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## Analysis of headache disorders in Spain during the period 2011-2016: Patient profile, healthcare management and direct medical costs

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# Analysis of headache disorders in Spain during the period 2011-2016: Patient profile, healthcare management and direct medical costs

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**ABSTRACT**

**Objectives:** To revise the number and characteristics of the Spanish population affected by headache disorders and the direct medical cost that these patients represent for the healthcare system. **Design:** A retrospective multicentre study. **Setting:** Records from all patients admitted with headache in primary and secondary care centres in Spain between 2011 and 2016 registered in a Spanish claims database. Direct medical costs were calculated using standardised average expenses of medical procedures determined by the Spanish Ministry of Health. **Results:** Data extraction claimed primary care records from 636,722 patients and secondary care records from 30,077 patients. Females represented 63% and 65% of all patients with headache in primary and secondary care respectively, with the exception of cluster headaches, a group with 60% male patients. No large shifts were observed over time in patients’ profile; contrarily, overall number of admissions increased 5 folds during the study period. Migraine was the cause for 28% of primary care consultations and 50% of secondary care admissions, and it was responsible for the largest portion of healthcare costs in 2016, a total amount of € 7,302,718. The estimated annual direct medical cost of headache disorders was € 10,716,086. **Conclusions:** Migraine was responsible for half of secondary care admissions linked to headache disorders. The total number of admissions increased 5 folds over a six year period, a raise likely to impact the direct medical costs associated to these disorders causing an increase in the total burden they represent for the Spanish National Healthcare System.

## Strengths and limitations

- The inclusion of primary and secondary care data allows a wider analysis of disease management.
- Patient records included all diagnoses registered upon admission, which permits a comorbidity analysis.
- The burden of prescription drugs could not be evaluated via this database.

**KEYWORDS:** Headache; Migraine; Claims database; Direct medical cost; Spain.



physicians, and anti-migraine treatments are used inadequately in an elevated percentage of cases [10]. Such investigations highlight the need to improve health protocols for headache symptoms in an effort to reduce its personal and economic burden. Hence, it is crucial to obtain updated epidemiologic data. Recent data examining the prevalence and characteristics of patients with headache and migraine is not available; additionally, previous statistics regarding the Spanish population were obtained via survey, with an assumed analytical error entailed. The aim of this study was to revise disease incidence and the profile of the Spanish population affected by headaches and migraine, contributing with novel data obtained from a Spanish claims database. A second objective was to evaluate the direct medical cost that these patients represent for the healthcare system, providing a basis for the optimisation of resource allocation.

## METHODS

### Data extraction

Records of inpatient and outpatient admissions due to headache were extracted from a Spanish Ministry of Health database that compiles data from private and public hospitals, and primary care centres covering all Spanish regions. The 9<sup>th</sup> and 10<sup>th</sup> revisions of the International Statistical Classification of Diseases and Related Health Problems, Clinical Modification (ICD9-CM and ICD10-CM) were used to claim all admissions registered with a principal diagnosis (admission motive) of headache, classified in accordance with The International Classification of Headache Disorders, 3rd edition (ICHD-3). Equally, four codes from The International Classification of Primary Care (ICPC) were used to claim



(examination, medication and surgery), nutrition, costs associated to personnel, medical equipment and resources. Data related to prescribed medication was not available

Data presentation is mainly descriptive. Statistical analyses were performed using Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA).

## RESULTS

### Patient profile

Four unique ICPC codes were used to identify patients with unspecified headache, migraine, specified tension-type headache and cluster headaches in primary care files, claiming 1,829,571 records. For hospitalisation records, 97 ICD9 and IC10 codes were clustered in 16 sets that identified 32,517 admissions between 2011 and 2016. Once indexed by patients' first admission, 636,722 single-patient primary care files and 30,077 hospitalisation files remained.

The analysis of single-patient data revealed a significant sex bias, with a higher percentage of female patients in most cases, with the exception of cluster headache, in which male patients represented the 61.67% in primary care and the 59.14% in hospitals (Table 1). The overall male and female rate in primary care was 37.47 vs. 62.53% while in secondary care it was 34.84 vs. 65.15%.

**Table 1 Number (N) and characteristics of patients diagnosed with headache disorders in primary and secondary care.**

Primary care	N	Females %	Age (SD)
Unspecified headache	383,464	64.54	39.22 (21.22)
Migraine	178,081	76.06	40.77 (16.18)
Tension-type headache	73,408	71.19	45.11 (18.17)

Cluster headache	1,769	38.33	47.60 (15.54)
<b>Secondary care</b>	<b>N</b>	<b>Females %</b>	<b>Age (SD)</b>
<b>Primary headaches</b>	29,514	65.32	36.40 (21.72)
Migraine	14,836	69.58	36.77 (21.55)
Without aura	1,511	73.06	31.95 (17.68)
With aura	6,234	69.60	36.87 (16.59)
Chronic migraine	480	82.71	41.07 (15.74)
Hemiplegic migraine	298	62.42	32.25 (18.00)
Menstrual migraine	30	100.00	32.17 (12.25)
Persistent aura without cerebral infarction	351	71.79	41.18 (15.72)
Persistent aura with cerebral infarction	34	70.59	42.47 (15.02)
Other forms of migraine <sup>a</sup>	871	59.47	30.92 (18.81)
Unspecified migraine	5,027	69.09	31.63 (19.46)
Tension-type headache	4,348	69.66	44.59 (21.90)
Trigeminal autonomic cephalalgias	981	47.30	43.85 (18.25)
Cluster headache	673	40.86	44.03 (17.90)
Hemicrania continua	308	61.36	45.21 (18.70)
Other specified headaches <sup>b</sup>	580	55.69	42.50 (19.65)
Unspecified headaches	8,732	58.63	35.17 (25.52)
<b>Secondary headaches</b>	563	55.95	44.35 (23.06)
Post-traumatic headache	317	45.11	41.89 (24.16)
Drug-induced headache	246	69.92	48.63 (20.97)

<sup>a</sup> With or without mention of status migrainosus. <sup>b</sup> Hypnic, primary cough, exercise and stabbing headache, headache associated with sexual activity.

Patients' age displayed great variability, although the mean age for most patients with classifiable syndromes remained between 30 and 50 years. Mean patients' age in secondary care slightly increased during the study period.

Primary care records allowed an analysis on patients' socioeconomic status. In all cases, around 60% of the patients had an income level of under € 18,000, while around 20% ranged between € 18,000 and € 99,999. Patients' employment status displayed a more irregular distribution, with a clear diminished percentage of pensioners (13.82%). The active population represented 38.38% of total patients, while not active or unemployed patients summed 32.50% of the total.

On the other hand, hospital records included a register of secondary diagnoses, utilised for the evaluation of disease comorbidities, which were evaluated for migraine and other headache types separately. In addition, data corresponding to male and female patients was analysed independently (Table 2). Overall, hypertension was the most common comorbidity, followed by disorders of lipid metabolism as hypertriglyceridemia and hyperlipidaemia. Slight differences appear between males and females in the diagnosis of hypothyroidism, anxiety and dysthymic disorder, primarily found in female patients. The frequency of hypertension and diabetes appeared increased in patients with migraine versus other headaches.

**Table 2 Secondary diagnoses found in patients with migraine and with other headache disorders (excluding migraine).**

Comorbidities	Males %		Females %	
	Migraine	Other headaches	Migraine	Other headaches
Essential hypertension	19.38	11.09	18.00	12.48
Disorders of lipid metabolism	14.61	11.57	15.50	14.12
Tobacco use disorder	9.17	11.73	13.71	14.30
Anxiety disorder	8.38	7.24	5.41	3.77
Diabetes mellitus	6.18	2.19	7.00	3.57

Hypothyroidism	5.86	5.05	1.16	1.13
Dysthymic disorder	5.55	4.26	2.53	1.55
Unspecified asthma	4.26	4.40	2.76	3.24
Depressive disorder	5.03	3.67	2.30	1.29
Vomiting	2.84	0.73	4.04	1.11

**Healthcare management**

Total admission data was analysed to obtain information on patients’ use of resources and management of the disease in both primary and secondary care. Persistent headache and migraine were controlled mostly in primary care facilities. It was in these centres where the highest number of admissions per patient was registered, an average of 2.8 for all headaches, 3.2 for migraine alone. Hospitalisations averaged one admission per patient in all cases.

The number of primary care admissions linked to headache disorders augmented considerably over time (Figure 1). The year 2011, 89,958 admissions were registered for all headache disorders, 26,459 for migraine alone; in contrast, the year 2016 those were 451,086 and 141,252, while the number of new patients remained stable.

In primary care, patients admitted with migraine represented 28.0% of the total, while in secondary care the proportion of patients with migraine raised up to the 49.7% (Figure 2A). The scrutiny of specialised care data alone showed a predominance of migraine with aura, followed by patients with tension-type headache (Figure 2B).

The vast majority of hospital admissions (90%) for headache disorders were due to emergencies and patients stayed hospitalised an average of 4.4 days. Posterior transfers

to other facilities were not significant, with 98% of the patients discharged to their residences.

The service to treat the most patients was neurology (51.85%), followed by paediatrics (22.33%) and internal medicine (16.53%). In all cases, procedures related to head and brain diagnostic imaging were predominant (Table 3).

