PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comorbidities in Patients with Migraine in Japan: A Cross-sectional Study Using Data from National Health and Wellness Survey
AUTHORS	Kikui, Shoji; Chen, Yirong; Ikeda, Ken; Hasebe, Miki; Asao, Keiko; Takeshima, Takao

VERSION 1 – REVIEW

REVIEWER	Serafini, Gianluca Sant'Andrea Hospital, Neurosciences
REVIEW RETURNED	07-Jul-2022

GENERAL COMMENTS	Thank you very much for asking me to review the present paper. This is, in summary, an interesting a cross-sectional online survey aimed to examine the association between migraine and various psychiatric and somatic comorbidities in Japan. The authors found that migraine patients were predominantly female and had significantly higher prevalence than matched non-migraine respondents to have psychiatric and somatic comorbidities. In addition, psychiatric comorbidities with >5% prevalence among migraine patients included depression, posttraumatic stress disorder, and anxiety disorders while gastrointestinal disorders were the most prevalent somatic comorbidity category. Also, other somatic comorbidities included allergies, insomnia, pre-menstrual syndrome, and anemia. Finally, migraine patients with more than 15 monthly headache days (MHDs) tended to have higher point estimates for PS-matched prevalence odds-ratio (POR). The authors may find my minor comments below. First, when throughout the Introduction section, the authors correctly focused on migraine, its relevance worldwide as well as its link with psychiatric/somatic comorbidities, the important association between psychiatric comorbidity and chronic headache/migraine might be further mentioned. In particular, research has systematically documented a strong bidirectional association between migraine and psychiatric disorders. Moreover, the relationship between migraine and post-COVID-19 psychopathology resulting in enhanced psychosocial impairment has often been clinically discussed rather than systematically studied. Thus, given the importance of this emergent researches in the field, i suggest to cite throughout the main text some relevant articles published upon this topic (PMID: 34766216; 20396640; 34149377). Moreover, as the most relevant aims/objectives of the present review paper have been reported extensively, the main hypotheses underlying this study should be reported in a similarly detailed manner.

	Furthermore, inclusion/exclusion criteria need to be comprehensively reported by the authors. Also, whether the study has been approved by the local review board is a matter of debate that should be specified within the main text. In addition, some statements throughout the manuscript such as: "Associations between migraines and psychiatric conditions have been hypothesized for neurotransmitters, such as serotonin, and ovarian hormonal influences, which might lead to serotonergic processing dysfunction and hypothalamic-pituitary-adrenal (HPA) axis dysregulation" are interesting but need to be more extensively developed. Here, the authors should provide more details to this specific regard. Moreover, the most relevant limitations/shortcomings of this study should be more comprehensively reported by the authors as the main caveats have been only partially described within the main text. Finally, what is the take-home message of this manuscript? While the authors reported that patients are more likely to have psychiatric and somatic comorbidities compared with matched non-migraine respondents, they could provide, in my opinion, their conclusive remarks in a more detailed manner for the readers. What are, specifically, the main implications of these findings? How the present results may be generalized? Here, some additional information are needed and might be useful for the general readership.

REVIEWER	Martelletti, Paolo Sapienza University of Rome
REVIEW RETURNED	16-Jul-2022

GENERAL COMMENTS	The authors present results extracted from a large Japanese database the 2017 NHWS where out of 30,001 respodents 378 individuals with migraine were extrapolated and compared with 1,512 non-migraine individuals. The aim of the study was to identify the presence of the most important comorbidity of migraine, the psychiatric comorbidity, on this database. The results confirm existing literature data in this area, although they have not been studied as thoroughly in the country surveyed. Also confirmed is the higher propensity for this comorbidity for patients with chronic migraine (+15 Monthly Migraine Days). I believe that the literature needs to be implemented and therefore suggest the inclusion of the following recent articles that focus on some interesting points in the topic: PMID: 35410119 PMID: 34261435 PMID: 31072313

REVIEWER	Altamura, Claudia Università Campus Bio-Medico di Roma
REVIEW RETURNED	05-Sep-2022

GENERAL COMMENTS	This is a well-conducted and well-described manuscript. Comorbidities are a relevant topic in migraine. I just have a few comments regarding the discussion section. A. Please discuss comorbidities based on commonly shared physiopathology with migraine (see PMID: 33958992). This would give a broader significance of the findings

	B. It would be interesting also to briefly discuss the possible implication of comorbidities on the new CGRP-targeted therapies.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Gianluca Serafini, Sant'Andrea Hospital Comments to the Author:

Thank you very much for asking me to review the present paper.

