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Epidemiology of diagnosed cluster headache in Norway

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Abstract

Background: Cluster headache (CH) is one of the most painful conditions in humans and there is limited epidemiological data on this debilitating condition.

Objectives: To describe the epidemiology of CH in Norway

Methods: We conducted a nationwide study to investigate the prevalence, incidence, and comorbidity of CH in Norway between January 1 2008 and December 31 2016. Treatment and outcome data from the Norwegian patient registry and the Norwegian prescription database were linked on an individual basis.

Results: Among 3,892,260 individuals ≥18 years old of age, we identified a total of 1891 patients with CH. The prevalence of CH was 48.6 per 100,000, and the male-to-female ratio was 1.47. The estimated incidence of CH was 3.0 per 100,000/year. Among patients with CH, increased age and sex adjusted odds ratios ([OR], all with *p*-values <0.0001, were observed for medication-induced headache (OR 50.7, 95% CI 36.7–69.9), migraine (OR 25.2, 95% CI 22.5–28.3), chronic posttraumatic headache (OR 22.2, 95% CI 12.8–38.45), history of cranial trauma (OR 1.9, 95% CI 1.5–2.4), somatoform disorders (OR 4.2, 95% CI 3.0–5.8), suicide attempt (OR 3.9, 95% CI 2.6–5.8), personality disorder (OR 3.6, 95% CI 2.6–4.9), bipolar disorder (OR 3.6, 95% CI 2.8–4.8), peptic ulcer (OR 2.8, 95% CI 2.3–3.3), depression (OR 2.8, 95% CI 2.4–3.1), substance abuse (OR 2.6, 95% CI 2.0–3.3), and cerebrovascular disease (OR 2.4, 95% CI 1.8–3.1). Use of opioid analgesics during the study period was more common among patients with CH compared to others (81% vs. 22%, sex and age adjusted OR 23.4, 95% CI 20.8–26.2, $p < 0.0001$).

Keywords

cluster headache, comorbidity, epidemiology, incidence, prevalence

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Introduction

Cluster headache (CH) is an excruciating and highly disabling primary headache disorder that is widely considered to be one of the most painful human conditions.[1,2] Further, CH has been associated with reduced quality of life, increased risk of depression, marked functional disability, and suicide.[1,3–6] There have been several studies assessing CH's prevalence (Table 1). There is limited high-quality epidemiological data on CH and methodologically rigorous population-based studies are scarce.[29] CH's comorbidity remains also insufficiently documented[30] (Table 2). This Norwegian nationwide study aims to investigate the prevalence and incidence of CH. Further, we sought to assess comorbidity and use of prescription drugs in patients with CH compared to the general population.

Methods

Ethical approval and waiver of the requirement for obtaining patient consent were granted by the Regional Committee for Medical Research (REK 2016/1504). Reporting is consistent with the STROBE statement (S1 Checklist).

Study population

This study was conducted within the 3.8 million inhabitants of Norway ≥18 years of age (2016 census) from January 1, 2008, to December 31, 2016. Two administrative registries were linked on an individual level by a unique 11-digit personal identifier. The registries linked were: (A) the Norwegian Patient Registry (NPR), which contains information about inpatient and outpatient treatment in Norwegian hospitals since 2008 with diagnoses coded according to the 10th revision of the International Classification of Diseases (ICD-10)[51] and (B) The Norwegian Prescription Database (NorPD), which contains information about all prescriptions dispensed in Norway since 2004 including type of drug according to the Anatomical Therapeutic Chemical classification system.[52,53] Diagnoses are registered for medications with reimbursement according to ICD-10 or the International Classification of Primary Care version 2 (ICPC-2). All residents ≥18 years during the study period included in NPR and/or NorPD were eligible for inclusion. Data from NPR and NorPD were de-identified before being provided to the study authors, and the exact dates for prescription dispensing and death were not made available to the authors. NPR receives data monthly and is used for reimbursement purposes, hospital statistics, and research.[54] Sensitivity, specificity, and positive predictive values for neurological diagnoses in NPR are found to be high, indicating that the registry is well suited for this epidemiological study.[51] Nonetheless, the NPR has not been specifically validated for headache diagnoses.

Outcome measures

The primary outcome measures were prevalence and incidence of CH according to ICD-10. The diagnoses screened in this study are presented in Supplementary Table 1. The ICD-10 code for CH (G44.0) is the same used for chronic paroxysmal hemicrania. A diagnostic criterion for chronic paroxysmal hemicrania is the prevention of attacks by indomethacin, and patients who had dispensed the arbitrary amount of >200 tablets were not considered to have CH. ICD-10 does not provide different codes for episodic and chronic CH.

In order to estimate incidence of CH we divided our database in two periods: period 1 (2008–2011) and period 2 (2012–2016). Patients who had not received the diagnosis CH in period 1 but who received the diagnosis in period 2 were used to calculate an incidence rate in the second period. Secondary endpoints were assessment for comorbidities and use of prescription drugs (Supplementary Table 2).

The Norwegian health care system. Norway has a public health care system with evenly distributed resources. Most patients with CH are treated by neurologists working in the public health care system. Those who are treated in the private sector are also registered in the NPR. Health authorities cover all inpatient treatment for patients with CH, and costs concerning established treatment options are not a concern for the individual patients. Except for a maximum annual deductible of 2185 Norwegian Kroner (210 USD, 2020), prescription drugs are provided to patients without further costs. This ensures access to medicines regardless of financial situation.

Statistics. Analyses were performed with R 3.1 (R-Foundation for Statistical Computing), SPSS 25.0 (IBM Corp., Chicago), and MySQL (Oracle). Due to multiple comparisons, statistical significance level was defined as $p \leq 0.001$ when investigating comorbidity and drug use in CH patients and people without CH in the NPR. For other statistical tests the statistical significance level was defined as $p \leq 0.05$. Exposure to a drug was defined as having occurred when the drug was prescribed. Patients were followed until death, emigration, or end of study period.