**Table 3 Percentage of admissions in which each medical procedure was performed.**

Procedures	% of admissions
Computerized axial tomography of head	41.86
Magnetic resonance imaging of brain	34.11
Injection or infusion of a therapeutic substance	11.26
Spinal tap	11.07
Microscopic examination of blood	10.49
Echoencephalography	9.52
Electrocardiogram	9.40
Electroencephalography	7.40
Routine chest x-ray	6.37
Arteriography of cerebral arteries	5.23

### **Direct medical cost**

The economic costs associated with patients' use of healthcare resources were evaluated for the year 2016 (Table 4). This calculation comprises the cost of secondary healthcare associated with a hospitalisation event, and is determined by the mean cost of medical procedures and hospitalisation days. Headache disorders summed a total annual cost of € 10,716,086. Migraine alone represented € 7,302,718 of the total annual cost.

**Table 4 Direct medical costs associated to secondary care for the year 2016.**

Headache disorders	Cost per patient	Total cost
<b>Primary headaches</b>	€ 2,796	€ 10,445,179
Migraine	€ 2,736	€ 7,302,718
Without aura	€ 2,752	€ 880,585
With aura	€ 2,674	€ 3,123,802
Chronic migraine	€ 3,132	€ 219,246
Hemiplegic migraine	€ 2,903	€ 142,247
Menstrual migraine	€ 2,019	€ 8,077
Persistent migraine aura without cerebral infarction	€ 2,554	€ 125,144
Persistent migraine aura with cerebral infarction	€ 3,843	€ 30,744
Other forms of migraine <sup>a</sup>	€ 2,933	€ 225,836
Unspecified	€ 2,757	€ 2,547,038
Tension-type headache	€ 2,803	€ 1,981,425
Trigeminal Autonomic Cephalalgias	€ 3,534	€ 653,752
Cluster headache	€ 3,712	€ 478,789
Hemicrania continua	€ 3,124	€ 174,963
Other specified headaches <sup>b</sup>	€ 2,941	€ 405,820
Unspecified	€ 2,742	€ 101,464
<b>Secondary headaches</b>	€ 2,913	€ 270,907
Post-traumatic headache	€ 2,695	€ 137,452
Drug-induced headache	€ 3,336	€ 133,455

<sup>a</sup> With or without mention of status migrainosus. <sup>b</sup> Hypnic, primary cough, exercise and stabbing headache, headache associated with sexual activity.

Finally, patients financing scheme was evaluated. As expected, the majority of patients were financed by the public health system (95.65%).

**DISCUSSION**

**Patient profile**

According to the Spanish Statistical Office, around 9.4% of the Spanish population annually suffers migraine or another frequent headache [7]. A national health survey from the year 2017 reported similar numbers, with a percentage of 5.1% affected males and 13.6% females [12]. In the same line are those found in the present study, with a male/female ratio of 37.47 to 62.53% and 34.84 to 65.15% in primary and secondary healthcare centres respectively. Equally, surveys show incidence rates that peak in patients between 35 and 45 years, which is confirmed by healthcare records [12], with no large shifts observed over time in patients' age and sex distribution [13].

In terms of patients' regional distribution, a prior survey described great variability among regions [14]; however that is not inferred from primary care records in which distribution was coincident with the regional population registers [15]. The influence of patients' socioeconomic status was not determining in this study either; while the majority of patients had an income level of under € 18,000, no direct links were found with their employment status.

Previous population-based studies have linked headaches to several comorbid conditions. Associations have been found with illnesses and disorders as hypertension, diabetes, hyperlipidaemia, asthma, obesity, hypothyroidism and depressive disorders [16-21]. Small differences have been observed among patients diagnosed with headache in the Spanish population, as well as slight differences between males and females.

### **Healthcare management**

Patients seeking medical attention for headache disorders in Spain were mostly handled in primary care centres. The number of patients registered in secondary care facilities was

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235 only 21% of the total patients registered in primary care, and referral to specialised care  
236 and emergency visits were in half of the cases due to migraine. Migraines with aura were  
237 predominant among patients receiving hospital inpatient and outpatient care, although  
238 aura has been found in only 30% of all patients with migraine [22].  
239 The prevalence of migraine increased from 6.5% in 2003 to 9.7% in 2012 [23]. This  
240 tendency, however, does not justify the raise in the number of admissions associated with  
241 headaches and migraine observed in this study, as it is the number of admissions per  
242 patient what appears to be increasing. Additionally, previous evaluations suggest that  
243 neurology consultations, predominant in this study, are mainly related to ineffective  
244 treatment or increased frequency of migraine attacks [24], which indicates the need to  
245 improve treatment protocols.

246 **Direct medical cost**

247 Altogether, headache disorders represent great personal and socioeconomic costs, though  
248 most evaluations have its focus on migraine. Migraine was ruled as the sixth leading cause  
249 of disability-adjusted life years (DALYs) worldwide in people between 25 and 39 years in  
250 2015, and it is estimated that those suffering from it have significantly lower health-  
251 related quality of life, increased work impairment, and require a more intensive  
252 healthcare resource utilization [25, 26]. To quantify the costs of this increased use of  
253 medical resources, previous studies used disease prevalence data as a primary approach.  
254 In this way, the direct cost of migraine in Spain was estimated to sum € 344 million in  
255 2004, including medical admissions and prescription medicine [27]. Posterior evaluations  
256 based on surveys measured costs per patient of € 1,092 to treat episodic migraine in 2012,

€ 920 when excluding medication costs [28], a cost significantly lower to that obtained in this study, where the costs of specialised admissions alone averaged € 2,800 per patient in 2016.

This study found similar costs to treat the distinct headache disorders. Earlier calculations assumed a much lower annual cost of TTH, around € 300 per person in 2011 [29]. In the same revision, the total burden of headaches in Spain was estimated over € 22 billion, including healthcare, medication costs and indirect costs (lost productivity). Herein, secondary care alone summed € 10,716,086. To add to this calculation is the burden linked to work productivity lost, a presumably significant sum, and medication.

This research is subject to several limitations. Direct medical costs were registered leaving out the expenses related to prescription medication, which need to be considered independently. Further research will be necessary to confirm the increasing tendency in medical costs and, as a consequence, the burden derived from headache disorders.

## CONCLUSIONS

Patients receiving specialised care represented around 21% of those treated in primary care, and as much as 28% of primary care consultations were due to migraine. In addition, this study shows the great importance of this condition in secondary care. The increasing number of primary care admissions associated with headache disorders is likely to provoke a raise in the direct medical costs associated, increasing the burden they represent for the Spanish National Healthcare System.

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279     **DECLARATIONS**

280     **Acknowledgements**

281     Not applicable

282     **Ethics approval and consent to participate**

283     Parameters such as health centres and medical history identifiers were re-coded prior to  
284     extraction to maintain records anonymised, with no access to identifying information, in  
285     accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. In  
286     such cases the Spanish legislation does not require patient consent and ethics committee  
287     approval (Law 14/2007, 3 July, on biomedical research, Spain).

288     **Availability of data and material**

289     The data that support the findings of this study is available from the Spanish Ministry of  
290     Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health  
291     Information) for researchers who meet the criteria for access to confidential data at  
292     <https://www.mscbs.gob.es/en/estadEstudios/estadisticas/cmbdAnteriores.htm>.

293     **Authors' contributions**

294     JD contributed to the investigation by analysing and interpreting the economic situation of  
295     headache disorders in Spain and was a major contribution in the intellectual content  
296     revision. AM analysed the evolution of headache and migraine over the study period and  
297     was a major contributor in writing the manuscript. All authors read and approved the final  
298     manuscript.

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388 **FIGURES**

389 **Figure 1. Annual number of primary care admissions linked all headache disorders and**  
390 **migraine alone.**

391 **Figure 2. A) Patients with migraine and other headaches in primary and secondary care.**

392 **B) Percentage of patients per headache type in secondary care. MA Migraine with aura,**  
393 **MWA Migraine without aura, CM Chronic migraine, TTH Tension-type headache, CH**  
394 **Cluster Headache.**

