Cluster headache and depression

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ABSTRACT

Objective: As cluster headache (CH) is often referred to as "suicide headache," we wanted to assess the prevalence of depression in CH 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 ICHD-III. We assessed depression using the Hospital Anxiety and Depression Scale (HADS-D) and the Center for Epidemiologic Studies Depression scale (CES-D) with supplementary questions to assess lifetime depression. Data were analyzed with logistic and linear regression models.

Results: Lifetime depression showed almost 3 times higher odds in CH patients (n = 462) than controls (n = 177) (odds ratio 2.77; 95% confidence interval 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.

Conclusions: CH is associated with an almost 3 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. *Neurology*® 2016;87:1899–1906

GLOSSARY

BMI = body mass index; **CES-D** = Centre for Epidemiologic Studies Depression scale; **CH** = cluster headache; **CI** = confidence interval; **HADS-D** = Hospital Anxiety and Depression Scale; **ICHD** = International Classification of Headache Disorders; **LUCA** = Leiden University Cluster Headache Analysis program; **OR** = odds ratio; **PSQI** = Pittsburgh Sleep Quality Index.

Cluster headache (CH) is a highly disabling headache disorder, typically represented by frequently recurring attacks of 15–180 minutes of unilateral, periorbital, 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 1 in 1,000 with a male to female ratio of 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 CH 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]

Supplemental data at Neurology.org

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CH shows several clinical, therapeutic, and pathophysiologic 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 pathophysiologic, 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 CH 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 program (LUCA) using validated questionnaires, and compared the results with those of 177 nonheadache 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, the details of which have been reported elsewhere.[18] In brief, using a dedicated website and 2 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 CH 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, 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 CH.[18,19] Recently, however, new ICHD-III criteria have been published, which have been shown to have no differences from the validity of the CH questionnaire.[20] Therefore, our diagnoses fulfill the ICHD-III criteria for CH.

Individuals without headache 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, CH, 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 who fulfilled the criteria of nonheadache 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, nonresponders received 2 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 Leiden University Medical Center. All participants provided written informed consent.

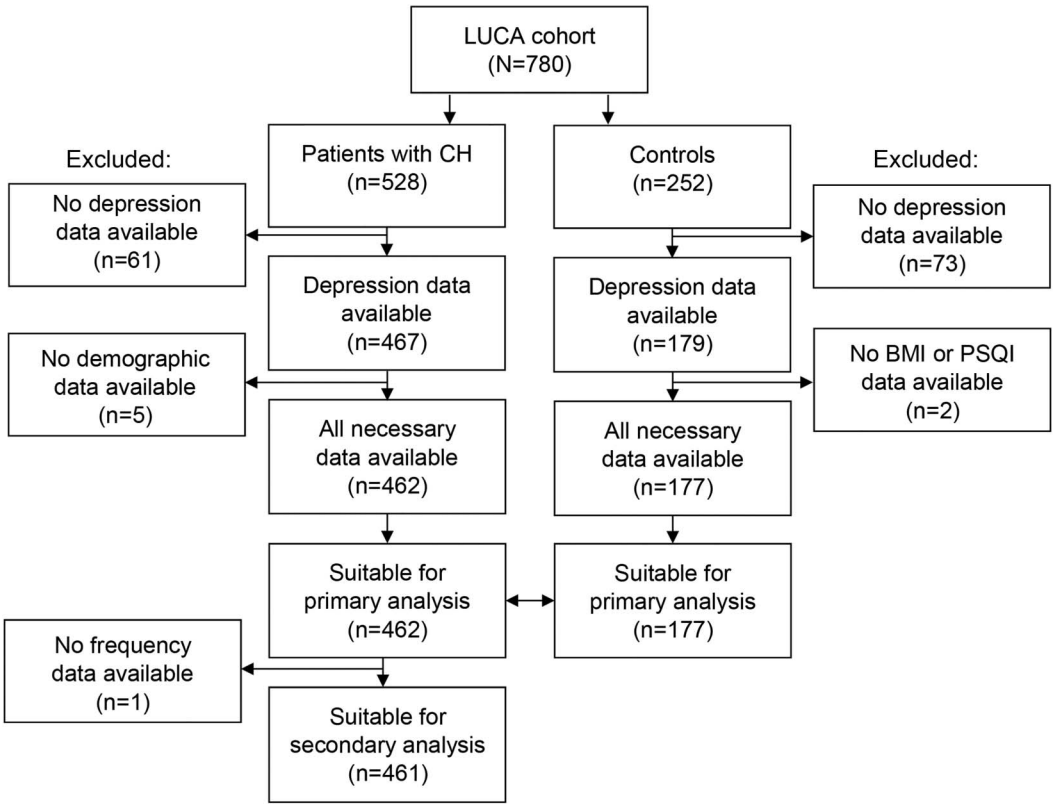
Measures. The extended CH questionnaire included questions that allowed us to divide between chronic (no attack-free periods of more than 1 month) and episodic (attack-free periods) CH, and to indicate whether the CH was active (last attack <1 month ago) or the participant was attack-free (last attack >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 4 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 behavior, questions were asked on sex, 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 cutoff scores for the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) and the Centre for Epidemiologic Studies Depression scale (CES-D), in combination with a previously used and published algorithm for depression and an additional question on depression diagnoses in the past (HADS-D ≥ 8, CES-D ≥ 16, or use of antidepressants with depression as indication, or having had the diagnosis of depression in the past).[14,15,21,22] 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 ± 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 χ^2 tests. We conducted a univariate logistic regression model to test the crude

