

# Epidemiology of headache in the Republic of San Marino

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**SUMMARY** An epidemiological survey on headache was performed in the Republic of San Marino, which is the smallest independent State in the world, located near the Adriatic Coast, within Italy. Among a random sample of 1500 inhabitants over 7 years of age the frequency of headache, severe headache and migraine in the previous year was 35.3%, 12.2%, 9.3% respectively for men, and 46.2%, 20.6%, 18% for women. The most common factors reported to provoke headache were emotional stress, physical strain, lack of sleep, particular foods or drinks and for women menstruation. Migraine patients differed from people without headache in that they had a higher consumption of coffee, more frequently reported bad sleep, allergic disease and previous appendectomy. Furthermore, migraine patients and severe headache sufferers had a higher diastolic blood pressure than non headache subjects.

Many studies have been performed on the epidemiology of headache and migraine. Extensive reviews on the matter are available.<sup>1-3</sup> However, no studies have been made to our knowledge, on a general population within the Mediterranean area. Here we present the results of a population survey performed in the Republic of San Marino.

## **Methods**

The Republic of San Marino is the smallest independent State in the world, located near the Adriatic Coast, within Italy. It is 22 square miles (57.2 square km) in area. On 31 December, 1984 there was a population of 21,792, 10,893 men and 10,899 women. The Republic is dominated by Mount Titano, 2460 feet above sea level. Most of the population live in San Marino, a mediaeval town on Mount Titano or in eight small villages spread over the territory. The Republic is therefore divided into nine zones, named "castles", according to each village and the town. A systematic random sample of 1500 inhabitants over 7 years of age was obtained from official records. Each subject was then invited by letter to present himself at the social centre of his castle to answer a questionnaire administered by two trained interviewers. The questionnaire was divided into eight parts.

The first three parts concerned general demographic findings, life habits and past medical history. The first question of the fourth part was: "Do you suffer or have you suffered over the past year from headache?" In the case of an affirmative answer the questionnaire was completed. Otherwise people were asked if they had suffered from headache in the past and if such headache was frequent or rare, at which age it had begun and ended and the questionnaire was stopped. Blood pressure was taken with a standard mercury manometer on the right arm, with the subject sitting, at the end of the third part of the questionnaire and before the first question of the fourth part. Interviewers were trained at the Headache Centre of our Clinic where they interviewed together 50 patients with headache under the supervision of a physician expert on headache. Subsequently they did 80 cross-interviews to volunteer inhabitants of San Marino encountered in government offices and 20 children in primary and junior schools. Agreement between the two interviewers ranged from 76% to 100% depending on single items. Agreement between the two interviewers on the major questions is shown in table 1. Among people who answered the questionnaire a random sample of 80 suffering from headache were invited to come forward to be interviewed and examined by a neurologist expert on headache. Sixty-one of them agreed to be examined. All 42 people who answered affirmatively to question No 65 were also interviewed (personally or by telephone) by two of us in order to ascertain classic migraine cases.

Among 346 people who refused to answer the questionnaire we interviewed 169 (84 men, 85 women) of them by telephone, asking if they suffered from headache and its severity. Distribution by age and sex of the whole popu-

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Table 1 *Main questions concerning headache and agreement between answers obtained by two interviewers*

No		% Agreement between interviewer
41	Do you suffer or have you suffered over the past year from headache?	99
52	Does anyone in your family suffer from headache (parents, siblings, children)?	96
53	How many headaches have you had in the past year?	
	1/day	100
	1/week	93
	1/month	96
	1/year	100
54	Does it last continuously, from morning to evening?	98
61	Headache onset is:	
	Always on the same side of the head	100
	Sometimes on one side, sometimes on the other	86
	Sometimes on one side, sometimes on both	89
	Always on both sides of the head or over all the head	96
62	Pain is:*	
	Like something throbbing	100
	Like something weighing down, pressing	90
	Other (stabbing, burning)	94
63	Pain is very bad—unable to do anything:	
	Never	97
	Sometimes	94
	Always, almost always	100
65	Minutes just before the start of a headache do you have disturbances of vision, tingling or loss of strength in a hand or part of the body, speech difficulties?	100
66	During headache do you have nausea and/or vomiting?	100

\*More than one answer was possible.

lation of the Republic of San Marino, the initial sample and people interviewed by questionnaire and-by telephone are shown in table 2. The survey was performed from 1 July 1983 to 30 June 1984.

