Chapter 3

Epidemiology of Headache

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Epidemiology has been defined as "the study of distribution and determinants of disease frequency in human populations." Epidemiologic studies may be categorized according to whether they focus on describing the distribution of disease in a population (descriptive studies) or on elucidating the determinants of disease (analytic studies) (41). Studies on headache epidemiology have primarily been descriptive, giving data on headache prevalence in men and women, in various age groups, among different races, and in different countries. Descriptive studies have also provided information on the personal and societal impact of headache in terms of economic costs and reduced quality of life. Recently, a number of analytic epidemiologic studies have been conducted with the explicit aim of studying causation by considering whether the risk of headache is different for those exposed and not exposed to some factor of interest.

In this chapter, we review some important results from descriptive studies on the prevalence and incidence of headache, and also review epidemiologic evidence relating to comorbid conditions and suspected risk factors. In addition, we focus on some analytic and design issues related to headache epidemiology, using specific studies from the epidemiologic literature to illustrate methodologic issues.

HEADACHE CASE DEFINITION

Irrespective of the design or the purpose of an epidemiologic study, it is necessary to define who has a certain diagnosis (is a case) and who does not. Case definition may be a particular problem in headache because headache diagnoses usually are made on the basis of subjective experiences without any objective signs or markers. Furthermore, there is some overlap in symptomatology between headache subtypes, and multiple headache types often coexist in the same individual. The most comprehensive and elaborate system for classifying headache disorders is the *International Classification of Headache Disorders,* 2nd edition (ICHD-2) (44). These provide specific criteria that are partly based on expert opinion and partly on systematic studies on reliability and validity. They represent an evolution of the criteria published by the International Headache Society (IHS) in 1988 (20). The introduction of these criteria provided a foundation for headache epidemiology that was lacking in earlier research and has made it possible to make meaningful comparisons between studies.

Although the introduction of standardized diagnostic criteria has helped to move forward population studies of headache disorders, the way in which these criteria are interpreted and applied (operationalized) has varied somewhat between studies. For example, many individuals have more than one headache type, most often both migraine and tension-type headache. The IHS classification requires that each headache occurring in the same individual receives a separate diagnosis and that secondary causes of headache are excluded. The issues of multiple headache types and secondary headaches have been handled in different ways in population studies. The gold-standard headache diagnosis is made by personal interview and examination by a neurologist using structured diagnostic criteria. However, this approach is expensive (71) and has been used in only a few population studies, usually with some modifications (5,6,23,28,52,83,106,113). Expert diagnosis has the advantage of assessing unlimited coexisting headaches types and diagnosing rare headache syndromes as well as secondary causes of headache (80,103–105,107). However, secondary causes of headache are uncommon in the general population (84) and multiple headache types are of less importance when the study aim is to identify only migraine sufferers. Screening instruments by lay interviewers have been shown to be accurate when the aim is to identify only the most common headache types (e.g., migraine and tension-type headache). For example, one method allowed the diagnosis of two headache types and had 85% sensitivity and 96% specificity for diagnosing migraine (111). A

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"recognition-based" questionnaire has also been used for mass screening of headache in adolescents. In this technique, descriptions of migraine and tension-type headache based on the IHS criteria were read to the pupils in connection with a clinical examination, and the pupils with recurrent headaches were then asked to indicate which headache most closely resembled their own headache (126).

The way in which *headache* is defined can influence study results. For example, higher headache prevalence is found in answer to a neutral question ("Do you have headache?") compared to questions involving some specification of headache degree ("Do you suffer from headache?" or "Do you have severe headache"?) (93). This is important when a question about headache is used to screen out non–headaches sufferers before the more specific questions about the features of the various headache types are posed. It has been found that those who answered "no" to the screening question about headache may nevertheless suffer from migraine, and that migraine prevalence increases after including screen-negative respondents (52). Ambiguities in the term *headache* may also be important when the term is translated, because it may have different connotations in other languages. This, as well as cultural differences relating to reporting pain, may contribute to variation in headache prevalence in different regions.

