PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of ischemic stroke in patients with migraine: A longitudinal follow-up study using a national sample cohort in Korea
AUTHORS	Choi, Hyo Geun; Lee, Sang-Yeon; Lim, Jae-Sung; Oh, Dong Jun; Kong, Il Gyu

VERSION 1 - REVIEW

REVIEWER	Matthias Eikermann Professor of Anaesthesia, Beth Israel Deaconess Medical Center and Harvard Medical School, USA
REVIEW RETURNED	16-Nov-2018

GENERAL COMMENTS	Lee et al are reporting a longitudinal follow-up study on the interesting and meaningful association between a diagnosis of migraine and risk of stroke utilizing a cohort of migraine patients and 1:4-matched controls. While there are strengths particularly resulting from the large cohort based on a complete, national patient sample and the long follow-up period, there are substantial limitations to study design and statistical analysis challenging the conclusions drawn in this study. I am concerned about a substantial lack of confounder control both in the main and subgroup analyses. Additionally, I miss sensitivity and exploratory analyses testing the robustness of the results and further examining the observed associations. Abstract Under the header “strengths and limitations” a summary of findings is provided without addressing strengths and limitations of the study. Introduction Instead of providing a short summary of the methods, hypotheses to be tested would be appreciated at the end of the introduction. Methods Matching variables are limited to age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. These covariates represent an important, but incomplete selection of potentially confounding variables. ICD-codes are available to the authors and there are various comorbidities in addition to hypertension, diabetes and dyslipidemia to be considered such as atrial fibrillation, right-left shunt, or comorbidities represented in the Charlson Comorbidity Index. Additionally, prescription data would be of interest, especially substances such as betablockers or

	antiplatelet drugs. Please refer to current literature, such as one of the papers on a pretty similar topic recently published in BMJ, 2017: doi: 10.1136/bmj.i6635. How do the authors justify utilizing the same confounder model for endpoints ischemic and hemorrhagic stroke? Please provide endpoint-specific models. Please provide descriptive statistics on migraine prevalence and stroke occurrence within subgroups analyzed. Strong association between migraine and ischemic stroke in young patients, specifically women? Would it be possible to examine the role of mediators such as oral contraceptive intake? Would it be possible to obtain more information on the stroke types and location and whether for example dissections were the underlying mechanism? It is important to differentiate between migraine with aura and without aura when drawing conclusions on the migraine- stroke association. Other observational studies have successfully discriminated between migraine with aura and migraine without aura based on ICD codes (BMJ, 2017: doi: 10.1136/bmj.i6635) and I would encourage the authors of this study to do the same. Table 1 The header for the case group is indicated as “psoriasis”. Please change to “migraine”. Figure 1 Please add information on exclusion criteria for controls.

REVIEWER	Teshamae Monteith, MD University of Miami, Miller School of Medicine, USA
REVIEW RETURNED	06-Dec-2018

GENERAL COMMENTS	The strength of the study is the large database and long term follow up. Were the patients with migraine selected if treated > 2 times or diagnosed greater than 2 times according to ICD-10? If treated >2 times, please explain the methodology. If diagnosed, please clarify. Please provide details on how patients with duplicate migraine diagnoses (chronic migraine, migraine without aura, migraine with aura) were assessed from the 45K patients with migraine. That should be reflected in the diagram. Please state why analysis was not done for migraine with aura and migraine without aura separately? This should be mentioned as a limitation. The prevalence of migraine estimated in the study appeared low and therefore may not be fully representative. In Table 1, why is psoriasis mentioned?

VERSION 1 – AUTHOR RESPONSE

First, we appreciate all of your valuable comments and suggestions. All revisions to the manuscript are shown in blue for the reviewers' convenience.

Reviewer: 1

Reviewer Name: Matthias Eikermann

Institution and Country: Professor of Anaesthesia, Beth Israel Deaconess Medical Center and Harvard Medical School, USA

Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below

Lee et al are reporting a longitudinal follow-up study on the interesting and meaningful association between a diagnosis of migraine and risk of stroke utilizing a cohort of migraine patients and 1:4-matched controls. While there are strengths particularly resulting from the large cohort based on a complete, national patient sample and the long follow-up period, there are substantial limitations to study design and statistical analysis challenging the conclusions drawn in this study.