Figure 1 Total study flow



BMI = body mass index; CH = cluster headache; LUCA = Leiden University Cluster Headache Analysis program; PSQI = Pittsburgh Sleep Quality Index.

association between the presence of CH and the odds of being depressed. Analyses were rerun, adjusting for sex, age, education, and BMI (model 1), and additively adjusting for PSQI score (model 2). Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs) 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 analyses of variance or independent-samples t tests. Differences in proportions were tested using χ^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 sex, 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% CIs 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.; Chicago, IL).

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 years), 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 nonresponders (n = 66) in age or sex. The secondary analysis was conducted in 461 participants with CH because of missing attack frequency data in one participant. Of the 252 controls in the LUCA database (mean age ± SD 45.0 ± 14.3 years), 177 (70.2%) filled out a depression questionnaire. Responders (n = 177) were slightly older than nonresponders (n = 75) (46.6 years vs 41.3 years; $p = 0.006$), but did not differ in sex (tables e-1, e-2, and e-3 at Neurology.org).

Descriptive data for participants with CH and nonheadache controls are shown in table 1. The 462 CH participants differed on several variables from the 177 healthy controls. CH participants more often were male 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 among CH, depression, and sleep disturbances. Participants with CH scored higher on all different subscales of the depression questionnaires,

Table 1 Baseline characteristics of the study population and comparison between 462 cluster headache (CH) patients and 177 controls

	Patients with CH (n = 462)	Controls (n = 177)	p
% Male	73.4	44.6	<0.001[a]
Age, y	49.2 ± 11.3	46.6 ± 14.3	0.03[a]
Marital status, %			0.006[a]
Single	12.8	20.3	
Cohabiting	15.6	22.6	
Married	66.2	53.1	
Divorced/widowed	5.4	4.0	
Education, y	13.0 ± 3.3	14.2 ± 3.5	<0.001[a]
BMI, kg/m^2	25.4 ± 3.6	24.1 ± 2.8	<0.001[a]
Pack-years	18.6 ± 16.8	4.8 ± 8.4	<0.001[a]
Caffeine (units per d)	6.6 ± 2.8	5.5 ± 2.5	<0.001[a]
Alcohol (units per wk)	7.6 ± 9.4	6.9 ± 7.6	0.28
HADS total score	10.8 ± 7.8	5.8 ± 5.2	<0.001[a]
HADS-D score	5.3 ± 4.3	2.6 ± 2.9	<0.001[a]
HADS-A score	5.6 ± 4.2	3.3 ± 2.9	<0.001[a]
CES-D score	11.5 ± 10.2	5.3 ± 6.2	<0.001[a]
Ever antidepressants (% yes)	22.5	10.2	<0.001[a]
Current antidepressants (% yes)	7.8	2.3	0.01[a]
Ever diagnosis depression (% yes)	16.7	8.4	0.007[a]
Lifetime depression (% yes)	43.9	15.8	<0.001[a]
PSQI score	6.3 ± 3.9	4.2 ± 2.8	<0.001[a]
Poor sleeper (% yes)[b]	58.4	37.3	<0.001[a]

Abbreviations: BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression scale; HADS = Hospital Anxiety and Depression Scale (A = anxiety scale; D = depression scale); PSQI = Pittsburgh Sleep Quality Index.
Values are percentages or means ± SD.
[a] Statistically significant difference, using χ^2 tests and independent-samples t tests as appropriate.
[b] Poor sleeper, defined as PSQI score >5.

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 a 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 OR of 4.17 compared with controls. This effect remained largely unchanged when adjusted for the covariates sex, age, education, and BMI (OR 4.08). After adjustment for PSQI score, the OR remained increased (OR 2.77).

Baseline comparison of CH subtypes. CH participants (n = 461) were divided into the following groups: (1) episodic active (n = 106); (2) episodic attack-free

Table 2 Logistic associations between cluster headache (CH) and lifetime depression in 462 participants with CH and 177 controls

	OR	95% CI	p
Univariate association	4.17	2.68-6.50	<0.001
Model 1			
Adjusted for sex, age, education, BMI	4.08	2.56-6.49	<0.001
Model 2			
Additively adjusted for sleep disturbances (PSQI score)	2.77	1.70-4.51	<0.001

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio; PSQI = Pittsburgh Sleep Quality Index.
All results were statistically significant.

