarrassed
 I experienced it daily and sometimes without a trigger
- 3.10.1 How old were you the first time you experienced flushing? Age years

3.11 Can any of the following give you a sudden sensation of warmth (flushing) (multiple answers)

No Yes

- Alcohol
- Hot food or drinks
- Spicy food
- Sunlight
- Hot and humid surrounds e.g. sauna or hot bath etc.
- Physical activity (e.g. sport)
- Psychological stress or emotional revolt (e.g. holding a speech in front of a large audience)
- Other: _____
- None of the above

3.12 Do you experience having thickened skin on your nose Yes No

4. ACNE

4.1 Have you experienced frequently having impure skin/pimples in the face after becoming an adult (above 25 years of age)

- No (Go to question 5)
- No, but I had acne when I was younger
- Yes, I have previously experienced pimples, which occurred after I became an adult, but I do not anymore
- Yes, and I still frequently experience having pimples

4.2 If yes, do they occur in relation to anything special?

- No Periods Alcohol Other _____

4.3 Where are these impurities/pimples typically located when you have them? (multiple answers)

- Forehead Cheeks Nose Chin Chest Back Shoulders Other _____

5. EYE SYMPTOMS

5.1 Do you frequently experience

No Yes

- red/bloodshot eyes
- watery/runny eyes
- foreign body sensation of the eyes
- stinging sensation in eye/eyes
- itching sensation in eye/eyes
- small, fine scales around eyelid margins
- thickened sensation of eyelid(s), which can be sore or red
- feeling the need to close eyes in the evening, in air-conditioned spaces, during flights etc.

5.2 If yes to any of the above, have you ever visited an ophthalmologist due to these symptoms? No Yes

5.3 Have you had the need to use viscous/watery eyedrops (artificial tears) for longer/shorter periods of time? No Yes

6. TREATMENT WITH CORTICOSTEROIDS/ADRENOCORTICAL HORMONE

6.1 Have you ever been treated with corticosteroids (also called adrenocortical hormone or prednisolone)?

- No, never (move on to question 7) Yes – creme/ointment Yes – pills Yes – syringe

6.2 Have you ever been treated with corticosteroids/adrenocortical hormone?

- No, never Yes, a short period of time (less than 1 month cumulated) Yes, a longer period (1-12 months cumulated)
- Yes, a long period (>12 months cumulated)

6.2.1 If yes, at what age were you when you were first treated with corticosteroids in the face? Age years

7. OTHER DISEASES AND TREATMENT

7.1 Has a doctor ever told you or someone in your family that you/they had any of the following diseases? (Only biologically related family members, i.e. not stepsister or stepparents)

SKIN

Rosacea

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Acne

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Seborrheic dermatitis

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Psoriasis

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Atopic dermatitis

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Non-melanoma skin cancer

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Malignant melanoma

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Urticaria (hives)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Any other skin disorder

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Please describe: _____

PSYCHIATRIC

Anxiety

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

If 'me', have you ever been treated for anxiety? No, never Yes, and I am still in treatment Yes, but I am no longer in treatment

Depression

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

If 'me', have you ever been treated for depression? No, never Yes, and I am still in treatment Yes, but I am no longer in treatment

Any other psychiatric disorder

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Please describe: _____

STOMACH AND GUT

Heartburn/reflux

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Inflammatory bowel disease (Crohn's disease/Ulcerative colitis)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Gluten intolerance/coeliac disease

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Do you frequently experience discomfort/bloating and changing bowel habits? (Irritated bowel syndrome)

No Rarely (few times a year) Monthly Weekly Daily

OTHER DISEASES

Type 1 diabetes

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Type 2 diabetes

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Sjogren's syndrome

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Metabolic disease

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

High cholesterol

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Hypertension (high blood pressure)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

If 'me', are you taking any treatment for hypertension? No Yes, pills, If yes, describe: _____

Raynaud's phenomenon

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

AIRWAYS

COPD (chronic obstructive pulmonary disease)

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Asthma

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Hay fever

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

NEUROLOGICAL

Parkinson's disease

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

Alzheimer's disease

no one me parent(s) sibling(s) child(ren) grandparent(s) grandchild(ren) parent(s) brother/sister(s) niece/nephew(s)

7.2 Do you often experience having cold nose and/or hands? No Yes, nose Yes, hands

7.3 Have you been diagnosed with/treated for any other diseases? No Yes, please describe: _____

8. SLEEP

8.1 How often do you find it difficult to fall asleep?

Once a month or less (never) 2-4 times a month one to several times a week daily

8.2 How often do you wake up earlier than what you intended (without being woken by an alarm or other noise)?

Once a month or less (never). 2-4 times a month one to several times a week daily