#### Definitions

Severe headache was recorded when people answered affirmatively (sometimes or always) to question No. 63. Common migraine was defined basically according to the

Ad Hoc Committee<sup>4</sup> when people reported at least two of positive family history, unilateral onset of pain (sometimes or usually) and nausea or vomiting during attacks (questions Nos. 52, 61, 66). Furthermore, in order to include only patients with recurrent attacks separated by free intervals we excluded patients with daily or continuous headache (questions Nos. 53, 54). Such diagnoses of severe headache and common migraine based on answers to questionnaire were compared with the final clinical diagnosis made by a neurologist on 61 people reinterviewed. As for severe headache, sensitivity was 0.95 and specificity 1.0, whereas for common migraine, values were 0.70 and 0.83 respectively. Results of the comparison between diagnosis made on the basis of the questionnaire and by the neurologist are shown in table 3. Any attempt to increase the specificity of the questionnaire by changing diagnostic criteria (for example, excluding positive family history) resulted in a severe loss of sensitivity. Discriminant analysis between migraine and non-migraine headache, including positive family history, onset of pain, quality of pain, nausea or vomiting and severity of pain, resulted in a higher severity of pain in the migraine group as the only significant discriminant factor.

Classic migraine was diagnosed by a neurologist, according to the Ad Hoc Committee,<sup>4</sup> on the basis of direct interview.

#### Results

##### Prevalence of headache

Of 1500 people sampled, 1144 (76.3%) agreed to be interviewed. Among these 528 (46.15%) reported that they had suffered from headache during the preceding year. Two hundred and nineteen (19.6%) said their headache was severe, while in 185 cases (16.1%) the diagnosis of common migraine was made. Among people interviewed by telephone, 46 (27.2%) reported headache during the preceding year, 11 (6.5%) severe headache and in 12 (7.1%) common migraine was diagnosed. On the basis of this information we estimated the frequency of headache, severe headache and migraine in the whole sample was 35.3%, 12.2%, 9.3% for men and 46.2%, 20.6%, 18% for women respectively. Distribution by age and sex is shown in

Table 2 *Whole population, initial sample, people interviewed by questionnaire or telephone, by age and sex*

Age (yr)	Whole population		Initial sample		Questionnaire*		Telephonic interview	
	Men N (%)	Women N (%)	Men N (%)	Women N (%)	Men N (%)	Women N (%)	Men N (%)	Women N (%)
7-10	617 (6)	617 (6)	25 (33)	29 (4)	21 (3.7)	27 (4.6)	—	—
11-15	965 (9.6)	877 (8.6)	66 (6.6)	77 (10)	51 (9)	64 (11)	8 (9.5)	7 (8.3)
16-20	1014 (10.1)	933 (9.2)	77 (10)	72 (9.7)	61 (10.8)	56 (9.6)	6 (7.1)	9 (10.7)
21-25	894 (9)	876 (8.6)	80 (10.4)	66 (8.9)	54 (9.6)	47 (8)	13 (15.4)	10 (4.7)
26-30	809 (8)	832 (8)	55 (7.2)	50 (6.8)	42 (7.5)	35 (6)	5 (5.9)	8 (9.4)
31-40	1566 (15.6)	1575 (15)	123 (16)	99 (13.4)	79 (14.07)	76 (13)	16 (19)	13 (15.4)
41-50	1418 (14)	1374 (13.5)	103 (13.5)	91 (12.3)	73 (13)	71 (12.2)	11 (13)	12 (14.1)
51-60	1224 (12.2)	1243 (12.2)	107 (14)	103 (13.8)	86 (15.3)	89 (15.2)	10 (11.9)	10 (11.7)
61-70	919 (9.2)	986 (9.8)	73 (9.5)	91 (12.3)	53 (9.4)	69 (11.8)	10 (11.9)	12 (14.1)
≥ 71	592 (6)	774 (7.6)	55 (7.2)	61 (8.2)	42 (7.4)	49 (8.4)	5 (6)	4 (4.7)
Total	10015 (100)	10151 (100)	763 (100)	737 (100)	562 (100)	582 (100)	84 (100)	85 (100)

\*Ten people were not able to answer the questionnaire because of some kind of handicap.

