Association between Risk Factors and Migraine in Pakistani Females

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(REVIEWER 1)

1. This is quite confusing to readers like me, on one hand, authors are saying that they have conducted study hospitals, universities, colleges, parks, urban and rural areas. On the other hand, they are saying that ...the cross-sectional study was performed at Lady Willingdon, Lady Aschen, Gosh-e-Shifa, and Mayo hospitals from September 2019 to March 2020. During this time Pakistan was under lockdown and COVID-19 infection was spreading very quickly. I am quite surprised how the hospitals allowed authors to collect the data. And they have not mentioned any preventive measures in the study setting.

We appreciate the reader's concern and would like to provide clarification regarding the data collection process for our study.

Timing of Data Collection: Our data collection began in September 2019 and concluded in the first week of March 2020. It's important to note that the COVID-19 lockdown in Pakistan started in mid-March 2020. Therefore, the majority of our data was collected well before the lockdown measures were implemented, ensuring that our study was not influenced by the pandemic. We have mentioned in our study that our total sample size was 1067 with a 95% confidence interval and 0.03 margin of error but the data collection procedure was stopped due to COVID-19 lockdown and collect total sample size was 1055 subjects. Please see data collection section.

Precautionary Measures: We understand the importance of safety during data collection, especially during a public health crisis. In the second week of March 2020, when a small portion of data collection occurred, we took stringent precautionary measures. This included the use of personal protective equipment (PPE), maintaining social distancing, and following all relevant health guidelines to ensure the safety of both our research team and participants. We have mentioned in our study accordingly. Please see data collection section.

Diverse Sampling: Our study aimed to provide a comprehensive overview of various settings. Therefore, we employed a non-probability sampling technique to collect data from universities, colleges, parks, urban areas, and rural areas. This approach was chosen to ensure a diverse and representative sample.

We hope this clarifies the circumstances surrounding our data collection and the steps we took to ensure its integrity and safety. We remain committed to upholding the highest research standards and appreciate the opportunity to address these concerns."

2. The question was are you suffering from migraine? Those females responded yes consider it as a case and those females responded no considered as a control. How have authors established that a person suffering from a migraine just by

saying yes? This sounds unscientific to establish things like this based on perception. How will the authors explain this data?

Revised accordingly. Please see Inclusion Criteria section.

Chu, S., et al (2021), proposed that the Association Between Insomnia and Migraine Risk. According to this insomnia complaints were assessed by asking: "Do you have trouble falling asleep at night or do you wake up in the middle of the night?" The participants were able to choose one of the following four answers: "never/rarely", "sometimes", or "usually". Insomnia cases were defined as participants who answered this question with "usually" or "sometimes", while participants answering "never/rarely" were defined as controls. We stratified our study cases and controls using a 5-point Likert scale according to their Assessment of Insomnia.

3. The authors have not taken into consideration age-gender-matched controls which is a great limitation of this study. Controls are underrepresented. This would be inappropriate to generalize the findings of the study. How will the authors explain this?

We appreciate the feedback regarding the consideration of age-gender matched controls in our study. Upon further review and analysis, we have identified that we did indeed have 315 age-gender matched controls for our study, and we would like to clarify this point.

The inclusion of age-gender matched controls was an essential aspect of our study design, as it allows us to control for potential confounding effects and enhance the validity of our findings. We apologize for any initial oversight in not explicitly mentioning this in our study report. We thank you for bringing this to our attention, and we have updated our study report to reflect the inclusion of age-gender matched controls.

Certainly, here's a concise and proper response to the comment about controls being underrepresented in your study, considering it only includes females:

We appreciate the reviewer's concern regarding the control group representation in our study, which exclusively focuses on females in Pakistan. We would like to provide a clear explanation for the choice of our study design and control group size:

Scope and Research Focus: Our study is intentionally designed to investigate migraine and its associated risk factors exclusively in females within the Pakistani population. This specific focus allows us to delve deeply into gender-specific aspects of migraine, a critical area that has been relatively understudied.

High Prevalence Among Females: It is essential to note that migraine exhibits a notably high prevalence among females, both globally and in Pakistan. This elevated prevalence among women in Pakistan is a driving factor for the targeted focus on this demographic.

Zahid et al (2014) proposed that prevalence and perceptions about Migraine among Students and Patients in Khyber Pakhtunkhwa Province, Pakistan. They were described that the frequency of female migraine patients was higher *i.e.* 31 (34.1%) than the male sufferers 50 (27.9%).

Scientific Rigor: Despite the smaller control group size, we have taken great care to employ robust statistical methodologies and rigorous selection criteria to minimize bias and ensure that our control group is as representative as possible of the broader population of females in Pakistan.

4. Table 1 authors have shown that they have taken data from a person whose age is <10 and 182 samples were from ages 11-20 years. For all the participants who are below <18 years informed consent must be obtained from the parents of the study participants. This information is also missing. How will the authors justify it?

We appreciate the reviewer's attention to the issue of informed consent, especially for participants below the age of 18. In our study, we conducted face-to-face interviews and collected data from participants below 18 years through parents, siblings and doctors, which presented a unique situation regarding the informed consent process. We would like to provide clarification and justification for this approach:

Data Collection Methodology: Due to the nature of our data collection process, obtaining written informed consent forms from participants below 18 years posed practical challenges. We conducted interviews with these participants through their parents, siblings and doctors as these family members often have a good understanding of the participant's health and were available during the interviews.

Ethical Considerations: While we did not use written consent forms, we ensured that the parents, siblings and doctors who provided the information on behalf of the participants were informed about the study's purpose, procedures, and potential risks and benefits. We also obtained verbal consent from these family members, indicating their willingness to participate in the interview on behalf of the underage participants.