Because headache diagnosis ultimately depends on self-report, the quality of recall is of crucial importance. It is likely that recall is biased toward the most recent and severe headaches (80). The effect of recall problems was illustrated in one study (10), in which 41% of individuals interviewed in middle life could not remember that they had reported aura at an earlier stage. Recall problems may also explain why the lifetime prevalence of migraine decreased with increasing age in the Copenhagen study (83).

Finally, the definition of the control group is of equal importance to the definition of the case group. Headache is experienced at least occasionally by the great majority of the population (83). Choosing a control group that is without headache is thus likely not the best strategy, because being truly headache free is relatively rare. Recall problems may be a problem when trying to define a control group with relatively little or no headache. One study showed that some persons who answered negatively to a direct question on whether they had headache had relatively frequent headache when asked to keep a headache diary (121). This indicates that in many studies, the control group, which is allegedly "without headache," may nevertheless have some. Therefore, some degree of misclassification of the controls as well as the cases is likely in most studies.

VALIDATION OF DIAGNOSTIC METHOD

In most headache epidemiologic studies, it is desirable to validate the headache diagnostic algorithm. This is ideally done by selecting a random sample of screen-positive and screen-negative individuals for a gold-standard diagnosis by a neurologist. By comparing the study diagnosis to the gold-standard diagnosis, the sensitivity (percent of true cases correctly identified) and specificity (percent of true noncases correctly identified) can be calculated (38,56,74,81). The sensitivity and specificity of the headache diagnosis affects the calculated rates of prevalence or incidence of disease in descriptive studies (e.g., [39]). In analytic studies, the usual effect of diagnostic error is to make measured associations between disease and risk factors more conservative because of imperfect differentiation between diseased and nondiseased individuals (bias towards the null hypothesis). In the context of a large population study (as opposed to a clinical diagnosis), a certain degree of imprecision is tolerable as long as the diagnostic error is unbiased.

A validation study should be done even if the questionnaire has already been validated, because one method may not be valid in other regions or countries, or at another time. The validation interview should be done in close temporal proximity to the main study so that any variation is caused by method and not to a change in the headache condition itself. In different validation studies, the degree of correspondence between the main study and the validation study is usually given by the *kappa value,* which is the observed agreement adjusted for the agreement rate expected by chance. For migraine diagnosis, the kappa values between clinical interview-based and questionnaire-based diagnoses of migraine has varied considerably, from 0.22 to 0.77 in various studies (38) with generally lower kappa values for tension-type headache.

SOURCE POPULATION AND SAMPLING

The *source population* is the population from which study participants are drawn. This is often a country, region, or city, but may also be schools, universities, or companies. The degree to which the results can be extrapolated to the general population depends on whether cases are representative of all cases and whether controls are representative of all noncases. A representative population can be obtained by drawing a sufficiently large random sample from the source population. Sometimes, however, a stratified sampling strategy is used to ensure that the study population resembles the source population with regard to some important features such as age, gender, race, or socioeconomic status (109).

Headache is a disorder that often does not lead to physician consultation (53,58,82,118). If the population of interest is headache sufferers in general, one may not get a representative sample by studying those who consult physicians, particularly those who consult headache specialists, because these patients likely have more frequent and severe headaches than the general population of

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headache sufferers, and they may also differ in many other respects.

The *participation rate,* namely, the proportion of the sampled population that actively participates in the study, can affect the degree to which the study population is representative of the source population. If headache is the main object of the study, individuals suffering from headache may be more likely to participate than non–headache sufferers, and the headache prevalence may be overrated. Likewise, if certain age or socioeconomic groups have a higher nonparticipation rate than the average, this may distort the results. A high participation rate is therefore important and it is also desirable that an evaluation of the nonparticipants is performed to assess whether they are different from the participating population with regard to age, gender, and socioeconomic status. In some cases, demographic information is available for the nonparticipants, and this information can be used to determine whether the nonparticipants are similar to the participants. Otherwise, the participating population can be compared to external sources of demographic data (e.g., census data for the country or town in which the study takes place) to determine whether the participating population appears to be reasonably representative. If participation is found to vary substantially by demographic characteristics, prevalence rates can be adjusted to compensate for differential participation (112).

