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Sex Differences in Clinical Features, Treatment, and Lifestyle Factors in Patients With Cluster Headache

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Abstract

Background and Objectives: Cluster headache is considered a male-dominated disorder, but we have previously suggested that females may display a more severe phenotype. Studies on sex differences in cluster headache have been conflicting, therefore this study, with the largest validated cluster headache material at present, gives more insights into sex-specific characteristics of the disease. The objective with this study was to describe sex differences in patient demographics, clinical phenotype, chronobiology, triggers, treatment, and lifestyle in a Swedish cluster headache population.

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Methods: Study participants were identified by screening medical records from 2014 – 2020, requested from hospitals and neurology clinics in Sweden for the International Classification of Diseases 10 code G44.0 for cluster headache. Each study participant answered a detailed questionnaire on clinical information and lifestyle and all variables were compared with regards to sex.

Results: 874 study participants with a verified cluster headache diagnosis were included. 575 (66%) were male and 299 (34%) were female and biological sex matched self-reported sex for all. Females were to a greater extent diagnosed with the chronic cluster headache subtype compared to males (18% vs 9%, P=0.0002). In line with this observation, female participants report longer bouts than male participants (P=0.003) and used prophylactic treatment more often (60% vs 48%, P=0.0005). Regarding associated symptoms, females experienced ptosis (61% vs 47%, P=0.0002) and restlessness (54% vs 46%, P=0.02) more frequently compared to males. More female than male study participants had a positive family history for cluster headache (15% vs 7%, P=0.0002). In addition, females reported diurnal rhythmicity of their attacks more often than males (74% vs 63%, P=0.002). Alcohol as a trigger occurred more frequently in males (54% vs 48%, P=0.01), while lack of sleep triggering an attack was more common in females (31% vs 20%, P=0.001).

Discussion: With this in-depth analysis of a well-characterized cluster headache population, we could demonstrate that there are significant differences between males and females with cluster headache which should be regarded at time of diagnosis and when choosing treatment options. The data suggests that females generally may be more gravely affected by cluster headache than males.

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Introduction

Cluster headache is a severely painful primary headache disorder characterized by unilateral, orbitally located head pain and is often accompanied by autonomic symptoms, such as lacrimation or ptosis, or a feeling of restlessness. During an active bout, headache attacks occur up to eight times per day and last between 15-180 minutes. In episodic cluster headache patients, active bouts are separated by symptom-free remission periods, whereas in chronic cluster headache patients, these remissions last less than three months per year.[1] As many as 1 per 500 are estimated to suffer from cluster headache, and although it is considered a male-dominated disease, the reported male-to-female ratio has shifted over the years from about

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6:1 before 1960 to 5.1-2.5:1 in 2018.[2–5] This shift is suggested to be an effect of lifestyle changes in both males and females, but possibly also due to increased recognition of the disease.[6]

A prominent feature of cluster headache is the striking diurnal and seasonal rhythmicity. For many patients, a cluster bout can arise during a certain time of the year while headache attacks recur with clock-like regularity at the same time of the day, leading to the premise that cluster headache is partly a disease of hypothalamic function and the circadian system.[7] The hypothalamus displays a large variety of functions, such as regulation of metabolic and neuroendocrine processes as well as sleep and circadian rhythm.[8] The suprachiasmatic nucleus (SCN), located within the hypothalamus, is considered the master clock of the brain orchestrating the daily cycles of behavior and physiology by synchronizing the peripheral circadian clocks of the body.[9] The peripheral clocks are regulated on a molecular level by so-called clock genes, including *Circadian Locomotor Output Cycles Kaput* (*CLOCK*) which has been associated with cluster headache.[10] In addition, studies could detect alterations in hormone levels for cluster headache patients, including melatonin, supporting a hypothalamic involvement in cluster headache.[11,12] These findings also pose the question how males and females with cluster headache are affected differently by the disease, specifically due to structural and functional sex differences in the hypothalamus.[13,14] Interestingly, the diurnal attack cycle is advanced by one hour in male as compared to female cluster headache patients, suggesting sex differences in cluster headache chronobiology.[15]

The literature is conflicting when comparing the clinical presentation of cluster headache in males and females. While some studies could not see major differences in clinical characteristics between the sexes, others have observed discrepancies in age at onset, pain location, attack duration, associated symptoms, and comorbid conditions, such as depression.[4,15–18]

Because there appears to be a clear divergence for various aspects of cluster headache in males and females, we performed an in-depth analysis of the so far largest validated cluster headache cohort. We examined and compared not only clinical phenotype and patterns of chronobiology, but also heredity, treatment, trigger and lifestyle factors between male and female cluster headache patients from Sweden.

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Methods

Study population

All included study participants were diagnosed with cluster headache and subtype by neurologists through structured interviews and clinical examination, according to the criteria of International Classification of Headache Disorders (ICHD), 3rd edition.[1] Study participants were identified between 2014 – 2020 by requesting medical records for the International Classification of Diseases (ICD) 10 code G44.0 for cluster headache from all major hospitals and neurology clinics over Sweden, as well as in conjunction with cluster headache patient visits to outpatient clinics. 430 of the participants were diagnosed by the experienced neurologists and co-authors A.S, C.S, or E.W at the Karolinska University Hospital. All medical records from G44.0 patients outside the Karolinska University Hospital catchment area (n=444) were read by co-authors A.S, C.S, or E.W to verify that the diagnosis fulfilled the criteria of the ICHD.[1] Patients identified outside the Karolinska University Hospital catchment area were recruited by being contacted by phone and/or mail and asked to complete a paper questionnaire. For patients attending outpatient clinics, the questionnaire was completed in relation to the visit. This study is focused on differences between biological sex (male/female) with regards to cluster headache. All participants have been genotyped for their biological sex and it matched their self-reported sex.