Q1) I am concerned about a substantial lack of confounder control both in the main and subgroup analyses. Additionally, I miss sensitivity and exploratory analyses testing the robustness of the results and further examining the observed associations.

[Response] Thank you for providing us the opportunity to clarify this important issue.

According to the reviewer's suggestion, we selected variables that might affect the association between migraine and stroke using the Charlson Comorbidity Index and subsequently performed the analysis with the added variables. However, the results were approximately equivalent when we employed the new model with the added variables compared to previous model without the added variables. Therefore, we believe that these participants were extracted homogeneously from both groups. Based on the present results, migraine exclusively appears to influence the risk of stroke.

Q2) Abstract: Under the header "strengths and limitations" a summary of findings is provided without addressing strengths and limitations of the study.

[Response] We identified the following submission guidelines for authors.

"An Article Summary, placed after the abstract, consisting of the heading 'Strengths and limitations of this study', and containing up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. They should not include the results of the study."

Thus, we have corrected the three bullet points to state the strengths and limitations of the study, but not the results of the study.

1. The strengths of the present study particularly result from the large cohort based on a complete, national patient sample and the long follow-up period.

2. We designed a cohort study to evaluate the risks of different types of stroke in migraineurs.

3. Migraine should be considered in assessments of the risk of ischemic stroke, particularly in young women.

4. Confounders linking migraine to stroke, such as cigarette smoking, obesity, and prescription information, were not available in the present cohort study based on claim data.

Q3) Introduction: Instead of providing a short summary of the methods, hypotheses to be tested would be appreciated at the end of the introduction.
[Response] We appreciate the reviewer's valuable comment.

According to your suggestion, we rephrased the end of the introduction as follows:

"Given the differences in the natures of hemorrhagic stroke and ischemic stroke in patients, including risk factors and genetic predispositions,[1 2] we hypothesized that the contributions of migraine to an increased risk of stroke differ according to the stroke type. Thus, stroke types should be analyzed separately. Additionally, stroke is a leading cause of mortality; therefore, validation of the association between migraine and stroke may facilitate treatment and prognosis in these cases. Herein, using a national Korean population-based sample cohort, we examined the association between migraine and different types of stroke."

Q4) Methods: Matching variables are limited to age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. These covariates represent an important, but incomplete selection of potentially confounding variables. ICD-codes are available to the authors and there are various comorbidities in addition to hypertension, diabetes and dyslipidemia to be considered such as atrial fibrillation, right-left shunt, or comorbidities represented in the Charlson Comorbidity Index. Additionally, prescription data would be of interest, especially substances such as betablockers or antiplatelet drugs. Please refer to current literature, such as one of the papers on a pretty similar topic recently published in BMJ, 2017: doi: 10.1136/bmj.i6635.
[Response] Thank you for the good suggestion.

1) Based on your comments, we added other diseases as confounders. Among the diseases represented in the Charlson Comorbidity Index, we selected some diseases that might be associated with migraine or stroke.

2) We opted to match the standard past medical histories of several patients to extract these participants homogeneously from both groups. Although the matching was not perfect, we made a greater effort to elicit a favorable comparison. According to the reviewer's comment, the associations between migraine and ischemic and hemorrhagic stroke might be more robust if we matched the further confounding factors indicated by the reviewer, particularly the prescription data, such as beta blockers or antiplatelet drugs. A recent meta-analysis of studies focusing the association between stroke and peripheral artery disease performed a regression analysis and the results suggested an association between a lower incidence of stroke and the prescription of antiplatelet drugs ($R^2 = 0.81$, $P < 0.01$), and statins ($R^2 = 0.85$, $P < 0.01$), but not antihypertensive medications.[3] However, currently, evidence for this association is limited. When we searched the PubMed and EMBASE databases using the keywords "([Migraine medication] AND ([stroke])" and limited the results to human-based studies published in the English language prior to January 2019, evidence of this association was limited. Moreover, we were unable to easily match participants based on prescription data, despite the large size of this population-based cohort study, because strict matching based on these characteristics increased the exclusion rate of the subjects due to the lack of control participants. Additionally, matching the use of medications according to duration was difficult due to heterogeneous medication profiles, such as doses and drug companies.

3) Per your recommendation, we added the current study (recently published in BMJ, 2017: doi: 10.1136/bmj.i6635)[4] proposing an association between migraine and an increased risk of perioperative ischemic stroke within 30 days of surgery.