TYPES OF EPIDEMIOLOGIC STUDIES

The study designs dealt with under the heading of epidemiology include both experimental and nonexperimental (observational) studies. Nonexperimental analytic study designs are often called observational because the investigator only observes those who are exposed or nonexposed. This is in contrast to experiments, clinical trials, or community interventions where the investigator assigns exposure to one group but not another. In this section, we discuss how various nonexperimental study designs have been applied to the field of headache epidemiology and give examples of the type of information these different designs can yield and some problems inherent in each of them (86).

In a *case series,* headache is described and often related to some other factor in a group of patients. Many interesting features of headache have been studied in this way. For instance, migraine attacks have been related to meteorologic factors (22), seasonal variation in daylight duration in polar areas (90), the menstrual cycle (110), the natural course of HIV infection (27), and seizures in epileptic patients (116). In addition, several studies have described the prevalence and special features of migraine and headache in patients with lupus (31), Tourette syndrome (50), idiopathic intracranial hypertension (117), glaucoma (75), and among visually impaired persons (47). Because there is no control group, only hypotheses about causal factors can be formulated on the basis of such studies.

With *correlational* (or ecologic) *studies,* the headache prevalence in a defined population is related to some other factor. By this method, relatively little used in headache epidemiology, it was found that headache among schoolchildren was more prevalent in districts with high unemployment (17), that headache prevalences in various parts of Greece correlated with mean temperatures (66), and that migraine was more prevalent at high altitude than at sea level in Peru (5). A limitation of this method is that exposure cannot be linked to particular individuals, and it is not possible to adjust for possible confounding factors.

In *cross-sectional surveys,* the disease status of individuals in the population is assessed at the same time as exposures of interest, such as demographic factors, comorbid conditions, or other suspected risk factors. A *prevalence study* is a cross-sectional study conducted to determine the proportion of the population that has a disease. Because headache usually varies considerably through life, it is important that a time span for the headache is determined. *Lifetime prevalence* measures the lifetime occurrence of headache. *Period prevalence* measures the proportion of individuals who have had headache during a defined period. *One-year prevalence* is often used because it is considered reasonably reliable, and it defines the proportion of the population that has an active disease, therefore being relevant for assessing the burden of headache in society.

Prevalence studies are probably the most common study type used in headache epidemiology. As can be seen from Table 3-1, prevalences differ widely between studies. Differences between studies using the same diagnostic criteria could be caused by differences in the age and gender distribution of the source populations, differences in the way in which the diagnostic criteria were operationalized, participation rates, or underlying differences in headache incidence or prognosis in different populations (93).

In virtually all studies in adults there is a higher proportion of headache sufferers among women than among men (see Table 3-1). Migraine prevalence typically increases in childhood and youth, is relatively stable and high in the third to the fifth decades, after which there is a marked decline in both sexes. Tension-type headache appears to be less related to age than migraine (97). A relatively typical age distribution of the 1-year headache prevalence in adults from a large population-based study in Norway is shown in Figure 3-1.

Studies in the United States and England have found higher prevalences of migraine among Caucasians (18,108), followed by African Americans and Asian Americans (111). In Singapore, the prevalence among the Chinese was lower than among the non-Chinese

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TABLE 3-1 Population-Based Studies on Prevalence of Headache in Various Parts of the World