9. SMOKING

9.1 Do you smoke? (one answer)

No, I have never smoked No, but I have previously smoked Yes, occasionally (less than 1 cigarette per day). Yes, daily

ANSWERS FROM DAILY SMOKERS

9.2 How many cigarettes do you smoke on average? (daily number of cigarettes)

Number of cigarettes Other, describe: _____

ANSWERS FROM OCCASIONAL SMOKERS

9.3 How many cigarettes do you smoke on average a week? (weekly number of cigarettes)

Number of cigarettes Other, describe: _____

ANSWERS FROM OCCASIONAL AND FORMER SMOKERS

9.4 Have you previously smoked every day? yes no

9.5 If yes, how much did you smoke on average a day?

Number of cigarettes Other, describe: _____

9.6 When did you stop smoking daily? (which year)

ANSWER FROM ALL SMOKERS

9.7 How old were you when you started smoking? (age in years) years

10. ALCOHOL

- 10.1 Have you been drinking alcohol in the past year? No Yes
- 10.2 How much was your average weekly intake during the past 12 months? (Write '0' if none) drinks per week

11. HEIGHT AND WEIGHT

- 11.1 What is your current height (without shoes)? _____ cm
- 11.2 What is your current weight without clothes and shoes? _____ kg

12. DERMATOLOGY LIFE QUALITY INDEX (DLQI)

- 12.1 Within the past week to what extent has your skin been itching, sore, hurting or stinging?
 Extremely Very A bit Not at all
- 12.2 Within the past week to what extent have you been embarrassed or shy because of your skin?
 Extremely Very A bit Not at all
- 12.3 Within the past week to what extent has your skin bothered you in terms of shopping or taking care of your house or back yard?
 Extremely Very A bit Not at all Not relevant
- 12.4 Within the past week to what extent has your skin affected the way you dress?
 Extremely Very A bit Not at all Not relevant
- 12.5 Within the past week to what extent has your skin affected your social activities or leisure activities?
 Extremely Very A bit Not at all Not relevant
- 12.6 Within the past week to what extent has your skin complicated your opportunities of exercise?
 Extremely Very A bit Not at all Not relevant
- 12.7 Within the past week has your skin prevented you from working or studying?
 Yes No Not relevant
- If "No", within the past week has your skin been a problem for you at work or during studies?
 Extremely Very A bit Not at all
- 12.8 Within the past week to what extent has your skin caused problems in relation to your partner, close friends or relatives?
 Extremely Very A bit Not at all Not relevant
- 12.9 Within the past week to what extent has your skin caused sexual problems?
 Extremely Very A bit Not at all Not relevant
- 12.10 Within the past week, has treatment of your skin caused problems, e.g. by making your home messy or dirty, or by being time consuming?
 Extremely Very A bit Not at all Not relevant

Appendix 2:

Semi-structured interview for diagnosing headache and migraine. Adapted from a validated interview from the Danish Headache Center (last updated November 18, 2012) for the purpose of interviewing patients without a diagnosis of migraine.

Semi-Structured Migraine and Headache Interview

0. Headache

0.1 Have you been diagnosed with migraine

Yes No

0.1.1 If yes, did anything happen in relation to debut of migraine?

Yes No

0.1.1.1 If yes – what happened

- Menarche
- Head trauma / Concussion
- Other _____

0.1.2 If NO:

0.1.2.1 Do you experience regular headaches?

0.1.2.1.1 If yes, how often (days per month) ____

0.1.2.1.2 Is the headache related to anything in particular

Yes No

0.1.2.1.3 If yes, what? _____

For all patients:

Do you ever experience headaches that are:

- | | Yes | No |
|-------------------------------------|----------------------------|----------------------------|
| a. Unilateral | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| b. Pulsating | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| c. Moderate/severe intensity | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| d. Aggravation by physical activity | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| e. Nausea | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| f. Vomiting | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| g. Photophobia | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| h. Phonophobia | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| i. Osmophobia | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |

Duration of the headache without medication:

- < ½ h 1
- ½ - 4 h 2
- 5 h – 23 h 3
- 1 - 3 days 4
- 4 – 7 days 5
- >7 days 6

1. MIGRAINE WITH AURA (MA)

a. Do you have migraine with aura?

