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ABSTRACT

Background: Migraine is a common and costly neurological disorder. The aim of this study was to quantify the costs of chronic (CM) and episodic migraine (EM) in Spain, evaluating the impact of psychiatric comorbidities and disability, and estimate the economic savings of reducing the number of migraine days by 50%.

Methods: This was an observational, cross-sectional analysis of data from migraine patients who participated in the Spanish Migraine Atlas. The participants were invited to complete a structured questionnaire including the following scales: Headache Needs Assessment (HANA), Hospital Anxiety and Depression Scale (HADs), and Migraine Disability Assessment Scale (MIDAS).

Results: 475 patients were included, 187 with CM (39.4%). Total costs per patient/year were: €16,578.2 ±€34,568.1 for CM and €6,227.8 ±€6,515.7 for EM. Moreover, a higher degree of disability according to MIDAS scale significantly increases the total cost of migraine, while the presence of psychiatric comorbidity increase costs for EM patients only. The reduction of one migraine day per month decreases average total costs by €744.14 per patient/year for EM and €663.20 per patient/year for CM, while reducing by 50% the number of migraine days, the economic savings would be €2,232.44 per patient/year (R^2=0.927) for EM and €6,631.99 per patient/year (R^2=0.886) for CM.

Conclusions: The costs associated with migraine are driven by migraine frequency and the degree of disability, while psychiatric comorbidity only influences the cost of EM patients. These results highlight the need to optimise migraine management to reduce the economic migraine burden. Future studies are needed to confirm our results.

Short running title: Estimating the Savings of a Migraine Free Life

Keywords: migraine, chronic migraine, costs, burden, quality of life, disability, psychiatric comorbidity.

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Atlas of Migraine in Spain was funded by Novartis.

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INTRODUCTION

Migraine is a common, disabling headache disorder, affecting 12% of the Spanish population (1) and represents the first cause of disability in people under 50 years of age (2). According to the ICHD-3 (3) , migraine is categorised as episodic (<15 days/month) and chronic (≥15 days/month).

Several studies conducted in the US and different countries across Europe, have shown that migraine, but chronic migraine (CM) in particular, causes considerable direct and indirect economic costs (4–11). Direct healthcare costs (DHC) represent the expenditure associated with medical resource utilisation, while indirect costs (IC) are defined as expenses incurred from productivity loss resulting from migraine. The economic burden of migraine varies greatly between countries (7), but IC accounted for the majority of the total cost in most studies (8,12,13). Moreover, migraine is associated with higher rates of comorbid psychiatric conditions that may influence total cost (14).

However, studies analysing the economic burden of migraine in Spain, including IC are scarce (8), and no studies have been carried out that assess the influence of comorbid anxiety and depression on costs. Additionally, data from previous studies were conducted more than 10 years ago (7,8), and these results do not include the direct non-health care costs (DNHC) borne by the patient. Therefore, it is necessary to update the direct and indirect cost of EM and CM and assess the impact of migraine frequency, headache-related disability, quality of life, and psychiatric comorbidity (anxiety and depression) on the economic burden of migraine.

The aim of the present study was i) to comparatively quantify the costs of CM and EM; ii) assess the impact of quality of life, psychiatric comorbidities, and disability over the economic burden of migraine and; iii) to estimate the economic savings when reducing the number of migraine days per patient per year by 50%.

METHODS

Study design

The Spanish Migraine Atlas 2018 was an initiative of the Spanish Patient's Association of Migraine and Headache (AEMICE), carried out by the Health & Territory Research Group (HTR) of the University of Seville, in collaboration with the Headache Study Group of the Spanish Neurological Society (GECSEN) and with the financial support of Novartis Spain.

