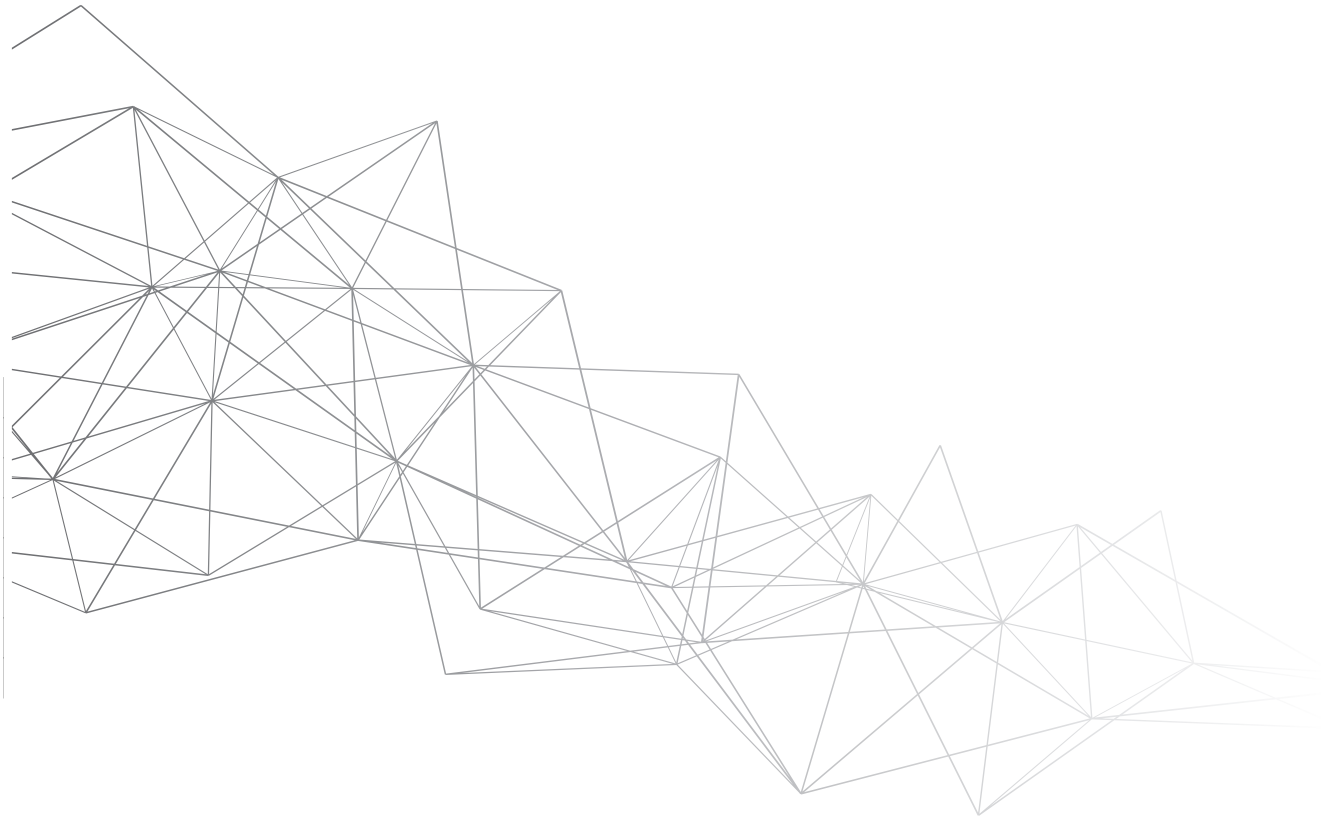
8 CHAPTER

Cluster headache and depression



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Neurology 2016 Nov 1;87(18):1899-1906
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Abstract

Objectives
As cluster headache (CH) is often referred to as 'suicide headache', we wanted to assess the prevalence of depression in cluster headache patients, and to investigate determinants of depression such as sleep disturbances.

Methods
In a cross-sectional, web-based, validated questionnaire study among 462 well-defined CH patients and 177 controls, we diagnosed CH according to the International Classification of Headache Disorders (ICHD-III). We assessed depression using the Hospital Anxiety and Depression Scale (HADS-D) and the Center for Epidemiologic Studies Depression scale (CESD) with supplementary questions to assess lifetime depression. Data were analysed with logistic and linear regression models.