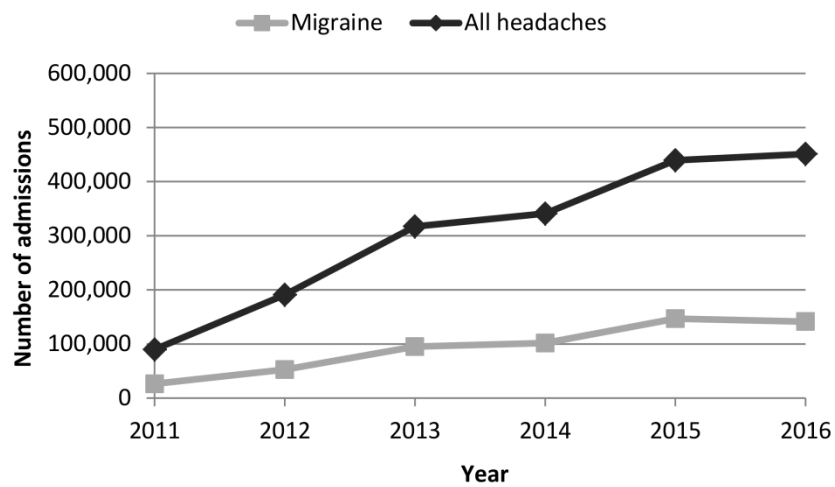


Figure 1. Annual number of primary care admissions linked all headache disorders and migraine alone.  
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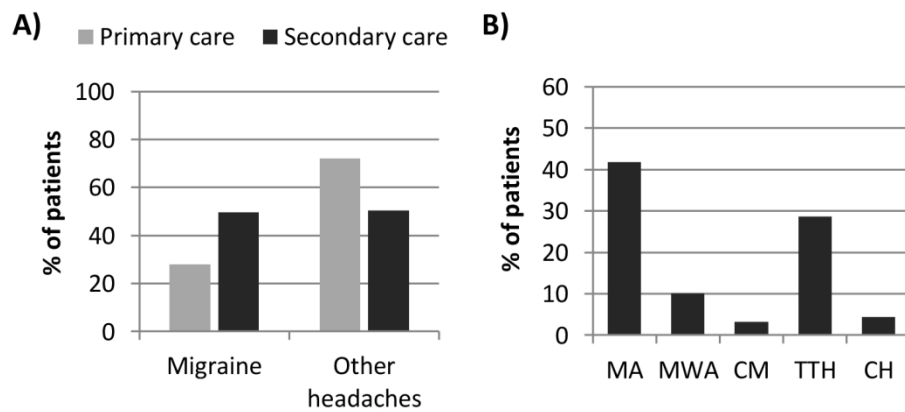


Figure 2. A) Patients with migraine and other headaches in primary and secondary care. B) Percentage of patients per headache type in secondary care. MA Migraine with aura, MWA Migraine without aura, CM Chronic migraine, TTH Tension-type headache, CH Cluster Headache.

139x70mm (300 x 300 DPI)

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## Analysis of the management and costs of headache disorders in Spain during the period 2011-2016: a retrospective multicentre observational study

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# Analysis of the management and costs of headache disorders in Spain during the period 2011-2016: a retrospective multicentre observational study

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2739 words

23 **ABSTRACT**

24 **Objectives:** To investigate the number and characteristics of the Spanish population  
25 affected by headache disorders and the direct medical cost that these patients represent  
26 for the healthcare system. **Design:** A retrospective multicentre observational study.  
27 **Setting:** Records from all patients admitted with headache in primary and secondary care  
28 centres in Spain between 2011 and 2016 that were registered in a Spanish claims  
29 database. Direct medical costs were calculated using the standardised average expenses  
30 of medical procedures determined by the Spanish Ministry of Health. **Results:** Data  
31 extraction claimed primary care records from 636,722 patients and secondary care  
32 records from 30,077 patients. Females represented 63% and 65% of all patients with  
33 headache in primary and secondary care respectively, with the exception of cluster  
34 headaches, a group with 60% of male patients. No large shifts were observed over time in  
35 patients' profile; contrarily, the number of cases per 10,000 patients attended in primary  
36 care increased 2 folds between 2011 and 2016 for migraine and 1.85 folds for other  
37 headaches. Migraine was the cause for 28% of primary care consultations and 50% of  
38 secondary care admissions, and it was responsible for the largest portion of healthcare  
39 costs in 2016, a total amount of € 7,302,718. The estimated annual direct medical cost of  
40 headache disorders was € 10,716,086. **Conclusions:** Migraine was responsible for half of  
41 secondary care admissions linked to headache disorders. The raise detected in the  
42 number of cases in primary care is likely to impact the direct medical costs associated to  
43 these disorders causing an increase in the total burden they represent for the Spanish  
44 National Healthcare System.

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**Strengths and limitations**

- The inclusion of primary and secondary care data allows a wider analysis of disease management.

- Patient records included all diagnoses registered upon admission, which permits a comorbidity analysis.

- The burden of prescription drugs could not be evaluated via this database.

**KEYWORDS:** Headache; Migraine; Claims database; Direct medical cost; Spain.

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67     **INTRODUCTION**

68     Headache disorders are extremely common, experienced by practically everyone at some  
69     moment in their lives. Annually, the percentage of adult population affected with  
70     headache is around 50% when the multiple types of headache are considered [1]. Primary  
71     headache disorders include migraine, tension-type headache (TTH), trigeminal autonomic  
72     cephalalgias (cluster headache and hemicrania continua) and others, including primary  
73     cough headache or those associated with sexual activity [2]. The most common form is  
74     TTH, which affects around 38% of the population [3]. Contrarily, trigeminal autonomic  
75     cephalalgias have a considerably low prevalence. For cluster headache it is less than 1%,  
76     yet, it is of raising interest due to the severity of its symptoms and its impact in patients'  
77     lives [4].

78     As for migraine, the estimated affected population remains around the 10% globally, with  
79     a 12.6% one-year prevalence in Spain [5, 6]; indeed, according to the Spanish Statistical  
80     Office, 5.1% of males and 13.6% of females were diagnosed with migraine or frequent  
81     headache in Spain in 2017 [7]. Migraine’s socioeconomic and personal impacts determine  
82     its relevance as it is considered a major cause of disability worldwide [8]. The primary  
83     migraine classification entails migraine with aura or without aura, with secondary  
84     classifications that include chronic migraine, hemiplegic migraine and of other origins [3].

85     Altogether, these disorders affect a large portion of the population, especially during  
86     working age, which implicates great public health repercussions and socioeconomic costs  
87     [9]. Medical surveys across Europe have shown deficiencies in the care that patients with  
88     persistent headache and migraine receive; the portion of patients with migraine lacking

medical treatment remains significant, and anti-migraine treatments are used inadequately in an elevated percentage of cases [10]. Such investigations highlight the need to improve health protocols for headache symptoms in an effort to reduce its personal and economic burden.

The availability of real-world evidence that reflects current practice is considered crucial for resource allocation decisions in public health and the revision of the established protocols and guidelines [11, 12]. Recent data examining the prevalence and characteristics of patients with headache and migraine is not available; additionally, previous statistics regarding the Spanish population were obtained via survey, with an assumed analytical error entailed. Hence, the interest on obtaining updated epidemiologic data regarding these conditions.

The aim of this study was to revise disease incidence and the profile of the Spanish population affected by headaches and migraine, contributing with novel data obtained from a Spanish claims database. A second objective was to evaluate the direct medical cost that these patients represent for the healthcare system, providing a basis for the optimisation of resource allocation.

## METHODS

### Data extraction

Records of inpatient and outpatient admissions due to headache were extracted from a Spanish Ministry of Health database that compiles data from private and public hospitals, covering around 90% of admissions, and primary care centres, covering around 10% of the

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111 Spanish population, from all Spanish regions [13, 14]. The 9<sup>th</sup> and 10<sup>th</sup> revisions of the  
112 International Statistical Classification of Diseases and Related Health Problems, Clinical  
113 Modification (ICD9-CM and ICD10-CM) were used to claim all admissions registered with a  
114 principal diagnosis (admission motive) of headache, classified in accordance with The  
115 International Classification of Headache Disorders, 3rd edition (ICHD-3). Equally, four  
116 codes from The International Classification of Primary Care (ICPC) were used to claim  
117 primary care records, corresponding to migraine alone, TTH, cluster headache and  
118 unspecified headaches. Within the database, any healthcare visit that is registered in the  
119 system is considered an admission. Primary care admissions are inherently outpatient and  
120 specialised care inpatient and outpatient admissions are discernible by the length of stay  
121 parameter. The records extracted corresponded to admissions from the years 2011 to  
122 2016, the last available data.

123 Parameters such as health centres and medical history identifiers were re-coded prior to  
124 extraction to maintain records anonymised, with no access to identifying information, in  
125 accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. In  
126 such cases the Spanish legislation does not require patient consent and ethics committee  
127 approval [15].

128 **Patient and Public Involvement**

129 No patient involved.

130 **Data analysis**

131 The complete admission data was used for both primary care and hospitalisation records  
132 to evaluate information on patients' nature of admission and discharge, length of stay,

services that treated the patients, and medical procedures utilised. Repeated records corresponding to separated admissions were eliminated for the analysis of patients' characteristics, relying on the first admission as the index event. The direct medical cost was calculated based on the standardised average expenses of admissions and medical procedures determined by the Spanish Ministry of Health, available for the year 2016. Cost is presented in total cost of all registered admissions and average cost per hospitalised patient. These figures include all expenses related to the admission: treatment (examination, medication and surgery), nutrition, costs associated to personnel, medical equipment and resources. Data related to prescription medication was not available.

Data presentation is mainly descriptive. The number of cases per 10,000 persons attended in primary care was calculated from the Ministry of Health database descriptive information [16]. Two-sample Z tests were used to test for differences in sample proportions, with a  $p < 0.05$  considered statistically significant. Statistical analyses were performed using Microsoft Excel® Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP. 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

## RESULTS

### Patient profile

Four unique ICPC codes were used to identify patients with unspecified headache, migraine, specified tension-type headache and cluster headaches in primary care files, claiming 1,829,571 records. For hospitalisation records, 97 ICD9 and IC10 codes were

clustered in 16 sets that identified 32,517 admissions between 2011 and 2016. Once indexed by patients' first admission, 636,722 single-patient primary care files and 30,077 hospitalisation files remained.