Q5) How do the authors justify utilizing the same confounder model for endpoints ischemic and hemorrhagic stroke? Please provide endpoint-specific models.

[Response] We apologize for the confusion.

1) We did not design two other studies but analyzed two different endpoints (ischemic and hemorrhagic stroke) using a single database. Although the natures of hemorrhagic stroke and ischemic stroke differ in patients, migraine and stroke are common neurovascular disorders that share underlying physiological processes, thus creating a common model to analyze different endpoints will enable a clear and easily explainable interpretation of their association.

2) Consistent with the model used in the present study, Kurth et al. designed a prospective cohort study to evaluate the risk of any stroke type in migraineurs.[5]

Q6) Please provide descriptive statistics on migraine prevalence and stroke occurrence within subgroups analyzed.

[Response] Thank you for the good suggestion. We added the descriptive statistics on migraine prevalence and stroke occurrence within the subgroups analyzed to the results section (supplementary table s1).

Q7) Strong association between migraine and ischemic stroke in young patients, specifically women? Would it be possible to examine the role of mediators such as oral contraceptive intake?

[Response] In our subgroup analysis, a strong association was observed between migraine and ischemic stroke in young patients, specifically young women. Based on a consensus statement from the European Headache Federation (EHF),[6] the use of combined hormonal contraceptives may further increase the risk of ischemic stroke in patients with migraine, specifically migraine with aura, supporting our results. As the reviewer suggested, the question of whether oral contraceptive intake further increases the risk of ischemic stroke in women taking oral contraceptives is quite interesting. Regrettably, we were unable to extract information on particular mediators, such as oral contraceptive intake, from the Korean claims database. Because oral contraceptive drugs are sold as over-the-

counter drugs in Korea, their use is not reflected in the claim data for evaluating their effects as mediators of the migraine-stroke association. We added this information to the discussion section.

Q8) Would it be possible to obtain more information on the stroke types and location and whether for example dissections were the underlying mechanism?

[Response] In fact, we were able to extract information about the stroke subtypes and locations from the database used in the present study. The impact of migraine on each type of pathophysiology might vary when considering different functional outcomes, survival, and recurrence according to stroke subtype.[7] However, in the present study, a profound distribution of stroke subtypes was not employed. The classification of the stroke type can lead to a significantly decreased incidence of each disease. Because an insufficient number of cases causes inappropriate comparisons due to lower statistical power, the profound distribution of stroke subtypes would hamper our ability to draw a clear conclusion from the available data. In particular, the absolute incidence of hemorrhagic stroke is very low in general practice; therefore, most studies do not provide information about subtypes, such as the presence of an aneurysm, although the association is positive in public health studies.[8]

Q9) It is important to differentiate between migraine with aura and without aura when drawing conclusions on the migraine- stroke association. Other observational studies have successfully discriminated between migraine with aura and migraine without aura based on ICD codes (BMJ, 2017: doi: 10.1136/bmj.i6635) and I would encourage the authors of this study to do the same.

[Response] Thank you for the helpful suggestion.

In response to the reviewer's suggestion, we discriminated between migraine with aura and migraine without aura based on ICD codes, as described in a previous study,[4] to draw profound conclusions regarding the migraine-stroke association. Compared with control subjects, participants who reported migraine with aura and migraine without aura had increased adjusted hazards ratios (HRs) of 1.44 (95% CI = 1.09 to 1.89) and 1.15 (95% CI = 1.06 to 1.24) for ischemic stroke, but not an increased risk of hemorrhagic stroke (as shown in Table 4).

Q10) Table 1:The header for the case group is indicated as "psoriasis". Please change to "migraine".

[Response] Thank you for noting this typographical error.

We changed the header for the case group to “migraine”.

Q11) Figure 1: Please add information on exclusion criteria for controls.

[Response] We appreciate the reviewer’s concern.

The information on exclusion criteria for controls was already included in the materials and methods section. Again, subjects in the control group who died before the index date were excluded. In both the migraine and control groups, participants with histories of hemorrhagic or ischemic stroke before the index date were excluded.

Reviewer: 2

Reviewer Name: Teshamae Monteith, MD

Institution and Country: University of Miami, Miller School of Medicine, USA

Please state any competing interests or state ‘None declared’: None.

Please leave your comments for the authors below

The strength of the study is the large database and long term follow up.