Results
Lifetime depression showed almost three times higher odds in CH patients (n=462) than controls (n=177) (OR 2.77, 95% CI 1.70-4.51). Chronic (n=67) vs. episodic (n=394) patients had a higher prevalence of lifetime depression and more sleeping problems. Current depression was associated with having active attacks (last attack < 1 month) (adjusted p=0.02), but no effect remained after correction for sleep disturbances.

Conclusion
Cluster headache is associated with an almost three times increased odds of lifetime depression. Current depression is highly prevalent in patients with active disease, in part related to sleep disturbances due to current nocturnal attacks.

Introduction

Cluster headache (CH) is a highly disabling headache disorder, typically represented by frequently recurring attacks of 15-180 minutes of unilateral, peri-orbital, excruciating pain associated with ipsilateral facial autonomic features and restlessness. (1) Nocturnal sleep-related attacks are highly prevalent, with 75% of all attacks starting between 9:00 pm and 10:00 am, leading to impaired sleep quality and quantity. (2) In about 85% of patients, headache attacks cluster in periods of several weeks to months, interspersing with attack-free periods of several months to years (episodic CH); in the remaining patients, long attack-free periods are absent (chronic CH). (1, 3, 4) The lifetime prevalence of CH is about one in 1000 with a male to female ratio is 4.3). (4, 5) Related to the low prevalence, many patients are diagnosed only after many years. (6, 7) The reduction of quality of life, social functioning, and socioeconomic status can be enormous in CH patients (depending on subtype, number of cluster periods, attack frequency, and response to treatment). (8)

Patients portray the excruciating pain of a cluster headache attack as being worse than any other pain they have ever experienced. The extreme nature of the pain has earned CH the title 'suicide headache'. Suicidal tendencies have been reported in 25-55% of patients. (9-11)

CH shows several clinical, therapeutical and pathophysiological similarities to migraine, another episodic headache disorder. Prospective long-term follow-up studies in patients with migraine and in patients with depression have shown that the risk of depression is increased in patients with migraine and *vice versa* the risk of migraine is increased in patients with depression. (12, 13) Such bidirectional comorbidity suggests shared underlying pathophysiological, possibly genetic mechanisms for both episodic brain conditions. (14, 15) Furthermore, many CH patients have a lack of sleep due to nocturnal attacks, potentially contributing to depressive symptoms. Previous small studies investigated the relationship between cluster headache and depression, but did not use specific and structured questionnaires for establishing a diagnosis of CH or depression. (10, 16, 17) We therefore wanted to assess whether depression is also a comorbid condition in CH. To this end we interviewed 462 well-characterized CH patients from the Leiden University Cluster Headache Analysis programme (LUCA) using validated questionnaires, and compared the results with those of 177 non-headache controls. Secondarily, we wanted to identify CH specific characteristics that are associated with depression.

Methods

Participants and study design

The present study was conducted as part of the LUCA project (Leiden University Cluster headache Analysis programme), the details of which have been reported elsewhere. (18) In brief, using a dedicated website and two validated web-based screening and diagnostic questionnaires, with a specificity of 88% to diagnose CH according to the International Classification of Headache Disorders (ICHD-III beta) criteria, (1) Dutch speaking persons between 18 and 80 years of age from The Netherlands were invited to participate in research on CH. A clinically confirmed diagnosis of cluster headache by a physician was available for 94% of the LUCA population. (18) For the remaining 6%, no clinically confirmed diagnosis was available, for instance because they never consulted a doctor. The questionnaires included, in addition to diagnostic questions, also questions regarding demographic factors, use of acute and prophylactic headache medications, and CH attack frequency. The CH questionnaire primarily was validated for the ICHD-II criteria for cluster headache. (18, 19) Recently, however, new ICHD-III criteria have been published, which have been shown to have no differences to the validity of the CH questionnaire. (20) Therefore, our diagnoses fulfil the ICHD-III criteria for CH.