The analysis of single-patient data revealed a significant sex bias, with a higher percentage of female patients in most cases, with the exception of cluster headache, in which male patients represented the 61.67% in primary care and the 59.14% in hospitals (Table 1). The overall male and female rate in primary care was 37.47 vs. 62.53% while in secondary care it was 34.84 vs. 65.15%.

**Table 1 Number (N) and characteristics of patients diagnosed with headache disorders in primary and secondary care centres.**

Primary care	N	Females %	Age (SD)
Unspecified headache	383,464	64.54	39.22 (21.22)
Migraine	178,081	76.06	40.77 (16.18)
Tension-type headache	73,408	71.19	45.11 (18.17)
Cluster headache	1,769	38.33	47.60 (15.54)
Secondary care	N	Females %	Age (SD)
<i>Primary headaches</i>	29,514	65.32	36.40 (21.72)
Migraine	14,836	69.58	36.77 (21.55)
Without aura	1,511	73.06	31.95 (17.68)
With aura	6,234	69.60	36.87 (16.59)
Chronic migraine	480	82.71	41.07 (15.74)
Hemiplegic migraine	298	62.42	32.25 (18.00)
Menstrual migraine	30	100.00	32.17 (12.25)
Persistent aura without cerebral infarction	351	71.79	41.18 (15.72)
Persistent aura with cerebral infarction	34	70.59	42.47 (15.02)
Other forms of migraine <sup>a</sup>	871	59.47	30.92 (18.81)
Unspecified migraine	5,027	69.09	31.63 (19.46)

Tension-type headache	4,348	69.66	44.59 (21.90)
Trigeminal autonomic cephalalgias	981	47.30	43.85 (18.25)
Cluster headache	673	40.86	44.03 (17.90)
Hemicrania continua	308	61.36	45.21 (18.70)
Other specified headaches <sup>b</sup>	580	55.69	42.50 (19.65)
Unspecified headaches	8,732	58.63	35.17 (25.52)
<b>Secondary headaches</b>	563	55.95	44.35 (23.06)
Post-traumatic headache	317	45.11	41.89 (24.16)
Drug-induced headache	246	69.92	48.63 (20.97)

<sup>a</sup> With or without mention of status migrainosus. <sup>b</sup> Hypnic, primary cough, exercise and stabbing headache, headache associated with sexual activity.

Patients' age displayed great variability, although the mean age for most patients with classifiable syndromes remained between 30 and 50 years. Mean patients' age in secondary care slightly increased during the study period.

Primary care records allowed an analysis on patients' socioeconomic status. In all cases, around 60% of the patients had an income level of under € 18,000, while around 20% ranged between € 18,000 and € 99,999. Patients' employment status displayed a more irregular distribution, with a clear diminished percentage of pensioners (13.82%). The active population represented 38.38% of total patients, while not active or unemployed patients summed 32.50% of the total.

On the other hand, hospital records included a register of secondary diagnoses, utilised for the evaluation of disease comorbidities, which were evaluated for migraine and other headache types separately. In addition, data corresponding to male and female patients was analysed independently (Table 2). Overall, hypertension was the most common

comorbidity, followed by disorders of lipid metabolism as hypertriglyceridemia and hyperlipidaemia. Significant differences appeared between males and females in the diagnosis of mood disorders (anxiety, depressive disorder and dysthymic disorder) and hypothyroidism, primarily found in female patients. The frequency of essential hypertension, diabetes, dysthymic and depressive disorders and vomiting was consistently and significantly higher in patients with migraine versus those with other headaches.

**Table 2 Secondary diagnoses found in patients with migraine and with other headache disorders (excluding migraine).**

Comorbidities	Females %		Males %	
	Migraine	Other headaches	Migraine	Other headaches
Essential hypertension	19.38 <sup>a d</sup>	11.09 <sup>a</sup>	18.00 <sup>d</sup>	12.48
Disorders of lipid metabolism	14.61 <sup>c</sup>	11.57	15.50 <sup>c</sup>	14.12
Tobacco use disorder	9.17 <sup>b d</sup>	11.73 <sup>b</sup>	13.71	14.30
Anxiety disorder	8.38 <sup>b c</sup>	7.24 <sup>b</sup>	5.41 <sup>d</sup>	3.77
Diabetes mellitus	6.18 <sup>b d</sup>	2.19 <sup>a</sup>	7.00 <sup>d</sup>	3.57
Hypothyroidism	5.86 <sup>b</sup>	5.05 <sup>b</sup>	1.16	1.13
Dysthymic disorder	5.55 <sup>b d</sup>	4.26 <sup>b</sup>	2.53 <sup>d</sup>	1.55
Unspecified asthma	4.26 <sup>b</sup>	4.40 <sup>b</sup>	2.76 <sup>c</sup>	3.24
Depressive disorder	5.03 <sup>b d</sup>	3.67 <sup>b</sup>	2.30 <sup>d</sup>	1.29
Vomiting	2.84 <sup>a d</sup>	0.73 <sup>b</sup>	4.04 <sup>d</sup>	1.11

<sup>a</sup> p value < 0.05, females vs. males; <sup>b</sup> p value < 0.001, females vs. males; <sup>c</sup> p value < 0.05, migraine vs. other headaches; <sup>d</sup> p value < 0.001, migraine vs. other headaches.

The most common comorbidities displayed in Table 2 were analysed in relation with age. Significant differences appeared among age groups. Hypertension was found in 28.34% of admissions in patients older than 36 years of age, while in those under 36 it was found in

1.51% of admissions ( $p<0.001$ ). The same effect was found for the disorders of lipid metabolism, diabetes, hypothyroidism, dysthymic and depressive disorders diagnosed in 16.56%, 8.75%, 6.06%, 6.71% and 6.14% of admissions in older patients respectively, and 0.81%, 0.24%, 1.50%, 1.47% and 0.85% of admissions in younger patients respectively ( $p<0.001$ ).

### 200 Healthcare management

201 Total admission data was analysed to obtain information on patients' use of resources and  
202 management of the disease in both primary and secondary care. Persistent headache and  
203 migraine were controlled mostly in primary care facilities. It was in these centres where  
204 the highest number of admissions per patient was registered, an average of 2.8 for all  
205 headaches, 3.2 for migraine alone. Hospitalisations averaged one admission per patient in  
206 all cases.

207 The number of primary care admissions linked to headache disorders in primary care  
208 augmented considerably over time. The year 2011, 89,958 admissions were registered for  
209 all headache disorders, 26,459 for migraine alone; in contrast, the year 2016 those were  
210 451,086 and 141,252, while the number of new patients remained stable. In addition, the  
211 number of cases per 10,000 individuals attended in primary care was calculated, which  
212 included new patients and successive visits (Figure 1). The number of cases per 10,000  
213 patients attended in primary care increased 2 folds between 2011 and 2016 for migraine  
214 and 1.85 folds for other headaches ( $p<0.001$ , 2011 vs. 2016).

215 In primary care, patients admitted with migraine represented 28.0% of the total, while in  
216 secondary care the proportion of patients with migraine increased to 49.7% (Figure 2A).

The scrutiny of specialised care data alone showed a predominance of migraine with aura, followed by patients with tension-type headache (Figure 2B). The vast majority of hospital admissions (90%) for headache disorders were due to emergencies and patients stayed hospitalised an average of 4.4 days. Posterior transfers to other facilities were not significant, with 98% of the patients discharged to their residences. The service to treat the most patients was neurology (51.85%), followed by paediatrics (22.33%) and internal medicine (16.53%). In all cases, procedures related to head and brain diagnostic imaging were predominant (Table 3).

**Table 3 Medical procedures performed in more than 5% of admissions.**

Procedures	% of admissions
Computerized axial tomography of head (CT scan)	41.86
Magnetic resonance imaging (MRI) of the brain	34.11
Injection or infusion of a therapeutic substance	11.26
Spinal tap	11.07
Microscopic examination of blood	10.49
Echoencephalography	9.52
Electrocardiogram	9.40
Electroencephalography	7.40
Routine chest x-ray	6.37
Arteriography of cerebral arteries	5.23

**Direct medical cost**

The economic costs associated with patients' use of healthcare resources were evaluated for the year 2016 (Table 4). This calculation comprises the cost of secondary healthcare associated with a hospitalisation event, and is determined by the mean cost of medical

procedures and hospitalisation days. Headache disorders summed a total annual cost of € 10,716,086. Migraine alone represented € 7,302,718 of the total annual cost.