This is, in summary, an interesting a cross-sectional online survey aimed to examine the association between migraine and various psychiatric and somatic comorbidities in Japan. The authors found that migraine patients were predominantly female and had significantly higher prevalence than matched non-migraine respondents to have psychiatric and somatic comorbidities. In addition, psychiatric comorbidities with >5% prevalence among migraine patients included depression, posttraumatic stress disorder, and anxiety disorders while gastrointestinal disorders were the most prevalent somatic comorbidity category. Also, other somatic comorbidities included allergies, insomnia, pre-menstrual syndrome, and anemia. Finally, migraine patients with more than 15 monthly headache days (MHDs) tended to have higher point estimates for PS-matched prevalence odds-ratio (POR).

The authors may find my minor comments below.

First, when throughout the Introduction section, the authors correctly focused on migraine, its relevance worldwide as well as its link with psychiatric/somatic comorbidities, the important association between psychiatric comorbidity and chronic headache/migraine might be further mentioned. In particular, research has systematically documented a strong bidirectional association between migraine and psychiatric disorders. Moreover, the relationship between migraine and post-COVID-19 psychopathology resulting in enhanced psychosocial impairment has often been clinically discussed rather than systematically studied. Thus, given the importance of this emergent researches in the field, i suggest to cite throughout the main text some relevant articles published upon this topic (PMID: 34766216; 20396640; 34149377).

Response: We thank Dr Gianluca for this comment and for the suggested references. We wish to clarify that this study was based on the population cohort from 2017 before the COVID-19 pandemic, as such any potential discussion on the relationship between migraine and post-COVID-19 psychopathology could not be discussed based on the findings.

Action: We have added the suggested references into the main text and updated the ***Introduction*** accordingly. The revised ***Introduction*** (page 4-5) now reads as:

"Previous reports demonstrated that approximately 90% of chronic migraine patients have at least one comorbidity.[5] A nationwide population-based study in the United States reported an association between migraine comorbidities and the intensity of headache pain and frequency.[6] It is important to take into consideration the comorbidities of migraine from diagnosis through to treatment.[7] The previously reported comorbidities of migraine include various psychiatric[8–11] and somatic conditions such as cardiovascular disorders,[12,13,6] gastrointestinal disorders,[6,14–16] allergy-related disorders,[6,17,18] sleep disorders,[6,19,20] and gynecological disorders.[21] A meta-analysis showed that the most frequently addressed comorbidities among migraine patients in clinical and population studies were depressive disorders, hypertension, and anxiety disorders.[22]

Studies have shown a strong bidirectional association between migraine and psychiatric conditions such as depression, anxiety, suicide risks,[9,10] and may have shared neuropathic mechanisms.[11,23] Similarly, somatic comorbidities such as those of cerebrovascular and metaboloendocrine (e.g., stroke, insulin sensitivity, hypothyroidism, endometriosis) also reportedly have bidirectional association with migraine.[23]"

PMID: 34766216 is now reference #9:

9. Ziplow J. The Psychiatric Comorbidities of Migraine in Children and Adolescents. Curr Pain Headache Rep 2021;25:69. doi:10.1007/s11916-021-00983-y

PMID: 20396640 is now reference #10:

10. Pompili M, Serafini G, Di Cosimo D, et al. Psychiatric comorbidity and suicide risk in patients with chronic migraine. Neuropsychiatr Dis Treat 2010;6:81–91. doi:10.2147/ndt.s8467

PMID: 34149377 is now reference #11:

11. Karsan N, Goadsby PJ. Migraine Is More Than Just Headache: Is the Link to Chronic Fatigue and Mood Disorders Simply Due to Shared Biological Systems? Front Hum Neurosci 2021;15:646692. doi:10.3389/fnhum.2021.646692

Moreover, as the most relevant aims/objectives of the present review paper have been reported extensively, the main hypotheses underlying this study should be reported in a similarly detailed manner.