Results

The average population in Norway ≥18 years of age during the study period was 3,892,260. The number of patients who received the diagnoses G44.0 was 2734. We identified a total of 1891 patients who fulfilled our criteria for having CH, providing a prevalence of CH of 48.6 per 100,000 (between January 1, 2008 and December 31, 2016). We identified 584 patients who received the diagnosis in the period between 2012 and 2016. The estimated incidence of CH was 3.0 per 100,000 per year.

Table 1. Incidence and prevalence of selected epidemiological studies on CH.[7–28,70]

	Incidence /100,000/ year	Prevalence /100,000	Sample	Ratio M:F	Comments	Year
Jurno ME et al.	—	41.4 (lifetime)	36,145	6.69:1	Questionnaire in a sample of the total of 126,284 inhabitants in the city of Barbacena (Brazil). The Family Health Strategy Program covers only 84,610.	2018
Hagen K et al.	—	400 (lifetime)	529	—	Merged data of HUNT3 ($n = 297$) and 4 ($n = 232$)	2018
Mengistu et al.	—	1298.7	231	1.06:1	Cross-sectional sample survey in Addis Ababa (Ethiopia). Three patients with CH in a sample of 231.	2013
Fischera et al.		124 (lifetime) 53 (1-year)		4.3:1 CCH 15:1 ECH 3.8:1	Meta-analysis of population-based studies. Ratio ECH:CCH was 6	2008
Katsarava et al.	—	119 (1-year)	3336	3:1	Population-based sample in Essen (Germany)	2007
Evers et al.	—	150 (1-year)	2291	—	A sample of 3425 inhabitants of Dortmund from 25 to 75 years was randomly selected and invited to participate (67% responded). Two males with CH were identified	2007
Ekbom et al.	—	151 (lifetime)	31,750	4.8:1	Lifetime prevalence on a twin sample, 41–67 years old.	2006
Karli et al.	—	80 (1-year)	2387	—	Among 1270 students in Turkey aged 12–14 and 1117 students aged 15–17 1 patient with ECH and 1 with CCH were identified	2006
Torelli et al.	—	279 (lifetime)	7522	1.3:1	Lifetime prevalence of the Italian population >14 years old.	2005
Black et al.	2.07 (overall) 4.25 (males)	—	—	5:1	Olmsted County (Minnesota in 1989–1990). The ratio M:F in this table has been calculated with merged data from Swanson et al.[15]	2005
Lin KH et al.	—	—	104	6.42:1	104 patients with ECH recruited from two major headache clinics in Taiwan.	2004
Sjaastad et al	—	326 (lifetime)	1838	6:1	Population of Vågå (18–65 years old). Seven patients with CH were identified. Conflicts of interest.	2003
Ekbom et al.	—	—	554	30–49 years: ECH 7.2:1 CCH 11.0:1 >50 years: ECH 2.3:1 CCH: 0.6:1	Patients with CH examined between 1963 and 1997	2002
Tonon et al.	2.5 (overall)	56 (lifetime)	26,628	—	Population of San Marino	2002
Manzoni et al.	—	—	482	Before 1960: 6.2:1 1960s: 5.6:1 1970s: 4.3:1 1980s: 3.0:1 1990s: 2.1:1	A decrease in the ratio M:F was observed to be parallel to a decrease in the ratio M:F for smoking and employment.	1998
Tekle et al.	—	30 (1-year)	15,500	—	Sample in an Ethiopian rural community $\geq$20 years old. Several methodological issues: linguistic problems and study carried out by proxies with little training.	1995
Swanson et al.	9.8 (overall) 15.6 (men) 4 (women)	—	—	4.2:1	Olmsted County (Minnesota 1919–1981).	1994
D'Alessandro et al.	—	69 (lifetime)	21,792	14.2:1	Population of San Marino. Several methodological problems as stated by Manzoni and Stovner (2010).	1986
Manzoni et al.	—	—	180	7.2:1	One hundred and sixty-one patients with ECH and 19 with CCH.	1983
Kudrow	—	—		ECH: 4.8:1 CCH: 6.3:1		1980
Ekbom et al.	—	90 (lifetime)	9803		Only 18-year old men. Only four out of nine patients had sought help.	1978
Horton	—	—	1176	6.7:1	Case series of patients with CH	1956

CH: cluster headache. ECH: episodic cluster headache. CCH: chronic cluster headache.

Table 2. Selected studies examining the comorbidity in cluster headache (CH).[3,30–50]