1 2

1.1 Visual aura

Yes No

- a. Are there visual disturbances? 1 2
- b. Unilateral 1 2
- c. Gradually progressing 1 2
- d. Scotoma 1 2
- e. Zig-zag lines (fortification) 1 2
- f. Flickering 1 2
- g. Preserved central vision 1 2
- h. Duration of gradual development _____min
- j. Duration of visual aura _____min

1.2 Sensory aura

Yes No

- a. Are there sensory disturbances? 1 2
- b. Unilateral 1 2
- c. Gradually progressing 1 2

Do the sensory disturbances involve:

- d. The face 1 2
- e. The tongue 1 2
- f. The hand 1 2
- g. The arm 1 2
- h. The foot 1 2
- i. The leg 1 2
- j. The body 1 2
- k. Duration of gradual development _____min
- l. Duration of visual aura _____min

1.3 Motor aura

Yes No

- a. Are there motor disturbances? 1 2
- b. Unilateral 1 2
- c. Gradually progressing 1 2

Do the motor disturbances involve:

- d. The face 1 2
- e. The tongue 1 2
- f. The hand 1 2
- g. The arm 1 2
- h. The foot 1 2
- i. The leg 1 2
- j. The body 1 2
- k. Duration of gradual development _____min
- l. Duration of visual aura _____min

1.4 Aphasia/

Speech disturbances

Yes No

- a. Are there speech disturbances? 1 2

Are the speech impairments due to:

- b. Problems articulating speech 1 2
- c. Problems finding the right words 1 2
- d. Problems understanding what people say 1 2
- e. Problematic for other people to understand your speech 1 2
- f. Duration of speech/aphasic disturbances _____min

- 1 **1.5 Basilar-type aura** Yes No
 2 a. Are there basilar/occipital
 3 symptoms? 1 2
 4 Are there:
 5 b. Bilateral pareses/parestesias 1 2
 6 c. Bilateral visual symptoms 1 2
 7 d. Dysarthria 1 2
 8 e. Vertigo 1 2
 9 f. Diplopia 1 2
 10 g. Tinnitus 1 2
 11 h. Hypacusia 1 2
 12 i. Decreased level of consciousness 1 2
 13 j. Ataxia 1 2

14
 15 **1.6 Succession of aura symptoms**

- 16 a. If more than 1 aura type, is the succession of the auras:
 17 Successive 1
 18 Simultaneously 2
 19 Not applicable (NA) 3

20
 21 **1.7 Aura with headache** Yes No

- 22 a. Do you have aura with headache 1 2
 23 b. Does the onset of the headache typically come:
 24 Before the aura 1
 25 After the aura 2
 26 Simultaneously with the
 27 aura 3
 28 c. How long time before/after the aura _____min

29
 30 **1.8 Aura without headache** Yes No

- 31 a. Do you have aura without
 32 headache 1 2

33
 34 **1.9 Migraine with aura over time**

- 35 a. Age at onset _____years
 36 b. Date of last attack _____
 37 c. No. of attacks within last year:
 38 0 1
 39 1-5 2
 40 6-12 3
 41 13-24 4
 42 25-36 5
 43 >36 6
 44 d. No. of lifetime attacks:
 45 1 1
 46 2-4 2
 47 5-9 3
 48 10-49 4
 49 50-100 5
 50 >100 6

2. MIGRAINE WITHOUT AURA (MO)

- a. Do you have migraine Yes No
 without aura? 1 2

2.1 Migraine without aura over time

- a. Age at onset _____years
 b. Date of last attack _____
 c. No. of attacks within last year:
 0 1
 1-5 2
 6-12 3
 13-24 4
 25-36 5
 >36 6
 d. No. of lifetime attacks:
 1 1
 2-4 2
 5-9 3
 10-49 4
 50-100 5
 >100 6

3. Migraine triggers

- a. Are there factors that Yes No NA
 can trigger a migraine attack? 1 2 3
 b. What type of migraine? **MO** **MA** **MA+MO**
 1 2 3

3.1. Can these factors trigger a migraine attack:

- Yes No
 a. Physical activity 1 2
 b. Light 1 2
 c. Stress 1 2
 d. Menstruation 1 2
 e. Alcohol 1 2
 f. Strong smells 1 2
 g. Lack of/too much sleep 1 2
 h. Other factors: _____

4. Chronic migraine (MA+MO)

During the past 3 successive months, have you had:

- a. Headache at least 15 days a Yes No
 month 1 2
 b. Migraine at least 8 days
 a month 1 2