**Table 4 Direct medical costs associated to secondary care for the year 2016.**

Headache disorders	Cost per patient	Total cost
<b>Primary headaches</b>	€ 2,796	€ 10,445,179
Migraine	€ 2,736	€ 7,302,718
Without aura	€ 2,752	€ 880,585
With aura	€ 2,674	€ 3,123,802
Chronic migraine	€ 3,132	€ 219,246
Hemiplegic migraine	€ 2,903	€ 142,247
Menstrual migraine	€ 2,019	€ 8,077
Persistent migraine aura without cerebral infarction	€ 2,554	€ 125,144
Persistent migraine aura with cerebral infarction	€ 3,843	€ 30,744
Other forms of migraine <sup>a</sup>	€ 2,933	€ 225,836
Unspecified	€ 2,757	€ 2,547,038
Tension-type headache	€ 2,803	€ 1,981,425
Trigeminal Autonomic Cephalalgias	€ 3,534	€ 653,752
Cluster headache	€ 3,712	€ 478,789
Hemicrania continua	€ 3,124	€ 174,963
Other specified headaches <sup>b</sup>	€ 2,941	€ 405,820
Unspecified	€ 2,742	€ 101,464
<b>Secondary headaches</b>	€ 2,913	€ 270,907
Post-traumatic headache	€ 2,695	€ 137,452
Drug-induced headache	€ 3,336	€ 133,455

<sup>a</sup> With or without mention of status migrainosus. <sup>b</sup> Hypnic, primary cough, exercise and stabbing headache, headache associated with sexual activity.

Finally, patients financing scheme was evaluated. As expected, the majority of patients were financed by the public health system (95.65%).

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240     **DISCUSSION**

241     **Patient profile**

242     According to the Spanish Statistical Office, around 9.4% of the Spanish population  
243     annually suffers from migraine or another frequent headache [7]. A national health survey  
244     from the year 2017 reported similar numbers, with a percentage of 5.1% affected males  
245     and 13.6% females [17]. In the same line are those found in the present study, with a  
246     male/female ratio of 37.47 to 62.53% and 34.84 to 65.15% in primary and secondary  
247     healthcare centres respectively. Equally, surveys have shown incidence rates that peak in  
248     patients between 35 and 45 years, which has been confirmed by healthcare records [17],  
249     with no large shifts observed over time in patients’ age and sex distribution [18].  
250     The influence of patients’ socioeconomic status was not determining in this study; while  
251     the majority of patients had an income level of under € 18,000, no direct links were found  
252     with their employment status.  
253     Previous population-based studies have linked headaches to several comorbid conditions.  
254     Associations have been found with illnesses and disorders as hypertension, diabetes,  
255     hyperlipidaemia, asthma, obesity, hypothyroidism and depressive disorders [19-24]. Small  
256     differences were observed between male and female patients, principally in the diagnosis  
257     of mood disorders and hypothyroidism, which appeared to play a more significant role in  
258     females as it has been described in the general population [25, 26]. Similarly, essential  
259     hypertension, diabetes, dysthymic and depressive disorders and vomiting were primarily  
260     diagnosed in patients with migraine versus other headaches. Age was too a determinant  
261     factor in the diagnosis of comorbidities; older patients were more likely to be diagnosed

with hypertension, disorders of lipid metabolism, diabetes, hypothyroidism, dysthymic and depressive disorders, while the diagnosis of tobacco use disorder, anxiety disorder, asthma and vomiting symptoms did not display this correlation.

### Healthcare management

Patients seeking medical attention for headache disorders in Spain were mostly handled in primary care centres. The number of patients registered in secondary care facilities was only 21% of the total patients registered in primary care, and referral to specialised care and emergency visits were in half of the cases due to migraine. Migraines with aura were predominant among patients receiving hospital inpatient and outpatient care, although aura has been found in only 30% of all patients with migraine [27].

The prevalence of migraine was estimated to increase from 6.5% in 2003 to 9.7% in 2012 [28]. Herein, primary care data inclusion increased a 70% during the study period, which explains the increase registered in the number of admissions [16]. Nonetheless, the number of cases per 10,000 patients attended in primary care increased significantly over the study period, including new patients and successive visits. Additionally, previous evaluations suggest that neurology consultations, predominant in this study, are mainly related to ineffective treatment or increased frequency of migraine attacks, which could indicate the need to improve treatment protocols [29].

Regarding the management of these disorders at the hospital level, recommendations call to avoid imaging for uncomplicated headache, while previous analysis revealed a tendency to perform unnecessary neuroimaging tests in patients that fall into that category [30, 31]. A study developed in 2014 in the north of Spain investigated the

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possible overuse of neuroimaging procedures in patients with chronic migraine in a headache clinic [32]. The number of tests performed was considered adequate, but CT scans were registered in 76% of admissions and MRI in 42% [32]. Further research will be necessary to determine the current application of such recommendations in Spain.

**Direct medical cost**

Updated real-world evidence plays a pivotal role in resource allocation decisions in public health [11, 12]. Hence, it appears crucial to measure not only patients' use of healthcare resources but the direct medical cost associated.

Altogether, headache disorders represent great personal and socioeconomic costs, though most evaluations have its focus on migraine. Migraine was ruled as the sixth leading cause of disability-adjusted life years (DALYs) worldwide in people between 25 and 39 years in 2015, and it is estimated that those suffering from it have significantly lower health-related quality of life, increased work impairment, and require a more intensive healthcare resource utilization [33, 34]. To quantify the costs of this increased use of medical resources, previous studies used disease prevalence data as a primary approach.

In this way, the direct cost of migraine in Spain was estimated to sum € 344 million in 2004, including medical admissions and prescription medicine [35]. Posterior evaluations based on surveys measured costs per patient of € 1,092 to treat episodic migraine in 2012, € 920 when excluding medication costs [36], a cost significantly lower to that obtained in this study, where the costs of specialised admissions alone averaged € 2,800 per patient in 2016. This cost is tightly associated with the number and nature of diagnostic tests; however, further research will be necessary to determine its utility and whether its use

should be adjusted. In addition, the distinct calculation methods used in both studies cannot be ruled out as the origin of cost fluctuation.

This study found similar costs to treat the distinct headache disorders. Earlier calculations assumed a much lower annual cost of TTH, around € 300 per person in 2011 [37]. In the same revision, the estimated total burden of headaches in Spain was over € 22 billion, including healthcare, medication costs and indirect costs (lost productivity). Herein, secondary care alone summed € 10,716,086. To add to this calculation is the burden linked to work productivity lost, a presumably significant sum, and medication.

A number of limitations may have influenced the results of this study. Direct medical costs were registered leaving out the expenses related to prescription medication, which need to be considered independently. Further research will be necessary to confirm the increasing tendency in medical costs and, as a consequence, the increasing burden derived from headache disorders.

## CONCLUSIONS

Patients receiving specialised care represented around 21% of those treated in primary care, and as much as 28% of primary care consultations were due to migraine. In addition, this study shows the great importance of migraine in secondary care. The increasing number of cases of headache disorders attended in primary care centres is likely to provoke a raise in the direct medical costs associated, increasing the burden they represent for the Spanish National Healthcare System.

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329     **Acknowledgements**

330     Not applicable

331     **Funding statement**

332     This research received no specific grant from any funding agency in the public, commercial  
333     or not-for-profit sectors.

334     **Competing interests statement**

335     The authors declare that they have no competing interests.

336     **Ethics approval and consent to participate**

337     Parameters such as health centres and medical history identifiers were re-coded prior to  
338     extraction to maintain records anonymised, with no access to identifying information, in  
339     accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. In  
340     such cases the Spanish legislation does not require patient consent and ethics committee  
341     approval (Law 14/2007, 3 July, on biomedical research, Spain).

342     **Data sharing statement**

343     The data that support the findings of this study is available from the Spanish Ministry of  
344     Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health  
345     Information) for researchers who meet the criteria for access to confidential data at  
346     <https://www.mscbs.gob.es/en/estadEstudios/estadisticas/cmbdAnteriores.htm>.

347     **Authors' contributions**

348     JD contributed to the investigation by analysing and interpreting the economic situation of  
349     headache disorders in Spain and was a major contribution in the intellectual content

revision. AM analysed the evolution of headache and migraine over the study period and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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**FIGURES**

**Figure 1. Annual number of cases of headache disorders and migraine alone registered per 10,000 primary care admissions.**

**Figure 2. A) Patients with migraine alone and other headaches in primary and secondary care. B) Percentage of patients per headache type in secondary care.** MA Migraine with aura, MWA Migraine without aura, CM Chronic migraine, TTH Tension-type headache, CH Cluster Headache.

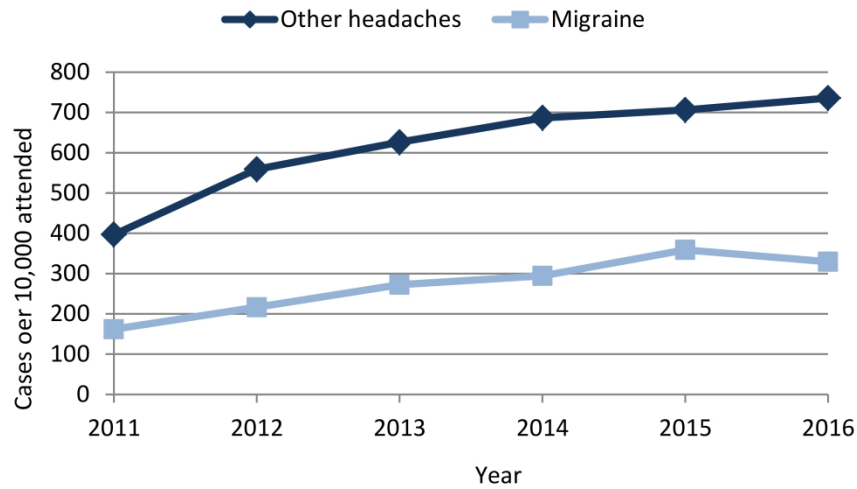


Figure 1 Annual number of cases of headache disorders and migraine alone registered per 10,000 primary care admissions.