Author	Comorbidities		Statistics			Comments	Year
			CH	Controls	*p*-value		
Lund et al.	Damaging alcohol intake		5%	1.5%	0.035	Study examining unhealthy lifestyle in 400 CH patients and 200 controls.	2019
	Higher BMI		26.1	24.2	<0.001		
	Cannabis regularly		2.25%	0%	0.033		
	Depression		32.0%	9.0%	<0.001		
	Hypertension		24.5%	12.5%	<0.001		
			OR[a] 2.4 (95% CI 1.5–3.9)		<0.001		
	Gastric ulcer		12.8%	3.0%	<0.001		
			OR[a] 4.7 (95% CI 2.0–11.3)		<0.001		
	Angina pectoris		6.0%	1.0%	0.005		
			OR[a] 7.0 (95% CI 1.6–30.0)		0.009		
	Cardiac infarction		3.5%	0%	0.007		
	Cerebral infarction		5%	1.5%	0.035		
			OR[a] 3.7 (95% CI 1.1–12.5)		0.039		
	Hypercholesterolemia		21.5%	11.5%	0.003		
			OR[a] 2.2 (95% CI 1.3–3.7)		0.002		
	Chronic bronchitis		7.0%	3.0%	0.046		
	Back problems		34.3%	14.0%	<0.001		
	Rheumatoid diseases		17.5%	7.0%	<0.001		
	Fibromyalgia		3.0%	0%	0.01		
Song et al.	Comorbid migraine		30 (15.6%)	—		Prospective multicenter registry study. One hundred and ninety-two patients with CH.	2019
Ji Lee M. et al.	Suicidality during attacks	Passive suicidal ideation	111 (64%)	—		One hundred and ninety-three CH patients recruited between 2016 and 2018. Patients with longer disease duration, higher HIT-score and Patient Health Question-9 score had a higher ictal suicidality.	2019
		Active suicidal ideation	62 (35.8%)	—			
		Suicidal planning	10 (5.8%)	—			
		Suicidal attempt	4 (2.3%)	—			
	Interictal suicidality	Passive suicidal ideation	7 (4%)	—			
		Active suicidal ideation	6 (3.5%)	—			
		Suicidal planning	5 (2.9%)	—			
		Suicidal attempt	2 (1.2%)	—			
	Suicidality between bouts	Passive suicidal ideation	0 (0%)	—			
		Active suicidal ideation	1 (1.9%)	—			
		Suicidal planning	1 (1.9%)	—			
		Suicidal attempt	0 (0%)	—			

(continued)

Table 2. (continued)

Author	Comorbidities	Statistics			Comments	Year
		CH	Controls	*p*-value		
Choong CK et al.	Depressive disorders	19.8%	10.0%	—	Retrospective analysis with 7589 CH patients and 30,341 controls from insurance claims.	2017
	Sleep disturbances	19.7%	9.1%	—		
	Anxiety disorders	19.2%	8.7%	—		
	Suicidal ideation	OR: 2.5 ($p < 0.0001$)				
	Drug dependence	OR: 2.8 (95% CI 2.3–3.4, $p < 0.0001$)				
Joshi et al.	Cigarette smoking	64%	32%	0.00077	Seventy-five patients met the diagnostic criteria for CH. There were 152 Controls.	2017
	Dental/TMJ problems	4%	0%	0.04		
	Depression	17%	7%	0.03		
	Deviated septum	7%	1%	0.03		
	Skin conditions	4%	19%	0.0008		
	Diabetes	0%	9%	0.002		
	Musculoskeletal problems	7%	16%	0.046		
	Other GI problems[b]	9%	24%	0.004		
Trejo-Gabriel-Galan et al.	CH contribution to global suicide rate	0.04/100.000 population-year 39% of all primary headaches			Suicide in primary headaches in 48 countries.	2018
Galan et al.	CH contribution to global attempted suicide rate	0.4/100.000 population-year 35% of all primary headaches				
Piacentini et al.	Personality disorders	92% of the patients had personality disorders. The most frequent were: obsessive–compulsive (30.8%), histrionic (26.9%), narcissistic (11.5%), paranoid (11.5%), avoidant (11.5%). Somatoform disorder was identified as a clinical syndrome in 15.4%.			Twenty-six consecutive inward patients with CH between 2014 and 2016 evaluated using the MCMI-III, 14 personality disorder scales and 10 clinical syndrome scales.	2017
Lasaosa et al.	Absence of nocturnal dipping[c]	48.5%	16.6%	0.004	Cross-sectional study assessing cardiovascular risk factors in 33 CH patients and 30 controls. Results are not adjusted for possible confounders.	2017
	Ever-smoker	45.5%	40%	0.042		
	IMT[d] 90th percentile	25%	4.5%	0.012		
	Pathological ankle-brachial index	69.7%	40.9%	0.034		
Munoz et al.	Personality traits	Obsessive–compulsive 52.5%, anxious 47.5%, histrionic 45%, schizoid 42.5%, impulsive 32.5%, paranoid 30.0%. OR for paranoid traits was 3.27 (95% CI 1.66–6.43, $p = 0.001$) for CH patients.			Eighty-five consecutive patients with CH and 164 patients with migraine as reference population.	2016
Louter et al.	Lifetime depression	OR: 2.77 (CI 1.7–4.5)			Cross-sectional, web-based, validated questionnaire study among 462 well-defined CH patients and 177 controls. OR adjusted by sex, age, education, BMI and sleep disturbances (PSQI score).	2016
	Ever antidepressants	22.5%	10.2	<0.001		
	Lifetime depression	43.9%	15.8%	<0.001		
	Poor sleeper	58.4%	37.3%	<0.001		

(continued)

Table 2. (continued)