Q1) Were the patients with migraine selected if treated > 2 times or diagnosed greater than 2 times according to ICD-10? If treated >2 times, please explain the methodology. If diagnosed, please clarify.

[Response] Thank you for providing us the opportunity to clarify this important issue.

In Korea, a physician may provide a temporary migraine diagnosis for subjects who are suspected of having migraines, because the physician should conduct appropriate lab tests or radiography to exclude similar diseases with common manifestations. In addition, a single assessment to confirm migraine may not be accurate due to the complex characteristics of headache. In Korea, all patients of the Korean nationality are covered by insurance; therefore, a follow-up evaluation is common practice in Korean clinics. If a subject had received a confirmed migraine diagnosis, he/she would receive routine therapy and a second migraine diagnosis in the next outpatient visit. Therefore, this study only included the patients who had received two or more migraine diagnoses prior to the index date to increase the validity of the migraine diagnoses.

Q2) Please provide details on how patients with duplicate migraine diagnoses (chronic migraine,

migraine without aura, migraine with aura) were assessed from the 45K patients with migraine. That should be reflected in the diagram.

[Response] Thank you for your good comments

In response to the reviewer's suggestion, we discriminated between patients with migraine with aura and migraine without aura based on ICD codes, as described in a previous study,[4] to draw profound conclusions on the migraine-stroke association. Compared with control subjects, participants who reported migraine with aura and migraine without aura had increased adjusted hazards ratios (HRs) of 1.44 (95% CI = 1.09 to 1.89) and 1.15 (95% CI = 1.06 to 1.24) for ischemic stroke, but not an increased risk of hemorrhagic stroke (as shown in Table 4).

Q3) Please state why analysis was not done for migraine with aura and migraine without aura separately? This should be mentioned as a limitation.

[Response] We added separate descriptions of the associations between different stroke types and migraine with and without aura.

Q4) The prevalence of migraine estimated in the study appeared low and therefore may not be fully representative.

[Response] Thank you for providing us an opportunity to clarify this important issue.

In this study, the incidence of migraine was 3.7% (41,585 of 1,125,691 participants) after employing a strict matching protocol. Before matching, the incidence of migraine in Korea was 4.1% (45,587 of 1,125,691 participants). This value is consistent with a previous cohort study in Korea, indicating the overall prevalence rates of migraine was 6.1%,[9] despite the use of different study designs. Given the global prevalence of migraine of approximately 8%–15%,[10 11] the incidence of migraine in Korea is relatively low because of limited data. Only patients with migraine who visited the hospital are recorded. In other words, data are not available for patients with weak migraine symptoms or patients who do not visit a hospital, leading to lower incidence. Based on a population-based epidemiologic study of migraine in Korea, only 24.4% of patients ever consulted doctor for headache and 3.3% of patients were prescribed a drug by a doctor.[12] We added these sentences to the discussion section.

Q5) In Table 1, why is psoriasis mentioned?

[Response] Thank you for noting this typographical error.

We changed the header for the case group to “migraine”.

References

1. Andersen KK, Olsen TS, Dehlendorff C, et al. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. Stroke 2009;40(6):2068-72. doi: 10.1161/STROKEAHA.108.540112
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S1. Subgroup analysis of migraine prevalence and stroke occurrence

Characteristics	Young men (20-39 years old, n = 15,550)			Young women (20-39 years old, n = 47,410)		
	Migraine (n = 3,110, %)	Non-Migraine (n = 12,440)	P-value	Migraine (n = 9,482)	Non-Migraine (n = 37,928)	P-value
Ischemic stroke			0.015*			< 0.001*
Yes	15 (0.48)	28 (0.22)		26 (0.27)	41 (0.11)	
No	3,095 (99.52)	12,412 (99.78)		9,456 (99.73)	37,887 (99.89)	
Hemorrhagic stroke		0.157		0.727		
Yes	14 (0.45)	36 (0.28)		16 (0.17)	58 (0.15)	
No	3,096 (99.55)	12,404 (99.72)		9,466 (99.73)	37,870 (99.85)	
Characteristics	Middle-aged men (40-59 years old, n = 22,090)			Middle-aged women (40-59 years old, n = 68,240)		
	Migraine (n = 4,418)	Non-Migraine (n = 17,672)	P-value	Migraine (n = 9,482)	Non-Migraine (n = 37,928)	P-value
Ischemic stroke			0.560			0.002*