Non-headache individuals willing to participate had to pass a screening questionnaire online via the research website. If this screening questionnaire did not show any indication for having migraine, cluster headache, chronic tension type headache or medication overuse headache, individuals were sent a subsequent in depth questionnaire. This second questionnaire again assessed possible headache complaints, together with demographic variables. Only individuals that fulfilled both the criteria of 'non-headache' in the screening and in depth questionnaire were considered eligible controls and were approached for this questionnaire study. Healthy controls were also sent web-based questionnaires on symptoms of (lifetime) depression, sleeping problems and demographic characteristics, identical to the questionnaires that were sent to the CH patients.

All patients diagnosed with CH and controls received an invitation to participate in a questionnaire with questions on symptoms of lifetime depression and sleeping problems. For all questionnaires, non-responders received two e-mail reminders. Participants without the needed internet skills were able to fill out the questionnaires on paper.

Standard Protocol Approvals, registrations, and patient consents

The LUCA and depression studies were approved by the Medical Ethics Committee of the Leiden University Medical Center. All participants provided written informed consent.

Measures

The extended CH questionnaire included questions which allowed to divide between chronic (no attack-free periods of more than one month) and episodic (attack-free periods) CH, and to indicate whether the CH was 'active' (last attack < 1 month ago) or the participant was 'attack-free' (last attack > 1 month ago). For episodic CH patients questions were asked on the mean frequency of attacks during the start-up phase, the bout and the recovery phase. Also, the mean duration of the remission phase was asked. For chronic CH patients the mean number of attacks per day was asked. We defined four groups of patients: 1) episodic active; 2) episodic attack-free; 3) chronic active; 4) chronic attack-free. The latter group is considered to be treated successfully for their chronic CH, although a return to episodic CH ('secondary episodic' CH) cannot be excluded. In order to be able to adjust for potential confounding effects of demographic variables and addictive behaviour, questions were asked on gender, age, marital status, ethnicity, education, body mass index (BMI), smoking, caffeine use and alcohol consumption.

Lifetime depression was measured as a dichotomous variable. We used validated cut-off scores for the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) and the Centre for Epidemiologic Studies Depression scale (CESD), in combination with a previously used and published algorithm for depression and an additional question on depression diagnoses in the past: [HADS-D ≥ 8, or CES-D ≥ 16, or use of antidepressants with as indication a depression, or having had the diagnosis depression in the past]. (14, 15, 21, 22) Both CH patients and controls filled out the same depression questionnaires, whereas the CH patients filled out additional questions on current headache status at the time of the depression questionnaire.

To correct for a potential confounding effect of sleep disorders, the Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep disturbances over the past month. The PSQI is designed to measure the quality and patterns of sleep in the past month and contains 19 self-rated questions, with a global scoring range of 0 to 21. Higher scores denote a poorer sleep quality. (23) Scores are also allowed to be dichotomized, with a score of >5 defining 'poor sleepers'. CH patients and controls filled out the same questionnaire.

Statistical method

We reported baseline characteristics as mean ± standard deviation (SD) or percentages. Differences in means between CH and control groups were tested with 2-sided independent samples *t*-tests. Differences in proportions were tested by x^2 tests. We conducted a univariate logistic regression model to test the crude association between the presence of CH and the odds of being depressed. Analyses were rerun, adjusting for gender, age, education and BMI (model 1), and additively adjusting for PSQI-score (model 2). Results were reported as odds ratios with 95% confidence intervals and corresponding *p*-values. Secondarily, baseline characteristics of the different CH subtypes (episodic/chronic, and active/attack-free) were reported as mean ± SD or percentages. We tested differences in means between CH subgroups with one-way ANOVAs or independent samples *t*-tests. Differences in proportions were tested using x^2 tests. A univariate linear regression model was conducted to test the crude association between the CH status (active/attack-free) and the score on the HADS-D depression questionnaire. Here also, analyses were rerun, adjusting for gender, age, education and BMI (model 1), for subtype (chronic/episodic) (model 2) and for PSQI-score (model 3). Subsequently, we investigated associations with current antidepressant use and current lithium use in an additional model. Results were reported as unstandardized regression coefficients (B) with 95% confidence intervals and corresponding *p*-values. For all analyses *p*-values of <0.05 were considered to indicate statistical significance. We performed all analyses by SPSS 17.0 (SPSS inc., IBM, USA).