Table 3 Comparison of diagnosis of migraine obtained by questionnaire and by clinical interview

	Questionnaire/clinical interview	
	Migraine	Non migrainous headache
Migraine	26	4
Non migrainous head	11	20

the fig. It can be seen that severe headache and common migraine show a similar trend, with a higher frequency among 41–50 year old men and among 31–60 year old women, and a rapid fall in frequency after 60 years of age in both sexes.

The differences in frequency of severe headache and common migraine between the two sexes were particularly evident among 31–60 year old people. No significant differences were found in frequency of severe headache and common migraine as far as education, work and marital status were concerned.

Classic migraine was confirmed in 12 people (seven females, five males) out of 42 who reported visual or other disturbances before headache. Most false positive cases were common migraine patients with non specific visual disturbances before or during attacks. No subjects with a headache suggesting classic migraine were found among people interviewed by telephone. Therefore the estimated prevalence of classic migraine in our sample was 0.6% for men, and 0.9% for women.

*Factors provoking headache*

As shown in table 4, the most common factors provoking headache among people who answered the questionnaire are emotional stress, physical strain, lack of sleep, particular foods or drinks (cheese, chocolate, tea, etc) and for women, menstruation.

There are also miscellaneous other factors, comprising cigarette smoking, weather changes, sinusitis, noise, etc. By comparing factors provoking headache among people with severe headache and with mild-moderate headache, we found that among men the difference was statistically significant for particular foods, drinks and other factors (mainly cigarette smoking) whereas among women, significantly related to severe headache were emotional stress, physical fatigue, lack of sleep and menstruation.

*Migraine, life habits and past medical history*

We compared people with migraine and people without headache concerning lifestyle and some aspects of medical history (table 5). In order to verify whether the two groups differed we used stepwise discriminant analysis<sup>5</sup> including age and sex as independent variables. As one can see (table 6), migraine patients differ significantly, with a higher consumption of coffee, more frequently reported bad sleep, allergic diseases (asthma, hay fever, skin eczema) and previous appendectomy.

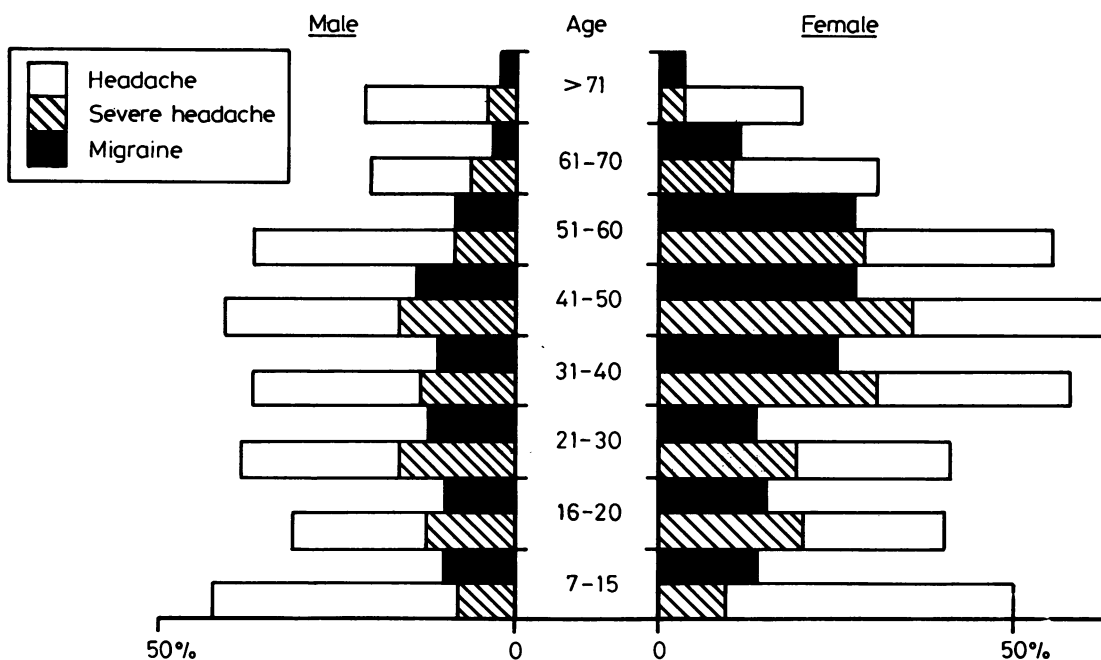


Fig Age and sex prevalence rates of headache, severe headache, and migraine estimated for the whole sample.

