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

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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

interviews. Additionally, blood and skin samples as well as pictures taken with normal and thermal cameras were collected. In this article we describe baseline data of the cohorts along with family history of migraine and rosacea, smoking, alcohol, body mass index (BMI) and dermatology life quality index (DLQI). Cohorts were not age- and sex-matched as they will not undergo direct comparison.

Future plans

COROCO and COMICO offer the possibility of studying epidemiology, risk factors, natural history and comorbidities in both disorders. We plan for longitudinal follow up through national Danish registries and to invite participants for a follow-up in 5-10 years. Unveiling a possible disease overlap between migraine and rosacea may also help in determining mechanisms behind both of these widespread and debilitating disorders.

Registration

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

Keywords

migraine, phenotype, rosacea

Strengths and limitations of this study

- 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

better characterize exact overlap of these diseases. Establishment of prospective patient cohorts with a physician-diagnosis of either migraine or rosacea will help confirm this connection and uncover possible risk factors and comorbidities in both.

COHORT DESCRIPTION

Study approval, registry and data availability

The study was approved by the Ethical Committee of the Capital Region of Denmark (H-17023750) and was registered at www.clinicaltrials.gov (NCT03872050). All participants provided written informed consent in accordance with the declaration of Helsinki anno 1964 with adjustments until 64th WMA General Assembly, Fortaleza, Brazil, October 2013. All data are under the supervision of the corresponding author and can be made available upon reasonable request.

Study population and setting

Two cohorts were established; Copenhagen Rosacea Cohort (COROCO) and Copenhagen Migraine Cohort (COMICO). Willing participants had to be aged 18 years or above. A physician-diagnosis of rosacea was needed to be included in COROCO, and a physician-diagnosis of migraine was needed to be included in COMICO. There were no exclusion criteria. All participants signed an informed consent upon enrollment.

Recruitment

Copenhagen Rosacea Cohort (COROCO)

Electronic Medical Records (EMR) were searched for adults who consulted a doctor for a diagnosis of rosacea at either *Department of Dermatology and Allergy at Gentofte Hospital* (between September 3rd, 2013 – May 5th, 2019) or *Department of Dermatology and Wound Healing Centre at Bispebjerg Hospital (*between January 1st, 2014 – November 21st, 2018). Diagnosis of rosacea was defined as one of the following ICD-10 codes: DL71, DL718A, DL719, DL718.[21]

A total of 790 patients were identified through EMR and invited to participate in the rosacea cohort. Five letters were not delivered due to wrong address, and invitations were thus delivered to 785 patients. Patients could respond through one of three routes: mailing the 'return envelope' (free of charge), sending an e-mail, or calling/texting a dedicated phone. The response rate was 46.8% (367 patients). Nine patients informed us that they did not want to participate due to illness, lack of time or because they did not believe to have rosacea. Of the 358 patients who responded positively to the invitation, we interviewed 274 patients before reaching the pre-specified inclusion number (see Figure 1 for details). An additional 35 patients with a prior diagnosis of rosacea were included via the Danish Headache Center at Rigshospitalet Glostrup or via online recruitment (www.forsøgsperson.dk). Interviews were performed in 309 patients, and after reviewing pictures, nine patients were excluded from analysis, as their symptoms could not clearly be attributed to rosacea. COROCO thus included a total of 300 patients. Interviews were performed between September 17th to 2018 to October 14th, 2019.

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.forsøgsperson.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

cheek, and mouth swab for DNA sampling. Procedures are described below. Patients only had to agree to the semi-structured interview to be eligible for the study.

INTERVIEW

A semi-structured interview was performed at the beginning of the visit. The interview was performed either by a medical doctor (author NW) or by trained senior medical students. All patients were asked questions based on two questionnaires.

Questionnaire – rosacea

Demographic information, comorbidities, family history, dermatology life quality index (DLQI) and presence of symptoms and manifestations of rosacea. If patients had a prior diagnosis of rosacea, first presenting symptom of rosacea, diagnostic delay and previous treatments were also collected (appendix 1). Patients were also evaluated with the National Rosacea Society Rosacea Clinical Scorecard.[22]

Questionnaire – migraine

A validated semi-structured questionnaire on diagnosis and subtyping of migraine[23] was adapted by author NW for the purpose of interviewing patients with no known migraine or headache (appendix 2). Questions included family history, headache/migraine and aura symptoms along with risk factors for headache/migraine. If patients had a diagnosis of migraine, migraine onset and headache frequency were collected.

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 25^0 lens. The camera has a range of -40^0C to $+150^0$C and temperature accuracy of +/- 1^0 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

corresponding to the facial area of the three branches of the trigeminus (forehead, cheeks, chin). An additional temperature measurement was performed on the tip of the nose (appendix 3). The measure point was matched to the size of the iris to adjust for differences in distances from which the pictures were taken.

Facial skin temperature has previously been investigated in both migraine and rosacea with unclear results.[24] We therefore offer baseline temperatures in a large group of patients with both disorders to determine whether previous findings reflect true differences or simply interindividual differences within patient groups.

Superficial stratum corneum sampling

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

Rosacea is characterized by local inflammation of the face, however, recent evidence suggests that the inflammation may be systemic.[25] Migraine has also been suggested to

involve inflammation, especially neuroinflammation, but possibly also systemic inflammation.[26]

Measurement of inflammatory markers from the skin will allow us to compare facial inflammation (cheek) to systemic inflammation (forearm) and to compare patients with migraine and rosacea to uncover a possible subclinical inflammation in both disorders. Furthermore, we hope to investigate whether there is a correlation between local/systemic inflammation, subtypes of rosacea and disease activity.

Genetics

Patients were not allowed to eat, drink, smoke, chew gum or clean teeth one hour before collection. All patients were instructed to rinse their mouth with water immediately before collection. For the analyses, one SK-1S DNA buccal swab (Isohelix, Harrietsham, U.K) was rubbed against cheek mucosa for 60 seconds before returning the swab to the supplied tube without touching the head of the swab. The shaft was broken on the edge of the tube which left the head of the swab in the tube. The tube was stored at -80° C until analysis.

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

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

were more frequent and heavy smokers than their peers,[44] and smoking has been suggested as a precipitating factor for migraine attacks.[45] Furthermore, a higher prevalence of non-migraine-specific headache has been found among current smokers.[46]

Smoking in rosacea is also debated. Some studies find a lower prevalence of smoking in patients with rosacea[47,48] and that smoking is protective against incident rosacea[49] whereas others find a higher prevalence of smoking.[50,51]. Past smoking has been associated with a higher risk of incident rosacea compared to never smokers,[38,49] perhaps due to an autoimmune response, but this needs further investigation. Smoking constricts the peripheral blood vessels, possibly masking rosacea which could be a reason for why we see a lower prevalence of current smoking in the rosacea group.

Alcohol

Regular intake of alcohol was less common in the migraine cohort (62.3%) than in the rosacea cohort (79.3%). In those with regular intake of alcohol, median average weekly intake for those in the migraine cohort was 2 items/week (IQR 1.0 – 3.0) and 4 items/week (IQR 1.0 – 9.0) for rosacea.

Alcohol is a common trigger of migraine attacks,[3,52–55] which was also one of the most commonly reported anecdotal reasons for alcohol abstinence in the migraine cohort.