Questionnaire

The questionnaire was composed of three parts consisting of both checklist and free text items (Table 1). The first part included personal, demographic, and medical information, the second part included questions designed to assess different clinical aspects of the disease, and the third part included questions related to lifestyle. The two questions on pain intensity respectively annual rhythmicity were added 2016 and were therefore not answered by all participants. Non-responders were reminded up to two times to participate in the study. All questionnaire data is self-reported except cluster headache diagnosis which was validated according to the criteria of the ICHD. All assessed variables compared with regards to sex are listed in Table 2.

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Statistical analysis

Welch's t-test was used to compare the means of continuous variables. Fisher's exact test, or chi-squared test for more than two categories, was used to compare proportions of categorical variables. All tests were two-tailed and $\alpha < 0.05$ was considered statistically significant. Analyses were performed using GraphPad Prism version 9.0.0 for Windows (GraphPad Software, San Diego, CA, USA, *www.graphpad.com*). All data are presented as either mean ± standard deviation (SD) or as proportions with odds ratio (OR) and 95% confidence interval (CI) for males versus females.

Standard Protocol Approvals, Registrations, and Patients Consents

The study was approved by the Swedish Ethical Review Authority in Stockholm, Sweden (diary number 2014/656-31/4). Written informed consent was obtained from all participants in the study.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator following the Karolinska Institutet data transfer agreement and General Data Protection Regulation (GDPR).

Results

To date, 1,484 individuals were recruited for inclusion in our cluster headache biobank of which 874 participated in this questionnaire study (Figure 1). 496 were excluded due to; deceased before study start (n=17), did not wish to participate (n=31) or had not replied at the specific time point of data collection (n=448), of which 293 (65.4%) were males and 155 (34.6%) females. Out of the remaining 988 individuals a G44.0 diagnosis could not be confirmed for 114. Of the 874 participants, all validated with a G44.0 diagnosis by the authors (A.S, C.S, or E.W) according to ICHD criteria, 575 (65.8%) were males and 299 (34.2%) were females. 186 (21.9%) reported to be in a cluster bout when answering the questionnaire. No individuals were removed due to missing data (eTable 1 in the Supplement). Demographic and clinical data as well as the subsequent statistics have been

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summarized in Table 2. The age at the time of completing the questionnaire differ slightly between male and female participants (51.3±13.9 vs. 49.0±15.0, *P*=0.028). Male and female participants do not differ in age at cluster headache onset, although there is a lower proportion of males with cluster headache onset below the age of 20 years compared to females (16.2% vs. 23.0%, *OR* [95% CI]:0.64 [0.44–0.92], *P*=0.020). We have previously reported that chronic cluster headache patients have a later mean disease onset than episodic cluster headache patients and this delay could be observed in both sexes in the present study (eFigure 1A).[19]

Regarding family history, significantly fewer males than females had a first- or second-degree relative also diagnosed with cluster headache (7.1% vs. 15.4%, OR [95% CI]:0.42 [0.27–0.66], *P*=0.0002).

Interestingly, the proportion of males with chronic cluster headache was lower than for females (9.4% vs. 18.4%, OR [95% CI]:0.46 [0.31–0.70], *P*=0.0002). In line with this observation, bout length, but not attack frequency or attack duration, differed between males and females (*P*=0.004) with female participants tending to have longer cluster headache bouts than male participants. Pain intensity was reported equally high for both sexes, and associated symptoms occurred similarly except for ptosis (47.0% vs. 60.5%, OR [95% CI]:0.58 [0.43–0.76], *P*=0.0002) as well as restlessness (45.6% vs. 53.9%, OR [95% CI]:0.72 [0.54–0.95], *P*=0.024) which were both more common in females. The mean body mass index (BMI) differed significantly between male and female participants (26.5±4.1 vs. 25.0±4.9, *P*<0.0001). In addition, fewer male than female participants suffer from self-reported migraine (12.5% vs. 29.4%, OR [95% CI]:0.34 [0.24–0.49], *P*<0.0001) and male participants suffered less from tension-type headache than female participants (44.3% vs. 57.6%, OR [95% CI]:0.58 [0.44–0.78], *P*=0.0002).

Presence of diurnal rhythmicity of attacks was less common in male than female cluster headache participants (364/575 [63.3%] vs. 220/299 [73.6%], OR [95% CI]:0.62 [0.46–0.85], *P*=0.002). Additionally, the number of attacks per two-hour time interval over 24 hours differed between males and females (*P*=0.002) with a higher frequency of nightly attacks in females (Figure 2A). We could not find a difference in the occurrence of annual rhythmicity of cluster headache bouts nor in the bout distribution by month of the year between the sexes (Figure 2B). Male and female participants differed slightly in self-reported chronotype; morning, evening or neither. Females tended to be morning types while more males tended to

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describe themselves as evening types (*P*=0.046). Since a shift in chronotype with age has been reported, we also analyzed chronotype in different age groups between males and females (eTable 2 in the Supplement).[20,21] Overall, we saw a difference in chronotypes by sex and age (*P*=0.001). In addition, hours of night sleep varied between males and females (*P*=0.017), especially more female participants got less than five hours of sleep per night.

When comparing acute and prophylactic treatments between male and female participants, both sexes generally used abortive medication at equally high proportions (>90% of the participants). In addition, we specifically compared different abortive medications (Figure 3A) and detected a less frequent use of oxygen by males compared to females (27.8% vs. 36.5%, OR [95% CI]:0.67 [0.49–0.92], *P*=0.013). Oxygen is not prescribed to smokers in Sweden, and it has been reported that cluster headache patients (both males and females) smoke more than the general population.[19] However, there was no difference in smoking habits between male and female participants (26.8% vs. 25.1%, *P*=0.63; eTable 3 in the Supplement). Regarding prophylactic treatment, significantly fewer males used preventive medication than females (47.7% vs. 60.2%, OR [95% CI]:0.60 [0.45–0.80], *P*=0.0005), although the use of specific prophylactic medications did not differ between the sexes (Figure 3B).