Data Source (Survey)

The questionnaire was prepared by the HTR research group, taking into account the opinion of a panel comprised of headache experts, psychologists and migraine sufferers and after a scientific literature review (15). In addition, the impact of migraine on quality of life, probability of psychiatric comorbidity, and disability levels were evaluated using different scales (16-18): Headache Needs Assessment (HANA), Hospital Anxiety and Depression Scale (HADs), and Migraine Disability Assessment Scale (MIDAS). The HANA scale is a migraine-specific quality of life instrument measuring two dimensions of the chronic impact of migraine: frequency and bothersomeness (16). This scale contains the following seven domains: i) anxiety/worry; ii) depression/discouragement; iii) self-control; iv) energy; v) function/work; vi) family/social activities; and vii) overall impact of migraine.

HADS is an instrument designed for screening potential anxiety and depression rather than grading the severity of anxiety and depression in the general population (17). The HADS questionnaire included 14 items, seven of which evaluate anxiety (HADS-A) and a further seven that evaluate depression (HADS-D). Each item is scored on a scale of 0–3, resulting in an overall score of 0–21 for both HADS-A and HADS-D to detect possible cases of depression and anxiety. According to the score obtained in the HADS scale it is possible to distinguish between no case: 0-7; borderline case: 8-10 and case: 11-21 for both anxiety and depression (17).

Additionally, disability was measured using the MIDAS scale, with a 5-item questionnaire designed to evaluate disability within the past three months (18). A score from 0–270 is used to indicate the overall level of disability due to migraine based on the following grading system: grade I, little or no disability (score of 0–5) ; grade II, mild disability (score of 6–10) ; grade III, moderate disability (score of 11–20); and grade IV, severe disability (score of ≥ 21)(19). The highest category is subdivided into grade IV-A, severe disability (scores of 21–40) and grade IV-B, describing a very severe (scores of 41–270).

In order to validate the whole questionnaire, one pilot test was carried out by 20 personal interviews of migraine patients, which contributed to the improvement of understanding and completing the survey. After this process, the final questionnaire consisted of 124 items. The complete questionnaire is available and can be consulted online as an annex to the Spanish Migraine Atlas report (15).

Between June and September 2017, an online cross-sectional survey was performed within the framework of the Spanish Migraine Atlas, including patients from all Spanish regions, using a non-probability sampling methodology. The questionnaire was disseminated through the AEMICE patient association and patients filled it out voluntarily and anonymously. This survey was performed in full accordance with the Spanish law on data protection. As this was not an interventional study, no ethics

committee approval was required. However, all patients agreed to their participation through informed consent, and provided consent for aggregated reporting of research findings, before completing the survey. Of a total of 2,653 patients with migraine who began the questionnaire, after the validation, screening and cleaning process, the valid sample was made up of 1,283 patients. However, as one of the objectives of the present study was to assess the impact of quality of life, psychiatric comorbidities and disability, we estimated only the costs produced by the patients who answered all questions including MIDAS, HADs, and HANA validated scales: total Migraine=475; EM=288; and CM=187 (Figure 1). All patients included had been seen by a doctor within the last year and had received a medical diagnosis of migraine. The classification between CM and EM was established using the number of headache days reported by patients.

[Insert Figure 1]

Variables

The questionnaire included variables related to healthcare service utilisation (diagnostic tests, medical visits, emergency visits, and hospital admissions), private service utilisation incurred by the patients (visits to private specialists and other complementary treatments for migraine), data related to the patient's labour productivity losses in the past year and the scores of HANA, HADS, and MIDAS.

Costs analysis

To assess the burden of migraine in Spain, the following were calculated: DHC, assumed by the national public health system; DNHC borne by the patient; and IC (20–24). In the present study, the IC were derived only from the patient's labour productivity losses due to medical visits, sick leave, and hospital admission days related to migraine in the economically active population, since this was the information included in the survey. Costs were calculated independently for patients with CM and EM. All costs were expressed in Euros referring to the year 2017, with the exception of the unit price per normal working hour in Spain, which was last updated in 2015 (25). The pharmacological costs were acquired from the economic study carried out in Spain in 2012 by Bloudek et al (7). The annual increase in the consumer price index of pharmaceutical products (26), was applied to the operating costs for 2010 used by Bloudek et al (7).