Alcohol is a commonly acknowledged trigger of rosacea flushing,[56–58] and intake of alcohol seems to be associated with a higher risk of incident rosacea,[47,59,60] though some studies failed to find significant associations between rosacea and alcohol intake.[38,61,62]

Body mass index

Median body mass index (BMI) was 24.6 (IQR 21.5 – 28.2) for the migraine cohort and 25.7 (23.1 – 29.0) for the rosacea cohort. Stratified into groups, underweight (BMI < 18.5) was seen in 3.3% (10 patients) of the migraine cohort and 1.3% (4 patients) of the rosacea cohort. Normal weight (BMI between 18.5 – 25) was found in 50.7% (154 patients) in the migraine cohort and 39.7% (119 patients) in the rosacea cohort. Overweight (BMI between 25 – 30) was found in 28.6% (87 patients) of the migraine cohort and 40.7% (122 patients) of the rosacea cohort. Obesity (BMI > 30) was found in 15.6% (53 patients) in the migraine cohort and 18.3% (55 patients) in the rosacea cohort.

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

BMI may be a risk factor for incident rosacea.[72,73] It has been suggested that metabolic disease[72] and cardiovascular comorbidities are more common in rosacea, though this is debated.[50,74–76] We do find more patients in the overweight group in our rosacea cohort compared to the migraine cohort, however, patients with both disorders may be present in both groups. Furthermore, as patients were not age- and sex-matched, more analyses are needed after proper phenotyping to rule out potential confounders in both groups.

DLQI

Median DLQI is 1 (IQR 0 – 2) for the migraine cohort and 2 (IQR 1 - 5) for the rosacea cohort. Stratified into groups, DLQI of 0-1 (no effect on quality of life) was present in 65.1% (198 patients) in the migraine cohort and 42.7% (128 patients) in the rosacea cohorts. DLQI between 2-5 (mild effect on quality of life) was present in 27.3% (83 patients) in the migraine cohort and 35.0% (105 patients) in the rosacea cohort. DLQI between 6-10 (moderate effect on quality of life) was found in 5.6% (17 patients) in the migraine cohort and 12.0% (26 patients) in the rosacea cohort. DLQI 11-20 (large effect on quality of life) was found in 2.0% (6 patients) in the migraine cohort and 10.0% (30 patients) in the rosacea cohort. DLQI 20 (extreme effect on quality of life) was not found in any of the 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)

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.

There is also a risk of selection bias, as patients were recruited primarily through specialist clinics where only the most severely affected patients are seen. As patients were not excluded from one of the cohorts if they had both diagnoses, comparison between groups is also problematic as differences and similarities may be attributed to both patient groups being present in both cohorts. Furthermore, it might be speculated that patients who identified with the investigated disorders, e.g. migraine patients who also identified with rosacea symptoms, or who had family members with the disease, were more prone to accept the invitation to participate. However, we believe that the fairly short one-time study-visit that could be combined with their outpatient visit was enough motivation in most cases. For rosacea, the disorder is relatively un-investigated, and patients seemed motivated to participate simply due to this fact.

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.

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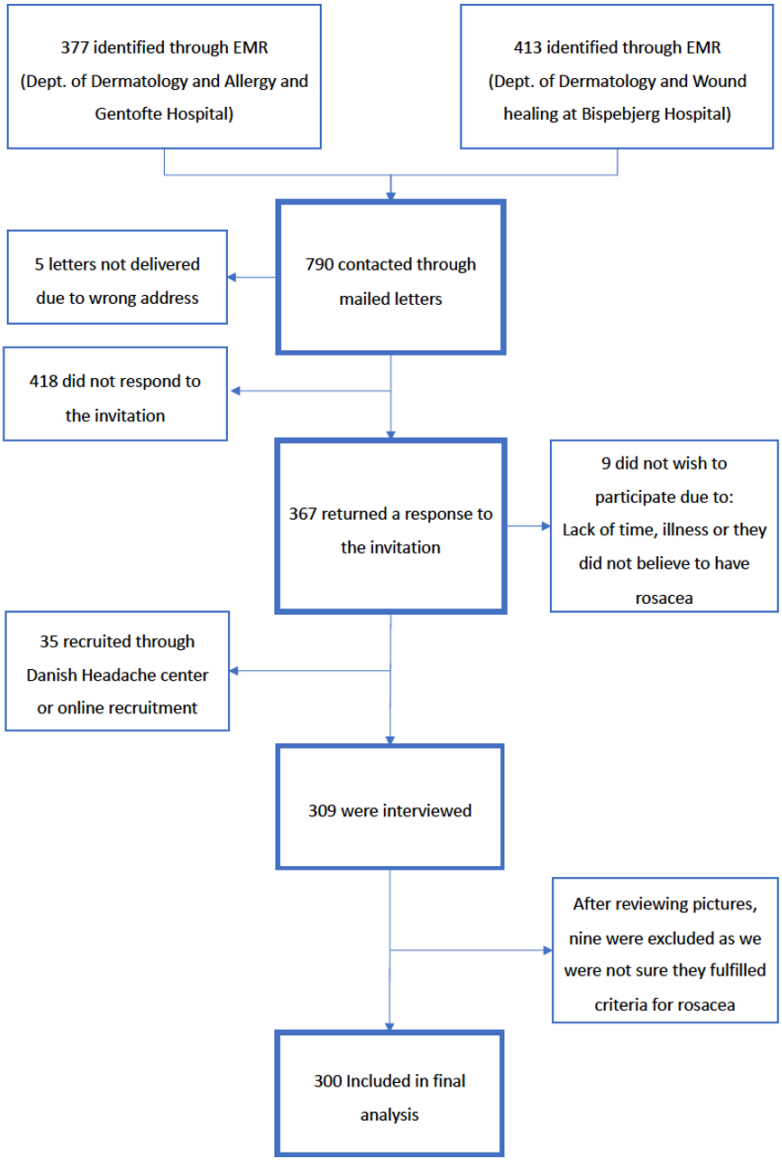


Figure 1. Flow chart detailing enrolment in COROCO. EMR = Electronic Medical Records.

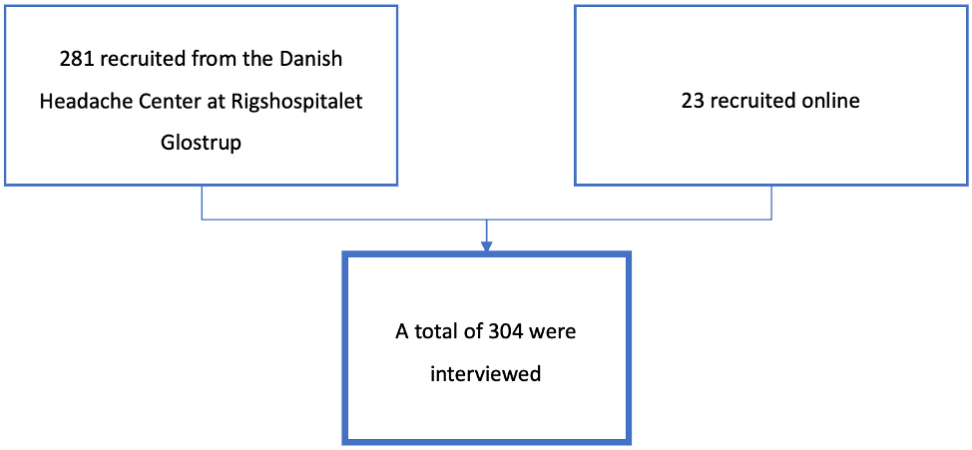


Figure 2: Flow chart detailing enrolment in COMICO.