Table 4 Factors blamed for provoking headache

	Men		Women	
	Severe headache (%)	Never severe headache (%)	Severe headache (%)	Never severe headache (%)
Emotional stress	37	39.3	61.7	48.4
Physically "over-doing it"	54.1	44.3	59.4	43.2
Lack of sleep	37.5	34.2	41.3	29.9
Too much sleep (NAP)	19.2	10.7	11.3	6.4
Day off work	5.5	6	4.9	2.6
Alcohol	12.3	14.9	6.9	3.9
Particular foods or drinks	31.5	17.6	29.2	20.5
Period	—	—	57	36.8
Others (miscellaneous)	44.6	29	25.4	27.3

\*People interviewed with questionnaire.  
(p from  $\chi^2$  Test).

### Headache and blood pressure

In seven out of nine "castles" blood pressure was determined in people over 15 years of age (879 subjects). People were divided according to answers in different groups. Differences among the means were evaluated by the Analysis of Covariance. As categorical independent variables (factors), different headache groups were selected (table 7). As metric independent variables (covariates), age and Body Mass Index (BMI) were considered (BMI = weight/height<sup>2</sup>). As dependent variables, diastolic and systolic arterial pressure were finally taken into account. By this procedure, differences among means

were evaluated after removing from the dependent variable the variation due to covariates. The statistical significance of differences among means was assessed by the modified *t* test associated with the Bonferroni method.<sup>6</sup> In table 7 significant differences are indicated (for  $p < 0.05$ ). Diastolic blood pressure was higher in the "migraine" group than the "no headache" group, in both men and women (table 7). Only in women was this pressure higher in the "headache with nausea and vomiting" group than in the "headache without nausea and vomiting" group. In both men and women diastolic arterial pressure was higher in the "headache always severe" group than in the "headache never severe" group.

Table 5 Migraine, life habits and medical history

	No headache (N = 603) (%)	Migraine (N = 185) (%)
Cigarette smoking:		
Never	73.6	71.1
1-10/day	11.6	11.8
11-20/day	9.5	12.8
21-40/day	4.6	3.2
> 40/day	0.7	0.2
Alcohol:		
Never	42.9	42.2
Less than 1 lt wine/day and/or rarely spirits	54.5	56.1
More than 1 lt wine/day and/or usually spirits	2.7	1.6
Coffee:		
Never	42.5	36.4
Less than 3/day	51.7	50.3
More than 3/day	5.8	13.4
Bad sleep	15.8	24.1
Use of sleeping pills:		
Never/rarely	96.7	91.9
Often	1.3	4.8
Always	2	3.2
Allergic disease	17.9	27.9
High blood pressure	9.7	11.3
Myocardial infarction	0.8	1.6
Stomach ulcer	7.1	7.5
Appendectomy	12.1	20.3
Cholecystectomy	1.7	1.1

### Discussion

There are many published studies on the prevalence of headache. However, this is the first investigation performed in a general population in South Europe. In order to make it comparable with other studies we decided to give the prevalence figures both for severe headache and migraine. Furthermore, we decided to ascertain diagnosis in all people with a possible classic migraine. In fact, severe headache is a social health

Table 6 Migraine, life habits and medical history. Results of discriminant analysis (versus no headache group)

Variables entered	Discriminant function coefficients	Partial F	p
Sex	1.353	26.0	<0.01
Age	-0.0214	10.4	<0.01
Cigarette smoking	0.179	1.3	NS
Coffee	0.611	7.7	<0.01
Bad sleep	0.782	4.5	<0.05
Sleeping pills	0.534	1.6	NS
Allergic diseases	0.546	8.1	<0.01
Appendectomy	0.773	4.3	<0.05
Constant	-4.245		

