

## Cluster headache prevalence: methodological considerations. A review of the literature

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**Abstract.** Cluster headache (CH), also known as “suicide headache”, is characterized by a distinctive periodic temporal pattern and by accompanying autonomic symptoms during the attacks. Epidemiological data for the general population are scarce: only five studies have been carried out until now on CH prevalence in the general population, with conflicting results (prevalence rates vary between 56 and 326 cases every 100,000 inhabitants). Recently, a study was performed to investigate a representative sample of the Italian general population aged over 14 years. Possible CH cases according to the diagnostic criteria of the 1988 International Headache Society (IHS) classification were screened out of a sample of 10,071 patients registered in the lists of seven general practitioners (GPs) in Parma, using a previously validated, specially designed self-administered questionnaire. The diagnosis of CH was confirmed in 21 subjects (nine women and 12 men). The estimated prevalence rate was 279/100,000 (95% CI: 173-427), 227/100,000 (95% CI: 104-431) in women and 338/100,000 (95% CI: 175-592) in men. Based on methodological considerations, we believe that a lifetime prevalence rate of 279/100,000 for a population aged over 14 years is a reliable figure and it is probably not much lower than in the whole general population, since some studies performed on large case series have shown that the onset of CH is not frequent under 14 years of age. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Headache, cluster headache, epidemiology, lifetime prevalence

### Introduction

Cluster headache (CH) is a type of primary headache so-called because its symptoms recur in clusters. There are two forms of CH: episodic CH, characterized by alternating *active periods*, with daily or almost daily attacks, and *remission periods* that are totally symptom free; and chronic CH, in which remission periods are absent or last less than one month (1). The attacks are extremely painful, so that CH is also commonly called *suicide headache*. The pain is always unilateral and confined to the orbital, supraorbital and temporal regions. The duration of the attacks varies between 30 and 180 minutes and is associated with a variety of accompanying autonomic symptoms (2-4). Even though CH has very distinctive clinical features that consistently characterize the attacks between pa-

tients and within the same patient and are therefore easy to detect, very few data are available on CH epidemiology, in particular in the general population. This is probably due to its low frequency in comparison with other forms of primary headache, such as migraine.

When a disease is fairly rare, for a variety of reasons, it does not raise interest among private and public sponsors. In addition, a fairly rare disease presents investigators with methodological problems in epidemiological studies, mainly due to the need to investigate very large samples that are representative of the general population.

Since the first reports on CH, opinions about its prevalence have widely varied. Regarded as a rare condition by some authors, CH was frequently diagnosed by others. In the early '50s, after investigating 4,634

subjects, Ogden (5) found that 100/100,000 subjects suffered from “histamine cephalgia”. However, Horton’s diagnostic criteria for histamine cephalgia could not be considered exhaustive enough to establish a CH diagnosis.

In this review we will consider all the currently available data on CH prevalence and comment on the study results, evaluating the investigational approaches used by the various authors.

### General population studies

Five studies have been carried out to date on CH prevalence in the general population. The discordance among the few currently available results is probably due less to actual differences in the studied populations than to a lack of consistency in the methods used for data collection in the different studies. Moreover, most studies were conducted prior to the 1988 International Headache Society (IHS) classification currently in use, and therefore the applied diagnostic criteria are not consistent (Tab. 1).

Ekbom et al. (6) investigated a sample of 10,400 18-year-old males, who were seen by a doctor for their pre-draft physical examination between October 1975 and May 1976. During the month preceding the mandatory medical visit for military recruitment, the young men received a questionnaire that they had to fill out and send back within a week. The questionnaire contained questions about a variety of diseases, as well as health and social conditions. There was also a question specially aimed at investigating whether the subject had suffered or was suffering from some form of recurrent headache. All subjects who answered af-