Author	Comorbidities		Statistics			Comments	Year
			CH	Controls	*p*-value		
Barloese et al.	Percentage of REM sleep		17.3%	23.%	0.0037	Polysomnography was performed on two nights in 40 CH patients during active bout and one night in 25 controls.	2015
	REM latency		2.0 h	1.2 h	0.0012		
	Arousals		7.34	14.1	0.003		
Liang JF et al.	Adjusted hazard ratio for depression	Control 1: 2692 age-, sex- and Charlson's score[e]-matched migraine patients	5.6 (95% CI 3.0–10.6), $p < 0.001$			Six hundred and seventy-three patients with CH and two different control groups. Median of 2.5 years follow-up.	2013
		Control 2: 2692 patients free from migraine	1.1 (95% CI 0.7–1.7), 0.77				
Rossi P et al.	Cannabis %		55.5	36.6	<0.0001	Comparative cross-sectional survey comparing lifetime use of illicit drugs in 210 patients (162 males) with CH and a representative sample of the Italian population (10,940 people). Only data for the male patients is presented (differences for illicit drugs for female patients was not statistically significant compared to the control sample).	2012
	Opioids %		5.5	2.3	0.01		
	Cocaine %		24.1	8.7	0.0001		
	Amphetamines %		12.9	3.7	0.0001		
	Ecstasy %		13.5	4.2	0.0001		
	Hallucinogens %		8.6	5	>0.05		
Luerding R et al.	Questionnaire for Measuring Factors of Aggression (FAF)		ANOVA for the subscale "self-aggression/depression" was significant ($F_{4,\ 123.}$ 5.771, $p < 0.001$), but not for other subscales or the sum scale.			Twenty-six patients with chronic, 25 with active episodic and 22 with episodic CH outside the active period were examined interictally with a validated questionnaire quantifying factors of aggression and compared with 24 migraine patients and 31 headache-free volunteers.	2012
Rozen TD et al.	Suicidality		55% of participants			Demographics, clinical characteristics, triggers, suicidality and personal burden in 1134 individuals that completed a web-based survey from October to December 2008 in the USA. No control group.	2012
	Age of onset		36% 21–30 y; 35% ≤20 y				
	Time delay to diagnosis		22% had a delay of ≥10 y.				
	Personal history of depression		24% of responders				
Robbins et al.	Depression (PHQ-9 ≥10)	ECH		6.3%		Forty-nine consecutive CH patients. EHC patients in and out of active attack periods had similar depression and anxiety scores.	2012
		CCH		11.8%			
	Anxiety (GAD-7 ≥ 10)	ECH		15.6%			
		CCH		11.8%			
Zidverc-Trajkovic et al.	Diabetes mellitus		OR: 4.2, $p = 0.035$			One hundred and thirty CH patients in Serbia. Control group: 982 patients with migraine. OR adjusted by gender, age and duration of headache.	2011

(continued)

Table 2. (continued)

Author	Comorbidities	Statistics			Comments	Year
		CH	Controls	*p*-value		
Lambru et al.	Prevalence of traumatic head injuries	38.5% in the CH group (OR 2.0 (95% CI 1.3 to 4.9).		23% in controls	Two hundred males with CH and 200 migraine controls.	2010
	Heavy alcohol	10.0%		0.5% migraine patients		
Van Alboom E et al.	Trigeminal neuralgia	16% of the patients had previously received the diagnosis trigeminal neuralgia			Eighty-five CH patients of 4 neurology outpatient clinics in Belgium. A mean delay of 44 months was reported, but 31% of the patients had to wait more than 4 years to receive the diagnosis.	2009
Pietrini et al.	Hypertension	35% of CH patients			Sixty consecutive CH patients. The authors did not find an increased prevalence of hypertension compared to the expected prevalence adjusted per age and gender.	2005
Graff-Radford et al.	Sleep apnea	80.6%			Thirty-one consecutive patients with episodic CH in active phase completed an overnight polysomnographic study.	2004
Kudrow L.	Peptic ulcer	Men with CH had a statistically significantly higher prevalence compared to controls			Cross-sectional survey study. One hundred and forty CH patients compared to controls from a headache clinic and healthy outpatients.	1976
	Coronary artery disease	No increased risk for CH patients compared to controls				

OR: odds ratio.

[a]Model adjusted by age, sex and group (CH/controls).

[b]Other GI (gastrointestinal) problems: other than celiac disease, GERD (gastroesophageal reflux disease). Only statistically significant differences found in the different studies presented in this table are included.

[c]Nocturnal dipping: normal decrease of 10–20% in nocturnal blood pressure.

[d]IMT: intima-media thickness (measured by carotid ultrasound).

[e]Charlson's score: method of predicting mortality by classifying or weighting comorbid conditions. MA+: migraine with aura; MA−: migraine without aura. MCMI-III: Millon Clinical Multiaxial Inventory-III.

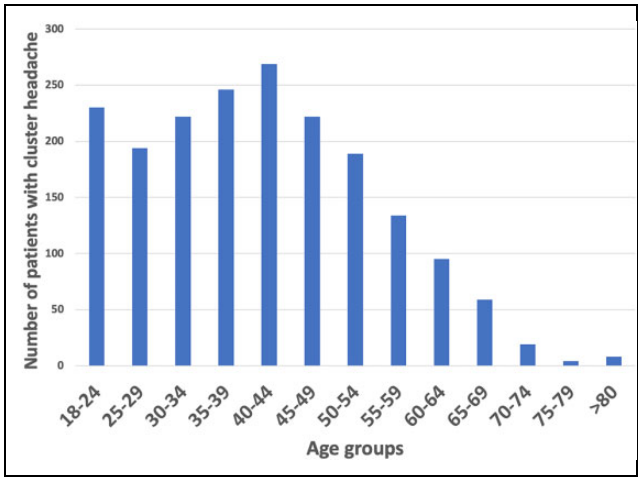

Figure 1. Age distribution of patients with CH in our nationwide sample.

Among 1891 patients with CH 1126 were men (59.5%), providing a male-to-female ratio of 1.47. The mean age of the whole population was 55.8 (±18.9) years. The median age of the patients with CH was 42 years (interquartile ratio: 20). Figure 1 shows the age distribution of patients with CH.

Forty-two patients with CH (2.2%) died between 2008 and 2016. The expected number of deaths in the CH group according to the mortality in the Norwegian population in 2016 adjusted for age and gender would have been 30.3 deaths in that period of time (HR: 1.4, CI 1.0–1.9, $p = 0.044$).