Table 7 Age and blood pressure (average + SD) in different groups

	N	Age (yr)	DBP	SBP
<i>Men:</i>				
No headache	209	40 ± 21	81 ± 15	} 134 ± 23
Headache	99	35 ± 17	82 ± 15	
Migraine	48	35 ± 17	85 ± 15	
Headache without nausea/vomit	108	34 ± 17	80 ± 14	128 ± 20
Headache with nausea/vomit	38	39 ± 15	88 ± 15	} 136 ± 21
Headache never severe	98	36 ± 17	82 ± 15	
Headache something severe	34	32 ± 15	82 ± 16	
Headache always severe	14	39 ± 16	89 ± 12	132 ± 20
<i>Women</i>				
No headache	188	42 ± 23	78 ± 17	} 130 ± 27
Headache	136	38 ± 20	78 ± 16	
Migraine	79	38 ± 18	81 ± 15	
Headache without nausea/vomit	129	36 ± 21	76 ± 17	129 ± 22
Headache with nausea/vomit	83	41 ± 15	83 ± 13	} 129 ± 20
Headache never severe	113	37 ± 22	76 ± 16	
Headache something severe	62	39 ± 17	80 ± 14	
Headache always severe	37	41 ± 14	85 ± 13	130 ± 19

\*p &lt; 0.05.

DBP, diastolic blood pressure; SBP, systolic blood pressure.

problem while classic migraine is a well featured disorder which leaves no doubt about the diagnosis. Common migraine, on the contrary, is a separate disorder from a diagnostic point of view, whose borderlines with tension headache and so-called mixed forms are ill-defined. Thus comparison with other studies on the prevalence of common migraine is difficult, since even slight changes in definition criteria (for example, pain *always* unilateral or *sometimes* unilateral) may lead to gross changes in sensitivity and specificity of the questionnaire. In our study, we tried to obtain a good specificity with a fairly good sensitivity, in order to avoid on the one hand the inclusion of too many false positive cases and on the other, the use of ambiguous terms such as "other vascular headaches". Discriminant analysis showed in our study that the main factor distinguishing between migraine and non migrainous headache is the intensity of pain. This finding agrees with other previous studies showing that the number of migraine features increases with the severity of pain.<sup>7</sup> However, we abandoned the idea of giving an operational definition of migraine as "recurrent severe headache" and decided to accept the best compromise possible with the definition of common migraine used in our questionnaire (sensitivity 0.70 and specificity 0.83) to give a description of the prevalence of migraine in our population.

The prevalence of headache in our study, although lower than that found in other reports,<sup>8-12</sup> shows that headache is a very common symptom in the Republic of San Marino.

For severe headache, our figures are lower than those found by Ziegler<sup>9</sup> in the USA, who, however, considered together severe ("in which subjects were able to carry on some work but with difficulty"), and disabling ("completely unable to perform work") headache, and those found by Nikiforow and Hokkanen<sup>10</sup> in Northern Finland, who, however, did not report the definition criteria of severe headache.

An indirect validation of our definition of "severe" headache is the finding that we previously reported in a paper on economic loss due to headache:<sup>12</sup> among 514 working people, 29% of those reporting severe headache sometimes or always had lost at least one working day in the previous year whereas the same was true only for 0.5% of those reporting that their headaches were never severe. Even reducing our figures to this percentage, we found that the prevalence of severe headache is 4.7% (3.5% for men and 5.9 for women). Comparison of our figures with those found by Ziegler *et al* in China<sup>13</sup> obtained as life-prevalences (and not as year-prevalence as in our study) of a headache severe enough to decrease activity by at least 50% shows that severe headache is more common in the Republic of San Marino, suggesting that social, environmental and genetic factors play a relevant role in determining severe headache onset.

The prevalence of common migraine in our study is similar to that found by Waters<sup>14</sup> and Waters and O'Connors<sup>8</sup> in England, Nikiforow in Finland<sup>15</sup> and Markush<sup>16</sup> in the USA. Recently, Bruyn,<sup>17</sup> reviewing reports on the epidemiology of migraine, stressed the many problems which may in some way bias results. However, in our study we validated the diagnosis of common migraine made by our questionnaire, and this confirms that most of our patients have de facto a common migraine. Furthermore, we probably lost many other patients with a poorly featured common migraine. Therefore we cannot agree with Bruyn who concluded that a realistic percentage of migraine sufferers among populations is 1.5-2%. Such a percentage is, on the contrary, realistic for classic migraine, whose prevalence may be better compared among different populations. However, attention should be paid, in our experience, to ascertain cases since many common migraine sufferers report non specific visual disturbances without the typical temporal pattern of classic migraine aura.