(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 sex, 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 CH (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

Table 3 Baseline characteristics of 461 people with cluster headache (CH) and comparison among 4 different subtypes

	Episodic (n = 394) active (n = 106)	Episodic, attack-free (n = 288)	Chronic (n = 67) active (n = 58)	Chronic, attack-free (n = 9)	p
% Female	31.1	23.3	32.8	33.3	0.25
Age, y	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, y	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
Pack-years	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[a]
No. of attacks per day in CCH patients	—	—	2.9 ± 3.5	1.5 ± 2.4	0.32
No. of attacks per day (start-up phase)	1.1 ± 1.4	0.9 ± 1.0	—	—	0.13
No. of attacks per day (bout)	3.3 ± 2.8	3.3 ± 2.4	—	—	0.90
No. of attacks per day (recovery phase)	1.0 ± 1.4	0.9 ± 1.0	—	—	0.53
Duration attack-free period, y	0.7 ± 0.9	1.9 ± 2.5	—	—	<0.001[a]
Time to last attack, y	0.03 ± 0.05	1.9 ± 3.3	0.01 ± 0.01	5.6 ± 8.3	<0.001[a]
HADS total score	11.5 ± 7.8	9.6 ± 7.0	15.0 ± 9.4	15.3 ± 9.6	<0.001[a]
HADS-D score	5.6 ± 4.2	4.6 ± 3.8	7.9 ± 5.5	7.2 ± 4.5	<0.001[a]
HADS-A score	5.8 ± 4.3	5.1 ± 3.9	7.1 ± 4.9	8.1 ± 5.6	0.002[a]
CES-D score	12.7 ± 9.7	9.8 ± 9.4	17.5 ± 11.9	14.8 ± 14.7	<0.001[a]
Lifetime depression (% yes)	51.9	37.5	63.8	33.3	0.001[a]
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[a]
Poor sleeper (% yes)	75.5	46.5	82.8	77.8	<0.001[a]

Abbreviations: BMI = body mass index; CCH = chronic cluster headache; CES-D = Center for Epidemiologic Studies Depression scale; HADS = Hospital Anxiety and Depression Scale (A = anxiety scale; D = 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.
[a] Statistically significant difference, using χ^2 tests and independent-samples *t* tests as appropriate.

Table 4 Linear associations between cluster headache (CH) status (active/attack-free) and current depression (Hospital Anxiety and Depression Scale, subscale depression, scores) in 461 participants with CH

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

Data are unstandardized regression coefficients (B) with 95% confidence intervals (CIs) and *p* values. Model 1 was adjusted for sex, age, education, and body mass index (BMI). Model 2 was additively adjusted for CH subtype (chronic/episodic). Model 3 was additively adjusted for Pittsburgh Sleep Quality Index (PSQI) score.
[a] Statistically significant results.
[b] Subsequent (separate) analyses with current lithium use and current use of antidepressants showed no changes in the significance of the other determinants.

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 CH.

CH patients had 3 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 CH sample than in the control group, the increased prevalence of depression in CH 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. Epidemiologic associations with depression have been described for a range of neurologic 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 CH patients is at least partially explained by poor sleep quality. The OR for depression dropped from 4.17 to 2.77 after adjustment for sleep disturbances. Current attacks of CH were 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 CH 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 CH patients. Only 23/133 (17%) of the 133/462 (28%) participants with CH who fulfilled the loose criterion for current depression (HADS-D $\geq$8) and only 14/56 (25%) of the 56/462 (12%) participants who fulfilled the stricter criterion for current depression (HADS-D $\geq$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 CH is associated with poor outcomes: depression and sleeping problems. This underlines the importance of adequate treatment for CH. Suicidal thoughts are frequently reported in patients with CH and could be related to the higher frequency of depression.[10,11] 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, CH.[33,34] The evidence for a causal relationship between head trauma and CH 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 socioeconomic backgrounds. Also, in line with previous epidemiologic 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 that are not specifically designed to diagnose clinical depression in individuals. However, we used validated cutoff values, which should provide a reliable differentiation between depressive and nondepressive persons.[21,22] CH 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. Finally, 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 CH may be important to prevent suicide in this 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.

AUTHOR CONTRIBUTIONS

M.A. Louter is principal investigator and contributed to design and conceptualization of the study, data collection, analysis and interpretation, as well as writing the first draft of the manuscript and revising. L.A. Wilbrink contributed to design and conceptualization of the study, data collection, analysis and interpretation, as well as writing the first draft of the manuscript together with M.A.L. and revising. J. Haan contributed to design and conceptualization of the study, as well as revising the first draft of the manuscript. E.W. van Zwet contributed to analysis and interpretation of the data. W.P.J. van Oosterhout contributed to data collection, as well as revising the manuscript for intellectual content. F.G. Zitman contributed to design and conceptualization of the study. M.D. Ferrari contributed to design and conceptualization of the study, interpretation of the data, as well as revising the manuscript for intellectual content. G.M. Terwindt contributed to design and conceptualization of the study, interpretation of the data, as well as revising the manuscript for intellectual content.

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DISCLOSURE

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