Response: We thank Dr Gianluca for this comment. We wish to clarify that the objectives of this study were to identify a list of potential psychiatric and somatic comorbidities as well as examine the association of between migraine and these potential comorbidities in Japan through the assessment of the prevalence odds ratio (POR) between migraine and the identified comorbidities reported in the study

Action: The objectives have been further expanded in the ***Introduction*** (Page 5) which reads as:

"Therefore, the objectives of this study were to identify a list of potential psychiatric and somatic comorbidities experienced by migraine patient as well as examine the association between migraine and these psychiatric and somatic comorbidities in Japan by assessing the prevalence odds ratio (POR) between migraine and these comorbidities, with reference to non-migraine individuals. The initial findings from this study on the potential comorbidities of migraine may provide insights to learning the etiology of migraine and help physicians and patients with effective migraine management and treatment."

Furthermore, inclusion/exclusion criteria need to be comprehensively reported by the authors.

Response: We thank Dr Gianluca for this comment.

Action: We have expanded the inclusion/exclusion criteria under the subsection ***Study population*** under ***Methods*** (Page 5-6), which reads as:

"The ICHD-3 like inclusion criteria also defines migraine respondents without aura as having at least five migraines in the past 6 months or self-reported physician diagnosis of migraine, migraine lasting for at least four hours but not more than 72 hours if untreated, experienced at least two migraine pain

symptoms (pain on one side of head; pulsating, throbbing or pounding pain; moderate-to-severe pain; or pain made worse by routine), and experienced at least in one migraine-related symptom (nausea and/or vomiting; light hypersensitivity; or sound hypersensitivity). Migraine with aura was defined as respondents having at least two migraines in the past 6 months or self-reported physician diagnosis of migraine, and experience migraine-related symptom (see spots, flashing lights; or heat waves) before or during the migraine. Respondents having migraine without aura or migraine with aura were also included as migraine patients in this study. Respondents who did not self-report migraine were classified as non-migraine respondents. There were no exclusion criteria."

Also, whether the study has been approved by the local review board is a matter of debate that should be specified within the main text.

Response and action: We thank Dr Gianluca for this comment. We wish to clarify that this database study has been reviewed and was granted exemption by the Public Health Research Foundation, Japan. The details of the local review board have been expanded and included under the ***Ethics approval and consent to participate*** (page 17), which reads as:

"This database study was also granted exemption by the Public Health Research Foundation (https://www.phrf.jp/), Japan."

In addition, some statements throughout the manuscript such as: "Associations between migraines and psychiatric conditions have been hypothesized for neurotransmitters, such as serotonin, and ovarian hormonal influences, which might lead to serotonergic processing dysfunction and hypothalamic-pituitary-adrenal (HPA) axis dysregulation" are interesting but need to be more extensively developed. Here, the authors should provide more details to this specific regard.

Response: We thank Dr Gianluca for this comment.

Action: We have further expanded the discussion on the ***Psychiatric comorbidities*** (page 14-15), which reads as:

"Psychiatric disorders that our study found associated with migraine such as PTSD, anxiety disorders, OCD and depression have been described in previous literature.[8–11] Various neurotransmitter systems and brain regions implicated in psychiatric disorders have been postulated to overlap with that in migraine.[7,11,23] Neurotransmitters such as serotonin and other monoamines, and ovarian hormonal influences, might lead to serotonergic processing dysfunction and hypothalamic-pituitary-adrenal (HPA) axis dysregulation which underlie most psychiatric disorders.[23] For instance, migraine patients exhibit ictal or interictal alterations in neurotransmitters blood levels which share common pathophysiology to depression, stress, and bipolar disorder.[7,23] Genetic factors could also potentially influence the association between migraine and psychiatric disorders. A genome-wide association study with over 1 million individuals found significantly overlapped genetic risks of migraine with psychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD) or depression.[30] Emerging functional neuroimaging hint at that possibility of long-term chronic migraine could alter brain activity and increase disease burden.[7,11] implying a need to understand the shared pathophysiology of psychiatric comorbidities and migraine to facilitate better management of both conditions among patients."