The costs related to medical visits, tests, and emergency room visits was obtained from the prices published in the Official Bulletins of the 17 Spanish Autonomous Communities. Average rates for 2017 were used due to the variability of prices between the different Autonomous Communities.

The DNHC were self-reported by patients, including costs for visits to private specialists, other complementary treatments for migraine including physical aerobic exercise; psychological treatment; acupuncture; and specific diet.

We estimated the financial savings from the 50% reduction in migraine days indirectly, using the average number of migraine days per month reported by patients who participated in this study and differentiating by migraine type.

Statistical analysis

Descriptive statistics (number of valid cases, mean, and SD) were calculated for all continuous variables and frequencies and percentages were calculated for categorical variables for the overall migraine, distinguishing between CM and EM.

For the annual cost, mean and SD were calculated distinguishing between CM and EM. The percentages of each of the costs were calculated using the cost of each category and the total cost per patient per year.

In addition, the cost comparison between CM and EM was carried out using the distribution established according to the HANA, HADS and MIDAS scales. The non-parametric Mann-Whitney analysis was used due to the absence of a normal distribution. Statistical significance was established at $p<0.05$.

In order to verify the relationship between costs and impact of migraine on quality of life (HANA) Pearson correlations were made for each of the costs for CM and EM ($r=0.337$ $p<0.001$).

A dot plot representing the values along a numeric line has been used to show possible accumulations, trends, variability, dispersion, and how the average total cost of migraine was distributed by number of days per month with a headache. Using Pearson's correlation coefficient, we measured the degree of association between the number of days with migraine per month and average total costs ($r= 0.763$, $p<0.001$). The average total costs relative to the number of migraine days per month have been estimated using simple linear regression.

RESULTS

We analysed data from 475 patients who fully completed the survey of whom 187 had CM (39.4%). The mean age was 36.83 (± 10.75) years, with 89.9% being women. Overall EM and CM groups were comparable with respect to age and gender. CM patients had a lower proportion of university degrees ($p=0.003$), higher unemployment ($p=0.036$), and were more likely to be members of a Spanish migraine patient association ($p=0.002$). CM patients are also more likely than EM patients to have depression

(32.1% vs 10.8%, p <0.001) or anxiety (56.15% vs 36.1%, p<0.001). According to MIDAS, those with CM are more likely to suffer severe disability than EM patients (p <0.001) (Table 1).

[Insert Table 1]

The average total cost for patients with migraine was €10,302.6± 22,808.7 per year, 55% corresponding to IC, 30% to DHC, and 15% to DNHC (Table 2). IC for patients with CM and EM are respectively: CM=€8,233.9 per year; EM=€3,891.6 per year (p<0.001). We observed a substantial variability of expenditure per person in hospital admissions.

[Insert Table 2]

Positive correlations were found between anxiety level and costs for EM. Thus, as the anxiety level increases (HADS-A), so does IC (p=0.011 and r=0.150) and total costs (p=0.003 and r=0.173). The same applied to depression level (HADS-D) and costs for EM patients, since as the depression value increases, so does DHC (p=0.005 and r= 0.164), IC (p<0.001 and r=0.302), and total costs (p<0.001 and r=306). We found no statistical correlation between anxiety or depression and costs for CM (Table 3).

Positive correlation between all types of cost and the HANA scale score were observed in CM and EM (table 3). A positive correlation between disability and total costs for EM and CM was also found (Table 3).

[Insert Table 3]

We have calculated average scores for anxiety and depression to show the relationship with each number of migraine days per month (chart S1, S2). In the case of MC, HADS values fluctuate with greater dispersion, while in EM case HADS values follow a linear trend with respect to migraine days per month."

[Supplementary materialFigure S1, Figure S2]

Table 4 shows how the total costs, DHC, DNHC, and IC of migraine increase as the MIDAS score increases, meaning that this relationship statistically significant (p<0.001 Kruskal Wallis test). Total costs are twice as high for the Grade IVB according to MIDAS for patients with CM.