firmatively to this question had to fill out an additional questionnaire to identify the form of primary headache during their medical visit. Overall, 9,610 subjects (92.4%) sent back the first questionnaire. Those who did not reply to the questionnaire were nonetheless investigated for the presence of headache during the medical visit. Data was collected on a total of 9,803 subjects. The diagnostic criteria applied for the diagnosis of CH were set up by Ekbom himself a few years earlier (7). Among the 436 subjects with recurrent headache, nine of them fulfilled the diagnostic criteria for CH – including eight with episodic CH and one with chronic CH – and their diagnosis was confirmed through a direct interview. The estimated lifetime prevalence was 90/100,000. Significantly, this was the first study not conducted on a clinical population. However, although the method used by the authors was such that CH cases could not be easily missed, the resulting prevalence rate cannot be applied to the general population. In fact, only 20–30% of the patients in large case series (2, 3) develop CH in the first and the second decade of life. Realistically, the 90/100,000 prevalence rate is therefore very close to the present one only in 18-year-old men.

In 1984 and in 1999, the entire population of the Republic of San Marino was investigated in two studies that used the same methodological approach. In the first survey, the authors (8) found a prevalence rate of 69/100,000 (128/100,000 in men and 9/100,000 in women) out of 21,792 inhabitants (10,823 men and 10,899 women); in the second survey (9), the estimated prevalence rate was 56/100,000 (115.3/100,000 in men) out of 26,628 inhabitants (13,008 men and 13,620 women).

The authors used four different methods to identify suspected sufferers, namely: i) they reviewed all clinical records of patients seen in the 15 years preceding the study by neurologists, ophthalmologists and ear-nose-throat specialists practicing in San Marino; ii) they asked all 15 San Marino GPs to indicate how many of their patients had CH; iii) they mailed all San Marino inhabitants a letter illustrating the features of CH and asking those who experienced a similar headache to call the study center; iv) they reviewed clinical records of San Marino citizens who were treated at the University Headache Center of Bologna – the

**Table 1.** Cluster headache prevalence: studies conducted in the general population

Author	Year	Sample (n)	Cluster headache cases (n)	Prevalence (n/100,000)
Ekbom et al. (6)	1978	9,803	9	90
D’Alessandro et al. (8)	1986	21,792	15	56
Tonon et al. (9)	2002	26,628	15	69
Sjaastad et al. (14)	2003	1,838	6	326
Torelli et al. (13)	2005	10,071	21	279

nearest referral center to San Marino. For subjects with suspected CH, the diagnosis was confirmed through a direct interview and was established according to the criteria of the Ad Hoc Committee on Classification of Headache (10) for episodic CH, and according to the criteria set by Ekbom and Olivarius (11) in the first study and those of the 1<sup>st</sup> edition of the IHS classification (12) in the second study for chronic CH. Fifteen CH cases (14 men and one woman) were detected in the first study published in 1986 (8) and 15 cases (all men, including six already found in the previous survey) in the second study published in 2002 (9). Analyzing the distribution of the detected CH cases with respect to the different detection methods, it appears that the most effective method was by far the review of the clinical records of the neurologists practicing in San Marino. With this method alone, the investigators detected as many as 14 out of the 15 cases in the first study and 13 out of the 15 cases in the second study.

If we compare the 15 cases in the first study with the 15 cases in the second study, we can see that seven cases were present in both studies, eight developed the headache after the first study, and eight were no longer there, including three who had died, three who no longer lived in San Marino, and two who had completely recovered.

Beside the fact that it is very difficult to say when a CH patient has completely recovered, the prevalence for this type of headache should always be calculated on a lifetime basis, given its distinctive time pattern. Therefore, it is not clear why the two “recovered” cases were not included among the cases in the second study.

The suspect that the investigators may have missed a considerable number of cases arises from the following considerations: i) it is almost impossible that nearly all subjects with CH in the general population were seen by a neurologist; indeed, from the few available data, it appears that less than half of subjects with CH seek medical treatment for their headache – only 38.1% (8/21) in the study conducted in Parma (13), 28.6% (2/7) in the Sjaastad et al. study (14), and 44.4% (4/9) in the Ekbom et al. study (6) had seen a doctor for CH at the time of the survey; ii) it is very odd that only one woman with CH – in a chronic form, no less – was found in the first study and no woman at all out