The main comorbid headache disorders in patients with CH were drug-induced headache, trigeminal neuralgia (TN), tension-type headache (TTH), migraine, atypical facial pain and chronic posttraumatic headache (Table 3 and Figure 2). Other common medical comorbidities were peptic ulcer, cerebrovascular disease, hemorrhagic complications, hypertension, thromboembolism, and chronic renal failure. The main psychiatric comorbidities were somatoform disorders, suicide attempt, personality disorders, bipolar disorders, depression and substance abuse. After adjusting by age and gender, there was no association with increased risk for intracranial hemorrhage, cognitive symptoms, chronic heart failure, atrial fibrillation, liver disease or diabetes mellitus.

Most of the CH patients had tried sumatriptan and prednisolone was dispensed in half of them (Table 4). Eighty-one percent (1539) of the CH patients were dispensed opioids during the study period versus 22% (854,470) of the rest of the population, unadjusted OR: 19.3 (CI: 17.2–21.7, $p < 0.0001$); adjusted OR by sex and age: 23.4 (95% CI 20.8–26.2 $p < 0.0001$). Seven CH patients (0.37%) had an occipital stimulator implanted between 2008 and 2016.

Discussion

In this nationwide study of CH, we report a prevalence of 48.6 per 100,000 and annual incidence of 3.0 per 100,000. We further show that CH is associated with a higher risk of potentially severe medical, and psychiatric comorbidities and higher use of opioid analgesics. High-quality population-based studies on prevalence, incidence, and comorbidity are scarce.[29,30] A population-based study based on direct interviews in a small, but well-defined geographical catchment area in Norway, found that 0.38% (7/1838) fulfilled the criteria of CH and that among these only two had consulted a physician.[7] In another study in Sweden, only four out of nine patients with CH had sought professional help[8] even though they had experienced CH for 6 years on average. This raises the possibility that our study underestimates the real prevalence. Prevalence in studies conducted in Africa range between 30 and 1298.7 per 100,000.[9,10] The lifetime prevalence of CH has been estimated around 0.2–0.3%.[55] Studies that report 1-year prevalence of CH have been criticized for possibly underestimating the real prevalence as some patients might not have bouts during the observation period. Our prevalence of 48.6 per 100,000 is lower than the median prevalence of 121.5 per 100,000 observed in other studies (Table 1). This might be due to several factors including selection bias, non-consulting, misdiagnosis, or lack of specialist visit between 2008 and 2016.

Few studies have reported incidence of CH (Table 1). Incidence rates vary between 2.1 and 9.8 per 100,000 per year.[11–13] Whereas the sample size of previous studies ranges between 104 and 36,145,[14] this study included the entire adult Norwegian population of more than 3.8 million individuals. The incidence of 3.0 per 100,000 per year is within the range of previous studies.

While early reports on CH reported up to a 14-fold male predominance,[15–17] later studies have detected more women with CH.[18,19] The decrease in the male-to-female ratio might be due to increased awareness of the possibility of other primary headache diagnoses in women other than migraine. Our observed male-to-female ratio of 1.47 seems consistent with more recent epidemiological studies,[18–20] and it is possible that methodologically more rigorous studies in larger populations have simply clarified a more accurate male to female ratio that in the past was overestimated.

Comorbid headache disorders

As seen in other reports,[56,57] our study suggested that medication-induced headache appears to be a major problem in CH patients. Unfortunately, there is no ICD-10 code that perfectly overlaps with the ICHD-3 diagnosis "Medication-overuse headache." The ICD-10 code that is more analogous is G44.4 ("Drug-induced headache"). Distinguishing atypical facial pain, TN and CH often represents a real challenge in daily clinical practice.[58–63] Fifty-eight patients with CH (3.1%) in our study also received a diagnosis of TN. This raises the possibility of diagnostic uncertainty. The same problem applies to the 47 patients (2.5%) with CH who also

Table 3. Unadjusted and adjusted odds ratios for age and sex for different comorbidities in our nationwide sample.