[Insert Table 4]

The results of the Pearson correlation (R=0.763 p<0.001) explain how increasing the number of days with migraine leads to an increase in average total costs (chart 1). According to the regression analysis, the annual average economic savings from the reduction of one day of migraine per month was estimated at €744.14 for EM and €663.20 for CM while the 50% reduction of days without migraine (corresponding to

6 days per month for EM and 20 days per month for CM) would lead to an average economic saving of €2,232.44 per year for EM and €6,631.99 per year for CM.

[Insert Figure 2]

DISCUSSION

The present study shows that migraine, but particularly CM, is associated with increased direct and IC. The annual cost for patients with CM is more than two and a half times as high as in those with EM, and the largest proportion of expenditure is due to IC. More importantly, we found that reducing one migraine day per month may save annually €744.14 per EM patient and €663.20 per CM patient, while the 50% reduction in days with migraine per month would lead to an average economic saving of €2,232.44 per year for EM and €6,631.99 per year for CM.

Our findings are in line with previous studies where the cost of CM was found to be approximately three times higher than EM (7,10,13). People with CM are more likely than those with EM to visit their primary care physician, neurologist, the emergency department, and be admitted to a hospital. Furthermore, patients with CM are less likely to be employed and the disability related to migraine is associated with a reduction in productivity at work. As estimated in other studies (8,13,27), IC represents the largest proportion of expenditure in our study, although there exist studies that do not corroborate the same results (10). These apparent contradictory results might be explained by the variability of costs in different national healthcare systems with different management strategies for migraine, but also due to the different methodologies used to recruit patients. Also, socio-demographic differences, particularly educational level and employment status may influence IC. In this study, most patients had university studies and were working, in contrast with the study of Messali et al. (10). In the present sample, the average cost savings per day without migraine was slightly higher in EM in comparison with CM patients. Our results may be explained because the proportion of unemployed individuals was higher in CM and this may influence the economic burden, as production loss at work represented the main part of the costs.

We observed that the burden of migraine and associated-costs are largely driven by migraine frequency but also by degree of disability, measured by the MIDAS scale as previously reported(28–30). The cost of migraine was much higher in subjects with CM and in those with moderate or severe disability compared to little disability. Our data are consistent with previous studies in which frequency and severity of migraine increase DHC (6,7,29,31), but also IC (8,13,27). Similarly, there is a statistically significant

relationship between the costs of migraine and quality of life, with higher costs associated with those who experience more limitations in their daily life (27).

In the present study the annual DHC was €5,910 for CM and €1,185 for EM patients, and the IC ranges from €3,891 (EM) to €8,233 (CM). In comparison with prior studies in Spain (7), DHC for CM has more than doubled, mainly due to the increase in emergency room visits and hospital admissions in patients analysed in the present study - while IC for EM remains similar. IC is also much higher than reported in another European study (8) that included patients from Spain. All these changes in cost, particularly in CM patients, may be explained by including patients with a more severe type of migraine, but also due to changes in chronic migraine management.

Comorbid psychiatric conditions are more frequent in patients with CM and, previous evidence suggests that it may contribute to the increase in costs (11,14). In our sample, anxiety and depression occur at high rates in CM compared with EM as previously reported (4,28). However, anxiety and depression were both associated with an increase in total cost, but only in patients with EM. In this study, we did not find a linear trend in the increase of depression and anxiety values with respect to costs. In other words, since depression and anxiety values are mostly high, it does not increase the costs in a statistically significant manner. It can be argued that patients with CM have been probably suffering anxiety or depression for a longer period than EM patients, and have developed different strategies to better cope with psychiatric comorbidity, reducing the influence on disability and cost. In accordance with our findings, previous studies reported that the presence of psychiatric comorbidity was not associated with an increase in the costs of migraine in Spain or France as it occurs in other European countries (7). However, the screening of anxiety and depression disorders was based in HADS scores and it is a not confirmed diagnosed based on a structured clinical interview. Therefore, we cannot exclude that some CM patients have been misclassified and this may influence our results. In patients with EM, interictal anxiety is associated with lost productive time (32)probably because the concern about suffering a new migraine attack may generate an increase in healthcare utilisation, a reduction in the patient's labour productivity, and as a consequence could increase healthcare costs. Future studies should examine whether medical costs in patients with migraine and psychiatric comorbidity could be decreased by improving the diagnosis and treatment of depression and anxiety.