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 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 aswer)

- ▭ **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
▭ Mirvaso (brimonidine tartrate) creme/gel	▭	▭	▭
▭ Finacea (azelaic acid) creme/gel	▭	▭	▭
▭ Metronidazole / metrocrem / rozex / robaz creme/gel	▭	▭	▭
▭ Oracea (doxycycline) tablet	▭	▭	▭
▭ Soolantra (ivermectin) creme	▭	▭	▭
▭ Tetracycline	▭	▭	▭
▭ Erythromycin (macrolide) tablet	▭	▭	▭
▭ Accutin / Isotretinoin tablet	▭	▭	▭
▭ Other: _____			

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 you 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 phychiatric 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 you 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 you 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 you 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	□ 1	□ 2
b. Pulsating	□ 1	□ 2
c. Moderate/severe intensity	□ 1	□ 2
d. Aggravation by physical activity	□ 1	□ 2
e. Nausea	□ 1	□ 2
f. Vomiting	□ 1	□ 2
g. Photofobia	□ 1	□ 2
h. Phonofobia	□ 1	□ 2
i. Osmophoabia	□ 1	□ 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		
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/parestesias	□ 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. 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

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. Photofobia	□ 1	□ 2
h. Phonofobia	□ 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 □ 1 No □ 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. Ca^{2+}-antagonists are efficient	□ 1	□ 2	□ 3
c. Angiotensin II receptor blockers are efficient	□ 1	□ 2	□ 3
d. ACE-inhibotors 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 □ 1 No □ 2

8. SECONDARY HEADACHES? Yes □ 1 No □ 2

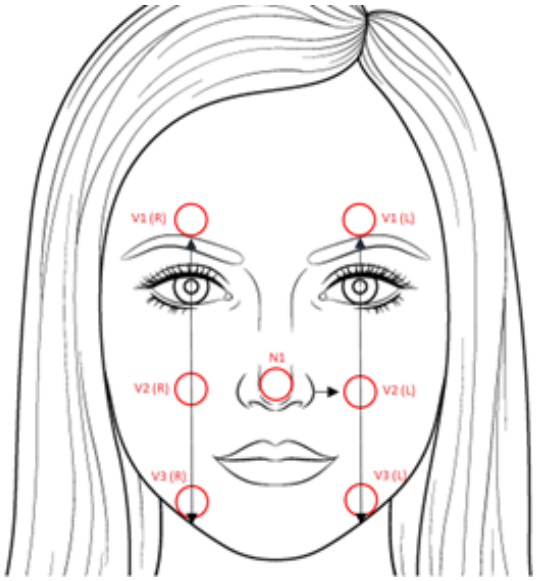
If yes, specify:_____

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: Guide for standardized measure of the three branches of the trigeminus on both sides of the face (forehead, cheeks, chin) and the tip of the nose. The circles were adjusted to be the same size as the pupil and iris to adjust for possible differences in sizes of the pictures. Guide was made by authors CC, DGZ and NW.



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

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

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MA is a consultant, speaker or scientific advisor for Alder, Allergan, Amgen, Eli Lilly, Lundbeck, Novartis, and Teva, primary investigator for Alder, Allergan, Amgen, Eli Lilly, Novartis and Teva trials. MA has no ownership interest and does not own stocks of any pharmaceutical company. MA serves as associate editor of Cephalalgia, associate editor of Headache, associate editor of the Journal of Headache and Pain. MA is President of the International Headache Society.

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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

interviews. Additionally, blood and skin samples as well as pictures taken with normal and thermal cameras were collected. In this article we describe baseline data of the cohorts along with family history of migraine and rosacea, smoking, alcohol, body mass index (BMI) and dermatology life quality index (DLQI). Cohorts were not age- and sex-matched as they will not undergo direct comparison.

Future plans

COROCO and COMICO serve as strong data sources that will be used for future studies on rosacea and migraine with focus on risk factors, occurrence, treatment, natural history, complications, comorbidities and prognosis.

Registration

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

Strengths and limitations of this study

- 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.
- Rosacea diagnoses are validated through pictures evaluated by three physicians and migraine diagnoses validated through semi-structured interviews.

- 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

better characterize exact overlap of these diseases. Establishment of prospective patient cohorts with a physician-diagnosis of either migraine or rosacea will help confirm this connection and uncover possible risk factors and comorbidities in both.

COHORT DESCRIPTION

Study approval, registry and data availability

The study was approved by the Ethical Committee of the Capital Region of Denmark (H-17023750) and was registered at www.clinicaltrials.gov (NCT03872050). All participants provided written informed consent in accordance with the declaration of Helsinki anno 1964 with adjustments until 64th WMA General Assembly, Fortaleza, Brazil, October 2013. All data are under the supervision of the corresponding author and can be made available upon reasonable request.

Study population and setting

Two cohorts were established; Copenhagen Rosacea Cohort (COROCO) and Copenhagen Migraine Cohort (COMICO). Willing participants had to be aged 18 years or above. A physician-diagnosis of rosacea was needed to be included in COROCO, and a physician-diagnosis of migraine was needed to be included in COMICO. There were no exclusion criteria. All participants signed an informed consent upon enrollment.

Recruitment

Copenhagen Rosacea Cohort (COROCO)

Electronic Medical Records (EMR) were searched for adults who consulted a doctor for a diagnosis of rosacea at either *Department of Dermatology and Allergy at Gentofte Hospital* (between September 3rd, 2013 – May 5th, 2019) or *Department of Dermatology and Wound Healing Centre at Bispebjerg Hospital (*between January 1st, 2014 – November 21st, 2018). Diagnosis of rosacea was defined as one of the following ICD-10 codes: DL71, DL718A, DL719, DL718.[21]

A total of 790 patients were identified through EMR and invited to participate in the rosacea cohort. Five letters were not delivered due to wrong address, and invitations were thus delivered to 785 patients. Patients could respond through one of three routes: mailing the 'return envelope' (free of charge), sending an e-mail, or calling/texting a dedicated phone. The response rate was 46.8% (367 patients). Nine patients informed us that they did not want to participate due to illness, lack of time or because they did not believe to have rosacea. Of the 358 patients who responded positively to the invitation, we interviewed 274 patients before reaching the pre-specified inclusion number (see Figure 1 for details). An additional 35 patients with a prior diagnosis of rosacea were included via the Danish Headache Center at Rigshospitalet Glostrup or via online recruitment (www.forsøgsperson.dk). Interviews were performed in 309 patients, and after reviewing pictures, nine patients were excluded from analysis, as their signs could not clearly be attributed to rosacea. COROCO thus included a total of 300 patients. Interviews were performed between September 17th to 2018 to October 14th, 2019.

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.forsøgsperson.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 at 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 entire visit; both interviews and clinical examination, was performed by either a medical doctor (author NW) or by senior medical students who were specifically trained to perform both.

Each visit lasted approximately 60 minutes and included interview, blood sample, pictures with digital and thermal cameras, superficial stratum corneum sampling of the forearm and cheek, and mouth swab for DNA sampling. Procedures are described below. Patients only had to agree to the semi-structured interview to be eligible for the study, as this was the essential part of the investigation; however, most patients agreed to all investigations.

INTERVIEW

A semi-structured interview was performed at the beginning of the visit based on two questionnaires. All participants were asked questions on both rosacea and migraine to confirm diagnosis and phenotype. All questionnaires were reviewed by author NW. In case of doubt about rosacea diagnosis, authors AE and JPT were consulted, and in case of doubt about migraine diagnosis, author MA was consulted.