Markush *et al*<sup>16</sup> found 9.1% of 451 women answered affirmatively to the question "does your vision blur or flicker just before the headache comes on?" However, they did not check whether an affirmative answer corresponded to a typical aura. Nikiforow<sup>15</sup> found 5.5% (2% for men and 8% for women) of classic migraine among a sample of 200 people in Finland. However, this sample represented

80% of people requesting examination by a neurologist, selected among 76-8% of the general population who originally responded to the survey. Therefore this percentage may be considerably reduced when applied to the whole population. The prevalence of classic migraine in our study is quite similar to that found by Manzoni *et al*<sup>18</sup> among hospital staff, thus confirming that its value is around 1% in our region. This finding suggests that further studies should be performed on large samples in order to verify whether classic migraine has different prevalence rates among other populations.

Distribution by age and sex of migraine and severe headache in our population duplicates findings from most similar studies. We would stress two findings: (1) migraine and severe headache have a similar distribution by age, supporting again the probability that most recurrent severe headaches are de facto migraine headache; (2) the increase in frequency of migraine and severe headache among women is particularly striking after 30 years of age. This finding suggests that puberty probably plays a minor role in the sex differential whereas pregnancy and childbirth, which may facilitate the appearance of migraine headache, as we previously reported,<sup>13</sup> may play a major role in increasing the frequency of both severe headache and migraine in women over 30. This finding is also supported by the long term changes in hormonal environment induced by pregnancy.<sup>20 21</sup>

Factors blamed for headache seem to differ between the sexes and between people with severe headache and people who never have severe headache. In women, emotional and physical stress, lack of sleep, and menstruation seem more related to the occurrence of severe headache, whereas in men this applies to dietary factors and miscellaneous other factors (mainly cigarette smoking and weather changes). Stress is also the commonest factor in other studies,<sup>10</sup> and our values are similar to those found in the Finnish population. Dietary factors, on the contrary, seem far more common in our population than in the studies of Paulin *et al*<sup>11</sup> and Nikiforow and Hokkanen,<sup>10</sup> where they were reported by 4% of headache sufferers. Whether this is a true difference or an over reporting of such factors in our population cannot be stated. However, changes in the frequency of provoking factors (particularly stress) among populations with different social, cultural and dietary customs may explain differences in the frequency of severe headache. Migraine sufferers seem to differ from people without headache in some of their lifestyle and past medical history. Higher coffee consumption among migraine patients may be explained by the beneficial effect that caffeine has on migraine.<sup>22</sup> Bad sleep is probably related to psychological disturbances which are frequently found

among migraine patients.<sup>23</sup> However, lack of sleep has also been reported as a provoking factor by a number of patients with severe headache in our study. This relationship between sleep disturbances and severe headache and migraine has not been previously stressed and further studies should be performed to verify whether sleep disturbance treatment may also improve headache in this subgroup of patients.

The association of migraine with allergic diseases in our study is in agreement with previously reported epidemiological findings of Ziegler<sup>9</sup> and with studies by Mural *et al*<sup>24</sup> and Egger *et al*<sup>25</sup> on food allergy among migraine patients. These findings suggest that an allergic mechanism may be operative in migraine.

The curiously more frequent appendectomy among migraine patients is difficult to explain. The most likely explanation is that migraine patients may have suffered in infancy from recurrent abdominal pain, that is considered to be an "equivalent" of migraine in childhood,<sup>26</sup> and because of this they more frequently underwent appendectomy.

The relationship between headache and blood pressure has been the subject of numerous studies giving controversial results. Walker,<sup>27</sup> in his general practice population of 5785 patients, found in those suffering from migraine significantly higher systolic and diastolic blood pressure, whereas Waters,<sup>28</sup> in a community study, did not find significant differences between patients complaining of headache or migraine and those without headache. More recently Markush *et al*<sup>16</sup> found among women that migraine is significantly associated with reported hypertension and Ziegler *et al*<sup>9</sup> found that reported hypertension among women is significantly associated with disabling or severe headache. In our study we did not find an association between migraine and hypertension but our patients with migraine or severe headache showed higher diastolic pressure. Although the number of differences do not have clinical implications, this finding may indicate a different cardiovascular regulation in migraine patients which may be related to their emotional reactivity.

The final picture to emerge from our results is that severe headache and migraine, which widely overlap in the general population, are disturbances for which several aetiological factors (emotional, dietary, allergic, hormonal, sleep-wake cycle disturbances) operate on the grounds of personal susceptibility. Whether these factors act in a common final way to determine headache or operate with different mechanisms is a matter for biological and clinical studies.

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