	Patients with CH		Control population					
	Absolut number	% ($N = 1891$)	Absolut number	% ($N = 4{,}663{,}893$)[b]	Unadjusted OR (95% CI)	*p*-value	Adjusted[a] OR (95% CI)	*p*-value
Drug-induced headache	39	2.1	1916	0.04	50.9 (37.0–70.1)	<0.0001	50.7 (36.7–69.9)	<0.0001
Trigeminal neuralgia	58	3.1	5390	0.1	27.2 (20.9–35.3)	<0.0001	36.9 (27.6–46.8)	<0.0001
Tension-type headache	225	11.9	23,210	0.5	26.8 (23.3–30.9)	<0.0001	25.9 (22.5–29.8)	<0.0001
Migraine	386	20.4	48,721	1.0	24.1 (21.6–7.0)	<0.0001	25.2 (22.5–28.3)	<0.0001
Atypical facial pain	47	2.5	5710	0.1	23.4 (17.5–31.3)	<0.0001	23.4 (17.5–31.3)	<0.0001
Chronic posttraumatic headache	13	0.7	1251	0.03	25.6 (14.8–44.5)	<0.0001	22.2 (12.8–38.45)	<0.0001
Somatoform disorders	36	1.9	20,436	0.4	4.4 (3.1–6.1)	<0.0001	4.2 (3.0–5.8)	<0.0001
Suicide attempt	25	1.3	13,758	0.3	4.5 (3.0–6.7)	<0.0001	3.9 (2.6–5.8)	<0.0001
Personality disorder	42	2.2	23,875	0.5	4.4 (3.2–6.0)	<0.0001	3.6 (2.6–4.9)	<0.0001
Bipolar disorder	52	2.7	32,410	0.7	4.0 (3.0–5.3)	<0.0001	3.6 (2.8–4.8)	<0.0001
Peptic ulcer	115	6.1	140,852	3.0	2.1 (1.7–2.5)	<0.0001	2.8 (2.3–3.3)	<0.0001
Depression	247	13.1	221,449	4.7	3.0 (2.6–3.42)	<0.0001	2.8 (2.4–3.1)	<0.0001
Substance abuse	74	3.9	55,044	1.2	3.4 (2.7–4.3)	<0.0001	2.6 (2.0–3.3)	<0.0001
Cerebrovascular disease	63	3.3	144,641	3.1	1.1 (0.8–1.4)	0.5992	2.4 (1.8–3.1)	<0.0001
Alcohol abuse	85	4.5	80,342	1.7	2.7 (2.1–3.3)	<0.0001	2.2 (1.8–2.7)	<0.0001
Bleeding[c]	135	7.1	218,388	4.7	1.6 (1.3–1.9)	<0.0001	2.2 (1.8–2.6)	<0.0001
Hypertension	234	12.4	508,338	10.9	1.1 (1.0–1.3)	0.0509	2.2 (1.9–2.5)	<0.0001
Thromboembolism	181	9.6	424,027	9.1	1.1 (0.9–1.2)	0.5255	2.1 (1.8–2.5)	<0.0001
Problems related to lifestyle	17	0.9	18,432	0.4	2.3 (1.4–3.7)	0.0008	2.0 (1.2–3.2)	0.0041
Chronic renal failure	62	3.3	164,258	3.5	0.9 (0.7–1.2)	0.5317	1.9 (1.5–2.5)	<0.0001
Previous cranial traumatism	73	3.9	91,316	2.0	2.0 (1.56–2.5)	<0.0001	1.9 (1.5–2.4)	<0.0001
Heart valve disease	50	2.6	145,725	3.1	0.8 (0.6–1.1)	0.2129	1.7 (1.3–2.2)	0.0004
Vascular disease	43	2.3	137,637	3.0	0.8 (0.6–1.0)	0.0754	1.6 (1.1–2.1)	0.0049
Intracranial hemorrhage	11	0.6	26,095	0.6	1.0 (0.6–1.9)	0.9141	1.9 (1.1–3.5)	0.0290
Cognitive symptoms	25	1.3	124,166	2.7	0.5 (0.3–0.7)	0.0003	1.6 (1.1–2.5)	0.0180
Chronic heart failure	32	1.7	159,354	3.4	0.5 (0.3–0.7)	<0.0001	1.4 (0.9–2.0)	0.0869
Atrial fibrillation	54	2.9	232,617	5.0	0.6 (0.4–0.7)	<0.0001	1.4 (1.0–1.8)	0.0333
Liver disease	30	1.6	59,846	1.3	1.2 (0.9–1.8)	0.2568	1.2 (0.8–1.7)	0.3176
Diabetes mellitus	82	4.3	238,345	5.1	0.8 (0.7–1.0)	0.1125	1.1 (0.9–1.4)	0.2604
Aggressive behavior	0	2.1	815	0.04	$1.3e{-}04$ (4.8^{-82}–3.7^{+73})	0.9218	4.1^{-05} (1.6^{-131}–1.0^{+122})	0.9457

[a]Adjusted for sex and gender.

[b]The total population in Norway over 18 years of age in 2016 was used in order to calculate ORs adjusted for sex and gender. OR: Odds ratio, CI: confidence interval.

[c]See Table 1 for ICD-10 codes included under "Bleeding."

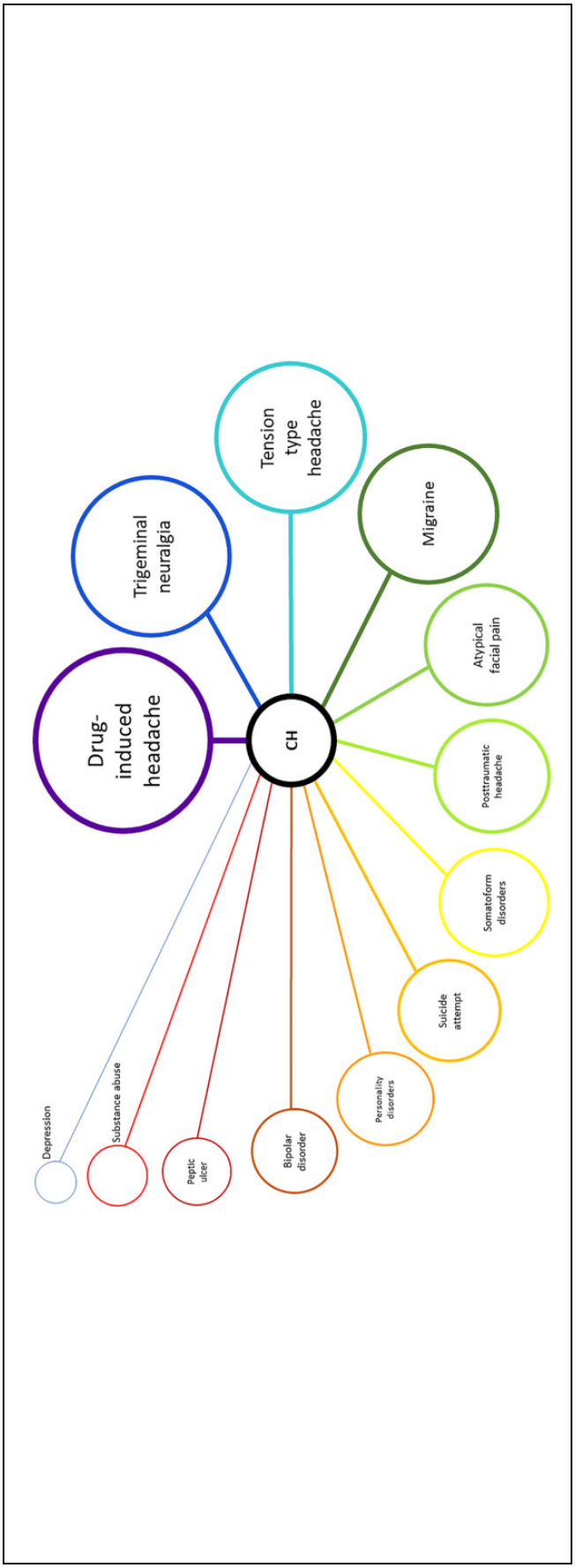

Figure 2. Visualization of the most common comorbid diagnosis found in this nationwide study (see Table 3 for further information). CH: cluster headache.