Migraine is underdiagnosed and undertreated worldwide (33,34). Currently, the proportion of migraine patients who receive triptans is very low and more than one in five candidates for preventive therapy do not receive it (34). Furthermore, it has been observed that inadequate acute migraine treatment is

associated with an increased risk of chronic migraine (35) and following management guidelines could reduce migraine days and disability in most patients (36). In the present study, we show that the reduction of only one migraine day per month may save €744.14 per patient per year for EM and €663.20 for CM. Therefore, adequate migraine management may not only reduce the number of migraine days, but could also have an enormous impact on the overall cost of migraine.

One of the strengths of the present study lies in the fact that to our knowledge it is the first exhaustive study analysing the health-economic consequences of migraine in Spain, including a considerable number of patients with CM. The present study includes information beyond that related to DHC by estimating the DNHC assumed by patients and the IC derived from labour productivity losses. In addition, three validated screening scales for disability (MIDAS), quality of life (HANA) and anxiety and depression (HADS) were applied, reducing bias against non-validated information.

This study is subject to certain limitations and therefore, the results of this research must be interpreted with caution. First of all, migraine diagnosis was based self-reported. Although all patients had previously been diagnosed by a physician, migraine diagnosis could not be confirmed. Another bias of the survey is that in order to be completed on an online platform, patients had to have Internet access in addition to having the necessary skills to deal with technology. In addition, a high proportion of patients accessed the survey through the AEMICE patient association so it is possible that patients with severe forms of migraine are overrepresented. Moreover, this is an observational cross-sectional study, thus the annual costs have been estimated based on the monthly costs declared by the patients at the time of the survey. Therefore, prospective studies with a higher number of patients may be needed to accurately estimate the annual savings of reducing the number of migraine days. In addition, the survey of the present study was long, that could explain the high non-response rates observed that may affecting the sample representativeness negatively. Finally, it should be noted that this survey did not include questions about the type of medication used. Therefore, this data was estimated based on previous studies that included Spanish patients (7) in which the unit price of medicines used refer to 2010. For the calculation of the final cost per medication, the annual increase of treatments in Spain from 2010 to 2017 was taken into account (26).

CONCLUSIONS

In Spain, in comparison with EM, CM is associated with greater migraine-related disability, higher cost, and lower quality of life. The cost of migraine is mainly driven by migraine frequency, while psychiatric comorbidity influences cost only in EM patients. Our findings show the significant annual saving of

reducing one migraine day per month (€744.14 for EM and €663.20 for CM), even further if this reduction is 50% of days without migraine would lead to an average economic savings of €2,232.44 for EM and €6,631.99 for CM, and highlights the potential impact of an adequate acute and preventive treatment on the overall economic burden of migraine. Future studies are needed to confirm our results.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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CAPTIONS FIGURES AND TABLE

FIGURES

Figure 1. Flow diagram of sample selection process

Figure 2. Distribution of the average total costs of migraine based on the number of days per month of self-reported migraine (N^{EM}: 288; N^{CM} :187)

TABLES

Table 1. Sociodemographic and psychiatric comorbidity of chronic (CM) and episodic migraine (EM)

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SUPPLEMENTARY MATERIAL

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Table 1. Sociodemographic and psychiatric comorbidity of chronic (CM) and episodic migraine (EM)