Questionnaire – rosacea

Demographic information, comorbidities, family history, dermatology life quality index (DLQI) and presence of rosacea features. If patients had a prior diagnosis of rosacea, first presenting sign or symptom of rosacea, diagnostic delay and previous treatments were

also collected (appendix 1). Patients were also evaluated with the National Rosacea Society Rosacea Clinical Scorecard.[22]

Questionnaire – migraine

A validated semi-structured questionnaire on diagnosis and subtyping of migraine[23] was adapted by author NW for the purpose of interviewing patients with no known migraine or headache (appendix 2). Questions included family history, headache/migraine and aura symptoms along with risk factors for headache/migraine. All patients; also those who claimed to have a previous diagnosis of migraine, were asked about headache characteristics to validate migraine diagnosis. If patients had a diagnosis of migraine, migraine onset and headache frequency were collected.

CLINICAL EXAMINATION

The following examinations were performed after the interview, and patients had therefore been sitting calmly for at least 30 minutes and drinking nothing but water, prior to examinations.

All examinations were performed on patients included in both COROCO and COMICO.

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 25^0 lens. The camera has a range of -40^0C to $+150^0$C and temperature accuracy of +/- 1^0 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 corresponding to the facial area of the three branches of the trigeminus (forehead, cheeks, chin). An additional temperature measurement was performed on the tip of the nose (appendix 3). The measure point was matched to the size of the iris to adjust for differences in distances from which the pictures were taken.

Facial skin temperature has previously been investigated in both migraine and rosacea with unclear results.[24] We therefore offer baseline temperatures in a large group of patients with both disorders to determine whether previous findings reflect true differences or simply interindividual differences within patient groups.

Superficial stratum corneum sampling

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

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

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

Furthermore, we hope to investigate whether there is a correlation between local/systemic inflammation, subtypes of rosacea and disease activity.

Genetics

Patients were not allowed to eat, drink, smoke, chew gum or clean teeth one hour before collection. All patients were instructed to rinse their mouth with water immediately before collection. For the analyses, one SK-1S DNA buccal swab (Isohelix, Harrietsham, U.K) was rubbed against cheek mucosa for 60 seconds before returning the swab to the supplied tube without touching the head of the swab. The shaft was broken on the edge of the tube which left the head of the swab in the tube. The tube was stored at -80° C until analysis.

The purpose of DNA collection was to perform a genome-wide association-study (GWAS) for the most common gene mutations in rosacea and migraine. A large meta-analysis of 375,000 individuals has located 38 loci relevant for migraine[27], whereas GWAS has only been done a few times in rosacea and only on populations selected from the '23andMe' customer base.[28,29] We will look at loci relevant to both migraine and rosacea in both patients groups to discover any potential overlaps. Analysis will not include genes listed on the ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing.[30]

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[31] and rosacea[32] 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.[33]

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

Findings are summarized in table 1 for COROCO and table 2 for COMICO.

Age and sex

COROCO

Median age was 51 years (interquartile range (IQR) 43.0 – 61.0) and there were 67.7% females in the cohort.

Rosacea usually affects individuals above age 30 years[9] with a peak onset between 45 – 60 years.[8] The sex distribution is more or less even, with only a tendency towards a female predominance.[8] COROCO thus resembles previous studies in rosacea.

COMICO

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

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

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

COROCO

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

Family history of migraine in the general population is usually underreported, [35,36] which may contribute to the low prevalence of family history of migraine in our rosacea cohort.

COMICO

Family history of migraine was found in 73.4% of those in the migraine cohort. Previous studies have found family history reports between 54-77%,[37,38] and we expect that patients with migraine are more aware of their family history and believe that this might be more or less the true prevalence of family history.

Family history of rosacea

COROCO

Family history of rosacea was 45% in the rosacea cohort. Family history in rosacea has previously been reported up to 55% compared to 12 - 17% in controls.[39,40] Rosacea is largely underestimated and often goes undiagnosed,[17,41,42] contributing to the low family history reports of rosacea. In our cohort, some patients stated that they suspected family members of having rosacea, but only definite diagnoses were included in our analysis, probably underestimating family history of rosacea in our cohorts.

COMICO

Family history of rosacea was 18.4% in the migraine cohort, corresponding to previous findings of 12 - 17% in controls.[39,40] As stated above, underdiagnosing of rosacea probably contributes to low family history reports in the migraine cohort as well.[17,41,42]

Smoking

COROCO

There were 13.0% current smokers in COROCO. The median pack-years for smokers were 24.6 years (IQR 13.3-26.0). A total of 36.6% were former smokers.

Smoking in rosacea is debated. Some studies find a lower prevalence of smoking in patients with rosacea,[43,44] and find smoking to be protective against incident rosacea,[45] whereas others find a higher prevalence of smoking.[46,47]. Past smoking has been associated with a higher risk of incident rosacea compared to never smokers,[39,45] perhaps due to an autoimmune response, but this needs further investigation. Smoking constricts the peripheral blood vessels, possibly masking rosacea which could be a reason for why we see a lower prevalence of current smoking in the rosacea group.

COMICO

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

Smoking in migraine is debated. A study from 1976 reports that smoking is unlikely to be related to migraine[48] whereas more recent research finds found an increased risk of migraine in past and current smokers.[49] Another study found that patients with migraine were more frequent and heavy smokers than their peers,[50] and smoking has been suggested as a precipitating factor for migraine attacks.[51]

Smoking in the general population in Denmark was 23% in 2018 (22% in women and 24% in men)[52], and it thus looks like we have a lower prevalence of smoking in our cohorts than in the background population. This could be because smoking cessation may trigger either rosacea or migraine, although there is no clear evidence of this, as stated above.

Alcohol

COROCO

Regular intake of alcohol was seen in 79.3% of COROCO with a median average intake of 4 items/week (IQR 1.0 – 9.0).

Alcohol is a common trigger of flushing in rosacea,[53–55] alcohol intake seems to be associated with a higher risk of incident rosacea,[43,56,57] though some studies have failed to confirm this association.[39,58,59]

COMICO

In COMICO, 62.3% regularly drank alcohol, with a median average intake of 2 items/week (IQR 1.0 – 3.0).

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

Body mass index

COROCO

Median body mass index (BMI) was 25.7 (23.1 – 29.0). Stratified into groups, underweight (BMI < 18.5) was seen in 1.3% (4 patients), normal weight (BMI between 18.5 – 25) was found in 39.7% (119 patients) , overweight (BMI between 25 – 30) was present in 40.7% (122 patients), and obesity (BMI > 30) was found in 18.3% (55 patients).

High BMI may be a risk factor for incident rosacea.[64,65] Metabolic disease[64] and cardiovascular comorbidities are more common in rosacea, though the causal relationship is debated.[46,66–68]

COMICO

Median BMI was 24.6 (IQR 21.5 – 28.2). Stratified into groups, underweight was seen in 3.3% (10 patients), normal weight was found in 50.7% (154 patients), overweight was seen in 28.6% (87 patients), and obesity was found in 15.6% (53 patients).

Obesity seems to be a risk factor for migraine,[69–72] and obesity and weight gain contributes to worsening of migraine, with the potential of turning episodic migraine into chronic migraine.[73–77] Patients for COMICO were primarily recruited through the Danish Headache Center, which is a highly specialized unit and 38.2% turned out to have chronic migraine, which may have contributed to a higher BMI in this group.