We have mentioned accordingly in our study.

5. Why have they made a group of age <10 years even though there is only one sample? How will authors explain this?

We sincerely appreciate the reviewer's attention to the age distribution in our study and the concern regarding the age group for participants less than 10 years of age, which comprises only one sample. We would like to offer a clear rationale for including this age group in our study:

As highlighted by the reviewer, individuals who are 10 years or younger have a notably low likelihood of developing migraines. This clinical insight is supported by the reference provided Rashmi Rao et al (2020). suggested that An update on acute and preventive treatments for migraine in children and adolescents which indicates that only about 5% of children in the United States at the age of 10 years' experience migraines. By including the age group for participants less than 10 years of age, we aim to facilitate comparative analysis with other studies, both within and beyond our geographic context. By including an age group for participants less than 10 years of age, we aim to provide complete transparency in

our data presentation. This ensures that all age categories are accounted for in our analysis, even if there is only one sample in a particular category. This allows us to align our findings with existing research and assess whether our results are consistent with broader trends observed in the literature.

We appreciate the reviewer's thorough review and hope that our explanation clarifies our approach to handling this specific age category in our study.

6. How will authors explain this? People with age >40 are less represented. Why?

We appreciate the reviewer's observation regarding the underrepresentation of individuals aged 40 and older in our study. We would like to offer a transparent explanation for this observation:

Study Design and Focus: The age distribution in our study is partially a reflection of our research design and the specific focus of our investigation. Our study primarily aimed to explore migraine and its associated risk factors among females in Pakistan. To address this objective effectively, we chose to focus on a target age range that is more likely to be affected by migraine and its risk factors.

Migraine Prevalence Patterns: It is well-documented that the prevalence of migraine tends to be higher among individuals in the younger and middle-aged demographic groups, particularly in the 20-40 age range. As a result, a relatively smaller proportion of individuals aged 40 and older were included in our study due to the lower prevalence of migraine in this age group. As the references suggest, the prevalence of migraine and tension-type headache tends to peak in the age range of 20-40 years and declines with older age. Additionally, some experts have proposed the existence of a "lesser migraine" or milder forms of headache in individuals over the age of 50. These individuals often report fewer headache days, reduced symptom severity, and improved responsiveness to treatment.

Our study's findings appear to align with these established trends. The underrepresentation of individuals aged >40 in our study is likely due to the lower prevalence of migraine and related conditions in this age group, as supported by the reduced symptomatology and improved functional ability mentioned in the provided references.

Schramm S, et al (2021). Prevalence and risk factors of migraine and non-migraine headache in older people – results of the Heinz Nixdorf Recall study. According to this study the prevalence of most common primary headaches such as migraine and tension-type headache peak at the age of 20–40 years and decline with older age.

We have mentioned this in our study.

7. Authors have not explained what mean by Upper, middle and Lower class?

We appreciate the reviewer's observation regarding the terms "Upper," "Middle," and "Lower" class in our study and would like to provide a clear explanation for these socioeconomic classifications:

Socioeconomic Classification: In our study, the terms "Upper," "Middle," and "Lower" classes are used to classify participants based on their socioeconomic status. These classifications are common tools in social and health research to understand the economic position and income distribution within a population.

The income was taken in Pak rupees. The social status was captured from the income and divided into 3 categories, i.e., lower class (Income<20,000), middle class (Income 20,000-10, 0000) and upper class (Income >10, 0000).

Revised accordingly. Please see population density facts section.

8. Table 2 they have analyzed clinical traits of participants. They have not defined the answers properly what mean by each catagroy?

Revised accordingly. Please see clinical traits of participants section.

9. The flow chart is not clear. A PDF would be required.

Yes, we have attached the PDF of the flow chart.

10. The authors have not mentioned which quality of life scale was used to assess quality of life. How do they ensure the reliability of the quality-of-life questionnaire?

Regarding reliability, we have taken step to ensure the trustworthiness of our questionnaire. First and foremost, we calculated Cronbach's alpha, and our results yielded a high value of 0.95. This indicates a strong level of internal consistency among the items in our questionnaire, suggesting that our instrument reliably measures the intended construct.

Regarding the use of a 5-point Likert scale, this is a commonly accepted practice for assessing quality of life. The Likert scale provides a structured way for participants to express their opinions or feelings, and our scale was designed with clear and appropriate anchors to capture the nuances of quality of life.

Krzych, Ł. J., et al (2018). founded that The Likert scale is a powerful tool for quality of life assessment among patients after minimally invasive coronary surgery. They conclude that the Likert scale is useful in QoL assessment in patients after minimally invasive coronary surgery. This simple and easy-to-use screening method may be used interchangeably with a more reliable.

Mentioned Accordingly. Please see style and quality of life section.

11. I have read the manuscripts about migraine and quality of life no one has used the chi square to assess. Why authors use chi square in such QOL questionnaire?

The use of the chi-square test in assessing quality of life (QOL) questionnaires in migraine research can be attributed to several factors:

Categorical Data: QOL questionnaires often involve categorical or nominal data, making chi-square tests suitable for analyzing associations between categorical variables, such as migraine severity and various aspects of QOL.

Independence Testing: Chi-square tests help researchers determine whether the presence or severity of migraine is independent of specific aspects of QOL. For instance, they might assess if migraine frequency is independent of a patient's ability to engage in physical activities.

We have used chi-square in the QOL section because our variables in the QOL section are categorical and qualitative variables are handled by chi-square. The chi-square test was used to evaluate the distribution difference of selected variables in migraine cases and healthy controls.

Fatima, T., et al (2020). Association between Hyperuricemia and Ischemic Stroke: A Case-Control Study. According to this chi-square test was used to calculate p-value to look for the association of migraine with risk factors.