In our questionnaire, we asked participants to list any possible triggers that could elicit a cluster headache attack during a bout in a free-text answer, and we categorized and summarized the most common answers for all participants, subdivided by sex, in Figure 4. There was no significant difference in reporting trigger factors as free-text answers between males and females (49.2% vs. 54.5%, *P*=0.15, data not shown). Alcohol was by far the most listed trigger among participants who reported trigger factors for their attacks (50.7%), and males reported more often than females that alcohol provoked a cluster headache attack (56.5% vs. 40.5%, OR [95% CI]:1.91 [1.29–2.81], *P*=0.001). Alcohol intake differed significantly between male and female participants with males generally consuming more alcohol than females (*P*<0.0001; see eTable 4 in the Supplement). This trend between sexes is also seen in the general Swedish population (Source: Statistics Sweden), although it appears that overall fewer participants have a high alcohol consumption while more participants have seldom, or no alcohol consumption compared to the general population. Interestingly, we could not see a difference in alcohol intake (*P*=0.25) nor alcohol as trigger factor (*P*=0.67, data not shown) when comparing males and females with chronic cluster headache. The second most described trigger factor for cluster headache attacks was stress

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(26.7%) which was not as common for males as for females (20.5% vs. 37.4%, OR [95% CI]:0.43 [0.28–0.66], *P*=0.0001). Other trigger factors that differed significantly between male and female participants were changes in weather/temperature or draft/gust (11.3% vs. 25.2%, OR [95% CI]:0.38 [0.23–0.63], *P*=0.0003), lack of sleep (8.1% vs. 14.7%, OR [95% CI]:0.51 [0.28–0.92], *P*=0.037), and food/drink (13.1% vs. 6.7%, OR [95% CI]:2.08 [1.06–4.20], *P*=0.040). Most described food items or non-alcoholic beverages that may trigger an attack were chocolate, sweets or food/beverages with high sugar content, coffee/tea, (strong) cheese, food with high salt content, and spicy/pungent food. In addition to free-text answers, participants with cluster headache were specifically asked whether alcohol, coffee/tea, or lack of sleep may trigger an attack. These specific questions confirmed the free-text answers: Alcohol as a trigger was more commonly reported by male participants (*P*=0.01) while lack of sleep triggered attacks in females more often than in males (*P*=0.001). There was no difference for coffee/tea as a trigger and 1.2% of the female participants reported hormone related factors, like menstruation, as a trigger.

Discussion

In this study, we methodically analyzed and compared demographic, clinical and lifestyle features between 575 male and 299 female participants with cluster headache from Sweden. We did not find a difference in mean age at onset between male (31.9 years) and female (31.8 years) participants, but a higher proportion of females with cluster headache onset below the age of 20 years which agrees with a study on cluster headache in the United States of America.[18] It is unclear why more female than male participants had an early onset of cluster headache. Interestingly, both male and female participants with chronic cluster headache showed a delay in disease onset with no difference between the groups (data not shown), except for a minor second peak at onset above 60 years. This data needs to be interpreted with care due to thinning down of the sample size but could suggest that females with late cluster headache onset suffer from a harsher form of the disease. Overall, we could not confirm a bimodal pattern for disease onset as reported in the American study, only an indication of two peaks for females with chronic cluster headache which has also been suggested in an Italian study.[22] This bimodal pattern has led to speculations on hormonal involvement in cluster headache, as these peaks coincide with menarche and menopause in females.[16] However, a study on the influence of for example menstruation and menopause could not find a clear association with cluster headache.[23]

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It was previously observed in a Danish study that both male and female cluster headache patients have a higher mean BMI compared to controls.[24] In our study BMI categories of male and female cluster headache participants were compared to the general Swedish population using publicly available health data from Statistics Sweden (eTable 5 in the Supplement). The mean BMI was higher for male cluster headache participants than for female participants (P<0.0001) which is also seen in the general population (P<0.0001). When comparing to the general population, we found a higher mean BMI for cluster headache (P<0.0001). Interestingly, this difference was only significant for male participants (P=0.009) but not for female participants (P=0.34). When analyzing the frequencies of the different BMI categories (underweight, normal, overweight, and obese) in participants and controls, we observed the same trend: Male, but not female, participants tend to be more overweight or obese compared to males (P=0.005) and females (P=0.66) in the general population. This suggests that especially males with cluster headache have a risk of being overweight, possibly due to a less healthy lifestyle.

Curiously, significantly more female (15%) than male (7%) participants had a first- or second-degree relative also diagnosed with cluster headache which is in concordance with two recently published review articles on family history of cluster headache where they noted a predominance of females with familial cluster headache.[25,26]

In addition, there was a preponderance of females (18%) over males (10%) with the chronic cluster headache subtype which has been observed in another Scandinavian cohort recently.[27] This is also reflected in longer cluster headache bouts for female participants compared to males which indicates that, although cluster headache is still considered a predominantly male disease, females may generally suffer from a more debilitating form of cluster headache. Nevertheless, the pain intensity during a cluster headache attack does not differ between sexes and is equally excruciating for both male and female participants, as previously reported.[4,15]

Generally, we could see that associated symptoms occurred with similar frequencies in males and females. Only ptosis and restlessness were more common in female participants which agrees with earlier studies (note that restlessness was phrased as “need to move”).[15,16] We could not confirm nausea to be more frequent in females with cluster headache, nor was nausea associated with migraine in our cluster headache cohort (data not shown).[16,18,28]

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The prevalence of migraine is found to be between 13.8–18% in Sweden with a majority of the affected being females.[29,30] As in the general population, fewer male than female cluster headache participants suffer from self-reported migraine (P<0.0001). Depending on which study we compare our data with, we could or could not find differences in the prevalence of migraine between the general Swedish population and Swedish cluster headache participants (eTable 6 in the Supplement). When comparing to Swedish twins in the PILOT study, both male and female cluster headache participants have a higher prevalence for migraine than controls [29]. This difference could not be seen in comparison to the OCTO-Twin or the GENDER study of Swedish twins except for female participants in our cluster headache cohort compared to females in the OCTO-Twin study.[30] As for other primary headache disorders, male cluster headache patients suffered less from tension-type headache than female patients (P=0.0002). In the PILOT study, the prevalence of tension-type headache for the general Swedish population is 10.9% for men and 15.7% for women which is quite a bit lower than in our cluster headache cohort (P<0.0001, data not shown).[29] However, population studies from other countries have found a higher prevalence of tension-type headache which indicates a high variability.[31,32] Since these data are not based on a clinical diagnosis but are self-reported, we need to be careful with interpreting these results. The Danish Headache Centre reported a high comorbidity of clinically diagnosed tension-type headache in migraine patients (67%), thus there may indeed be an increased incidence of other types of headaches in primary headache patients.[33] To our knowledge, comorbidity of tension-type headache with cluster headache has not been reported previously. Our findings suggest that females with cluster headache are more likely to suffer from other primary headache disorders in addition to cluster headache.