DLQI

COROCO

Median DLQI was 2 (IQR 1 - 5). Stratified into groups, DLQI of 0-1 (no effect on quality of life) was present in 42.7% (128 patients). DLQI between 2-5 (mild effect on quality of life) was present in 35.0% (105 patients). DLQI between 6-10 (moderate effect on quality of life) was found in 12.0% (26 patients), and DLQI between 11-20 (large effect on quality of life) was found in 10.0% (30 patients). DLQI 20 (extreme effect on quality of life) was found in 0.3% (1 patient).

Interestingly, we find a very low impact of rosacea on daily quality of life. There may be a number of reasons for this. One, DLQI is an immediate view on quality of life during the past week. Rosacea is fluctuating and patients may not have had a lot of symptoms at the time of the interview, and thus a low DLQI. Second, many patients reported to have previously been very affected by their rosacea, but they were now less affected, either due to acceptance of their symptoms, or because they had been effectively treated. Thirdly,

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)

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.

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)
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.

Future plans

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

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,[79] 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 features, first presenting sign/symptom and later onset of other rosacea features 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 rosacea feature sometimes many years prior to

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

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 DGZ collected data for the study. NW and JHH performed the analysis under supervision of AE. NW drafted the manuscript. All authors reviewed and edited the manuscript. All authors approved the final manuscript.

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Figure captions

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

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

Appendices

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.

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.

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.

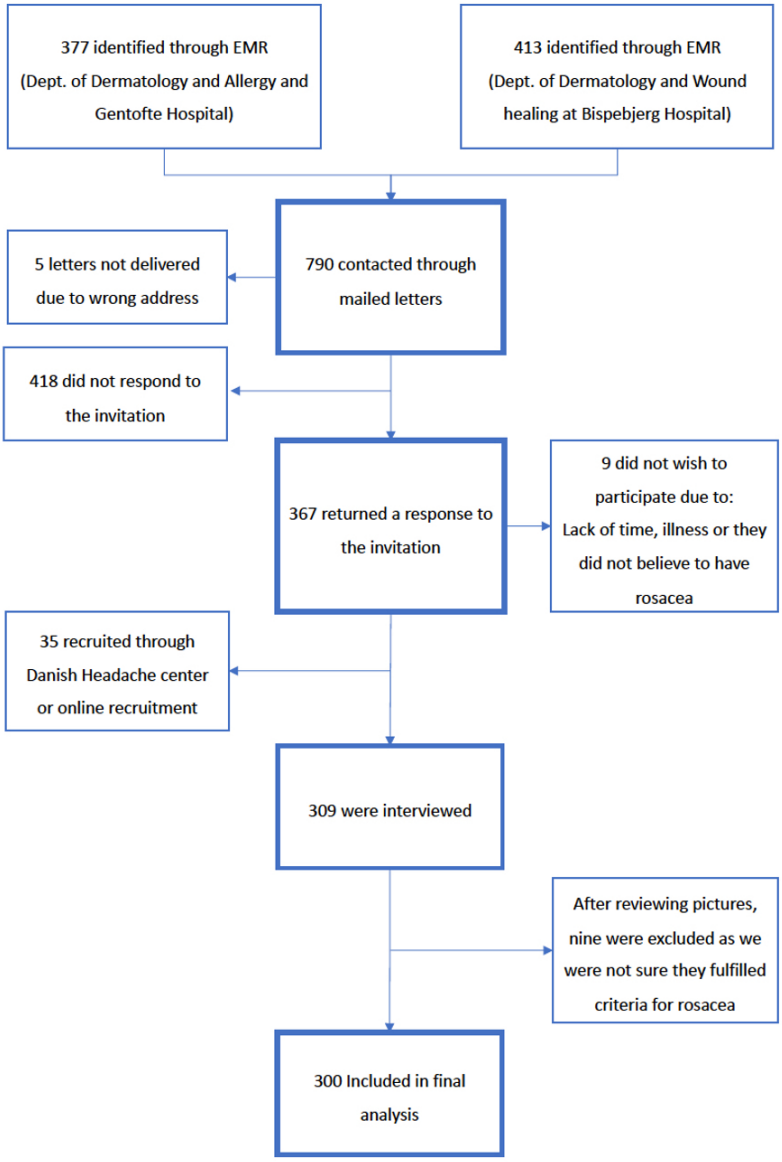


Figure 1. Flow chart detailing enrollment in Copenhagen Rosacea Cohort (COROCO). EMR, Electronic Medical Records.

150x225mm (150 x 150 DPI)

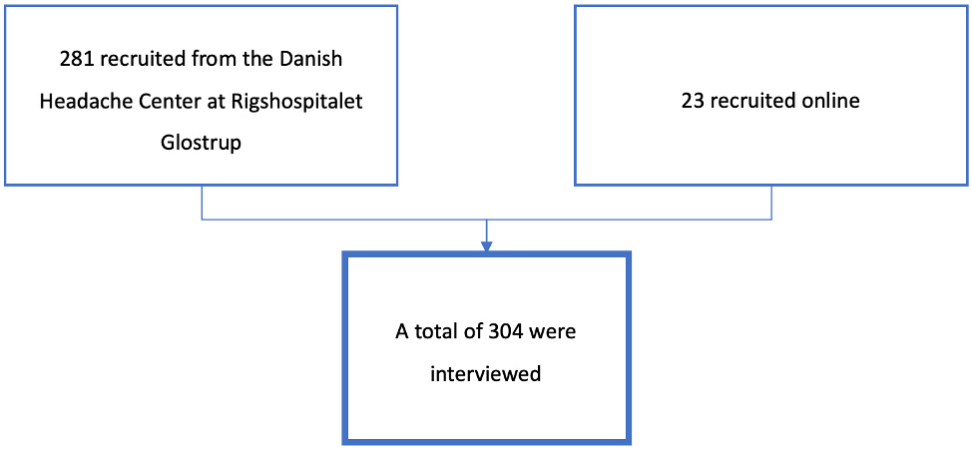


Figure 2. Flow chart detailing enrollment in Copenhagen Migraine Cohort (COMICO).

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 aswer)

- ▭ **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
▭ Mirvaso (brimonidine tartrate) creme/gel	▭	▭	▭
▭ Finacea (azelaic acid) creme/gel	▭	▭	▭
▭ Metronidazole / metrocrem / rozex / robaz creme/gel	▭	▭	▭
▭ Oracea (doxycycline) tablet	▭	▭	▭
▭ Soolantra (ivermectin) creme	▭	▭	▭
▭ Tetracycline	▭	▭	▭
▭ Erythromycin (macrolide) tablet	▭	▭	▭
▭ Accutin / Isotretinoin tablet	▭	▭	▭
▭ Other: _____			

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 you 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 phychiatric 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 <u>DAILY SMOKERS</u>

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

Number of cigarettes ▭▭ Other, describe: _____

ANSWERS FROM <u>OCCASIONAL SMOKERS</u>

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

Number of cigarettes ▭▭ Other, describe: _____

ANSWERS FROM <u>OCCASIONAL AND FORMER SMOKERS</u>

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 you 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 you 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 you 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	□ 1	□ 2
b. Pulsating	□ 1	□ 2
c. Moderate/severe intensity	□ 1	□ 2
d. Aggravation by physical activity	□ 1	□ 2
e. Nausea	□ 1	□ 2
f. Vomiting	□ 1	□ 2
g. Photofobia	□ 1	□ 2
h. Phonofobia	□ 1	□ 2
i. Osmophoabia	□ 1	□ 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		
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/parestesias	□ 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. Photofobia	□ 1	□ 2
h. Phonofobia	□ 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. Ca^{2+}-antagonists are efficient	□ 1	□ 2	□ 3
c. Angiotensin II receptor blockers are efficient	□ 1	□ 2	□ 3
d. ACE-inhibotors 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