Yes	68 (1.54)	294 (1.66)		138 (1.46)	409 (1.08)	
No	4,350 (98.46)	17,378 (98.34)		13,648 (98.54)	54,952 (98.92)	
Hemorrhagic stroke		0.157		0.727		
Yes	34 (0.77)	127 (0.72)		78 (0.82)	291 (0.77)	
No	4,384 (99.23)	17,545 (99.28)		13,570 (99.18)	54,301 (99.23)	
Characteristics	Old men (≥ 60 years old, n = 14,740)			Old women (≥ 60 years old, n = 39,895)		
	Migraine (n = 2,948)	Non-Migraine (n = 11,792)	P-value	Migraine (n = 7,979)	Non-Migraine (n = 31,916)	P-value
Ischemic stroke			0.015*			0.002*
Yes	205 (7.0)	756 (6.4)		512 (6.4)	1,766 (5.5)	
No	2,743 (93.0)	11,036 (93.6)		7,467 (93.6)	30,150 (94.5)	
Hemorrhagic stroke		0.157		0.465		
Yes	50 (1.7)	155 (1.3)		103 (1.3)	446 (1.4)	
No	2,898 (98.3)	11,637 (98.7)		7,876 (98.7)	31,470 (98.6)	

* Chi-square test; differences were considered significant at P < 0.

VERSION 2 – REVIEW

REVIEWER	Matthias Eikermann Beth Israel Deaconness Medical Center and Harvard Medical School
REVIEW RETURNED	26-Jan-2019

GENERAL COMMENTS	It is unclear how the authors have handled the request of optimized confounder control. The authors should pay more emphasize to this most important point and write a little less defensive response letter where they describe specifically how the results change with the addition of additional confounders. Also, please describe better how you believe you can ensure the migraine was not diagnosed as part of the stroke work-up.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Matthias Eikermann

Institution and Country: Beth Israel Deaconness Medical Center and Harvard Medical School

Please state any competing interests or state 'None declared': none

Q1) It is unclear how the authors have handled the request of optimized confounder control. The authors should pay more emphasize to this most important point and write a little less defensive response letter where they describe specifically how the results change with the addition of additional confounders.

[Response] We are sorry not to have conveyed our meaning to the reviewers clearly.

Again, we appreciated for providing us the opportunity to clarify this important issue. According to the reviewer's suggestion, we have been tried to adjust confounders using the Charlson Comorbidity Index. However, Charlson Comorbidity index was included cerebral vascular disease (independent variable of this study), and diabetes (matched variable of this study).1 We agree your opinion that Charlson Comorbidity index is useful methods. Therefore, we selected some of them as confounders in this study.

Specifically, based on literature review, we performed the analysis with added variables that might affect the association between migraine and stroke, such as congestive heart failure,2 myocardial infarction,3 peripheral vascular disease,4 pulmonary disease,5 liver disease,6 and depression histories.7 8 Thus, the new model was adjusted for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories. Notably, crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke were not changed before and after adding new variables (as presented below). Moreover, given no difference between the Crude and the adjusted hazard ratios, it can be thought that there was no significant difference in other parts of the baseline confounders except for migraine.

Previous model

Crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke

Characteristics	Hemorrhagic stroke				Ischemic stroke			
	Crude	P-value	Adjusted†	P-value	Crude	P-value	Adjusted†	P-value
Migraine		0.369		0.371		<0.001*		<0.001*
Yes	1.06 (0.93-1.21)		1.06 (0.93-1.21)		1.17 (1.09-1.26)		1.18 (1.10-1.26)	
No	1.00		1.00		1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories

New model

Crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke

Characteristics	Hemorrhagic stroke				Ischemic stroke			
	Crude	P-value	Adjusted†	P-value	Crude	P-value	Adjusted†	P-value
Migraine		0.369		0.172		<0.001*		<0.001*
Yes	1.06 (0.93-1.21)		1.10 (0.96-1.25)		1.17 (1.09-1.26)		1.17 (1.08-1.25)	
No	1.00		1.00		1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories

Q2) Also, please describe better how you believe you can ensure the migraine was not diagnosed as part of the stroke work-up.

[Response] We appreciate the reviewer's valuable comment.