Country, Author	Year	Age Range (y)	Number of Respondents	Study Method	Time Period Prevalence	Headache		
						Men	Women	Overall
Europe								
Austria, Lampl et al. (51)	2003	≥15	997	Personal interview	1 year	43.6	54.6	49.4
Croatia, Zivadinov et al. (123)	2001	15–65	3794	Personal interview	1 year			65.2
Denmark, Rasmussen et al. (83)	1991	25–64	740	Personal interview	Lifetime	93	98	96
Finland, Sillanpää and Anttila (101)	1984	14	3863	Questionnaire	1 year	65	71	68
France, Michel et al. (63)	1996	>18	9411	Questionnaire	3 months	39	58	49
France, Henry et al. (42)	2002	≥15	10585	Personal interview	Lifetime			29.2
Germany, Göbel et al. (32)	1994	>18	4061	Questionnaire	Lifetime			71.4
Greece, Mitsikostas et al. (66)	1996	15–75	3501	Questionnaire	1 year	19.0	40.0	29
Italy, Prencipe et al. (76)	2001	≥65	833	Personal interview	1 year	36.6	62.1	51
Italy, Camarda and Monastero (16)	2003	≥65	1031	Personal interview	1 year	16.5	26.3	21.8
Norway, Hagen et al. (39)	2000	≥20	51383	Questionnaire	1 year	29.1	46.8	38.6
Norway, Zwart et al. (125)	2003	13–19	8984	"Recognition-based"	1 year	21.0	36.5	29.1
San Marino, Benassi et al. (9)	1986	≥7	1145	Questionnaire	1 year	39.8	52.4	43.3
Spain, Bassols-Farres et al. (7)	2002	≥18	1964	Telephone interview	0.5 year	71.5	85.6	78.6
Sweden, Dahlöf and Linde (24)	2001	18–74	1668	Telephone interview	1 year	43	57	62
Sweden, Carlsson (17)	1996	7–16	1144	Questionnaire	Not stated			26
Turkey, Ozge et al. (74)	2003	8–16	5562	Personal interview	Not stated			49.2
UK, Abu-Arafeh and Russell (3)	1993	5–15	2165	Questionnaire	1 year			66
UK, Boardman et al. (11)	2003	≥18	2662	Questionnaire	Lifetime 3 months	90.2 62.0	94.4 76.8	92.6 70.3
The Americas								
Brazil, Barea et al. (6)	1996	10–18	538	Personal interview	1 year	77.9	87.9	82.9
Ecuador, Sachs et al. (88)	1985	0–60+	1113	Personal interview	Not stated	2.6	10.9	6.8
Mexico, Garcia-Pedroza et al. (30)	1991	<10–60+	700	Questionnaire	Lifetime	8.9	10.6	13.9
Puerto Rico, Miranda et al. (65)	2003	<20–<50	1610	Telephone interview	1 year	27	40	35.9
US, Linet et al. (55)	1989	12–29	10169		4 weeks	91	95	
US, Duckro et al. (26)	1989	≥21	500	Telephone interview	Lifetime	20.4	11.2	15.8

(*continued*)

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TABLE 3-1 Population Based Studies on Prevalence of Headache in Various Parts of the World (Continued)

Country, Author	*Year*	*Age Range (y)*	*Number of Respondents*	*Study Method*	*Time Period Prevalence*	*Headache*		
						Men	*Women*	*Overall*
US, Cook et al. (21)	1989	≥65	3811	Personal interview	1 year	36	53	
US, Kryst et al. (48)	1994	≥20	1759	Telephone interview	1 year	11.5	14.5	13.4
US, Stewart et al. (109)	1992	12–80	20468	Questionnaire	Not stated	13.9	27.3	
Africa								
Nigeria, Osuntokun et al. (72)	1992	0–80+	18954	Questionnaire	Lifetime			51
Tanzania, Matuja et al. (60)	1995	20–40+	1540	Questionnaire	1 year	51	60	53
Zimbabwe, Levy (54)	1983	5–60+	5028	Questionnaire	Not stated	17.6	27.0	20.2
Asia								
Israel, Abramson et al. (2)	1980	15	4899	Personal interview	Not stated	70.8	80.7	75.8
India, Shivpuri et al. (99)	2003	11–15	1305	Questionnaire	Not stated	18	21	19.5
Japan, Sakai and Igarashi (89)	1997	≥15	4029	Telephone interview	1 year			55.6
Korea, Roh et al. (85)	1998	≥15	2500	Telephone	1 year			68
Saudi Arabia, Abdul Jabbar et al. (1)	1997	15–60+	5891	Personal interview	Not stated			8
Singapore, Ho and Ong (43)	2001	≥12	2096	Personal interview	Lifetime			83.7
Taiwan, Lu et al. (59)	2000	13–15	4436	Questionnaire	Lifetime	81.3	87.9	84.6
Taiwan, Wang et al. (119)	2000	≥15	3377	Questionnaire	1 year	50	72	62

population (43). In a meta-analytic study of many prevalence surveys, the relative contributions of racial, geographic, and methodologic factors to the great variations in headache and migraine prevalence have been assessed (93).

Prevalence studies have also given data on attack frequencies, duration and severity (e.g., [24]; [83]). In addition, the impact of headache on public health can be studied by adding questions about influence on work and leisure activities, absenteeism, and so on (see Chapter 4).