Chronobiology clearly differs between males and females with cluster headache. More female (74%) than male (63%) participants report diurnal rhythmicity of their attacks and although both sexes have a peak of attacks occurring at nighttime, females were more likely to have cluster headache attacks at night and during the early morning hours while the lowest frequency of attacks for females was around lunchtime. For males, attack occurrence was more spread out throughout the 24-hour day. Annual rhythmicity of cluster bouts occurred roughly in 50% of both sexes which agrees with previous observations.[15] The distribution of cluster bouts throughout the year shows a clear peak in fall as well as a smaller peak in spring for both sexes. A study on an arctic cluster headache population found that cluster bouts more likely started around the equinoxes in March and September, times of the year when the daily

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change of natural light is most noticeable and the SCN increases in size.[34,35] Intriguingly, a preliminary study from Portugal could find an increase in *CLOCK* gene expression in cluster headache patients at the September equinox.[36] These findings suggest an involvement and possible dysregulation of circadian rhythm in cluster headache producing specific diurnal as well as annual attack patterns.

Nocturnal sleep duration differed significantly between males and females. Most male participants slept 6-7 hours per night while female participants had a large variance in sleep duration. A higher proportion of females (13%) slept less than 5 hours per night compared to males (8%) which could be explained by the more frequent nighttime cluster headache attacks. Studies on sex differences for sleep in the general population report longer sleep duration for females.[37] In addition, more females than males report inadequate sleep which, together with the observation that males more likely function well with less than seven hours of sleep, suggests that females may be more susceptible to clinical symptoms from sleep difficulties and could potentially be more debilitated by nocturnal cluster headache attacks.[38,39]

With respect to treatment for cluster headache attacks, there was no difference in use of acute medication between male and female participants except for oxygen which was reported more frequently in females (37%). We could exclude smoking as a factor contributing to a lower use of oxygen in males (28%). It remains unclear why female cluster headache participants in Sweden use oxygen more often than males to abort cluster headache attacks. Other studies rather report the opposite, and although efficacy does not seem to differ between the sexes, a slower response has been observed in females.[40,41] The use of prophylactic medication during cluster headache bouts was higher in female (60%) compared to male (48%) participants which is not surprising considering that significantly more females suffer from chronic cluster headache.

To reduce bias, participants were asked to write down specific triggers for their cluster headache attacks during a bout instead of presenting them with a list of possible trigger factors. The response rate to this question was similar between males and females, therefore unlikely that one sex recalled possible triggers better than the other. Alcohol was the most common trigger to elicit an attack among those reporting triggers, and more males (57%) than females (40%) reported alcohol as a trigger which concurs with previous reports.[15,18] As to why this is, a possible explanation could be that male episodic cluster headache

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participants consume more alcohol than female episodic cluster headache participants and they may not reduce their alcohol intake as much during a bout as females. However, our data does not differentiate between alcohol consumption during and out of bout but rather reflects general intake. We could not directly compare alcohol intake between cluster headache participants and the general Swedish population due to different definitions (eTable 6 in the Supplement), but it appears that both male and female cluster headache participants have a lower alcohol consumption than the general Swedish population which would contradict a Danish study on lifestyle of cluster headache patients.[24] However, we think that a reduced alcohol intake in cluster headache participants seems rational considering that alcohol is a very common trigger for headache. In addition, our data suggests that cluster headache participants with a high disease burden have very low alcohol consumption.

Other often reported trigger factors were stress and lack of sleep which were both more frequently reported by females (38% and 15%) than by males (21% and 8%). Research has pointed out sex differences in stress response mechanisms. Females have been reported to be more vulnerable to stress-induced hyperarousal, a state of increased agitation, restlessness, and sleep disruption, while males are more afflicted with stress-induced cognitive deficits as well as structural and functional changes in brain regions critical for cognition.[42] Perhaps, stress-induced arousal may, among other things, lead to sleep deprivation and consequently contribute to triggering a cluster headache attack in females. This is also supported by the higher frequency of restlessness seen during attacks in female participants. In addition, when cluster headache participants were specifically asked whether sleep deprivation elicits an attack, 31% of the females and only 20% of the males said yes, indicating that females with cluster headache are more sensitive to disrupted sleep. Interestingly, a Korean study on sex differences reports higher perceived psychological stress in female compared to male cluster headache participants.[4]

The causal relationship between attack triggers and cluster headache is still unclear and some triggers may be associated wrongly. For example, both stress and relaxation (after stress) are mentioned as separate trigger factors, although they are interconnected. Additionally, in migraine, many premonitory symptoms may be misinterpreted as triggers, for example chocolate and the craving for sweets or chocolate.[43] In cluster headache, although not as pronounced, premonitory symptoms have also been reported and could therefore underlie the same misinterpretation by participants.[44]

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The findings of this study reveal distinct differences in chronobiology and disease burden between the sexes. Cluster headache in females present with more pronounced diurnal rhythmicity and may affect females much more in their everyday life, as demonstrated by nightly attacks disrupting their sleep and overall longer cluster headache bouts leading to the need for more prophylactic treatment. In addition, females are more likely to get cluster headache if they have a family history for the disease, and female cluster headache participants more likely suffer from other headache disorders. Finally, females may be more susceptible to stress and sleep deprivation as triggers for their cluster headache attacks. Our study indicates that male participants generally have a less healthy lifestyle, underlined by a higher BMI and tobacco consumption than the general population as well as a higher alcohol intake than females.

