PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Migraine and the risk of cardiovascular and cerebrovascular events: A meta-analysis of 15 cohort studies including 1,099,003 subjects
AUTHORS	Mentias, Amgad Elgendy, Islam Elgendy, Akram Qazi, Abdul Barakat, Amr F. Saad, Marwan Mohsen, Ala Abuzaid, Ahmed Mahmoud, Ahmed

VERSION 1 – REVIEW

REVIEWER	Simona Sacco Department of Applied Clinical Sciences and Biotechnology University of L'Aquila Italy
REVIEW RETURNED	22-Nov-2017

GENERAL COMMENTS	Authors performed an updated meta-analysis of cohort studies assessing the association between migraine and vascular events. Authors found that subjects with migraine had a higher risk of stroke and myocardial infarction (MI) compared with non-migraineurs, while migraine with aura was associated with a higher risk of stroke and all-cause mortality. Overall, the study lacks novelty as it is mostly the update of previous work in which several points have already been discussed. Please find below my observations. ● The main flaw of this study is the lack of novelty as several meta-analyses are available on this same topic. Results are confirmatory of what is already known by those meta-analyses. ● Authors addressed the association between migraine with different vascular outcomes, performed specific analyses for gender, migraine type and subtypes of vascular events. Consequently, most of the material (even when relevant) of this study is provided as supplement. I do not think this is good as the main results should be available in the published paper. ● Authors performed a meta-analysis including 1,099,003 subjects, while a previous meta-analysis of cohort studies addressing the risk of stroke in subjects with migraine compared with non-migraineurs (Neurol Sci 2017;38:33-40) included 2,221,888 subjects. I suggest providing reasons for that discrepancy. Besides, I suggest discussing the differences between the previous and the present

	meta-analysis with regard to the risk of stroke in subjects with migraine. ● Authors state in the Introduction that they evaluated the association of migraine with "a wide range of outcomes"; however, they only assessed the association of migraine with cardiac and cerebral events. The present study does not evaluate the association of migraine with other vascular events, including peripheral arterial events and venous thrombosis. That should be pointed out. ● Authors included cohort studies with a migraine arm and a non-migraine one. Among non-migraineurs, a proportion of subjects with non-migraine headache may have been included depending on the study design. The comparison between subjects with migraine and subjects with non-migraine headaches may have affected results and may have increased the clinical heterogeneity of studies. I suggest discussing that point. ● Authors state in the Methods that they preferred the evaluation of all-cause over vascular mortality because all-cause mortality "is considered a preferable outcome in the evaluation of cardiovascular disease". Was all-cause mortality preferred to vascular mortality also because of a stronger statistical effect due to higher numbers? ● At the end of page 5, the abbreviations RR and HR should be explained. Do Authors think that the difference between RR and HR among the included studies may be a source of methodological heterogeneity? If so, I suggest discussing that point. ● Authors state in the Methods (page 6) that they used the I2 statistic to evaluate the degree of heterogeneity. According to the Cochrane Handbook for Systematic Reviews of Interventions, heterogeneity in meta-analyses has three components, namely statistical, clinical, and methodological. The I2 only assesses statistical heterogeneity. Therefore, I suggest using the term "statistical heterogeneity" each time the I2 results are shown. Besides, I suggest adding to the Discussion some considerations about clinical and methodological heterogeneity. ● Authors presented the results of both adjusted and unadjusted analyses. I suggest adding in the Discussion section some considerations about the different (or similar) results of the adjusted and the unadjusted results. ● Authors found that the risk of MI and all-cause mortality, but not that of stroke, increased with increasing length of follow-up. A previous meta-analysis already found that the risk of MI increases with follow-up length in migraineurs compared with non-migraineurs (Eur J Neurol 2015;22:1001-1011), while the risk of stroke appeared stable over time. That difference between the risk of stroke and that of MI is an important point that can be better discussed. ● Authors should also clarify what this study adds considering the available meta-analysis addressing the association between migraine and hemorrhagic stroke. ● An important source of between-study clinical heterogeneity is race/ethnicity. ● I suggest replacing the term "gender" with "sex" throughout the manuscript, as "sex" is related to biological characteristics, while "gender" is related to cultural characteristics. ● I suggest mentioning the results of case-control studies assessing the association between migraine and vascular diseases, in order to point out whether the results of the more robust cohort studies are comparable or different.

REVIEWER	Hemang Panchal

	East Tennessee State University, Johnson City, TN, USA
REVIEW RETURNED	23-Nov-2017

GENERAL COMMENTS	This is a well performed meta-analysis study. My comments are as below. - How was the adjusted and unadjusted analysis performed? Did you have patient level data? What variables were adjusted? - In addition to definition of migraine and aura, I believe the definitions of outcomes also varied between studies which is not unusual for any meta-analysis study. However, it will be worth mentioning the outcomes definitions provided in original studies. How was the stroke diagnosed? How was MI diagnosed?