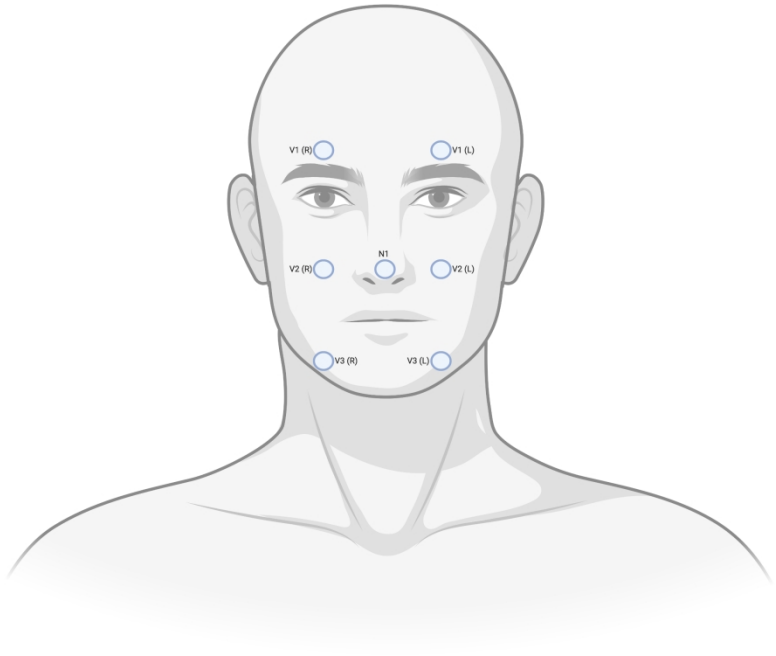
8. SECONDARY HEADACHES?	Yes	No
	□ 1	□ 2

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)

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

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

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

currently smoked and 36.6% were former smokers. Regular intake of alcohol was present in 79.3% (median 4 items/week (IQR 1.0 – 9.0). Median body mass index (BMI): 25.7 (IQR 23.1 – 29.0). Median DLQI: 2 (IQR 1 - 5).

COMICO: 88.5% women (median age 41 years (IQR 29.5 – 51.0)). Family history of migraine: 73.4%. Family history of rosacea: 18.4%. There were 17% who currently smoked and 26.0% former smokers. Regular intake of alcohol was present in 62.3% (median intake: 2 item/week (IQR 1.0 – 3.0)). Median BMI was 24.6 (IQR 21.5 – 28.2). Median DLQI was 1 (IQR 0 – 2).

Future plans

COROCO and COMICO serve as strong data sources that will be used for future studies on rosacea and migraine with focus on risk factors, occurrence, treatment, natural history, complications, comorbidities and prognosis.

Registration

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

Strengths and limitations of this study

- Copenhagen Rosacea Cohort (COROCO) and Copenhagen Migraine Cohort (COMICO) are large cohorts of adults with either physician-diagnosed migraine or

rosacea that are phenotyped through face-to-face interview by trained professionals.

- Rosacea diagnoses are validated through pictures evaluated by three physicians and migraine diagnoses validated through semi-structured interviews.
- 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 above the age of 30 years.[8,9] The 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 disorders.[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

better characterize exact overlap of these diseases. Establishment of prospective patient cohorts with a physician-diagnosis of either migraine or rosacea will help confirm this connection and uncover possible risk factors and comorbidities in both.

COHORT DESCRIPTION

Study approval, registry and data availability

The study was approved by the Ethical Committee of the Capital Region of Denmark (H-17023750) and was registered at www.clinicaltrials.gov (NCT03872050). All participants provided written informed consent in accordance with the declaration of Helsinki anno 1964 with adjustments until 64th WMA General Assembly, Fortaleza, Brazil, October 2013. All data are under the supervision of the corresponding author and can be made available upon reasonable request.

Study population and setting

Two cohorts were established; Copenhagen Rosacea Cohort (COROCO) and Copenhagen Migraine Cohort (COMICO). Willing participants had to be aged 18 years or above. A physician-diagnosis of rosacea was needed to be included in COROCO, and a physician-diagnosis of migraine was needed to be included in COMICO. There were no exclusion criteria. All participants signed an informed consent upon enrollment.

Recruitment

Copenhagen Rosacea Cohort (COROCO)

Electronic Medical Records (EMR) were searched for adults who consulted a doctor for a diagnosis of rosacea at either *Department of Dermatology and Allergy at Gentofte Hospital* (between September 3rd, 2013 – May 5th, 2019) or *Department of Dermatology and Wound Healing Centre at Bispebjerg Hospital (*between January 1st, 2014 – November 21st, 2018). Diagnosis of rosacea was defined as one of the following ICD-10 codes: DL71, DL718A, DL719, DL718.[21]

A total of 790 patients were identified through EMR and invited to participate in the rosacea cohort. Five letters were not delivered due to wrong address, and invitations were thus delivered to 785 patients. Patients could respond through one of three routes: mailing the 'return envelope' (free of charge), sending an e-mail, or calling/texting a dedicated phone. The response rate was 46.8% (367 patients). Nine patients informed us that they did not want to participate due to illness, lack of time or because they did not believe to have rosacea. Of the 358 patients who responded positively to the invitation, we interviewed 274 patients before reaching the pre-specified inclusion number (see Figure 1 for details). An additional 35 patients with a prior diagnosis of rosacea were included via the Danish Headache Center at Rigshospitalet Glostrup or via online recruitment (www.forsøgsperson.dk). Interviews were performed in 309 patients, and after reviewing pictures, nine patients were excluded from analysis, as their signs could not clearly be attributed to rosacea. COROCO thus included a total of 300 patients. Interviews were performed between September 17th, 2018 – October 14th, 2019.

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.forsøgsperson.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 at 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 entire visit; both interviews and clinical examination, was performed by either a medical doctor (author NW) or by senior medical students who were specifically trained to perform both.

Each visit lasted approximately 60 minutes and included interview, blood sample, pictures with digital and thermal cameras, superficial stratum corneum sampling of the forearm and cheek, and mouth swab for DNA sampling. Procedures are described below. Patients only had to agree to the semi-structured interview to be eligible for the study, as this was the essential part of the investigation; however, most patients agreed to all investigations.

INTERVIEW

A semi-structured interview was performed at the beginning of the visit based on two questionnaires. All participants were asked questions on both rosacea and migraine to confirm diagnosis and phenotype. All questionnaires were reviewed by author NW. In case of doubt about rosacea diagnosis, authors AE and JPT were consulted, and in case of doubt about migraine diagnosis, author MA was consulted.

Questionnaire – rosacea

Demographic information, comorbidities, family history, dermatology life quality index (DLQI) and presence of rosacea features. If patients had a prior diagnosis of rosacea, first presenting sign or symptom of rosacea, diagnostic delay and previous treatments were

also collected (appendix 1). Patients were also evaluated with the National Rosacea Society Rosacea Clinical Scorecard.[22]

Questionnaire – migraine

A validated semi-structured questionnaire on diagnosis and subtyping of migraine[23] was adapted by author NW for the purpose of interviewing patients with no known migraine or headache (appendix 2). Questions included family history, headache/migraine and aura symptoms along with risk factors for headache/migraine. All patients; also those who claimed to have a previous diagnosis of migraine, were asked about headache characteristics to validate migraine diagnosis. If patients fulfilled criteria for a diagnosis of migraine, migraine onset and headache frequency were collected.