Results

Study flow and descriptives

The total study flow is shown in figure 1. All eligible persons with CH within the LUCA database (n=528) received a depression questionnaire (mean age ± SD: 48.8 ± 11.7), of which ultimately 467 returned questionnaires (88.4% response rate). The primary analysis was conducted in 462 participants with CH, because of missing demographic data in 5 patients. Responders (n = 462) did not differ from non-responders (n = 66) for age or gender. The secondary analysis was conducted in 461 participants with CH because of missing attack frequency data in one subject. Of the 252 controls in the LUCA database (mean age ± SD: 45.0 ± 14.3), n=177 (70.2%) filled out a depression questionnaire. Responders (n=177) were slightly older than non-responders (n=75), (46.6 years *v.* 41.3 years; p = 0.006), but did not differ in gender (supplementary tables e-1, e-2. e-3).

Descriptive data for participants with CH and non-headache controls are shown in Table 1. The 462 CH participants differed on several variables from the 177 healthy

controls. CH participants more often were males and married, were slightly older, had a lower educational level and slightly higher BMI, smoked substantially more pack years, and tended to use more caffeine. Furthermore, they showed increased scores on depression and anxiety scales and were more likely to report increased use of antidepressants, having received a diagnosis of depression in the past and experiencing sleeping problems.

The association between CH, depression and sleep disturbances

Participants with CH scored higher on all different subscales of the depression questionnaires, more often had lifetime depression and more often used or had used antidepressants (table 1). They also scored higher on the PSQI questionnaire (indicating worse sleep quality), and more often could be qualified as 'poor sleeper'. As shown in table 2 and figure e-1, the logistic regression analyses of the association between CH and the odds of depression showed in the crude model, an odds ratio of 4.17 compared with controls. This effect remained largely unchanged when adjusted for the covariates gender, age, education and BMI (OR 4.08). After adjustment for PSQI-score, the odds ratio remained increased (OR 2.77).

Baseline comparison of CH subtypes

CH participants (n=461) were divided in the following groups: 1) episodic active (n=106); 2) episodic attack-free (n=288); 3) chronic active (n=58); 4) chronic attack-free (n=9). Differences in alcohol use, duration of attack-free periods, time to last attack and all different depression and sleep subscales were observed. In general, participants with chronic CH had more symptoms of depression, and worse sleep quality, when compared to participants with episodic CH (table 3).

The association between active CH and current depression

As shown in table 4 and figure e-2, participants with active CH scored 1.81 points higher on the current depression questionnaire (HADS-D) than attack-free CH patients. This effect remained after adjustment for covariates gender, age, education and BMI (model 1). After adjustment for CH subtype (episodic or chronic), the effect decreased (B -1.02) (model 2). After adjustment for PSQI score (model 3), no effect remained (B -0.04). These results indicate an association between the current activity of CH and current depression, with involvement of current sleep disturbances.

Determinants of depression in CH patients

As shown in table 4, model 3, determinants of current depression in CH participants were: a lower educational level, having chronic CH and a higher PSQI sum score. Use of lithium might indicate more severe cluster headache (as it may be prescribed as a second line prophylactic treatment), more severe depression (as it may be prescribed as an additive to antidepressants if other treatments fail), or both. Additional analyses of current use of lithium indeed showed an association with depression scores, without changing the *p*-values for the other determinants. Subsequent analyses with current antidepressant use showed an association with depression scores, without changes in the significance of *p*-values of the other determinants.

Discussion

This is a large study on the prevalence of depression in a large sample of patients with cluster headache (CH).

CH patients had three times higher odds for depression than controls. Patients with active or chronic CH had higher depression scores than patients with CH who were attack free. Our finding that CH is associated with increased prevalence of depression is well in line with results from earlier smaller studies which, however, did not use specific and structured questionnaires for CH and depression. (10, 16, 17) Considering that depression is more prevalent among women and that there were proportionally much fewer women in the cluster headache sample than in the control group, the increased prevalence of depression in cluster headache is even more striking.

