PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Analysis of the management and costs of headache disorders in Spain during the period 2011-2016: a retrospective multicentre observational study
AUTHORS	Darbà, Josep; Marsà, Alicia

VERSION 1 – REVIEW

REVIEWER	Deanna Saylor Johns Hopkins University School of Medicine Baltimore, MD USA University of Zambia School of Medicine Lusaka, Zambia
REVIEW RETURNED	11-Nov-2019

GENERAL COMMENTS	Darba and Marsa present a retrospective analysis of healthcare claims data in primary and secondary care centers in Spain from 2011-2016 that show an increasing burden of headache on the Spanish healthcare system both in turns of number of healthcare visits/admissions and costs. This work is important as it continues to provide evidence of the increasing burden of headache and provide a basis for a call to action to improve headache management in diverse settings. However, addressing the following concerns would significantly strengthen the manuscript and its impact: GENERAL COMMENTS: - There are grammatical errors scattered throughout the manuscript. I would recommend careful review by an English editor. ABSTRACT: Please change the objective from "To revise..." to "To investigate" or "To evaluate," etc. INTRODUCTION: Please define what is meant by primary care and secondary care facilities. To me, primary care facilities are outpatient facilities and do not have admissions. However, the authors refer to admissions to primary care facilities in the results. As such, please define for readers outside of Spain how these facilities are classified. METHODS: 1.) Please indicate what percentage of hospitals and primary care centers in Spain are included in the database used (i.e. were all Spanish hospitals and primary care centers included in this study? If not, what types of facilities were omitted?). 2.) The authors state in the Data Analysis section that repeated records corresponding to multiple admissions were eliminated. I think this only refers to the patient demographic information, but it would be good to clarify here whether all admissions were included in healthcare cost and utilization analyses.

	3.) For the admission cost per patient, was this the cost per patient hospitalized (i.e. cost per admission) or per all patients that carried a headache diagnosis during this time period? Please clarify. RESULTS: 1.) The text indicates that some conditions, including anxiety, depression and hypothyroidism, are more common in females but Table 2 reflects that they are more common in males. Please clarify. 2.) Please add p values to Table 2. DISCUSSION: 1.) The authors report no regional differences in headache distribution in the discussion, but these results are in the results section. Please add them to the results section. 2.) What does it mean that "small differences have been observed among patients diagnosed with headache in the Spanish population" in relation to co-morbidities. Was there a difference between the prevalence of these co-morbidities in the headache population and the general population? If these data are available, they should be included in the Results section. If not, it would be helpful to know if there was an age effect of co-morbidities. For example, was hypertension common in young migraineurs or just older people with migraines who might be expected to have hypertension regardless of their migraine status? If the distribution of hypertension, diabetes and dyslipidemia is known by age in the Spanish population during the same time period, this analysis would significantly strengthen the manuscript. 3.) In the healthcare management section, it would be useful to discuss if there were any other time period changes that could explain the increase in admissions during the time period studied. Any changes to the national healthcare system? Any reason to think that more people were captured in the database in 2016 than 2011? etc. etc. 4.) In general, the Discussion would be strengthened if the authors postulated some reasons for their most remarkable findings - that of the significantly increased admission rate and costs - and also possible solutions for each trend.

REVIEWER	Lorenzo Falsetti Azienda Ospedaliero-Universitaria "Ospedali Riuniti" di Ancona, Italy
REVIEW RETURNED	13-Jan-2020

GENERAL COMMENTS	The paper by Darba et al addresses to a commonly analysed problem, the direct medical cost and healthcare management of headache disorders. The concept that headache and migraine increase directly and indirectly costs is not new and has already been extensively discussed in several other papers, some specifically conducted in the EU (i.e.: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1468-1331.2011.03612.x). Authors should discuss what is novel in their research in respect to already published material. One interesting point in the current paper is the number and the type of instrumental evaluations performed in this setting (Table 3): according to current guidelines, several of the reported procedures are useless in the setting of the headache disorders. This concept has already been discussed in several other papers, however authors should discuss about this topic in their work, since this aspect is very important in the management of headache disorders. Moreover, since the diagnosis of headache and migraine is mainly clinical and usually does not require further instrumental examination, authors should

	discuss briefly on the reason of the high rate of unnecessary instrumental examination performed. English form is poor, and I recommend a correction by a native-English speaker. The caption of Table 3 ("Table 3: Percentage of admissions in which each medical procedure was performed") is unclear and needs revising.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Deanna Saylor

Darba and Marsa present a retrospective analysis of healthcare claims data in primary and secondary care centers in Spain from 2011-2016 that show an increasing burden of headache on the Spanish healthcare system both in turns of number of healthcare visits/admissions and costs. This work is important as it continues to provide evidence of the increasing burden of headache and provide a basis for a call to action to improve headache management in diverse settings. However, addressing the following concerns would significantly strengthen the manuscript and its impact:

GENERAL COMMENTS:

- There are grammatical errors scattered throughout the manuscript. I would recommend careful review by an English editor.

English has been revised throughout the manuscript.

ABSTRACT: Please change the objective from "To revise..." to "To investigate" or "To evaluate," etc.

Objective has been modified.

INTRODUCTION: Please define what is meant by primary care and secondary care facilities. To me, primary care facilities are outpatient facilities and do not have admissions. However, the authors refer to admissions to primary care facilities in the results. As such, please define for readers outside of Spain how these facilities are classified.

Primary care facilities are indeed outpatient facilities, thus, the confusion originates from the use of the term "admission". In the Spanish system, we consider admission any healthcare visit that is registered in the system. Primary care admissions are always outpatient, and in specialised care, outpatient admissions are discernible by using the length of stay data. We have defined these terms in the manuscript lines 118-121.