The strengths of this study are the large sample size, the largest reported to date, and a well-defined and representative cohort where all participants have been diagnosed with cluster headache by a neurologist, according to the ICHD. Cluster headache prevalence was recently reported to be 0.054% in individuals of working age in Sweden.[45] This corresponds to approximately 5,400 individuals and more than 25% of these have been contacted to participate in this study. Participants were recruited via different channels (medical records, outpatient clinics) which may reduce the risk of only including participants with high disease burden. The sex distribution among non-responders at the specific time point of data collection (65.4% males and 34.6% females) was similar to the responder group (65.8% males and 34.2% females), making it unlikely that results are influenced by differential participation by sex. There are limitations to our study. All data is self-reported which may introduce recall bias in relation to e.g., medication and if the participant was in or out of bout. Our study did not include, and thereby did not consider, persons whose biological sex characteristics and self-reported sex are not synonymous. Sex bias in diagnosis could potentially contribute to the observed differences in severity. Cluster headache is still considered to be a disorder of males and may thereby making it more difficult for females with milder symptoms to be diagnosed with cluster headache than males which could contribute to the higher relative frequency of e.g., chronic cluster headache in females. In addition, this is an observational study where causality is difficult to infer from the associations found.

In conclusion, this is the largest study on sex differences in verified cluster headache patients to date which may help to increase our understanding in which manner the disorder manifests

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differently in males and females. Cluster headache is still often misdiagnosed in females, perhaps because certain features of the disease in female patients resemble a migraine-like phenotype. It is therefore of utmost importance for physicians to be aware of these sex differences when working in the clinic and meeting headache patients to be able to give the most effective treatment as fast as possible.

http://links.lww.com/WNL/C534

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Table 1. Questions to study participants.

Nr	**Question**
1	Social security number or assigned code:
2	Age:
3	Height (cm) and Weight (kg):
4	Birthplace and country:
5	Nationality:
6	Sex: □ Female □ Male
7	Profession / occupation:
8	Do you suffer or have you ever suffered from cluster headache? □ Yes. Which year did the disease first emerge? ……… □ No (go to question 23) Who performed the diagnosis? □ Neurologist □ Other physician
9	What medication do / did you use for cluster headache? Select the ones that you usually use / used. *Acute*: <u>Injection</u> □ Imigran □ Sumatriptan SUN <u>Nasal spray</u> □ Imigran □ Zomig <u>Tablet</u> □ Maxalt □ Sumatriptan □ Citodon □ Zomig □ Relpax □ Treo Comp □ Anervan Novum (tablet/suppository) □ Oxygen □ Other, which?……………………………… *Preventive or for attack abortion during the active period*: □ Verapamil/Isoptin □ Lithionit □ Prednisolon □ Sandomigrin □ Topimax/Topiramat □ Other, which? ……………………………………………………………………………
10	What form of cluster headache do / did you suffer from? □ Episodic □ Chronic *<u>Definition Episodic Cluster Headache</u>* *Recurring cluster headache attacks cumulated in periods. Cluster periods last from seven days up to a year. There should be symptom-free period of three months or more between cluster periods.* *<u>Definition Chronic Cluster Headache</u>* *Recurring cluster headache attacks during one year or more without interruption, or with short symptom-free intermissions which last less than three months.*
11.	How many attacks <u>per day</u> do you typically have during active periods (so-called cluster bouts)?

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	□ Less than 1 □ 1 - 2 □ 3 - 5 □ 6 or more
12.	For how long does an attack last? □ 15 – 30 min □ 30 min – 120 min □ 2 – 3 hours □ 3 – 5 hours □ 5 – 12 hours □ more than 12 hours
13.	For how long do your cluster bouts usually last? □ Less than 1 week □ 1 week – 1 month □ 1 – 2 months □ 2 – 4 months □ 4 – 7 months □ 7 – 12 months □ More than 12 months
14a.	How many cluster bouts do you usually have throughout one year? □ 0 □ 1 □ 2 □ 3 □ 4 or more
14b	How many cluster bouts have you had in total? □ 1 □ 2 □ 3 or more □ I have/had chronic cluster headache, i.e. recurring attacks for more than a year without remission for at least three months
14c.	On which side of the head is your pain located? □ Always on the right □ Always on the left □ Sometimes right, sometimes left
15.	During a headache attack do you also experience □ Redness of the eye □ Tearing of the eye □ Drooping eyelid □ Nasal congestion □ Runny nose □ Restlessness □ Difficulties lying still □ Nausea or vomiting □ Increased pain when taking the stairs/exercising
16.	Are you currently in a cluster bout? □ Yes □ No
17.	At what time(s) of day do your attacks usually occur? □ 00:00 – 02:00 □ 02:00 – 04:00 □ 04:00 – 06:00 □ 06:00 – 08:00 □ 08:00 – 10:00 □ 10:00 – 12:00 □ 12:00 – 14:00 □ 14:00 – 16:00 □ 16:00 – 18:00 □ 18:00 – 20:00 □ 20:00 – 22:00 □ 22:00 – 00:00 □ Random times
18a.	If you have recurring cluster bouts, do they usually appear during a specific time of year? □ Yes □ No (go to question 19)
18b.	During which season(s) do you often have your cluster bout(s)? □ Winter □ Spring □ Summer □ Autumn
18c.	During which month(s) do you most often have your cluster bout(s)? □ January □ February □ March □ April □ May □ June □ July □ August □ September □ October □ November □ December
19.	Have you experienced anything specific to trigger an attack during a bout?