CLINICAL EXAMINATION

The following examinations were performed after the interview, and patients had therefore been sitting calmly for at least 30 minutes and drinking nothing but water, prior to examinations.

All examinations were performed on patients included in both COROCO and COMICO.

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 25^0 lens. The camera has a range of -40^0C to $+150^0$C and temperature accuracy of +/- 1^0 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 corresponding to the facial area of the three branches of the trigeminus (forehead, cheeks and chin). An additional temperature measurement was performed on the tip of the nose (appendix 3). The measure point was matched to the size of the iris to adjust for differences in distances from which the pictures were taken.

Facial skin temperature has previously been investigated in both migraine and rosacea with unclear results.[24] We therefore offer baseline temperatures in a large group of patients with both disorders to determine whether previous findings reflect true differences or simply interindividual differences within patient groups.

Superficial stratum corneum sampling

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

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

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

Furthermore, we hope to investigate whether there is a correlation between local/systemic inflammation, subtypes of rosacea and disease activity.

Genetics

Patients were not allowed to eat, drink, smoke, chew gum or clean teeth one hour before collection. All patients were instructed to rinse their mouth with water immediately prior to collection. For the analyses, one SK-1S DNA buccal swab (Isohelix, Harrietsham, U.K) was rubbed against cheek mucosa for 60 seconds before returning the swab to the supplied tube without touching the head of the swab. The shaft was broken on the edge of the tube which left the head of the swab in the tube. The tube was stored at -80° C until analysis.

The purpose of DNA collection was to perform a genome-wide association-study (GWAS) for the most common gene mutations in rosacea and migraine. A large meta-analysis of 375,000 individuals has located 38 loci relevant for migraine[27], whereas GWAS has only been done a few times in rosacea and only on populations selected from the '23andMe' customer base.[28,29] We will look at loci relevant to both migraine and rosacea in both patients groups to discover any potential overlaps. Analysis will not include genes listed on the ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing.[30]

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 linked to both migraine[31] and rosacea[32] and has been suggested to be related to disease pathology. CGRP is relatively well-described in migraine, and CRGP-antibodies have recently proven beneficial in preventive treatment of migraine.[33]

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

Findings to date

Findings are summarized in table 1 for COROCO and table 2 for COMICO.

COROCO

Age and sex

Median age was 51 years (interquartile range (IQR) 43.0 – 61.0) and there were 67.7% females in the cohort.

Rosacea usually affects individuals above age 30 years[9] with a peak onset between 45 – 60 years.[8] The sex distribution is more or less even, with only a tendency towards a female predominance.[8] COROCO thus resembles previous studies in rosacea.

Family history of migraine

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

Family history of migraine in the general population is usually underreported, [34,35] 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 45% in the rosacea cohort. Family history of rosacea in patients with rosacea has previously been reported in up to 55%, compared to 12 - 17% in controls.[36,37] Rosacea is largely underestimated and often goes undiagnosed,[17,38,39] contributing to low family history reports of rosacea. In our cohort, some patients stated

that they suspected family members of having rosacea, but only definite diagnoses were included in our analysis, probably underestimating family history of rosacea.

Smoking

There were 13.0% current smokers in COROCO. The median pack-years for smokers were 24.6 years (IQR 13.3-26.0). A total of 36.6% were former smokers.

Smoking in rosacea is debated. Some studies find a lower prevalence of smoking in patients with rosacea,[40,41] and find current smoking to be protective against incident rosacea,[42] whereas others find a higher prevalence of smoking.[43,44]. Smoking constricts the peripheral blood vessels, possibly masking rosacea which could be a reason for why we see a lower prevalence of current smoking in the rosacea group. Interestingly, past smoking has been associated with a higher risk of incident rosacea compared to never smokers,[36,42] perhaps due to an autoimmune response, but this needs further investigation.

Alcohol

Regular intake of alcohol was seen in 79.3% of COROCO with a median average intake of 4 items/week (IQR 1.0 – 9.0).

Alcohol is a common trigger of flushing in patients who already have rosacea.[45–47] Intake of alcohol seems to be associated with a higher risk of incident rosacea in some studies,[40,48,49] though other studies have failed to confirm this association.[36,50,51]

Body mass index

Median body mass index (BMI) was 25.7 (23.1 – 29.0). Stratified into groups, underweight (BMI < 18.5) was seen in 1.3% (4 patients), normal weight (BMI between 18.5 – 25) was found in 39.7% (119 patients), overweight (BMI between 25 – 30) was present in 40.7% (122 patients), and obesity (BMI > 30) was found in 18.3% (55 patients).

High BMI may be a risk factor for incident rosacea.[52,53] Metabolic disease[52] and cardiovascular comorbidities are more common in rosacea, though the causal relationship is debated.[43,54–56]

Dermatology Life Quality Index (DLQI)

Median DLQI was 2 (IQR 1 - 5). Stratified into groups, DLQI of 0-1 (no effect on quality of life) was present in 42.7% (128 patients). DLQI between 2-5 (mild effect on quality of life) was present in 35.0% (105 patients). DLQI between 6-10 (moderate effect on quality of life) was found in 12.0% (26 patients), and DLQI between 11-20 (large effect on quality of life) was found in 10.0% (30 patients). DLQI 20 (extreme effect on quality of life) was found in 0.3% (1 patient).

Interestingly, we find a very low impact of rosacea on daily quality of life. There may be a number of reasons for this. One, DLQI is an immediate view on quality of life during the

past week. Rosacea is fluctuating and patients may not have had a lot of symptoms at the time of the interview, and thus a low DLQI. Second, many patients reported to have previously been very affected by their rosacea, but they were now less affected, either due to acceptance of their symptoms, or because they had been effectively treated. Thirdly, 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.

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.

COMICO

Age and sex

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

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

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

Family history of rosacea

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

Smoking

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

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

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

Alcohol

In COMICO, 62.3% regularly drank alcohol, with a median average intake of 2 items/week (IQR 1.0 – 3.0).

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

Body Mass Index

Median BMI was 24.6 (IQR 21.5 – 28.2). Stratified into groups, underweight was seen in 3.3% (10 patients), normal weight was found in 50.7% (154 patients), overweight was seen in 28.6% (87 patients), and obesity was found in 15.6% (53 patients).

Obesity seems to be a risk factor for migraine,[69–72] and obesity and weight gain contributes to worsening of migraine, with the potential of turning episodic migraine into chronic migraine.[73–77] Patients for COMICO were primarily recruited through the Danish Headache Center, which is a highly specialized unit and 38.2% turned out to have chronic migraine, which may have contributed to a higher BMI in this group.

Dermatology Life Quality Index (DLQI)

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 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)

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.

Future plans

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

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,[79] 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 features, first presenting sign/symptom and later onset of other rosacea features 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 rosacea feature sometimes many years prior to interview. In those with either rosacea or migraine, there is a higher chance that they will

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

Collaboration

For future potential collaborations and secondary use of the data, the corresponding 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.

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Figure captions

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

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

Appendices

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.

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.

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.