We can only speculate on why CH patients have increased prevalence of depression. As 85% of participants with CH had nocturnal attacks, lack of sleep might have been a contributing factor. Despair and stress because of relentlessly recurring pain attacks is another possible factor. Finally, hypothalamic dysfunction may offer a good explanation as depression (24), sleep disorders (25) and CH (26-28) have been associated with both functional and structural changes in this part of the brain. Epidemiological associations with depression have been described for a range of neurological disorders, in particular those associated with chronic pain. (29) Whether and to what extent the underlying mechanisms are similar remains to be studied.

Depression in cluster headache patients is at least partially explained by poor sleep quality. The odds ratio for depression dropped from 4.17 to 2.77 after adjustment for sleep disturbances. Current attacks of cluster headache was associated

with current depression, but this effect disappeared after adjustment for sleep disturbances. Participants were not wrongly considered as depressed due to sleeping problems, as the HADS questionnaire, in contrast to other instruments that measure depressive symptoms, contains no questions about this issue. It seems more likely that CH, depression and sleeping disturbances are intertwined. There is evidence that sleeping problems can be a risk factor for depression (30), and sleeping problems in cluster headache patients are caused by CH attacks that typically occur at night.

Another striking and clinically potentially relevant finding of our study was that, in all likelihood, depression was considerably underdiagnosed and undertreated in cluster headache patients. Only 23/133 (17%) of the 133/462 (28%) participants with cluster headache who fulfilled the loose criterion for current depression (HADS-D ≥ 8) and only 14/56 (25%) of the 56/462 (12%) participants who fulfilled the stricter criterion for current depression (HADS-D ≥ 11) were treated with antidepressants.

Our data suggest that current attacks are associated with increased symptoms of depression, and worse sleep quality. Therefore, we may conclude that unsuccessful treatment of cluster headache is associated with poor outcomes: depression and sleeping problems. This underlines the importance of adequate treatment for cluster headache. Suicidal thoughts are frequently reported in patients with cluster headache and could be related to the higher frequency of depression. (10, 11) Unfortunately we have no information on suicidal thoughts in our study population, but this would be an important topic for future research.

In patients with migraine, comorbid depression is a risk factor for migraine chronification. (15, 31, 32) Interestingly, in the present study, participants with chronic CH scored substantially higher on all depression subscales than those with episodic CH. However, due to the cross-sectional nature of our study, we cannot distinguish between cause and consequence. Likewise, we cannot determine whether depression and CH show bidirectional comorbidity. This would require long-term, prospective follow-up studies which are challenging because of the low incidence and prevalence of CH.

Strengths of our study include the large sample size for such a rare condition, the use of validated diagnostic questionnaires for CH (18) and the detailed information on depression. Head trauma has been associated with both depression and, in a few cases, cluster headache. (33, 34) The evidence for a causal relationship between head trauma and cluster headache is, however, limited and the relation, if any, seems rare. We therefore believe that the lack of information on a history of head trauma is unlikely to have affected the results. Possible limitations of our study are that our LUCA population is predominantly Dutch/Caucasian, of relatively

young age, recruited via the internet, and on average well-educated. We therefore cannot extrapolate our studies to other ethnic groups or populations from different socio-economic backgrounds. Also, in line with previous epidemiological studies, participants with CH more frequently were male and heavy smokers than non-CH controls. (5, 11) It seems unlikely that these differences have materially affected the results, as we adjusted all analyses for these differences. Another possible limitation is that depression was measured with questionnaires which are not specifically designed to diagnose clinical depression in individuals. However, we used validated cut-off values, which should provide a reliable differentiation between depressive and non-depressive persons. (21, 22) Cluster headache patients showed increased anxiety which might have contributed to the increased comorbid prevalence of depression. Unravelling the exact role of anxiety should be a topic of future research. Lastly, due to the cross-sectional character of this study no firm conclusion could be drawn regarding the direction of the comorbidity.

Early detection of comorbid depression in cluster headache may be important to prevent suicide in this unbearably painful primary headache disorder. Longitudinal bidirectional follow-up studies, although challenging, will be necessary to investigate the relationship in time between CH and depression, to answer the question on causal relationship.