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	□ Yes □ No If yes, what? ....
20.	Have you experienced anything specific to <u>trigger a cluster period</u>? □ Yes □ No If yes, what? ....
21.	How do / did you usually experience the pain during a cluster headache attack before taking medication? □ Unbearable □ Severe □ Moderate □ Mild
22.	Which intensity does the cluster headache have at its worst? *Mark on a scale between 0–10 where 0 = no pain and 10 = worst possible pain.* **0** · **1** · **2** · **3** · **4** · **5** · **6** · **7** · **8** · **9** · **10**
23a.	Do you suffer from migraine? □ Yes □ No (go to question 24)
23b.	Which type of migraine? □ Migraine with aura □ Migraine without aura □ Don’t know
24.	Do you get tension–type headache occasionally? □ Yes □ No
25.	Do you suffer from any other neurological disorder? □ Yes □ No If yes, which one and when did the disease start? ....
26a.	Do you have any relative with a cluster headache diagnosis? □ Yes. How are you related? .... □ No
26b.	Do you have any relative with a migraine diagnosis? □ Yes. How are you related? .... □ No
27.	Do you smoke? □ Yes, since .... □ No, have never smoked □ No, but smoked previously
28.	Do you use snus? □ Yes, since .... □ No, have never used snus □ No, but used snus previously
29a.	Have you experienced alcohol as a trigger for a cluster headache attack? □ Yes □ No
29b.	Alcohol habits: How many standard units of alcohol do you drink when you use alcohol? One standard unit of alcohol: 15 cl table wine, 33 cl strong beer, 50 cl beer, 8 cl dessert wine or 4 cl liquor. □ Don’t consume alcohol □ Rarely drink alcohol (<1 glass/week) □ 1 – 2 glasses/week □ 3 – 4 glasses/week □ ≥1 glass/day
30a.	Have you experienced that coffee and/or black/green tea may trigger a cluster headache attack? □ Yes □ No
30b.	Coffee/tea habits: Do you drink coffee and/or black/green tea regularly? □ No □ Yes, 2 – 6 cups/week □ Yes, ≥ 4 cups/day

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	□ Yes, ≤ 1 cup/week □ Yes, 1 – 3 cups/day
30c.	Have you experienced that coffee / beverages containing caffeine may alleviate a cluster headache attack? □ Yes □ No
31.	Have you ever been exposed to concussion / excessive violence against the head? □ Yes □ No If yes, when? ....
32a.	How much do you sleep per night? □ < 5 hours per night □ > 6 < 7 hours per night □ > 5 < 6 hours per night □ > 7 < 8 hours per night □ > 8 hours per night
32b.	If you have answered Yes to question 8, may lack of sleep trigger an attack? □ Yes □ No
32c.	If you have answered Yes to question 8, may sleep trigger an attack? □ Yes □ No
33.	Would you consider yourself a morning or evening person? □ Morning □ Evening □ Neither
34a.	At what time do you usually go to sleep in the evening? □ 20:00 – 21:00 □ 21:00 – 22:00 □ 22:00 – 23:00 □ 23:00 – 00:00 □ 00:00 – 01:00 □ 01:00 – 02:00 □ 02:00 – 03:00 □ ....:00 – ...:00 □ Random times
34b.	At what time do you usually go up in the morning? □ 04:00 – 05:00 □ 05:00 – 06:00 □ 06:00 – 07:00 □ 07:00 – 08:00 □ 08:00 – 09:00 □ 09:00 – 10:00 □ 10:00 – 11:00 □ ....:00 – ...:00 □ Random times

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Table 2. Demographic and clinical characterization of Swedish cluster headache patients.

	All	Males	Females	*P* - value
Number of individuals (% of All)	874	575 (65.8)	299 (34.2)	–
Interview age (years)	50.5 ± 14.3 (17–83)	51.3 ± 13.9 (17–83)	49.0 ± 15.0 (17–83)	**0.028**
Interview age groups (years)				
<30	8.8	6.6	13.0	
30-39	15.8	16.3	14.7	
40-49	20.3	20.7	19.4	**0.037**
50-59	25.6	25.6	25.8	
60-69	20.5	20.7	20.1	
≥70	9.0	10.1	7.0	
Age at onset (years)	31.9 ± 13.6 (6–70)	31.9 ± 13.1 (6–69)	32.0± 14.4 (11–70)	0.99
Age at onset groups (years)				
<20	18.6	16.2	23.1	
20-29	33.2	35.7	28.4	
30-39	20.4	20.9	19.4	0.08
40-49	14.7	14.6	14.9	
50-59	9.3	9.6	9.0	
≥60	3.8	3.1	5.2	
Heredity	10.0	7.1	15.4	**0.0002**
Chronic CH	12.5	9.4	18.4	**0.0003**
Attacks per day				
<1	6.9	7.4	6.0	
1-2	42.6	43.5	41.1	0.61
3-5	37.5	36.9	38.6	
>5	13.0	12.2	14.4	
Attack duration (min)				
15-30	18.4	17.5	20.2	
30-120	50.9	53.7	45.7	0.10
120-180	17.7	17.1	18.7	
>180	13.0	11.6	15.4	
Bout length (months)				
0-1	28.5	29.8	26.0	
1-2	30.7	31.9	28.3	
2-4	21.1	22.5	18.3	**0.003**
4-7	6.2	5.2	8.0	
7-12	4.9	4.2	6.3	
>12	8.7	6.4	13.0	
Pain intensity*[a]	9.26 ± 0.98 (5–10)	9.24 ± 1.01 (5–10)	9.30 ± 0.95 (6.5–10)	0.62
Associated symptoms				
Conjunctival injection	58.1	59.8	54.8	0.17
Lacrimation	74.7	75.0	74.2	0.87
Ptosis	51.6	47.0	60.5	**0.0002**
Nasal congestion	50.8	49.6	53.2	0.32
Rhinorrhoea	47.3	45.7	50.2	0.23
Restlessness	48.4	45.6	53.8	**0.022**
Nausea*[a]	22.8	20.1	27.1	0.16
BMI	26.0	26.5	25.0	**<0.0001**
Migraine	18.3	12.5	29.4	**<0.0001**
Tension-type headache	47.5	43.1	55.9	**0.0004**
Diurnal rhythmicity	66.8	63.3	73.6	**0.002**
Annual rhythmicity*[b]	50.0	49.4	50.9	0.81
Chronotype				
Morning	31.7	30.3	34.4	
Intermediate	29.2	27.7	32.1	**0.046**
Evening	39.1	42.1	33.4	
Hours of night sleep				
<5	9.7	8.1	12.7	
5-6	17.3	16.8	18.5	**0.017**
6-7	37.7	41.1	31.2	
>7	35.3	34.0	37.7	
Use of acute treatment	92.7	93.2	91.6	0.41
Use of prophylactic treatment	51.9	47.7	60.2	**0.0005**
Trigger Alcohol				**0.01**
Yes	52.1	54.4	47.5	