METHODS:

1.) Please indicate what percentage of hospitals and primary care centers in Spain are included in the database used (i.e. were all Spanish hospitals and primary care centers included in this study? If not, what types of facilities were omitted?).

Governmental methodological reports declare the inclusion of around 90% of the admissions registered in Spanish hospitals and specialised centres, excluding psychiatric hospitals, highly specialised hospitals and long-term care institutions. For primary care, the estimated coverage is around the 10%. This is now specified in the manuscript line 110.

2.) The authors state in the Data Analysis section that repeated records corresponding to multiple admissions were eliminated. I think this only refers to the patient demographic information, but it would be good to clarify here whether all admissions were included in healthcare cost and utilization analyses.

Yes that is only for the analysis of patients' profile. This information is now clarified in lines 134-135.

3.) For the admission cost per patient, was this the cost per patient hospitalized (i.e. cost per admission) or per all patients that carried a headache diagnosis during this time period? Please clarify.

The cost per patient is only valid for patients hospitalised during the study period. This information is now clarified in lines 138-139.

RESULTS:

1.) The text indicates that some conditions, including anxiety, depression and hypothyroidism, are more common in females but Table 2 reflects that they are more common in males. Please clarify.

Titles in Table 2 were mistaken and have been amended.

2.) Please add p values to Table 2.

P values have been added to the table and results have been discussed in more detail.

DISCUSSION:

1.) The authors report no regional differences in headache distribution in the discussion, but these results are in the results section. Please add them to the results section.

As stated in the discussion, we did not find differences in the diagnosis of this condition among regions. However, we have noticed that the primary care database cannot ensure the same level of coverage among Spanish regions. For this reason, we believe it is preferable to avoid any conclusions regarding patients' region of origin and preserve the reliability of the data. We have removed this observation from the discussion section.

2.) What does it mean that "small differences have been observed among patients diagnosed with headache in the Spanish population" in relation to co-morbidities. Was there a difference between the prevalence of these co-morbidities in the headache population and the general population? If these data are available, they should be included in the Results section. If not, it would be helpful to know if there was an age effect of co-morbidities. For example, was hypertension common in young migraineurs or just older people with migraines who might be expected to have hypertension regardless of their migraine status? If the distribution of hypertension, diabetes and dyslipidemia is known by age in the Spanish population during the same time period, this analysis would significantly strengthen the manuscript.

This statement referred to the differences observed between diagnostic groups and males and females. There is currently no data that allows comparability with the general population. Thus, comorbidities were analysed in relation with age, dividing the population in two groups based on mean age. The interesting data resulting from this analysis is now in the manuscript lines 192-199.

3.) In the healthcare management section, it would be useful to discuss if there were any other time period changes that could explain the increase in admissions during the time period studied. Any changes to the national healthcare system? Any reason to think that more people were captured in the database in 2016 than 2011? etc. etc.

We have had the change to revise database data inclusion information, noticing that, even though specialised care data inclusion was stable over the years, the primary care dataset increased its total patient number considerably between 2011 and 2016. This led to a major misinterpretation of the data that has been amended, discussion line 269.

To avoid misconceptions, Figure 1 was deleted and instead a new figure was added representing the number of cases per 10,000 persons attended in primary care, eliminating any effect derived from these shifts in data inclusion.

4.) In general, the Discussion would be strengthened if the authors postulated some reasons for their most remarkable findings - that of the significantly increased admission rate and costs - and also possible solutions for each trend.

Discussion has been revised and the most significant findings further discussed and contextualised.

Reviewer: 2

Reviewer Name: Lorenzo Falsetti

The paper by Darba et al addresses to a commonly analysed problem, the direct medical cost and healthcare management of headache disorders. The concept that headache and migraine

increase directly and indirectly costs is not new and has already been extensively discussed in several other papers, some specifically conducted in the EU (i.e.: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1468-1331.2011.03612.x).

Authors should discuss what is novel in their research in respect to already published material.

The direct medical cost associated with headache disorders has been previously measured in Europe and also in Spain. However, there is a growing interest on obtaining updated information regarding the population characteristics, treatment strategies and costs, which are all contemplated in this study. Additionally, the present study analyses a broader population, based on data obtained from a database recorded at the healthcare centre level. This has been emphasised in the manuscript lines 93-99 and discussion.

One interesting point in the current paper is the number and the type of instrumental evaluations performed in this setting (Table 3): according to current guidelines, several of the reported procedures are useless in the setting of the headache disorders. This concept has already been discussed in several other papers, however authors should discuss about this topic in their work, since this aspect is very important in the management of headache disorders. Moreover, since the diagnosis of headache and migraine is mainly clinical and usually does not require further instrumental examination, authors should discuss briefly on the reason of the high rate of unnecessary instrumental examination performed.

This concept has been discussed in the discussion section, lines 276-283.

English form is poor, and I recommend a correction by a native-English speaker.

English has been revised throughout the manuscript.

The caption of Table 3 ("Table 3: Percentage of admissions in which each medical procedure was performed") is unclear and needs revising.

Caption has been changed to "Medical procedures performed in more than 5% of admissions".

VERSION 2 – REVIEW

REVIEWER	Deanna Saylor Johns Hopkins University School of Medicine Baltimore, MD USA
REVIEW RETURNED	21-Jan-2020

GENERAL COMMENTS	The authors have appropriately addressed my prior concerns, and the manuscript has been strengthened as a result.

REVIEWER	Lorenzo Falsetti Internal and Subintensive Medicine Department, Azienda Ospedaliero-Universitaria "Ospedali Riuniti" di Ancona
REVIEW RETURNED	23-Jan-2020

GENERAL COMMENTS	Data presentation, discussion and English form improved in this version. I recommend to further review the English form in this version. The final revision should be performed by a native-English speaker.