Figure 1 : total study flow

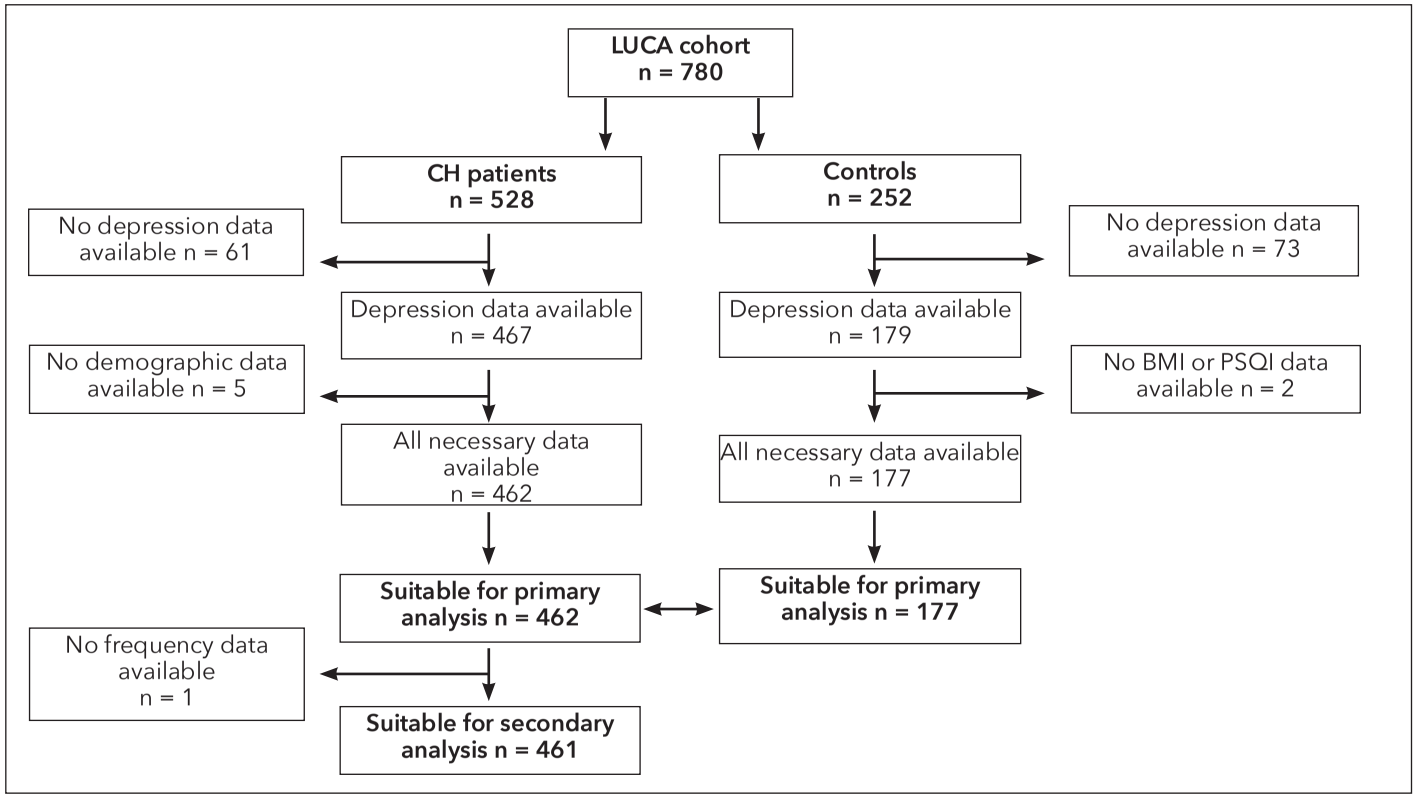

Table 1: Baseline characteristics of study population and comparison between 462 CH patients and 177 controls.