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No	44.3	43.1	46.5	
Unsure	3.7	2.4	6.0	
Trigger Coffee/Tea				
Yes	5.9	5.9	6.0	0.73
No	91.3	91.7	90.6	
Unsure	2.7	2.4	3.3	
Trigger Lack of sleep				
Yes	23.3	19.7	30.4	**0.001**
No	45.1	47.8	39.8	
Unsure	31.6	32.5	29.8	

Data presented as mean ± standard deviation (range) or as percentage. Heredity includes first- and second-degree relatives with cluster headache. Pain intensity was rated on a scale from 0-10 with 0 = no pain to 10 = worst imaginable pain. *P*-Values were calculated to compare males and females. *Only asked to study participants collected after 2016 based on [a]302 individuals (184 males/118 females) or [b]290 individuals (178 males/112 females) for whom detailed information was available. BMI: Body Mass Index.

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Figure titles and legends

Figure 1. Flow diagram showing inclusion and exclusion of cluster headache patients for study participation. 1,484 individuals were recruited for inclusion in our cluster headache biobank. 496 were excluded due to; deceased before study start (n=17), did not wish to participate (n=31), or had not replied at the specific time point of data collection (n=448). A G44.0 diagnosis could not be confirmed in 114 and in total 874 study participants validated with a G44.0 diagnosis participated in this questionnaire study.

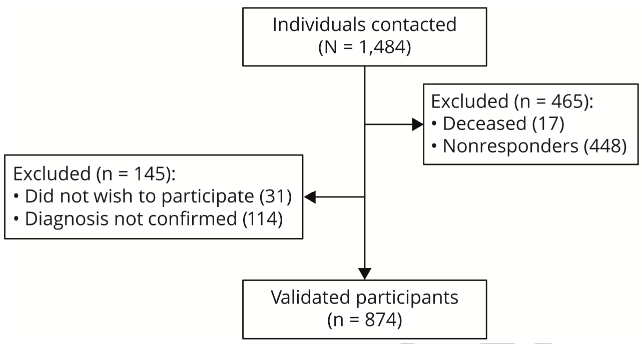

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Figure 2. Diurnal and annual reoccurrence of cluster headache attacks and bouts. (**A**) Participant frequency of attack distributions over 24 hours in two-hour intervals for patients reporting diurnal rhythmicity. Data from 565 cluster headache participants (350 males/215 females). Attack distribution by time of day differs significantly between males and females (*P*=0.002). (**B**) Participant frequency of bout distribution over the year in months for patients reporting annual rhythmicity. Data from 145 cluster headache participants (88 males/57 females). Bout distribution by month did not differ between males and females (*P*=0.72).

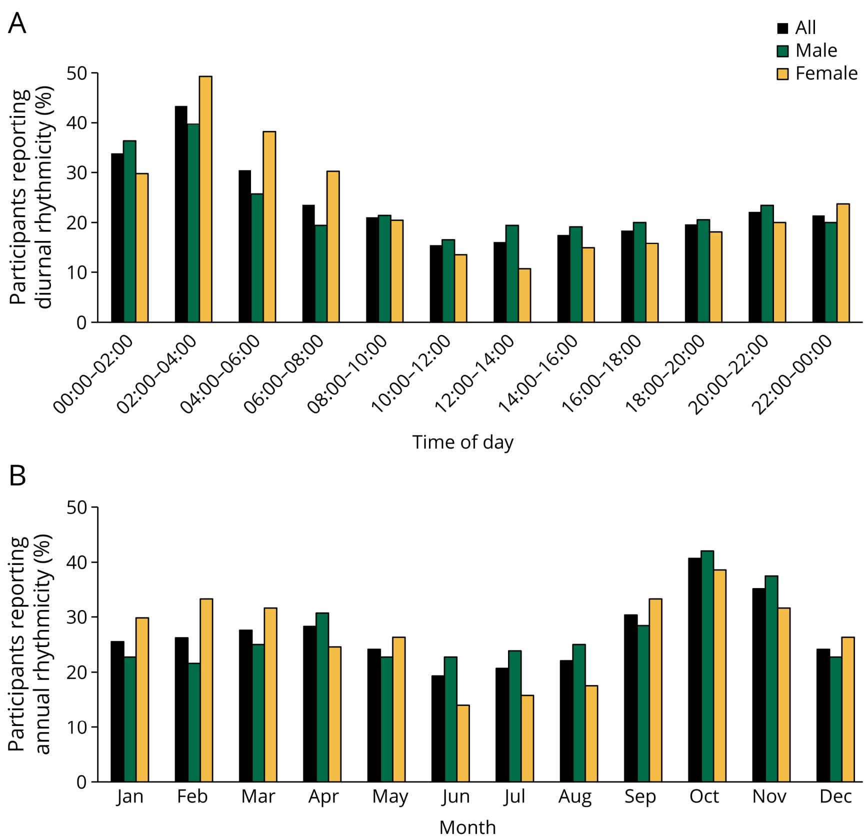

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Figure 3. Acute and prophylactic treatments in cluster headache participants. (**A**) Most used medication for attack abortion among participant who report using acute treatment. Data from 810 cluster headache participants (536 males/274 females). *Oxygen was more commonly used by females compared to males (*P*=0.013). (**B**) Most used preventive medication among cluster headache participants who report using prophylactic treatment (n= 454, 274 males/180 females).