Table 4. Drugs currently or previously tried by patients with cluster headache (CH).

Drug	Number of patients with CH	% of patients with CH
Sumatriptan	1807	95.6
Zolmitriptan	464	24.5
Prednisolone	953	50.4
Verapamil	917	48.5
Lithium	152	8.0
Topiramate	260	13.8
Valproic acid	115	6.1
Melatonin	399	21.1
Gabapentin	345	18.2
Pregabalin	172	9.1
NSAIDs (any)	1713	90.6
Botox	61	3.2
Opioids		
Total (any opioid)	1539	81.4
Morphine	69	3.6
Hydromorphone	1	0.1
Oxycodone	259	13.7
Oxycodone and naloxone	29	1.5
Ketobemidone	114	6.0
Ketobemidone and antispasmodics	56	3.0
Pethidine	58	3.1
Fentanyl	54	2.9
Dextropropoxyphene	26	1.4
Buprenorphine	107	5.7
Codeine and paracetamol	1343	71.0
Tramadol and paracetamol	46	2.4
Tramadol	905	47.9
Tapentadol	26	1.4

NSAIDs: nonsteroidal anti-inflammatory drugs.

received the diagnosis atypical facial pain. In one study, 16% of the patients with CH initially received the diagnosis of TN before it was revised to CH.[31]

Migraine was a common comorbidity in our sample (20.4% vs. 1.0% of people without CH in the NPR). TTH was also more common in CH patients (11.9% vs. 0.5% of people without CH in the NPR). Population-based studies have shown a 1-year prevalence of 43.1% for TTH and of 18.1% for migraine.[21] Other authors have found that 15.6% of patients with CH had comorbid migraine.[32] Most patients with TTH or migraine are not seen by neurologists in our country and that these are less likely to be registered as ICD-10 diagnosis by specialist health care services. This might be the reason why the percentage of people without CH who were diagnosed with migraine was lower than in population-based studies.

As reported by others,[33] we found that patients with CH were more likely to be diagnosed with traumatic head injuries and chronic posttraumatic headache. Due to the observational design of our study we cannot make any causal inferences.

Psychiatric comorbidities

We identified several severe psychiatric comorbidities to be more frequent in CH patients. Somatoform disorders were reported in 15% of patients in an Italian case series[34]; a figure that is similar to population-based prevalence rates. However, only 2% of patients with CH in our study were diagnosed with somatoform disorders, raising suspicion that clinicians in Norway underreport somatoform disorders in the presence of other severe conditions such as CH. Most of the literature has focused on suicidal ideation rather than on suicide attempts in CH[30,35–37] (Table 2). Twenty-five (1.3%) of the patients with CH in our study had made a suicide attempt that was serious enough to receive specialized care (vs. 0.3% of the population without CH). We might not have detected cases that did not seek help or where a suicidal attempt was not documented. Between 2008 and 2016 there were a total of 5069 deaths by suicide in Norway.[64] Patients with CH in this study had a higher risk of attempting suicide, putting these patients in a high-risk group. Our dataset did not have information about cause of death and thus we cannot know how many patients with CH did commit suicide during the study period.

Several studies report increased depression scores in CH patients[3,30,38–41] and depression was a common diagnosis among patients with CH in our sample (%) but lower than most other studies (Table 2). The actual prevalence of depression in our sample might be higher if patients with CH were screened directly.

In this sample, 2.2% of patients with CH received a personality disorder diagnosis (vs. 0.5% of the population without CH). Other authors have reported a much higher prevalence of personality disorder[34,42] when studying CH patients directly with neuropsychological tests (Table 2). Further, we found that patients with CH were twice as likely to receive diagnoses of problems related to lifestyle (ICD-10 code Z72) and life-management difficulty (ICD-10 Z73) compared to the population without CH. ICD-10 codes Z72 and Z73 (Supplementary Table 1) include problems such as lack of physical exercise, inappropriate diet and eating habits, problems related to socioeconomic and psychosocial circumstances, and so on. Substance abuse was also increased in patients with CH. Heavy alcohol consumption has been reported in up to 10% of patients with CH.[33] Diagnoses of alcohol abuse registered by specialized health care services was higher in patients with CH (4.5% vs. 1.7% in people without CH) with numbers in line with another Scandinavian study.[38] Cigarette smoking has also been documented to be increased among patients with CH.[39,43] Unfortunately, we could not collect good quality data on this topic since the coding praxis among specialist health care

services in Norway does not constantly register whether a patient smokes.

Comorbid medical diseases

Peptic ulcer has been described to have a significantly higher prevalence in men with CH compared to those without CH[44] and this was also true in our study. This might be related to the common use of nonsteroidal anti-inflammatory drugs (NSAIDs, which had been dispensed for 90.6% of our patients) and prednisolone (dispensed for 50.4% of the patients). It is noteworthy that half of the patients with CH had never tried prednisolone. Oral corticosteroids are often used for transitional prophylaxis but its level of evidence is low.[65] CH patients also had an increased risk for chronic renal failure which might be related to the common use of NSAIDs. Patients with CH had a two-fold increased risk of hemorrhagic complications (e.g. acute bleeding due to gastric ulcer or a duodenal ulcer, hematemesis, melaena, and hematuria; Supplementary Table 1) compared to people without CH in the NPR. We did not find an association between intracranial hemorrhage and CH after adjusting for age and sex.