REVIEWER	Giuseppe Biondi-Zoccai Sapienza University of Rome, Italy
REVIEW RETURNED	24-Nov-2017

GENERAL COMMENTS	The authors report an interesting systematic review on the risk of migraine, pooling adjusted risk estimates from published studies. The authors have registered their protocol, followed appropriate methodological guidelines, searched extensively, abstracted and appraised appropriately the primary studies, and used extensive and validated analytical methods. Accordingly, their results are solid and valid within the realms of the primary data feeded in. I have no major comments. I would only suggest to explore other potential moderators (eg drug therapy) and discuss them in detail (for instance, NSAIDs could be the cause of adverse events, at least in part). Also, it would be interesting to provide stratified analyses by publication or enrolment year, to check whether the effects are more or less pronounced in recent cohorts.

REVIEWER	James Brophy McGill University
REVIEW RETURNED	29-Nov-2017

GENERAL COMMENTS	Title: Migraine and the risk of cardiovascular and cerebrovascular events: A meta-analysis of 15 cohort studies including 1,099,003 subjects Summary: A systematic review and meta-analysis of cohort studies showing an association between migraine headaches and a long-term increased risk of cardiovascular and cerebrovascular events. Main comments: I found this is to be a well-organized, well performed and well written paper. The authors have appropriately followed and used all the conventional quality metrics including PRIMSA, MOOSE and Newcastle-Ottawa checklists. I have been asked to particularly review the statistical aspects of the paper. Hera again I found the work to be of high quality and have only a few queries/comments/suggestions. 1. In the abstract and throughout the paper, the authors refer to mean follow-up. Although I haven't looked at the distribution of the individual 15 studies, I suspect that they should be using the median

	with IQR. 2. The abstract conclusion is succinct as desired but perhaps too much so. I think there should be a mention of the limitations, especially given the heterogeneity that is seen with the abstract results (I2 >60%). 3. Page 7 MACCE the authors report adjusted RR 1.42, 95% CI 1.26-1.60 and 1.39, 95% CI 1.24-1.57, for high quality studies. Given that there are forcibly less studies in the high quality sensitivity analysis how can the 95% CI be narrower? 4. The same issue occurs on page 8 line 15 where the restricted sensitivity analysis gives adjusted HR 1.39, 95% CI 1.21-1.60 compared to the unrestricted adjusted analysis gives HR 1.45, 95% CI 1.26-1.66. 5. Although PHS and WHI reported hemorrhagic and ischemic strokes separately they come from the same study and I think they should appear within the subsection of total strokes. Studies that reported only 1 type of stroke are obviously suspect from a quality viewpoint and this should be stated. 6. Page 8 line 53 "Subgroup analysis according to gender did not illustrate any differences according to gender (Supplemental Figure 3)." I think this is a significant negative finding and that the quantitative result should be reported in the main text. 7. Page 8 line 55 "The heterogeneity of MI risk was improved by meta-regression by follow-up duration, with evidence of higher risk of MI as the duration of follow-up was increased (P=0.02)" I don't think simply reporting p values is helpful in assessing the strength of the evidence, the actual effect size and associated uncertainty should be reported. 8. Page 9 line 41 Discussion "we demonstrated that migraine might be associated…" I think the data says it is associated. Although I do accept and respect the authors' concern about what is its implication, the statement as written is unclear. 9. The authors should mention as a limitation that the power of the funnel plot to detect publication bias is limited in the scenarios where there are few studies.

VERSION 1 – AUTHOR RESPONSE

Comments from the Associate Editor:
We would like to thank the Associate Editor for the constructive feedback.

While I agree with Sacco that we know this already, the authors could really work harder at explaining what this adds to previous reviews (are estimates more refined for example?).
We have provided in the fifth paragraph of the Discussion further explanations on how this meta-analysis is different from prior meta-analyses on this topic "To the best of our knowledge, the current meta-analysis represents the largest and most updated meta-analysis of cohort studies evaluating the association between migraine and cardiovascular and cerebrovascular outcomes. The strengths of this study include: the large sample size, the use of adjusted summary estimates which attempted to minimize the risk of confounding, and the wide variety of analyses which were conducted to assess for the reasons of statistical heterogeneity among the included studies. Unlike other meta-analyses which focused on one outcome such as mortality [10], MI and angina [43], ischemic stroke [57], haemorrhagic stroke [58], or any stroke [59], this meta-analysis evaluated a wide range of cardiovascular and cerebrovascular outcomes. In addition, we included only cohort studies, which are considered of higher evidence as compared to case-control studies. By using the totality of evidence to date, this meta-analysis provided more refined estimates for the outcome of stroke and demonstrated a significant association between migraine and the risk of MI as compared with the

prior meta-analysis by Schürks et al [9]. Although a recent meta-analysis of cohort studies which included 2,221,888 participants demonstrated that migraine was associated with a higher risk of stroke, particularly ischemic stroke, but there was no difference in the risk of haemorrhagic stroke [59], unlike our meta-analysis. The difference in the inclusion criteria could explain these differences. In our meta-analysis, we excluded the study by Gelfand et al [28], since this study enrolled only pediatric subjects (i.e., ~1.6 million subjects)."