If prevalence studies are repeated on the same population, it is possible to detect changes in headache prevalence over time. An increasing headache prevalence from 1974 to

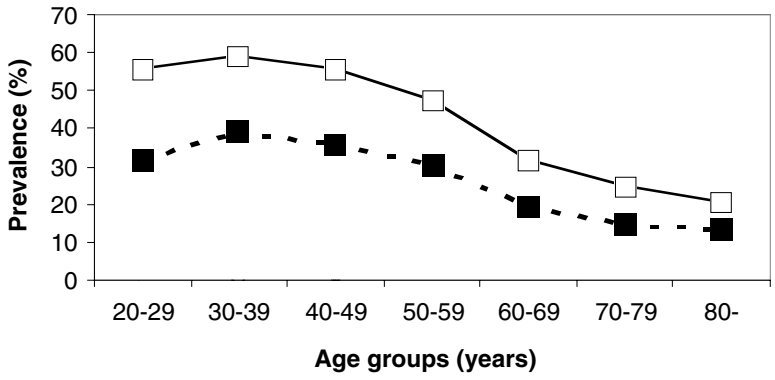

FIGURE 3-1. Age distribution of 1-year prevalence of headache (open squares, women; closed squares, men) among 51,383 adults from the HUNT study 1995–1997 in Nord-Trøndelag county, Norway (39). (Figure made by Knut Hagen, MD, PhD, Norwegian University of Science and Technology, Trondheim, Norway.)

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1992 has been found among 7-year old school children in Finland (100), and of medically recognized migraine in the United States during the 1980s (87). However, two large, methodologically similar studies conducted in the United States 10 years apart found that the prevalence of migraine was unchanged during this time period (56).

If a study is repeated on the same individuals, it is possible to calculate headache *incidence*, that is, the number of new ("incident") cases in a defined population, accumulated over several years, or per time period. With this method, the incidence of cluster headache in San Marino has been calculated (2.5/100,000 per year [114]). Among Swedish schoolchildren who were given questionnaires 2 years apart, the 2-year cumulative headache incidences was 43%, 37%, and 32% among those who were 8, 11, or 13 years old at the first investigation (12). Most studies reporting headache incidence rates at different ages have not used repeated investigations, but have relied on retrospective data of age at onset. Because of recall errors, this may lead to an overestimation of incidences at older ages (80), a phenomenon referred to as *telescoping* (14).

Cross-sectional studies may also be used to assess associations between headache and suspected risk factors and other disorders. This has been done with regard to psychosocial, psychiatric, gynecologic, endocrinologic, and hematologic, as well as arteriosclerotic risk factors, other pain conditions and consumption of analgesics (2,4,13,18,21,33–35,40,46,61,78,79,102,109,123,124).

In *case-control studies,* a group of headache sufferers is compared with a control group (healthy persons or individuals with some other disorders) with regard to either a suspected cause or some other clinical features or factors. Examples of observations from case-control studies include the finding that hypertension was more prevalent among headache patients from an outpatient clinic than among controls from the general population (19), that body mass index was higher and socioeconomic status lower among patients with chronic daily headache than among those with episodic headache (94), and that head trauma was reported somewhat more often (not statistically significantly) among patients with chronic headache than among other headache patients (8).

The case-control method has also been used to compare the prevalence of headache among subjects with or without another disorder. In this way it was found that migraine was more frequent among patients with Ménière's disease (77), with transient global amnesia (95), Behçet's disease (67), and schizophrenia (49). No increase in headache prevalence was found among patients with systemic lupus erythematosus (98). Some case-control studies have investigated whether obstructive sleep problems may be associated with headache. There was a higher proportion of snorers among individuals with chronic daily headache than among individuals with episodic headache (92), and headache was more prevalent among patients referred to polysomnography for obstructive sleep apnea than among controls (91,115).

In case-control and cross-sectional studies, both disease and suspected cause are measured at the same point in time. Hence, it is not always possible to be certain that exposure to the risk factor of interest preceded the onset of illness. This is a particular problem when considering exposures that change as a result of illness such as psychiatric factors and medication overuse. For this reason, studies of putative risk factors that may both precede and follow the onset of headache are best studied in studies with a prospective design, such as cohort studies.