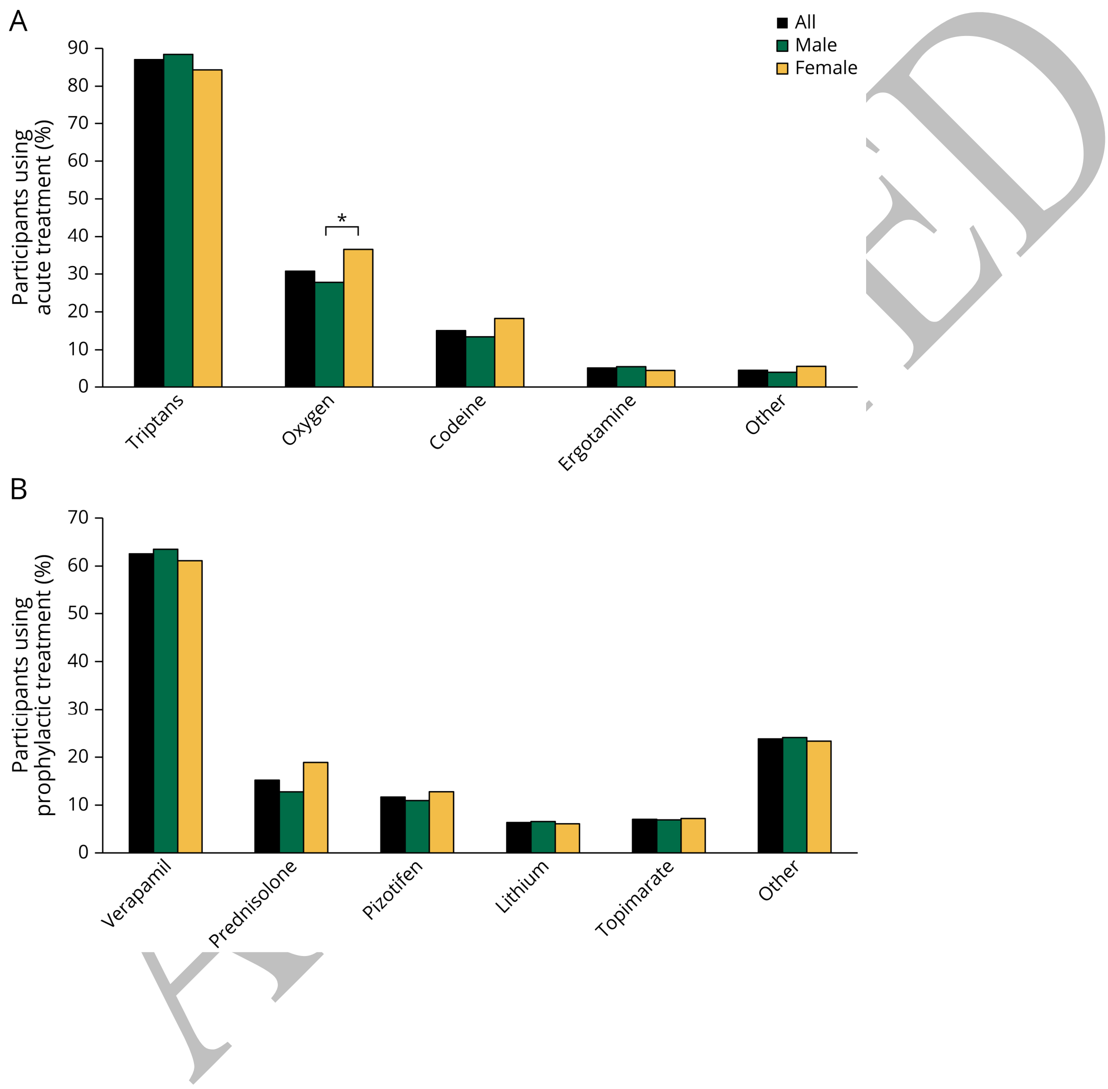

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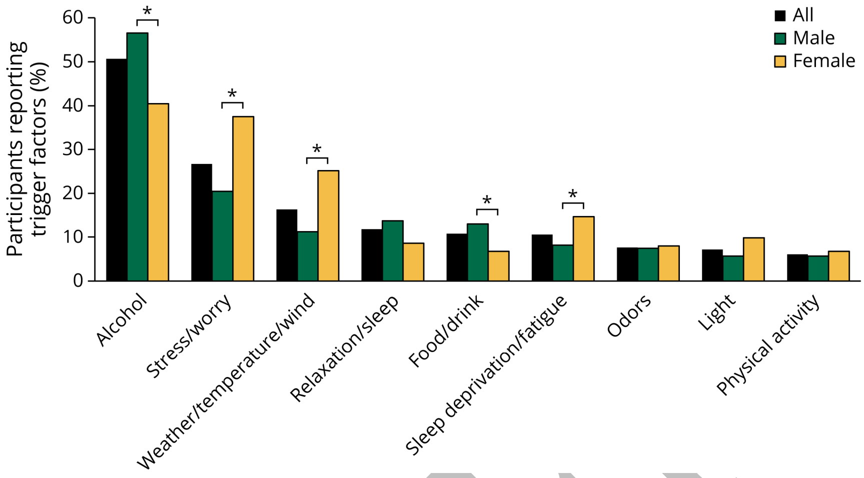
Figure 4. Most common trigger factors for cluster headache attacks during a bout for study participants reporting specific triggers (free-text answers). 446 cluster headache participants (283 males/163 females) reported yes to specific trigger factors. *Significant differences between males and females who report trigger factors were found for alcohol (*P*=0.001), stress/worry (*P*=0.0001), weather/temperature/wind (*P*=0.0003), food/drink (*P*=0.040), and sleep deprivation (*P*=0.037).



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Sex Differences in Clinical Features, Treatment, and Lifestyle Factors in Patients With Cluster Headache

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