Variables	Values (means ± SD) or N (%)			
Socio-demographic:	CM (n=187)	EM (n=288)	M (n=475)	P-value
Age, years ± SD	36.4 ± 11.1	37.1 ± 10.5	36.8 ± 10.7	0.368
Female (%)	170 (90.9)	257 (89.2)	427 (89.9)	0.554
Having a Partner, Yes (%)	114 (61.3)	179 (62.4)	293 (61.9)	0.090
University studies n (%)	79 (42.2)	172 (59.9)	251 (53.0)	0.003*
Job status, Unemployed	27 (14.5)	39 (13.5)	66 (13.9)	0.036*
Follower of Migraine Associations	39 (21.0)	30 (10.5)	69 (14.6)	0.002*
Psychiatric comorbidity:				
Depression (HADS)*				
Case score	60 (32.1)	31 (10.8)	91 (19.2)	
Borderline case	43 (23.0)	57 (19.8)	100 (21.0)	<0.001*
No case	84 (44.9)	200 (69.4)	284 (59.8)	
Anxiety (HADS)*				
Case score	105 (56.1)	104 (36.1)	209 (44.0)	
Borderline case	45 (24.1)	75 (26.0)	120 (25.3)	<0.001*
No case	37 (19.8)	109 (37.8)	146 (30.7)	
*Disability (MIDAS**)*	83.4 ± 65.5	29.7 ± 27.5	50.9 ± 53.2	<0.001*

Notes: The unemployment rate is calculated by dividing the number of unemployed by the active population.

Abbreviations: SD = Standard Deviation; CM = Chronic Migraine; EM= Episodic Migraine; M= Migraine

* HADS= Hospital Anxiety and Depression Scale (Scoring Case: 0-7; Borderline case: 8-10; No case: 11-21).

** MIDAS= Migraine Disability Assessment (Little or No Disability: 0-5; Mild Disability: 6-10; Moderate Disability: 11-20; Severe Disability: 21+).

Table 2. Direct and indirect costs per person during 1 year among CM and EM patients (euros 2017)

Cost typology	M (n=475) Mean(± SD)	CM (n=187) Mean(± SD)	EM (n=288) Mean(± SD)	p-value
Direct Health Care Cost	**3,045.5 (± 20,225.7)**	**5,910.6 (±31,981.2)**	**1,185.1 (±1,985.3)**	**<0.001***
Medical visits (HCP)	**330.9(±503.5)**	**535.9 (± 683.4)**	**197.8 (± 266.3)**	**<0.001***
Primary care physician	143.9 (±269.2)	226.7 (±374.6)	90.2 (±146.2)	**<0.001***
Neurologist	178.9 (±346.8)	295.1 (±488.1)	103.5 (±172.5)	**<0.001***
Paediatrician	1.1(±17.5)	1.8 (±24.9)	0.6 (± 10.0)	0.756
Otorhinolaryngologist	7.0 (±42.5)	12.3 (±59.6)	3.5 (± 25.4)	0.051
Diagnostic testing	**135.9 (**± 263.8)	**199.0 (±332.2)**	**94.9 (±197.9)**	**<0.001***
Computed Tomography	60.6 (± 127.0)	81.8 (±150.7)	46.7(±106.9)	**0.003***
Magnetic resonance	66.1 (± 155.5)	100.5(±192.7)	43.8(±120.8)	**<0.001***
Lumbar puncture	9.2 (±66.4)	16.6(±89.7)	4.3(±44.8)	**0.045***
Emergency room visits	**635.7 (±1655.9)**	**1,064.9 (± 2,442.0)**	**357.0 (±682.6)**	**<0.001***
Emergencies (visits)	587.0 (±1637.0)	990.6(±2429.3)	324.9 (±652.8)	**<0.001***
Emergency (test)	48.7 (±206.7)	74.3(±282.7)	32.1 (±134.2)	**0.012***
Computed tomography	27.9 (±135.3)	47.3 (±198.6)	15.4(±65.3)	**0.002***
Magnetic resonance	14.2 (±78.5)	22.0 (±98.5)	9.2(±61.8)	0.055
Spinal tap, or lumbar puncture	6.5(±63.6)	5.0 (±50.8)	7.6(± 70.7)	0.760
Hospital admissions	**1.592,9 (±18.780,8)**	**3.486,5 (±29.819,7)**	**363,3 (±1.549,5)**	**<0.001***
Treatments	**327,51[a]**	**624,28[a]**	**172,08[a]**	
Direct Non-Health Care Cost	**1.656,0 (± 2.204,3)**	**2.433,7 (±2.897,3)**	**1.151,0 (± 1.391,0)**	**<0.001***
Medical visits	33.3 (± 111.8)	57.0 (±146.7)	18.0 (±78.1)	**<0.001***
Complementary treatments	29.6 (± 65.0)	45.3 (±77.3)	19.4 (±53.4)	**<0.001***
Preventive Treatments	44.7 (± 56.2)	64.8 (±77.2)	31.7 (±30.2)	**<0.001***