	CH patients (n=462)	Controls (n=177)	p-value
Gender (% male)	73.4%	44.6%	**<0.001**
Age (years)	49.2 ± 11.3	46.6 ± 14.3	**0.03**
Marital status			**0.006**
% single	12.8%	20.3%	
% cohabiting	15.6%	22.6%	
% married	66.2%	53.1%	
% divorced / widowed	5.4%	4.0%	
Education (years)	13.0 ± 3.3	14.2 ± 3.5	**<0.001**
BMI (kg/m^2)	25.4 ± 3.6	24.1 ± 2.8	**<0.001**
Packyears	18.6 ± 16.8	4.8 ± 8.4	**<0.001**
Caffeine (units per day)	6.6 ± 2.8	5.5 ± 2.5	**<0.001**
Alcohol (units per week)	7.6 ± 9.4	6.9 ± 7.6	0.28
HADS total score	10.8 ± 7.8	5.8 ± 5.2	**<0.001**
HADS-D score	5.3 ± 4.3	2.6 ± 2.9	**<0.001**
HADS-A score	5.6 ± 4.2	3.3 ± 2.9	**<0.001**
CESD score	11.5 ± 10.2	5.3 ± 6.2	**<0.001**
Ever antidepressants (% yes)	22.5%	10.2%	**<0.001**
Current antidepressants (% yes)	7.8%	2.3%	**0.01**
Ever diagnosis depression (% yes)	16.7%	8.4%	**0.007**
Lifetime depression (% yes)	43.9%	15.8%	**<0.001**
PSQI score	6.3 ± 3.9	4.2 ± 2.8	**<0.001**
Poor sleeper (% yes)*	58.4%	37.3%	**<0.001**

CH, Cluster Headache; BMI, Body Mass Index; HADS, Hospital Anxiety and Depression Scale (D: depression scale; A: anxiety scale); CES-D, Centre for Epidemiologic Studies Depression Scale; PSQI, Pittsburgh Sleep Quality Index. Values are percentages or means ± SD. P-values depicted in bold indicate a statistical significant difference, using x^2 tests and independent samples t-tests appropriately.

* Poor sleeper defined as PSQI-score >5

Table 2: Logistic associations between CH and lifetime depression in 462 participants with CH and 177 controls.

	OR	95% CI	p-value
Univariate association	**4.17**	**2.68 – 6.50**	**<0.001**
Model 1 *Adjusted for gender, age, education, BMI*	**4.08**	**2.56 – 6.49**	**<0.001**
Model 2 *Additively adjusted for sleep disturbances*	**2.77**	**1.70 – 4.51**	**<0.001**

Data are Odds Ratios (OR) with 95% confidence intervals and p-values. Model 1 was adjusted for gender, age, education and BMI. Model 2 was additively adjusted for PSQI-score. Values depicted in bold indicate statistical significant results.

Table 3: Baseline characteristics of 461 people with CH and comparison between 4 different subtypes

	Episodic (n=394)		Chronic (n=67)		p-value
	Active (n=106)	Attack-free (n=288)	Active (n=58)	Attack-free (n=9)	
Gender (% female)	31.1%	23.3%	32.8%	33.3%	0.25
Age (years)	48.2 ± 12.1	50.1 ± 11.1	47.5 ± 10.8	44.8 ± 9.8	0.16
Marital status					0.23
% single	19.8%	9.7%	10.3%	33.3%	
% cohabiting	16.0%	15.6%	15.5%	11.1%	
% married	59.4%	68.8%	69.0%	55.6%	
% divorced / widowed	4.7%	11.1%	5.2%	0.0%	
Education (years)	12.9 ± 3.4	13.1 ± 3.4	12.5 ± 3.0	12.9 ± 3.2	0.60
BMI (kg/m^2)	25.1 ± 3.9	25.5 ± 3.4	25.6 ± 4.2	27.4 ± 4.4	0.29
Packyears	19.3 ± 17.9	18.3 ± 16.7	18.7 ± 16.1	18.8 ± 13.3	0.97
Caffeine (units per day)	6.6 ± 2.9	6.7 ± 2.8	6.1 ± 2.5	5.9 ± 2.1	0.41
Alcohol (units per week)	7.2 ± 9.1	8.2 ± 8.9	5.0 ± 8.3	13.2 ± 22.4	**0.03**
Number of attacks per day in CCH patients	.	.	2.9 ± 3.5	1.5 ± 2.4	0.32
Number of attacks per day (start-up phase)	1.1 ± 1.4	0.9 ± 1.0	.	.	0.13
Number of attacks per day (bout)	3.3 ± 2.8	3.3 ± 2.4	.	.	0.90
Number of attacks per day (recovery phase)	1.0 ± 1.4	0.9 ± 1.0	.	.	0.53
Duration attack-free period (years)	0.7 ± 0.9	1.9 ± 2.5	.	.	**<0.001**
Time to last attack (years)	0.03 ± 0.05	1.9 ± 3.3	0.01 ± 0.01	5.6 ± 8.3	**<0.001**
HADS total score	11.5 ± 7.8	9.6 ± 7.0	15.0 ± 9.4	15.3 ± 9.6	**<0.001**
HADS-D score	5.6 ± 4.2	4.6 ± 3.8	7.9 ± 5.5	7.2 ± 4.5	**<0.001**
HADS-A score	5.8 ± 4.3	5.1 ± 3.9	7.1 ± 4.9	8.1 ± 5.6	**0.002**
CESD score	12.7 ± 9.7	9.8 ± 9.4	17.5 ± 11.9	14.8 ± 14.7	**<0.001**
Lifetime depression (% yes)	51.9%	37.5%	63.8%	33.3%	**0.001**
Ever antidepressants (% yes)	28.3%	18.4%	31.0%	33.3%	0.05
Current antidepressants (% yes)	9.4%	6.3%	13.8%	0.0%	0.17
PSQI score	7.5 ± 3.9	5.2 ± 3.3	9.0 ± 4.5	7.8 ± 5.1	**<0.001**
Poor sleeper (% yes)	75.5%	46.5%	82.8%	77.8%	**<0.001**