Moreover, the most relevant limitations/shortcomings of this study should be more comprehensively reported by the authors as the main caveats have been only partially described within the main text.

Response: We thank Dr Gianluca for this comment.

Action: We have expanded the limitations of the study in the ***Discussion*** which reads as (page 17),

"Although ICHD-3 like criteria were created for this study using available self-reported data as objective classification criteria and to minimize misclassification, discrepancies between the criteria used in this study and the formal ICHD-3 criteria still exist. As such, the interpretation of the findings in this study would only be valid in comparison with the groups defined within this study. Additionally, NHWS is an online survey and thus respondents without access to internet or internet-related technology (such as those with more severe comorbidities or older respondents) were not included in the study and may not be well-represented in this study. Lastly, patient demographics such as gender and lifestyle could potentially influence the association of migraine with psychiatric and/or somatic comorbidities which was not explored and warrants further investigation."

Finally, what is the take-home message of this manuscript? While the authors reported that patients are more likely to have psychiatric and somatic comorbidities compared with matched non-migraine respondents, they could provide, in my opinion, their conclusive remarks in a more detailed manner for the readers. What are, specifically, the main implications of these findings? How the present results may be generalized? Here, some additional information are needed and might be useful for the general readership.

Response: We thank Dr Gianluca for this comment. We wish to clarify that the take-home message of this manuscript was to provide insights to facilitate effective management and treatment of migraine in clinical practice in Japan. This has been described under ***Clinical Implications*** (page 16-17), which implied the need for consideration of comorbidities when choosing appropriate treatment regimens for managing migraine and the associated comorbidities simultaneously.

Furthermore, this study identified a list of comorbidities that were found to be associated with migraine among respondents with self-reported migraine in Japan, some of which are novel comorbidities, previously not identified in the Japan's Clinical Guidelines for Chronic Headache. These included comorbidities such as obsessive-compulsive disorder (OCD), gastrointestinal comorbidities, sleep comorbidities, and gynecological comorbidities.

Action: We have revised the ***Clinical Implications*** (page 17-18) and the ***Conclusion*** (page 19) to provide a more detailed conclusion. The revised text read as:

Clinical implications: *(Pages 17-18)*

"Although some of the associations are not solidly established with potential pathological explanation, the findings from this study appear to have clinical importance. Various comorbidities are at high prevalence among migraine patients. Migraine patients may experience impairment for daily life and loss of productivity not only because of the migraine but also its comorbidities. In the treatment of migraine, comorbidities may influence therapeutic choices in two ways. First, by taking comorbidities into consideration, medication regimens could be selected to treat for both migraine and comorbidities simultaneously. Second, therapeutic options for migraine may be limited if there are comorbidities as contraindications to migraine medications.[40] Therefore, accounting for comorbidities which could complicate care in clinical practice is warranted when considering appropriate therapeutic options for migraine management.[24,40] Additionally, with the growing migraine prevalence,[2] elucidating the

associated comorbidities may provide insights to the shared physiopathology with migraine which could facilitate effective management and treatment of migraine.[7]"

Conclusion: *(Page 19)*

"Our study found that migraine patients are more likely to have psychiatric and somatic comorbidities compared with matched non-migraine respondents, some of which are novel ones previously unreported (e.g., OCD, gastrointestinal comorbidities, sleep comorbidities, gynecological comorbidities) in Japan. This study showed that migraine patients in Japan face an additional comorbid burden and provided insights to types of comorbidities that patients with migraine may suffer. As such, accounting for comorbidities, which could usually complicate care, when treating migraine would help in good clinical practice and improve outcomes among migraine patients."

VERSION 2 – REVIEW

REVIEWER	Serafini, Gianluca Sant'Andrea Hospital, Neurosciences
REVIEW RETURNED	26-Oct-2022

GENERAL COMMENTS	In the revised manuscript, the authors addressed successfully most of the major questions raised by Reviewers improving both the main structure and quality of the present paper. I have no further additional comments.

REVIEWER	Altamura, Claudia Università Campus Bio-Medico di Roma
REVIEW RETURNED	26-Oct-2022

GENERAL COMMENTS	Thank you for responding to my comments.