	Physical activity	17.9 (± 40.7)	20.9 (±55.9)	16.0 (±26.4)	0.662
	Diet	18.9 (± 52.0)	27.3 (± 57.3)	13.5 (±47.5)	**<0.001***
	Psychological treatment	15.7 (± 52.1)	25.5 (±74.2)	9.4 (± 28.4)	0.124
Indirect Costs		**5,601.1 (±7,556.9)**	**8,233.9 (±9,406.5)**	**3,891.6 (±5,433.4)**	**<0.001***
TOTAL COST patient/year		**10,302.6 (± 22,808.7)**	**16,578.2 (± 34,568.1)**	**6,227.8 (± 6,515.7)**	**<0.001***

[a] Pharmacological costs were updated, using the year over year growth of IPC for pharmaceutical products (INE,2017), starting from the costs (year 2010) extracted from the study by Bloudek et al (7).

Abbreviations: SD = Standard Deviation; CM = Chronic Migraine; EM= Episodic Migraine; M= Migraine

Table.3. Correlation between HADS score, HANA score, MIDAS score and annual cost per patient. (N^{CM}:187), (N^{EM}: 288)

	DHC				DNHC			
	CM	P-value	EM	P-value	CM	P-value	EM	P-value
HADS Anxiety	-0.066	0.371	0.098	0.098	0.017	0.814	0.085	0.149
HADS Depression	-0.064	0.386	0.164	**0.005***	-0.041	0.578	0.021	0.718
HANA	0.165	**0.024***	0.231	**<0.001***	0.171	**0.020***	0.121	**0.041***
MIDAS	0.241	**0.001***	0.199	**0.001***	0.153	**0.036***	0.196	**0.001***
	IC				TC			
	CM	P-value	EM	P-value	CM	P-value	EM	P-value
HADS Anxiety	0.014	0.852	0.150	0.011*	-0.056	0.449	0.173	0.003*
HADS Depression	0.112	0.127	0.302	<0.001*	-0.032	0.665	0.306	<0.001*
HANA	0.234	0.001*	0.301	<0.001*	0.230	0.002*	0.348	<0.001*
MIDAS	0.121	0.099	0.277	<0.001*	0.268	<0.001*	0.334	<0.001*

* Pearson Correlation

Abbreviations: DHC=Direct Health Costs; DNHC=Direct Non-Health Costs; IC=Indirect Costs; TC= Total Cost; CM=chronic migraine; EM=episodic migraine

Table 4. Associations between MIDAS grade and annual cost per migraine patient

Migraine								
MIDAS	TC (euro)	P-value	DHC (euro)	P-value	DNHC (euro)	P-value	IC (euro)	P-value
Grade I	3.657,5	<0.001*	1.284,3	<0.001*	1.180,0	<0.001*	1.193,3	<0.001*
Grade II	3.988,5		651,5		958,1		2.378,9	
Grade III	5.245,5		1.090,3		896,1		3.259,1	
Grade IV A	8.215,8		1.499,4		1.650,4		5.066,0	
Grade IV B	16.146,0		5.668,4		2.189,7		8.287,8	
Episodic Migraine								
Grade I	3.123,6	<0.001*	742,7	<0.001*	965,2	0.060	1.415,7	<0.001*
Grade II	3.149,2		549,2		846,2		1.753,8	
Grade III	5.121,2		1.013,8		938,6		3.168,8	
Grade IV A	6.921,2		1.379,1		1.317,7		4.224,4	
Grade IV B	9.600,3		1.657,4		1.401,7		6.541,3	
Chronic Migraine								
Grade I	5.411,9	0.015*	3.063,6	0.024*	1.885,7	0.008*	462,5	0.136
Grade II	12.171,6		1.648,2		2.050,0		8.473,4	
Grade III	6.489,1		1.855,0		471,4		4.162,6	
Grade IV A	11.766,5		1.829,5		2.562,9		7.374,2	
Grade IV B	19.076,9		7.464,4		2.542,5		9.069,9	