In *cohort studies,* two groups are selected on the basis of whether they have been exposed to a suspected cause or not and are followed and monitored for the occurrence of the outcome of interest. It is important that knowledge about the disease (headache) is not used to define the cohorts, and disease status should be determined in a blinded manner without knowledge of prior exposure status. The primary advantage of cohort studies is that exposure is measured before the onset of illness.

In cohort studies, it can be demonstrated that some baseline conditions or exposures are risk factors for incident headache, for example, that depression is a risk factor for migraine but not other headaches after 2 years (13), low systolic blood pressure is a risk factor for headache and migraine 11 years later (36), but whiplash trauma or concussion are not risk factors for headache 1 year or more after the trauma (64,69,70,96), Similarly, headache or migraine have been found to be risk factors for incident stroke in several cohorts (15,45,62). Interestingly, one study has demonstrated that women with migraine and headaches have a lower mortality than those without headache (120).

BIAS AND CONFOUNDERS IN HEADACHE EPIDEMIOLOGY

The true association of a disorder to some exposure may be distorted by bias and confounding. *Selection bias* (related to who participates in the study as a case or control) can result from poor participation or sampling, misdiagnosis of disease status, and loss to follow up. One well-known example is called *Berkson's* or *admission-rate* bias, resulting from the increased likelihood that individuals with multiple conditions will seek medical care compared to those with one condition (29). Thus, if patients with hypertension and headache are more likely to be referred to a headache outpatient clinic than those with headache alone, a study based on a clinical sample of headache patients might find a spurious or exaggerated association between headache and hypertension. *Information bias* (related to the information about or measurement of

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exposure) includes measurement problems caused by defective instrumentation, nonblinded investigators, or differences in recall between groups. The last may explain why individuals with migraine were more likely to (correctly) report a family history of migraine than individuals without migraine, which—in this case—results in a spurious or increased familial aggregation of migraine (73). The ultimate effect of bias in a study depends on whether or not the bias is differential (whether the bias is different for cases and controls), the study design, the magnitude of the bias, and other factors.

A *confounder* is a third factor that can explain the association between an exposure and a disorder. For example, it has been reported that migraine sufferers have an increased risk of ischemic stroke. If migraine sufferers were on average heavier and had higher blood pressure than controls, their increased risk of stroke might be caused by the presence of these other (confounding) factors rather than a biological relationship between migraine and stroke. For a factor to be a confounder, it must be related to the exposure (e.g., migraine sufferers are heavier), must be related to the outcome (e.g., heavier individuals have a higher risk of stroke even if they do not have migraine), and must not be on the "causal pathway" between exposure and outcome (e.g., migraine leads to weight gain). Confounding can lead to the appearance of an association where one does not exist (positive confounding) or to the disappearance of a true association (negative confounding). Age and gender are important potentially confounding factors in headache epidemiologic studies as well as for most other diseases. Socioeconomic status is another potentially confounding factor, at least in the United States; studies here have found that migraine is more prevalent in individuals with lower income or educational attainment (18,109). However, measures of socioeconomic status were not found to be associated with migraine in most European studies (25,32,52,68,78) except in one large prospective study, in which low socioeconomic status predicted frequent or chronic headache 11 years later (37).

THE CHALLENGE FOR HEADACHE EPIDEMIOLOGY

Epidemiology has already contributed considerably to our understanding of headache. Epidemiologic research has demonstrated the magnitude of the public health impact of headache and has provided clues to causes and pathophysiologic mechanisms. The large variation in headache prevalences between different populations is intriguing. Although some of this variation has been shown to be caused by underlying demographic differences in the studied populations (93), methodologic differences in the way in which diagnostic criteria are operationalized can also influence prevalence (57). To make meaningful comparisons between different studies, it is necessary that the methods in headache epidemiology be standardized, including how to define the source population, sampling, case ascertainment and phrasing of questions, and how to avoid biases and to deal with possible confounders. Such standardization requires an international initiative. If real variations in headache prevalence between different populations or in the same population at different times are found, it would be a large stride toward the identification of the most important genetic and environmental determinants of headache. This could hopefully lead to better treatment and prevention of the disorder.

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