296x209mm (300 x 300 DPI)

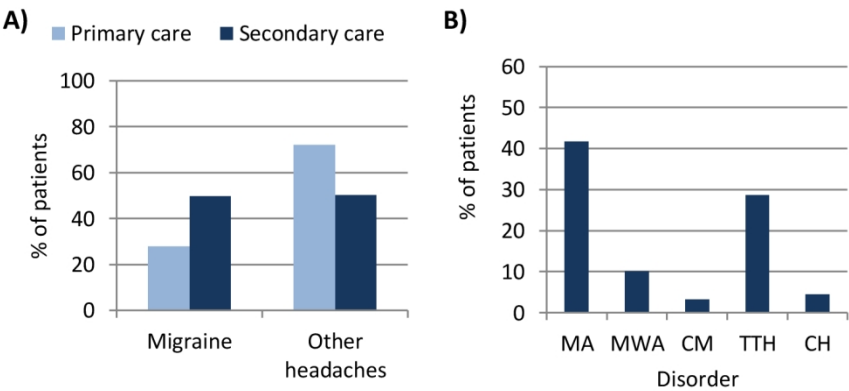


Figure 2 A) Patients with migraine alone and other headaches in primary and secondary care. B) Percentage of patients per headache type in secondary care. MA Migraine with aura, MWA Migraine without aura, CM Chronic migraine, TTH Tension-type headache, CH Cluster Headache.

150x70mm (300 x 300 DPI)

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
<b>Title and abstract</b>					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title and abstract	<p>RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.</p> <p>RECORD 1.2: If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract.</p> <p>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.</p>	Abstract
<b>Introduction</b>					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Lines 93-99		
Objectives	3	State specific objectives, including any prespecified hypotheses	Lines 100-104		
<b>Methods</b>					
Study Design	4	Present key elements of study design early in the paper	Line 108		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Lines 108-111		

Participants	6	<p>(a) <i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants</p> <p>(b) <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case</p>	Not applicable	<p>RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.</p> <p>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.</p> <p>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.</p>	Lines 111-118
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Line 131	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Not applicable
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Lines 131-142.		

Bias	9	Describe any efforts to address potential sources of bias	Not applicable		
Study size	10	Explain how the study size was arrived at	Not applicable		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Line 143-149.		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Line 143-149.		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Lines 123-127.

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Not applicable
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Not applicable
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study ( <i>e.g.</i> , numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Lines 152-157.	RECORD 13.1: Describe in detail the selection of the persons included in the study ( <i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Not applicable
Descriptive data	14	(a) Give characteristics of study participants ( <i>e.g.</i> , demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time ( <i>e.g.</i> , average and total amount)	Not applicable		
Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure	Not applicable		

		category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Not applicable		
<b>Discussion</b>					
Key results	18	Summarise key results with reference to study objectives	Discussion section		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Lines 314-318.	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Not applicable
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	Discussion section		

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion section		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding statement		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Not applicable

\*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langman SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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# BMJ Open

## Analysis of the management and costs of headache disorders in Spain during the period 2011-2016: a retrospective multicentre observational study

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Keywords:	NEUROLOGY, Migraine < NEUROLOGY, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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1 Analysis of the management and costs of headache disorders in Spain during  
2 the period 2011-2016: a retrospective multicentre observational study

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23 **ABSTRACT**

24 **Objectives:** To investigate the number and characteristics of the Spanish population  
25 affected by headache disorders and the direct medical cost that these patients represent  
26 for the healthcare system. **Design:** A retrospective multicentre observational study.  
27 **Setting:** Records from all patients admitted with headache in primary and secondary care  
28 centres in Spain between 2011 and 2016 that were registered in a Spanish claims  
29 database were included in the analysis. Direct medical costs were calculated using the  
30 standardised average expenses of medical procedures determined by the Spanish Ministry  
31 of Health. **Results:** Data extraction claimed primary care records from 636,722 patients  
32 and secondary care records from 30,077 patients. Females represented 63% and 65% of  
33 all patients with headache in primary and secondary care respectively, with the exception  
34 of cluster headaches, a group with 60% of male patients. No large shifts were observed  
35 over time in patients' profile; contrarily, the number of cases per 10,000 patients attended  
36 in primary care increased 2 folds between 2011 and 2016 for migraine and 1.85 folds for  
37 other headaches. Migraine was the cause for 28% of primary care consultations and 50%  
38 of secondary care admissions, and it was responsible for the largest portion of healthcare  
39 costs in 2016, a total amount of € 7,302,718. The estimated annual direct medical cost of  
40 headache disorders was € 10,716,086. **Conclusions:** Migraine was responsible for half of  
41 the secondary care admissions linked to headache disorders. The raise detected in the  
42 number of cases registered in primary care is likely to impact the direct medical costs  
43 associated to these disorders causing an increase in the total burden they represent for  
44 the Spanish National Healthcare System.

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**Strengths and limitations**

- The inclusion of primary and secondary care data allows a wider analysis of disease management.

- Patient records included all diagnoses registered upon admission, which permits a comorbidity analysis.

- The burden of prescription drugs could not be evaluated via this database.

**KEYWORDS:** Headache; Migraine; Claims database; Direct medical cost; Spain.

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3 89 persistent headache and migraine receive; the portion of patients with migraine lacking  
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5 90 medical treatment remains significant, and anti-migraine treatments are used  
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8 91 inadequately in an elevated percentage of cases [10]. Such investigations highlight the  
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11 92 need to improve health protocols for headache symptoms in an effort to reduce their  
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13 93 personal and economic burden.

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15 94 The availability of real-world evidence that reflects current practice is considered crucial  
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18 95 for resource allocation decisions in public health and the revision of the established  
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20 96 protocols and guidelines [11, 12]. Recent data examining the prevalence and  
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23 97 characteristics of patients with headache and migraine is not available; additionally,  
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25 98 previous statistics regarding the Spanish population were obtained via survey, with an  
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28 99 assumed analytical error entailed. Hence, the interest on obtaining updated epidemiologic  
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30 100 data regarding these conditions.

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32 101 The aim of this study was to revise disease incidence and the profile of the Spanish  
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34 102 population affected by headaches and migraine, contributing with novel data obtained  
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37 103 from a Spanish claims database. A second objective was to evaluate the direct medical  
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40 104 cost that these patients represent for the healthcare system, providing a basis for the  
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42 105 optimisation of resource allocation decisions.  
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## 46 47 107 **METHODS**

### 48 49 108 **Data extraction**

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52 109 Records of inpatient and outpatient admissions due to headache were extracted from a  
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54 110 Spanish Ministry of Health database that compiles data from private and public hospitals,  
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111 covering around 90% of admissions, and primary care centres, covering around 10% of the  
112 Spanish population, from all Spanish regions [13, 14]. The 9<sup>th</sup> and 10<sup>th</sup> revisions of the  
113 International Statistical Classification of Diseases and Related Health Problems, Clinical  
114 Modification (ICD9-CM and ICD10-CM) were used to claim all admissions registered with a  
115 principal diagnosis (admission motive) of headache, classified in accordance with The  
116 International Classification of Headache Disorders, 3rd edition (ICHD-3). Equally, four  
117 codes from The International Classification of Primary Care (ICPC) were used to claim  
118 primary care records, corresponding to migraine alone, TTH, cluster headache and  
119 unspecified headaches. Within the database, any healthcare visit that is registered in the  
120 system is considered an admission. Primary care admissions are inherently outpatient and  
121 specialised care inpatient and outpatient admissions are discernible by the length of stay  
122 parameter. The records extracted corresponded to admissions from the years 2011 to  
123 2016, the last available data.

124 Parameters such as health centres and medical history identifiers were re-coded prior to  
125 extraction to maintain records anonymised, with no access to identifying information, in  
126 accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. In  
127 such cases the Spanish legislation does not require patient consent and ethics committee  
128 approval [15].

129 **Patient and Public Involvement**

130 Patients were not directly involved in the design, planning and conception of this study.

131 **Data analysis**

The complete admission data was used for both primary care and hospitalisation records to evaluate patients' nature of admission and discharge, length of stay, services that treated the patients, and medical procedures utilised. Repeated records corresponding to separated admissions were eliminated for the analysis of patients' characteristics, relying on the first admission as the index event. The direct medical cost was calculated based on the standardised average expenses of admissions and medical procedures determined by the Spanish Ministry of Health, available for the year 2016. Cost is presented in total cost of all registered admissions and average cost per hospitalised patient. These figures include all expenses related to the admission: treatment (examination, medication and surgery), nutrition, costs associated to personnel, medical equipment and resources. Data related to prescription medication was not available.