Abbreviations: DHC=Direct Health Costs; DNHC=Direct Non-Health Costs; IC=Indirect Costs; TC=Total Cost.

Figure 1. Flow diagram of sample selection process

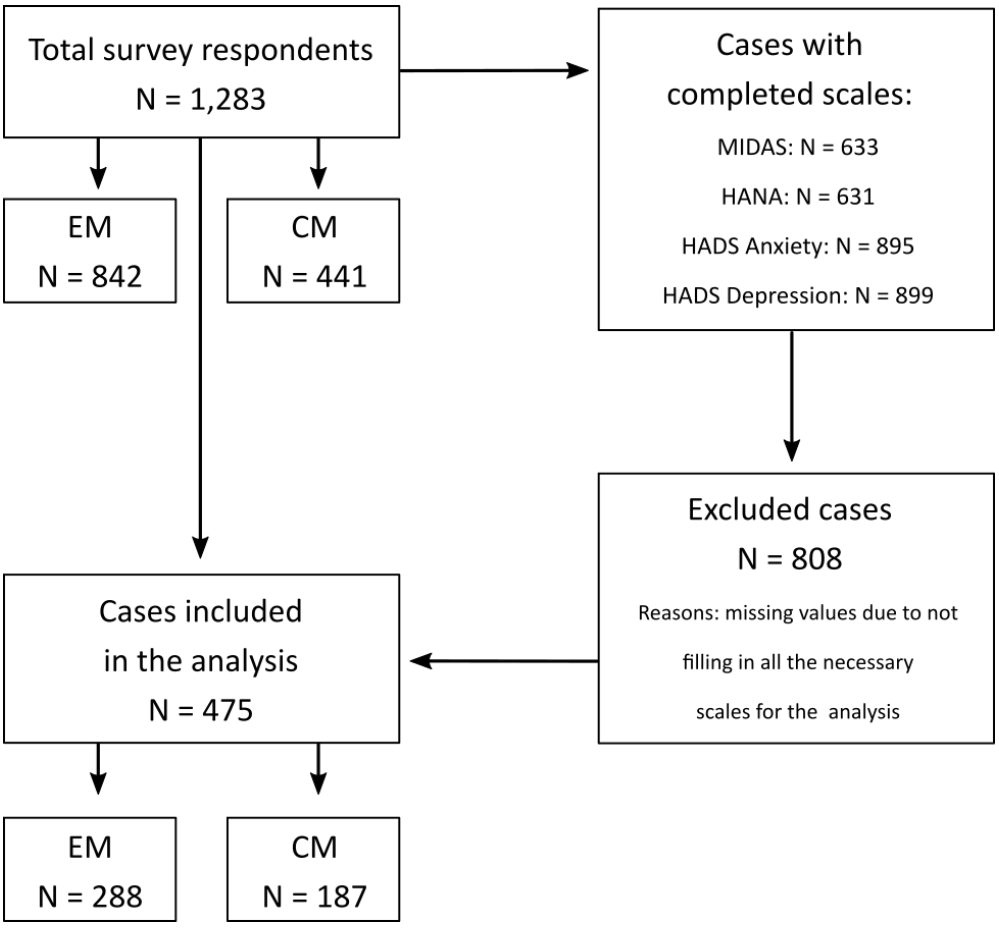

Figure 2. Distribution of the average total costs of migraine based on the number of days per month of self-reported migraine (N^{EM}: 288; N^{CM} :187)