of a total of 13,000 women was found in the second study; iii) the thorough screening of the population was done using a method – sending a letter to all inhabitants – that was as unreliable as it was deceptive. In order to validate this method, the authors randomly checked 90 subjects and were satisfied that 84 had received the letter and understood its content. However, they did not seek out the percentage of those who did not call back the center, even though they had received and understood the letter and had identified themselves as CH sufferers. In fact, their percentage was certainly high, because only eight of the 15 subjects with CH in the first study and one of the 15 subjects with CH in the second study replied to the letter. Moreover, of the eight subjects with CH who replied to the letter in the first study, six were CH cases that were also included in the second study, but only one of those replied to the letter in the second study, while five did not. The San Marino studies merely indicate a CH prevalence rate in the general population of at least 56-69/100,000, but, based on the above considerations, this figure may be much lower than the actual one.

In an extensive epidemiological study performed on the population of a small Norwegian county (14), the authors investigated a sample of 2,065 dalesmen aged from 18 to 65 years, living in Vågå County. Among them, 1,838 (88.6%) were interviewed through a specially designed face-to-face questionnaire. Headache diagnosis was established according to the criteria of the 1<sup>st</sup> edition of the IHS classification (12). The survey enabled investigators to identify six subjects with CH (one woman and five men) and the estimated lifetime prevalence rate was 326/100,000 (558/100,000 in men and 106/100,000 in women).

The only Italian survey was performed in Parma between 2002 and 2003 (13). We investigated a sample of 10,071 subjects aged over 14 years, including all patients registered in the practices of seven GPs in Parma. This survey was divided into two stages: a first stage to screen cases with suspected CH and a second stage to evaluate each suspected CH case and to confirm the diagnosis through a direct interview at the Parma Headache Center. During the screening stage, the subjects were given a specially designed, previously validated self-administered questionnaire (15) to be completed in three successive and different steps. A

total of 7,522 subjects (74.7%; 3,971 women and 3,551 men) responded to the questionnaire in their GP's office (n = 3,338; 1,885 women and 1,453 men), at home by mail (n = 1,914; 1,030 women and 884 men), or by phone (n = 2,270; 1,056 women and 1,214 men). Out of the 111 identified "suspected cases" (76 women and 35 men), 105 were seen by a neurologist and six were contacted by phone. The diagnosis of CH was confirmed in 21 subjects (nine women and 12 men), including seven that were already being treated at our center for CH, according to the diagnostic criteria of the 1<sup>st</sup> edition of the IHS classification (12). Seventeen patients were affected by episodic CH and four – all men – by chronic CH. The estimated prevalence rate was 279/100,000 in general (95% CI: 173-427), 227/100,000 for women (95% CI: 104-431) and 338/100,000 for men (95% CI: 175-592).

Our data are in agreement with those of the Vågå study conducted in Norway and we believe that the lifetime prevalence shown in a population aged over 14 years is a reliable figure, because: the initial sample was large and representative enough of Parma's general population aged over 14 years; the 74.7% response rate allows for results that are truly representative of the entire population; the screening questionnaire had been validated and had been proved to be reliable in detecting cases with suspected CH (15); and, the final diagnosis of CH was made according to the IHS criteria (12) using a direct interview by a (headache) neurologist. Moreover, our estimated prevalence rate is probably not much lower than in the entire general population, because some studies carried out on large case series have shown that the onset of CH is infrequent under 14 years of age (2-4).

### Mathematically extrapolated data

With reference to the methodological difficulties arising from studies aimed at investigating the distribution of a disease that is fairly infrequent in the general population, some authors have derived their epidemiological data from mathematical extrapolations: Kudrow (3), Heyck (16), and Swanson (17) calculated CH prevalence using this method, but they found conflicting rates (Tab. 2).

**Table 2 - Cluster headache prevalence: data from extrapolations**

Author	Year	Sample	Prevalence (n/100,000)
Heyck H (16)	1977	Clinical population	40
Kudrow L (3)	1980	Clinical population	240
Swanson et al. (17)	1994	General Population	401

Kudrow (3) estimated a prevalence rate of 240/100,000 (400/100,000 in men and 80/100,000 in women), based on Ekbom's (6) findings, on the mean age of males in his own sample of 425 subjects with CH, on the distribution of 18-year-old males in the general population of the United States in 1980, on the male-to-female ratio in his own patient group (M:F = 5.5:1), and considering the disease distribution as homogeneous in the different US geographic areas.