BMI, Body Mass Index; CCH, Chronic CH; ECH, Episodic CH; HADS, Hospital Anxiety and Depression Scale (D: depression scale; A: anxiety scale); CES-D, Centre for Epidemiologic Studies Depression Scale; PSQI, Pittsburgh Sleep Quality Index. Active,

last attack ≤1 month; Attack-free, no attacks for > 1 month. Values are percentages or means ± SD. P-values depicted in bold indicate a statistical significant difference, using x^2 tests and independent samples t-tests appropriately.

Table 4: Linear associations between CH status (active / attack-free) and current depression (HADS-D scores) in 461 participants with CH.

	B	95% CI	p-value
Univariate association			
CH status (attack free vs. active)	**-1.81**	**-2.62 - -1.00**	**<0.001**
Model 1			
CH status (attack free vs. active)	**-1.74**	**-2.54 - -0.94**	**<0.001**
Gender (female vs. male)	-0.26	-1.15 – 0.62	0.56
Age	-0.006	-0.04 – 0.03	0.73
Years of education	**-0.25**	**-0.37 - -0.13**	**<0.001**
BMI	0.05	-0.06 – 0.15	0.39
Model 2			
CH status (attack free vs. active)	**-1.02**	**-1.89 - -0.14**	**0.02**
Gender (female vs. male)	-0.31	-1.19 – 0.56	0.48
Age	-0.003	-0.04 – 0.03	0.88
Years of education	**-0.24**	**-0.35 - -0.13**	**<0.001**
BMI	0.03	-0.07 – 0.14	0.56
CH subtype (chronic vs. episodic)	**2.27**	**1.08 – 3.45**	**<0.0**
Model 3			
CH status (attack free vs. active)	-0.04	-0.86 - 0.79	0.93
Gender (female vs. male)	-0.76	-1.56 - 0.05	0.07
Age	-0.004	-0.04 - 0.03	0.82
Years of education	**-0.17**	**-0.27 - -0.06**	**0.002**
BMI	0.04	-0.06 - 0.14	0.40
CH subtype (chronic vs. episodic)	**1.49**	**0.39 - 2.58**	**0.008**
PSQI sumscore	**0.47**	**0.37 – 0.57**	**<0.001**
Subsequent analyses:*			
Current lithium use	**1.35**	**0.26 – 2.45**	**0.02**
Current use of antidepressants	**2.50**	**1.17 – 3.82**	**<0.001**

Data are unstandardized regression coefficients (B) with 95% confidence intervals and p-values. Model 1 was adjusted for gender, age, education and BMI. Model 2 was additively adjusted for CH subtype (chronic/episodic). Model 3 was additively adjusted for PSQI-score. Values depicted in bold indicate statistical significant results.

* Subsequent (separate) analyses with current lithium use and current use of antidepressants showed no changes in the significance of the other determinants.

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