5. Tension-type headache

Do you have tension-type headaches Yes No
 1 2

5.1 Headache characteristics Yes No

- a. Bilateral 1 2
- b. Pressing 1 2
- c. Mild/moderate intensity 1 2
- d. Aggravation by physical activity 1 2
- e. Nausea 1 2
- f. Vomiting 1 2
- g. Photophobia 1 2
- h. Phonophobia 1 2

5.2 Duration of headache

- < ½ h 1
- ½ - 4 h 2
- 5 h - 23 h 3
- 1 - 3 days 4
- 4 - 7 days 5
- >7 days 6

5.3 Tension-type headache over time

- a. Headache days within last year:
 - 0 1
 - 1-7 2
 - 8-14 3
 - 15-30 4
 - 31-179 5
 - ≥180 6
- b. No. of tension-type headache days during the three last months: _____ days
- c. If ≥45 headache days, are the days evenly spaced out Yes No
 1 2

6. MIGRAINE TREATMENT (MA+ MO)

6.1 Treatment of migraine attacks

- | | Yes | No | NA |
|--|----------------------------|----------------------------|----------------------------|
| a. Triptans are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| b. Regular painkillers (NSAID, Paracetamol etc.) are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| c. Ergotamine drugs are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| d. Other drug(s) _____ | | | |

6.2 Use of medication

- a. No. of days of triptan-use per month _____
- b. No. of days of regular painkiller-use per month _____

6.3 Prophylactic treatment of migraine

- | | Yes | No | NA |
|---|----------------------------|----------------------------|----------------------------|
| a. Beta-blockers are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| b. Ca ²⁺ -antagonists are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| c. Angiotensin II receptor blockers are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| d. ACE-inhibitors are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| e. Anti-epilepsy drugs are efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| f. Antidepressive medication (mirtazapine) is efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| g. Hormone treatment is efficient | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |
| h. Other drug(s) _____ | | | |
| g. Are you currently receiving prophylactic treatment(s) for migraine | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 | <input type="checkbox"/> 3 |

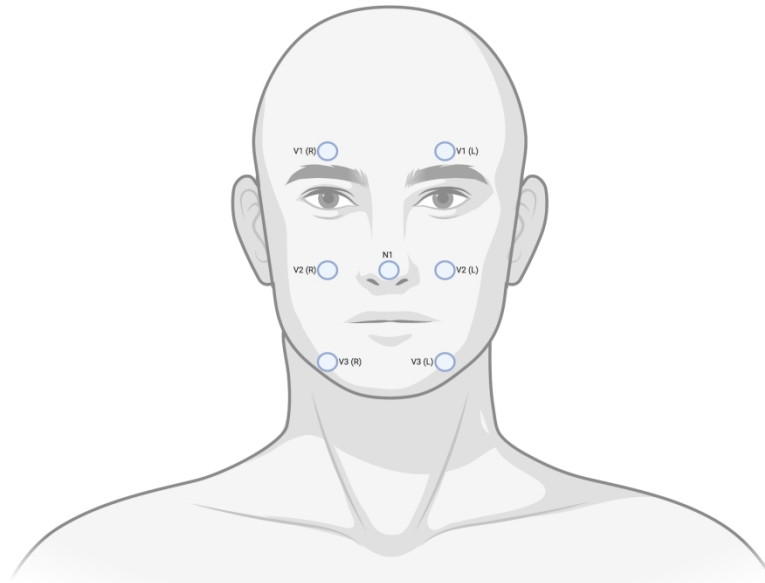
8. SECONDARY HEADACHES? Yes No
 1 2

If yes, specify: _____

11. Migraine within the family

- | | Yes | No |
|-------------------------------|----------------------------|----------------------------|
| a. Mother has/had migraine | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| b. Father has/had migraine | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| d. Siblings have/had migraine | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |
| e. Children have/had migraine | <input type="checkbox"/> 1 | <input type="checkbox"/> 2 |

Interview conducted by: _____



Appendix 3. Reference for evaluating thermal pictures. Each side of the face will be evaluated at areas corresponding to the three branches of the trigeminal nerve (forehead, cheeks, chin) and on the tip of the nose. Measurements will be performed on small areas (circles) rather than single points, to obtain an average from each area. To ensure correct ratio, circles were adjusted to match the pupil and iris of each picture. V1, ophthalmic nerve; V2, maxillary nerve; V3, mandibular nerve; R = right; L = left.

254x177mm (300 x 300 DPI)