Heyck (16) estimated a prevalence rate of 40/100,000, based on the number of CH and migraine cases seen in his own Headache Center and on the prevalence of migraine in the general population. He then applied a simple mathematical proportion to the figure thus obtained.

In his study on CH prevalence, Swanson (17) investigated the 6,476 inhabitants of Olmsted County, Minnesota, and identified 26 CH cases. Considering the age at onset of CH and the average duration of the disease, and applying a mathematical formula to these parameters, the extrapolated prevalence was 401/100,000. In spite of the inherent limitations of this study method, this is the only extrapolation that did not use reference data taken from other case series.

Although some of the previously mentioned data are in agreement with those emerging from population studies, by definition, mathematical extrapolations produce only approximate results, since they are affected by the inaccuracy of the procedure.

### Data from prevalence studies on other forms of headache

Additional indications on CH prevalence come from epidemiological studies on other forms of primary

**Table 3.** Cluster headache prevalence: studies conducted in developing countries

Author	Year	Sample (n)	Cluster headache cases (n)	Prevalence (n/100,000)
Zhao et al. (19)	1988	246,812	14	6
Tekle Haimanot et al. (20)	1995	15,000	5	33
Alders et al. (21)	1996	595	—	—

headache. In a study conducted in Denmark in the '90s, Rasmussen (18) found a CH prevalence rate of 100/100,000. The study was performed on a representative sample of the Copenhagen population, consisting of 740 subjects aged from 25 to 64 years from 11 neighborhoods in the western area of the city. Although this provides some kind of reference for epidemiological data on lifetime and last-year prevalence rates of the major forms of idiopathic headache, i.e. migraine and tension-type headache, the number of subjects considered in the study was not large enough to investigate the frequency of a rare condition such as CH.

Studies conducted on a few populations in developing countries indicate prevalence rates varying between 0 and 33/100,00 (Tab. 3); a survey conducted by Zhao et al. (19) on 246,812 inhabitants of 21 Chinese provinces, revealed a prevalence rate of 6/100,000; a study carried out by Tekle Haimanot et al. (20) in an Ethiopian community, showed that 33/10,000 inhabitants suffered from CH; and finally, the survey by Alders et al. (21), did not find any case of CH in a sample of 595 subjects recruited from urban and rural areas in Malaysia. The lower frequency of CH recorded in these studies might reflect a less common occurrence of the disease in socially and economically underdeveloped nations, or it might be the expression of a typical cultural attitude of populations that are reluctant in revealing their health problems.

### Studies of selected populations

While few reports in the literature on general population studies are present, many investigations have been carried out on variously sized selected popula-

**Table 4 -** Cluster headache prevalence: data from selected population

Author	Year	Sample	Prevalence (n/100,000)
Heyck H (16)	1977	Clinical population	40
Hardman RA (22)	1966	General practitioner's patients	—
Ogunyemi AO (23)	1984	Universitary students	229 (M)
Mitsikostas DD et al. (24)	1994	Monks	—
Muniz et al. (25)	1995	Universitary students	2500 (M)
Mitsikostas DD et al. (26)	1996	Universitary students	—

tions (22-26). No cases of CH were found among 588 medical students from Athens (26), nor in a community of 449 Greek monks aged under 50 years (24), who were accustomed to distinctive sleep-wake cycles and adopted a special diet. By contrast, Muniz et al. (25) found a 2.5% rate of the disease in a restricted group of 96 university students. In spite of the interest aroused by studies in subjects with particular lifestyles, the rates found are very discordant, proving that these epidemiological data are scarcely reliable (Tab. 4).

### Conclusion

In conclusion, although few studies have been carried out so far on the general population, based on the methodological considerations reported in this review, we believe that a lifetime prevalence rate of 279/100,000 for a population aged over 14 years is the most reliable figure.

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