Data presentation is mainly descriptive. The number of cases per 10,000 persons attended in primary care was calculated from the Ministry of Health database descriptive information [16]. Two-sample Z tests were used to test for differences in sample proportions, with a  $p < 0.05$  considered statistically significant. Statistical analyses were performed using Microsoft Excel® Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP. 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

## RESULTS

### Patient profile

Four unique ICPC codes were used to identify patients with unspecified headache, migraine, specified tension-type headache and cluster headaches in primary care files,



Unspecified migraine	5,027	69.09	31.63 (19.46)
Tension-type headache	4,348	69.66	44.59 (21.90)
Trigeminal autonomic cephalalgias	981	47.30	43.85 (18.25)
Cluster headache	673	40.86	44.03 (17.90)
Hemicrania continua	308	61.36	45.21 (18.70)
Other specified headaches <sup>b</sup>	580	55.69	42.50 (19.65)
Unspecified headaches	8,732	58.63	35.17 (25.52)
<b>Secondary headaches</b>	563	55.95	44.35 (23.06)
Post-traumatic headache	317	45.11	41.89 (24.16)
Drug-induced headache	246	69.92	48.63 (20.97)

<sup>a</sup> With or without mention of status migrainosus. <sup>b</sup> Hypnic, primary cough, exercise and stabbing headache, headache associated with sexual activity.

Patients' age displayed great variability, although the mean age for most patients with classifiable syndromes remained between 30 and 50 years. Mean patients' age in secondary care slightly increased during the study period.

Primary care records allowed an analysis of patients' socioeconomic status. In all cases, around 60% of the patients had an income level below € 18,000, while in around 20% this ranged between € 18,000 and € 99,999. Patients' employment status displayed a more irregular distribution than patients' income, with a clear diminished percentage of pensioners (13.82%). The active population represented 38.38% of total patients, while not active or unemployed patients summed 32.50% of the total.

On the other hand, hospital records included a register of secondary diagnoses, utilised for the evaluation of disease comorbidities, which were evaluated for migraine and other headache types separately. In addition, data corresponding to male and female patients

was analysed independently (Table 2). Overall, hypertension was the most common comorbidity, followed by disorders of lipid metabolism as hypertriglyceridemia and hyperlipidaemia. Significant differences appeared between males and females in the diagnosis of mood disorders (anxiety, depressive disorder and dysthymic disorder) and hypothyroidism, primarily found in female patients. The frequency of essential hypertension, diabetes, dysthymic and depressive disorders and vomiting was consistently and significantly higher in patients with migraine versus those with other headaches.

**Table 2 Secondary diagnoses found in patients with migraine and with other headache disorders (excluding migraine).**

Comorbidities	Females %		Males %	
	Migraine	Other headaches	Migraine	Other headaches
Essential hypertension	19.38 <sup>a d</sup>	11.09 <sup>a</sup>	18.00 <sup>d</sup>	12.48
Disorders of lipid metabolism	14.61 <sup>c</sup>	11.57	15.50 <sup>c</sup>	14.12
Tobacco use disorder	9.17 <sup>b d</sup>	11.73 <sup>b</sup>	13.71	14.30
Anxiety disorder	8.38 <sup>b c</sup>	7.24 <sup>b</sup>	5.41 <sup>d</sup>	3.77
Diabetes mellitus	6.18 <sup>b d</sup>	2.19 <sup>a</sup>	7.00 <sup>d</sup>	3.57
Hypothyroidism	5.86 <sup>b</sup>	5.05 <sup>b</sup>	1.16	1.13
Dysthymic disorder	5.55 <sup>b d</sup>	4.26 <sup>b</sup>	2.53 <sup>d</sup>	1.55
Unspecified asthma	4.26 <sup>b</sup>	4.40 <sup>b</sup>	2.76 <sup>c</sup>	3.24
Depressive disorder	5.03 <sup>b d</sup>	3.67 <sup>b</sup>	2.30 <sup>d</sup>	1.29
Vomiting	2.84 <sup>a d</sup>	0.73 <sup>b</sup>	4.04 <sup>d</sup>	1.11

<sup>a</sup> p value < 0.05, females vs. males; <sup>b</sup> p value < 0.001, females vs. males; <sup>c</sup> p value < 0.05, migraine vs. other headaches; <sup>d</sup> p value < 0.001, migraine vs. other headaches.

The most common comorbidities displayed in Table 2 were analysed in relation with age. Significant differences appeared among age groups. Hypertension was found in 28.34% of

admissions in patients older than 36 years of age, while in those under 36 it was found in 1.51% of admissions ( $p<0.001$ ). The same effect was found for the disorders of lipid metabolism, diabetes, hypothyroidism, dysthymic and depressive disorders, diagnosed in 16.56%, 8.75%, 6.06%, 6.71% and 6.14% of admissions in older patients, respectively, and 0.81%, 0.24%, 1.50%, 1.47% and 0.85% of admissions in younger patients, respectively ( $p<0.001$ ).

### Healthcare management

Total admission data was analysed to obtain information on patients' use of resources and management of the disease in both primary and secondary care. Persistent headache and migraine were controlled mostly in primary care facilities. It was in these centres where the highest number of admissions per patient was registered, an average of 2.8 for all headaches, 3.2 for migraine alone. One admission per patient was registered, on average, in specialised centres.

The number of primary care admissions linked to headache disorders in primary care augmented considerably over time. The year 2011, 89,958 admissions were registered for all headache disorders, 26,459 for migraine alone; in contrast, the year 2016 those were 451,086 and 141,252, while the number of new patients remained stable. In addition, the number of cases per 10,000 individuals attended in primary care was calculated, which included new patients and successive visits (Figure 1). The number of cases per 10,000 patients attended in primary care increased 2 folds between 2011 and 2016 for migraine and 1.85 folds for other headaches ( $p<0.001$ , 2011 vs. 2016).

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215 In primary care, patients admitted with migraine represented 28.0% of the total, while in  
216 secondary care the proportion of patients with migraine was 49.7% (Figure 2A). The  
217 scrutiny of specialised care data alone showed a predominance of migraine with aura,  
218 followed by patients with tension-type headache (Figure 2B).

219 The vast majority of hospital admissions for headache disorders (90%) were due to  
220 emergencies and patients stayed hospitalised an average of 4.4 days. Posterior transfers  
221 to other facilities were not significant, with 98% of the patients discharged to their  
222 residences.

223 The service to treat the most patients was neurology (51.85%), followed by paediatrics  
224 (22.33%) and internal medicine (16.53%). In all cases, procedures related to head and  
225 brain diagnostic imaging were predominant (Table 3).

226 **Table 3 Medical procedures performed in more than 5% of admissions.**

Procedures	% of admissions
Computerized axial tomography of head (CT scan)	41.86
Magnetic resonance imaging (MRI) of the brain	34.11
Injection or infusion of a therapeutic substance	11.26
Spinal tap	11.07
Microscopic examination of blood	10.49
Echoencephalography	9.52
Electrocardiogram	9.40
Electroencephalography	7.40
Routine chest x-ray	6.37
Arteriography of cerebral arteries	5.23

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228 **Direct medical cost**

The economic costs associated with patients' use of healthcare resources were evaluated for the year 2016 (Table 4). This calculation comprises the cost of secondary healthcare associated with a hospitalisation event, and is determined by the mean cost of medical procedures and hospitalisation days. Headache disorders summed a total annual cost of € 10,716,086. Migraine alone represented € 7,302,718 of the total annual cost.

**Table 4 Direct medical costs associated to secondary care for the year 2016.**

Headache disorders	Cost per patient	Total cost
<b>Primary headaches</b>	€ 2,796	€ 10,445,179
Migraine	€ 2,736	€ 7,302,718
Without aura	€ 2,752	€ 880,585
With aura	€ 2,674	€ 3,123,802
Chronic migraine	€ 3,132	€ 219,246
Hemiplegic migraine	€ 2,903	€ 142,247
Menstrual migraine	€ 2,019	€ 8,077
Persistent migraine aura without cerebral infarction	€ 2,554	€ 125,144
Persistent migraine aura with cerebral infarction	€ 3,843	€ 30,744
Other forms of migraine <sup>a</sup>	€ 2,933	€ 225,836
Unspecified	€ 2,757	€ 2,547,038
Tension-type headache	€ 2,803	€ 1,981,425
Trigeminal Autonomic Cephalalgias	€ 3,534	€ 653,752
Cluster headache	€ 3,712	€ 478,789
Hemicrania continua	€ 3,124	€ 174,963
Other specified headaches <sup>b</sup>	€ 2,941	€ 405,820
Unspecified	€ 2,742	€ 101,464
<b>Secondary headaches</b>	€ 2,913	€ 270,907
Post-traumatic headache	€ 2,695	€ 137,452
Drug-induced headache	€ 3,336	€ 133,455

<sup>a</sup> With or without mention of status migrainosus. <sup>b</sup> Hypnic, primary cough, exercise and stabbing headache, headache associated with sexual activity.



females. These findings were in line with previous estimations in the general population [25, 26]. Similarly, essential hypertension, diabetes, dysthymic and depressive disorders and vomiting were primarily diagnosed in patients with migraine versus other headaches. Age was another determinant factor in the diagnosis of comorbidities; older patients were more likely to be diagnosed with hypertension, disorders of lipid metabolism, diabetes, hypothyroidism, dysthymic and depressive disorders, while the diagnosis of tobacco use disorder, anxiety disorder, asthma and vomiting symptoms did not display this correlation.