Many CH patients in this study had not tried all available therapeutic options[65–67] (Table 4). A detailed medication history, focusing on the drugs that have been tried before, the maximal dose and duration of treatment, as well as partial efficacy and side effect profile, may improve and expand treatment options. Most of the patients with CH had tried at least one opioid. There is no good evidence to recommend the use of opioids in the acute or chronic treatment of CH[65] and clinicians should be especially careful when prescribing opioids because of the risk of habituation, dependence, substance use disorders, comorbid psychiatric disorders, and suicide risk in this population.[68]

In a series of 400 patients with CH compared to 200 controls, CH patients had a higher risk for cerebral infarction.[38] In the previous material, only patients between 18 and 65 years of age were included while we included all patients $\geq$18. In our patients with CH, risk of thromboembolism was doubled compared to the rest of the population (Table 3). The use of intravenous dihydroergotamine has been linked to increased rate of venous thrombosis both in patients with migraine and CH.[69] Unfortunately, we could not document how many patients with CH, migraine or the rest of the population were treated with intravenous dihydroergotamine during the study period as this is not registered in NorPD. Several cardiac conditions have previously been reported to be more prevalent in patients with CH.[38] In our data, patients with CH had an increased risk of developing vascular disease (i.e. coronary artery disease, atherosclerosis, aneurysm or dissection of big arteries and vascular dementia; Supplementary Table 1) or heart valve disease, however this is not a consistent finding in the literature.[44] The prevalence of chronic heart failure or atrial fibrillation were not increased in CH patients in our study after adjusting for age and sex. Vascular risk factors and lifestyle-related factors (alcohol and tobacco abuse) in patients with CH appear to be common, and a clinical evaluation to assess the risk for stroke, heart disease or thromboembolism should be an essential part of the follow-up in most CH patients.

Strengths and limitations

The major strength of this study is the large nationwide sample size collecting real world data in a relatively rare, but important condition. To our knowledge, the sample size exceeds any previous study.

The main limitation of this study is the observational design. Since data are based on diagnostic codes set in clinical practice, the results may be affected by the quality of coding practice.

The ICD-10 code for CH is the same used for chronic paroxysmal hemicrania. There is a possibility that the real prevalence of CH has been underestimated if some of the patients who dispensed more than 200 tablets of indomethacin actually had CH. ICD-10 does not differentiate between episodic and chronic CH. Future studies using ICD-11 will be able to differentiate between these two forms of CH.

Participants who had received the diagnosis G44.0 (CH) only once were also considered cases. Since there was no longitudinal assessment, some of these diagnoses might have been corrected outside the study period and changed to other ICD-10 diagnoses. This is also true for comorbidities detected in our study and some of them might have been misdiagnoses.

The calculation of incidence was limited by the fact that some patients in the 2008–2011 period may have received the diagnosis before 2008, and falsely been registered as "new patients" in this dataset.

In this study, data from January 1 2008 to December 31 2016 was included. The Norwegian patient registry uses ICD-10 codes which do not have a complete overlap with ICHD criteria. ICHD-II criteria were used in the specialist health care system between 2008 and 2013. ICHD-III Beta criteria were used between 2013 and 2016.

Validation of diagnoses and drug exposure in a representative subgroup of patients, would have strengthened our results. Still, previous validation studies have shown that NPR is adequately complete and correct to provide data for neurological epidemiological studies.[51]

Conclusion

In this nationwide epidemiological study of cluster headache, we report a prevalence of 48.6 per 100,000 and annual incidence of 3.0 per 100,000. We further show that patients with CH have a higher risk of potentially severe medical and psychiatric comorbidities and higher use of opioid analgesics. This places this patient population at substantial risk of serious adverse health outcomes, beyond the disability caused by the headache disorder. This study emphasizes the need to systematically and comprehensively evaluate these

patients from a general medical and psychiatric perspective in addition to a neurological evaluation. There is a risk that some or many of these diseases may be overlooked or not carefully searched for because of the very severe and highly disabling nature of the headache disorder itself.

Conclusion and relevance

CH was associated with higher risk of medical and psychiatric comorbidities, suicide attempts, and opioid use. In addition to deliberate and evidence-based management of CH, screening and appropriate management of comorbid diseases may improve overall outcome in patients with CH. Limitations include those inherent to observational studies including the inability to make causal inferences, assumptions regarding drug exposure, and the possibility of residual confounding.

Clinical implications

- In this Norwegian nationwide study, the prevalence of CH was 48.6 per 100,000 and the incidence was 3.0 per 100,000/year.
- The most common medical comorbidity was migraine requiring hospital specialist care (20.4% vs. 1.0% of people without CH).
- The most common non-headache medical comorbidity was hypertension (12.4% vs. 10.9% of people without CH). The most common psychiatric comorbidity was depression (13.1% vs. 4.7% of people without CH), and 1.3% of the patients had attempted suicide (vs. 0.3% of people without CH). A history of substance abuse was more common (3.9% vs. 1.2% of people without CH).
- The drug most commonly used was sumatriptan (95.6% of the patients). Most of the patients had been prescribed opioids at some point (81.4%).
- Cluster headache is a devastating headache disorder with potentially severe medical and psychiatric comorbidities.

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Author contributions

All authors read and approved the final manuscript. JC is the guarantor and was involved in planning the study, collection of the data, statistics, and writing of the manuscript. SG and ET gave the original concept of the study and were involved in writing of the manuscript. ØS and JC performed the statistical data analyses. MM and DD revised the final manuscript and were involved in the scientific organization of the study.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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