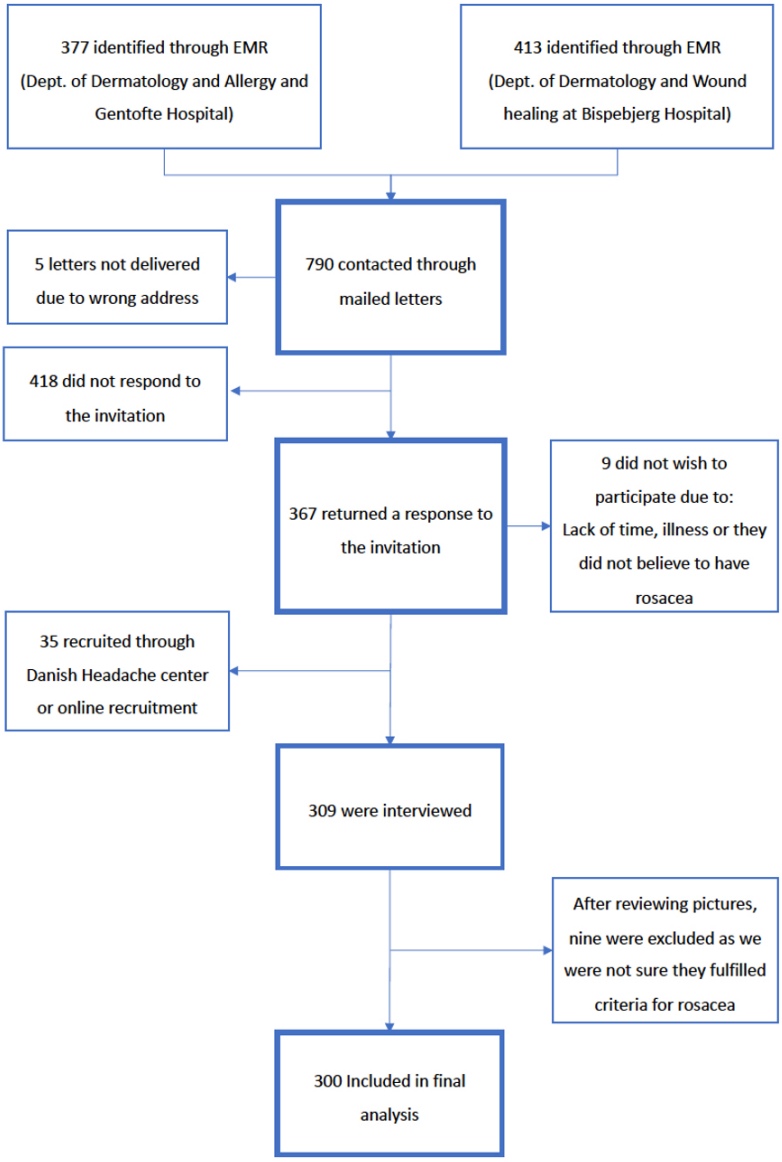


Figure 1. Flow chart detailing enrollment in Copenhagen Rosacea Cohort (COROCO). EMR, Electronic Medical Records.

150x225mm (150 x 150 DPI)

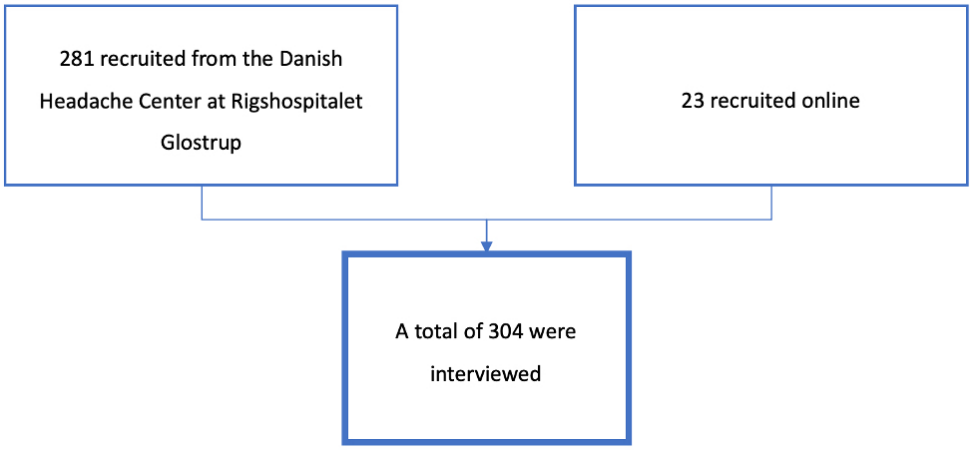


Figure 2. Flow chart detailing enrollment in Copenhagen Migraine Cohort (COMICO).

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 aswer)

- ▭ **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
▭ Mirvaso (brimonidine tartrate) creme/gel	▭	▭	▭
▭ Finacea (azelaic acid) creme/gel	▭	▭	▭
▭ Metronidazole / metrocrem / rozex / robaz creme/gel	▭	▭	▭
▭ Oracea (doxycycline) tablet	▭	▭	▭
▭ Soolantra (ivermectin) creme	▭	▭	▭
▭ Tetracycline	▭	▭	▭
▭ Erythromycin (macrolide) tablet	▭	▭	▭
▭ Accutin / Isotretinoin tablet	▭	▭	▭
▭ Other: _____			

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 you 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 phychiatric 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 you 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 you 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 you 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	□ 1	□ 2
b. Pulsating	□ 1	□ 2
c. Moderate/severe intensity	□ 1	□ 2
d. Aggravation by physical activity	□ 1	□ 2
e. Nausea	□ 1	□ 2
f. Vomiting	□ 1	□ 2
g. Photofobia	□ 1	□ 2
h. Phonofobia	□ 1	□ 2
i. Osmophoabia	□ 1	□ 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		
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/parestesias	□ 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. Photofobia	□ 1	□ 2
h. Phonofobia	□ 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. Ca^{2+}-antagonists are efficient	□ 1	□ 2	□ 3
c. Angiotensin II receptor blockers are efficient	□ 1	□ 2	□ 3
d. ACE-inhibotors 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

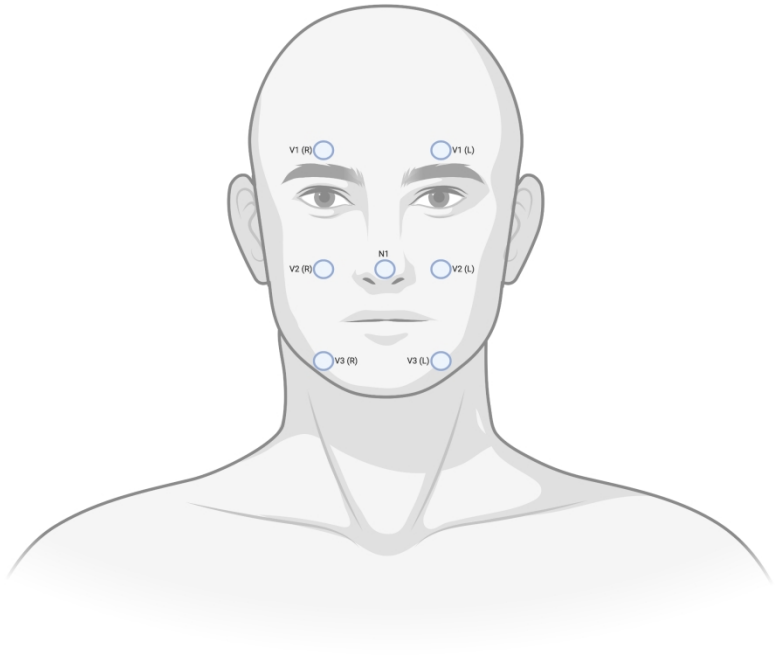
8. SECONDARY HEADACHES?	Yes	No
	□ 1	□ 2

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)