1) We considered the order of time (temporal relation) between hemorrhagic or ischemic stroke and development of migraine. In other words, we had information about the onset of both migraine and hemorrhagic or ischemic stroke in all participants. Based on this, among both the migraine and control groups, the participants who had a history of hemorrhagic or ischemic stroke prior to their development of migraine were excluded from this study. This detail of the participant selection process in the present study has been illustrated in Figure 1.

2) If migraine was one of subclinical manifestations of ischemic stroke, the frequency of stroke can be high exclusively after migraine compared to control. Based on Kaplan-Meier graph we illustrated, the cumulative incidence of ischemic stroke is increasing over time during the follow-up period, suggesting the migraine was not diagnosed as part of the stroke evaluation.

References

1. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. American journal of epidemiology 2011;173(6):676-82.

2. Adelborg K, Szepligeti SK, Holland-Bill L, et al. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. BMJ 2018;360:k96. doi: 10.1136/bmj.k96

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8. Vuralli D, Ayata C, Bolay H. Cognitive dysfunction and migraine. J Headache Pain 2018;19(1):109. doi: 10.1186/s10194-018-0933-4

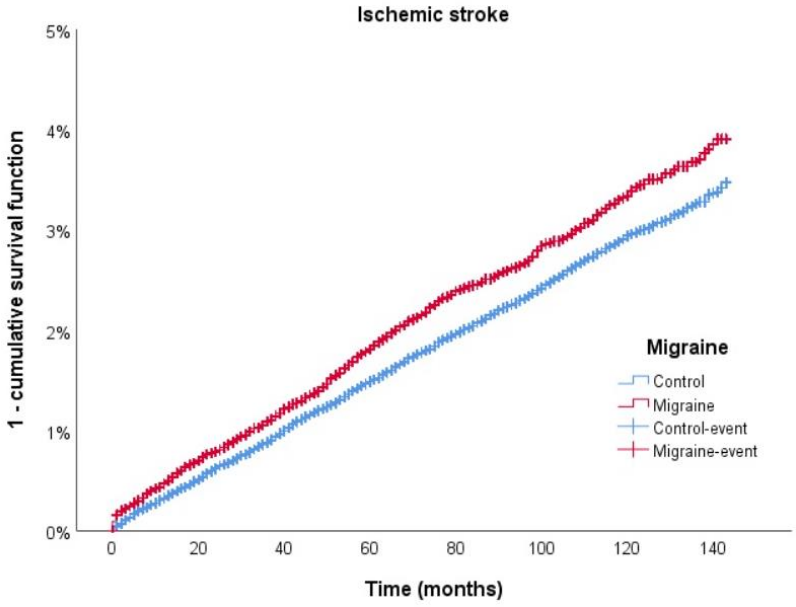
Q2) Also, please describe better how you believe you can ensure the migraine was not diagnosed as part

of the stroke work-up.

[Response] We appreciate the reviewer's valuable comment.

1) We considered the order of time (temporal relation) between hemorrhagic or ischemic stroke and development of migraine. In other words, we had information about the onset of both migraine and hemorrhagic or ischemic stroke in all participants. Based on this, among both the migraine and control groups, the participants who had a history of hemorrhagic or ischemic stroke prior to their development of migraine were excluded from this study. This detail of the participant selection process in the present study has been illustrated in Figure 1.

2) If migraine was one of subclinical manifestations of ischemic stroke, the frequency of stroke can be high exclusively after migraine compared to control. Based on Kaplan-Meier graph we illustrated, the cumulative incidence of ischemic stroke is increasing over time during the follow-up period, suggesting the migraine was not diagnosed as part of the stroke evaluation.



References

1. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *American journal of epidemiology* 2011;173(6):676-82.

2. Adelborg K, Szepligeti SK, Holland-Bill L, et al. Migraine and risk of cardiovascular diseases: Danish

population based matched cohort study. *BMJ* 2018;360:k96. doi: 10.1136/bmj.k96

3. Mahmoud AN, Mentias A, Elgendy AY, et al. Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects. *BMJ Open* 2018;8(3):e020498. doi: 10.1136/bmjopen-2017-020498
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5. Graif Y, Shohat T, Machluf Y, et al. Association between asthma and migraine: A cross-sectional study of over 110 000 adolescents. *The clinical respiratory journal* 2018;12(10):2491-96.
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