### **Healthcare management**

Patients seeking medical attention for headache disorders in Spain were mostly handled in primary care centres. The number of patients registered in secondary care facilities was only 21% of the total patients registered in primary care, and referral to specialised care and emergency visits were in half of the cases due to migraine. Migraines with aura were predominant among patients receiving hospital inpatient and outpatient care, although aura has been found in only 30% of all patients with migraine [27].

The prevalence of migraine was estimated to increase from 6.5% in 2003 to 9.7% in 2012 [28]. Herein, primary care data inclusion increased a 70% during the study period, which explains the increase registered in the number of admissions [16]. Nonetheless, the number of cases per 10,000 patients attended in primary care increased significantly over the study period, including new patients and successive visits. Additionally, previous evaluations suggest that neurology consultations, predominant in this study, are mainly related to ineffective treatment or increased frequency of migraine attacks, which could indicate the need to improve treatment protocols [29].

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281 Regarding the management of these disorders at the hospital level, recommendations call  
282 to avoid imaging for uncomplicated headache, while previous analysis revealed a  
283 tendency to perform unnecessary neuroimaging tests in patients that fall into that  
284 category [30, 31]. A study developed in 2014 in the north of Spain investigated the  
285 possible overuse of neuroimaging procedures in patients with chronic migraine in a  
286 headache clinic [32]. The number of tests performed was considered adequate, but CT  
287 scans were registered in 76% of admissions and MRI in 42% [32]. Further research will be  
288 necessary to determine the current application of such recommendations in Spain.

289 **Direct medical cost**

290 Updated real-world evidence plays a pivotal role in resource allocation decisions in public  
291 health [11, 12]. Hence, it appears crucial to measure not only patients' use of healthcare  
292 resources but the direct medical cost associated.  
293 Altogether, headache disorders represent great personal and socioeconomic costs, though  
294 most evaluations have its focus on migraine. Migraine was identified as the sixth leading  
295 cause of disability-adjusted life years (DALYs) worldwide in people between 25 and 39  
296 years in 2015, and those suffering from it are known to have a significantly lower health-  
297 related quality of life, increased work impairment and to require a more intensive  
298 healthcare resource utilization [33, 34]. To quantify the costs of this increased use of  
299 medical resources, previous studies used disease prevalence data as a primary approach.  
300 In this way, the direct cost of migraine in Spain was estimated to sum € 344 million in  
301 2004, including medical admissions and prescription medicine [35]. Posterior evaluations  
302 based on surveys measured costs per patient of € 1,092 to treat episodic migraine in 2012,

€ 920 when excluding medication costs [36], a cost significantly lower to that obtained in this study, where the costs of specialised admissions alone averaged € 2,800 per patient in 2016. This cost is tightly associated with the number and nature of diagnostic tests; however, further research will be necessary to determine its utility and whether its use should be adjusted. In addition, the distinct calculation methods used in both studies cannot be ruled out as the origin of cost fluctuation.

This study found similar costs to treat the distinct headache disorders. Earlier calculations assumed a much lower annual cost of TTH, around € 300 per person in 2011 [37]. In the same revision, the estimated total burden of headaches in Spain was over € 22 billion, including healthcare, medication costs and indirect costs (lost productivity). Herein, secondary care alone summed € 10,716,086. To add to this calculation is the burden linked to work productivity lost, a presumably significant sum, and medication.

A number of limitations may have influenced the results of this study. Direct medical costs were registered leaving out the expenses related to prescription medication, which need to be considered independently. Further research will be necessary to confirm the increasing tendency in medical costs and, as a consequence, the increasing burden derived from headache disorders.

## CONCLUSIONS

Patients receiving specialised care represented around 21% of those treated in primary care, and as much as 28% of primary care consultations were due to migraine. In addition, this study shows the great importance of migraine in secondary care. The increasing



Information) for researchers who meet the criteria for access to confidential data at <https://www.mscbs.gob.es/en/estadEstudios/estadisticas/cmbdAnteriores.htm>.

### Authors' contributions

JD contributed to the investigation by analysing and interpreting the economic situation of headache disorders in Spain and was a major contribution in the intellectual content revision. AM analysed the evolution of headache and migraine over the study period and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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463

464 **FIGURES**

465 **Figure 1. Annual number of cases of headache disorders and migraine alone registered**  
466 **per 10,000 primary care admissions.**

467 **Figure 2. A) Patients with migraine alone and other headaches in primary and secondary**  
468 **care. B) Percentage of patients per headache type in secondary care.** MA Migraine with  
469 aura, MWA Migraine without aura, CM Chronic migraine, TTH Tension-type headache, CH  
470 Cluster Headache.

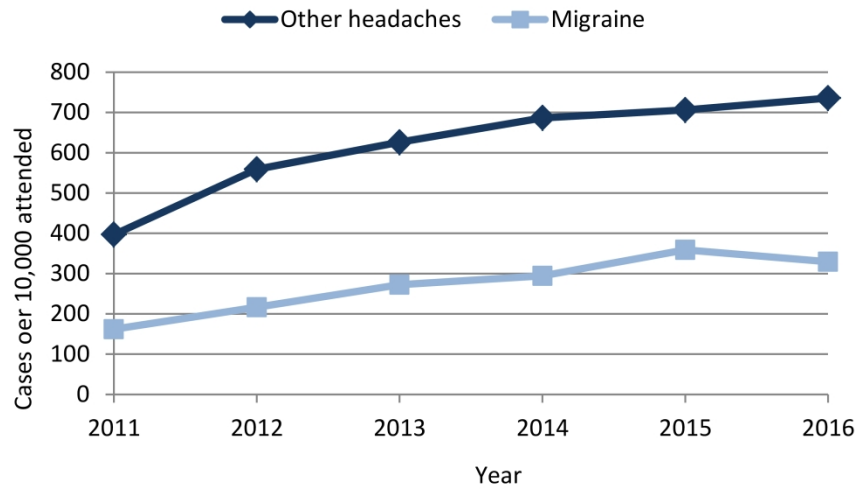


Figure 1 Annual number of cases of headache disorders and migraine alone registered per 10,000 primary care admissions.

296x209mm (300 x 300 DPI)

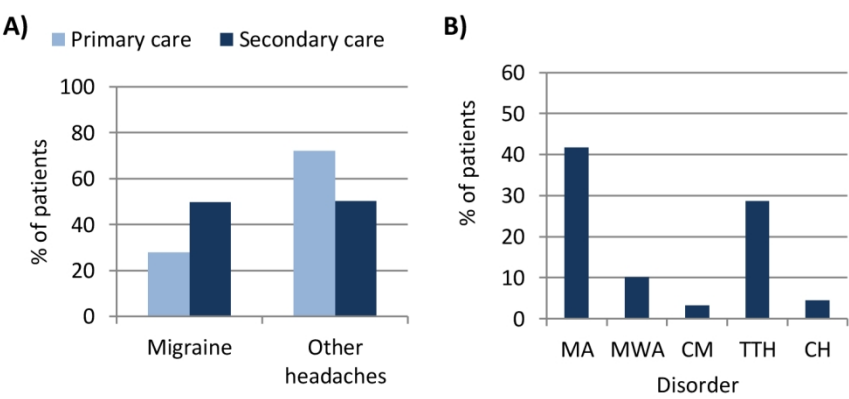


Figure 2 A) Patients with migraine alone and other headaches in primary and secondary care. B) Percentage of patients per headache type in secondary care. MA Migraine with aura, MWA Migraine without aura, CM Chronic migraine, TTH Tension-type headache, CH Cluster Headache.

150x70mm (300 x 300 DPI)

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
<b>Title and abstract</b>					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title and abstract	<p>RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.</p> <p>RECORD 1.2: If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract.</p> <p>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.</p>	Abstract
<b>Introduction</b>					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Lines 93-99		
Objectives	3	State specific objectives, including any prespecified hypotheses	Lines 100-104		
<b>Methods</b>					
Study Design	4	Present key elements of study design early in the paper	Line 108		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Lines 108-111		

Participants	6	<p>(a) <i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants</p> <p>(b) <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case</p>	Not applicable	<p>RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.</p> <p>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.</p> <p>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.</p>	Lines 111-118
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Line 131	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Not applicable
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Lines 131-142.		

Bias	9	Describe any efforts to address potential sources of bias	Not applicable		
Study size	10	Explain how the study size was arrived at	Not applicable		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Line 143-149.		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Line 143-149.		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Lines 123-127.

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Not applicable
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Not applicable
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study ( <i>e.g.</i> , numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Lines 152-157.	RECORD 13.1: Describe in detail the selection of the persons included in the study ( <i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Not applicable
Descriptive data	14	(a) Give characteristics of study participants ( <i>e.g.</i> , demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time ( <i>e.g.</i> , average and total amount)	Not applicable		
Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure	Not applicable		

		category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Not applicable		
<b>Discussion</b>					
Key results	18	Summarise key results with reference to study objectives	Discussion section		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Lines 314-318.	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Not applicable
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	Discussion section		

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion section		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding statement		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Not applicable

\*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langen SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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