I also found the search strategy rather thin and didn't find any reference to a detailed search strategy in the supplementary material.
In the Supplemental Table 1, we have provided the search strategy which was used to search the Pubmed and Cochrane Central Register of Controlled Trials.

They might want to update the search as it's 1 year old and I easily found a few additional studies:

Am J Med. 2017 Jun;130(6):738-743. doi: 10.1016/j.amjmed.2016.12.028. Epub 2017 Jan 19.
Migraine Headache and Long-Term Cardiovascular Outcomes: An Extended Follow-Up of the Women's Ischemia Syndrome Evaluation.
https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_28109970&d=DwIFaQ&c=pZJPUDQ3SB9JplYbifm4nt2lEVG5pWx2KikqINpWlZM&r=8kPQd5DZnZCwBAX86gmu-7p_TyB6ciCVliLliJ-RsE4&m=WNfnTPAnFSWnbpuzoHSHCF43DFIJhRbsXXfEP0M5Uro&s=OSTCO0QzA5_i7o5KXM4lMhlyTABIgCUZYIX-r8oBvvI&e=

Brain. 2017 Oct 1;140(10):2653-2662. doi: 10.1093/brain/awx223.
Migraine and risk of stroke: a national population-based twin study.
https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_28969391&d=DwIFaQ&c=pZJPUDQ3SB9JplYbifm4nt2lEVG5pWx2KikqINpWlZM&r=8kPQd5DZnZCwBAX86gmu-7p_TyB6ciCVliLliJ-RsE4&m=WNfnTPAnFSWnbpuzoHSHCF43DFIJhRbsXXfEP0M5Uro&s=OFZemWXpnosQN1TTfv76bu3QzC0GQYngpnpoSOeiLrw&e=

We would like to thank the Associate Editor for providing these references. We have performed an updated search and found no additional studies which met our inclusion criteria besides these 2 studies. We have updated Figure 1, and the first paragraph of the Results to reflect this "The initial search yielded 2,836 articles (Figure 1), of which 2,758 were excluded upon revision of the titles and abstracts. Among the remaining 78 studies, 43 were excluded due to case control or cross sectional design, 8 studies evaluated subclinical brain changes, 5 studies reported earlier results in overlapping cohorts, [23–27] 3 studies restricted the inclusion to a certain age group either pediatric [28] or elderly subjects (>65, and 50 years respectively). [29,30] One study was excluded since it focused only on cardiac related mortality [31]. Eighteen articles reporting 16 studies were included in the final analysis with a total number of 1,152,407 subjects: 394,942 migraineurs and 757,465 non-migraineurs. [5–8,11,12,21,22,32–41]"

We would like to point out that we had initially included the WISE study in our meta-analysis however at the time of conducting the analysis, only the abstract has been available, we have updated the reference list with the updated reference.

We have included the study by Lantz et al and have updated all the corresponding analyses for stroke.

I would also like to see some clinical insight in the discussion. For instance, migraine is now included in the latest version of the UK's eminent cardiovascular risk prediction tool:

BMJ. 2017 May 23;357:j2099. doi: 10.1136/bmj.j2099.
Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study.
https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_28536104&d=DwIFaQ&c=pZJPUDQ3SB9JplYbifm4nt2lEVG5pWx2KikqINpWlZM&r=8kPQd5DZnZCwBAX86gmu-7p_TyB6ciCVliLliJ-RsE4&m=WNfnTPAnFSWnbpuzoHSHCF43DFIJhRbsXXfEP0M5Uro&s=FiWrFyOcPgAi2sUte0x3zjnCTjExF_rTPN4uzvnnW98&e=

In the fourth paragraph of the Discussion, we have provided some further insight into the clinical implications of the findings of this study "The findings from this meta-analysis demonstrated that migraine, particularly with aura, is a risk factor for future cardiovascular and cerebrovascular events, namely stroke and MI. In the updated United Kingdom QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease, a history of migraine with or without an aura has been recently included as an additional clinical variable. [54] However this updated risk prediction score does not take into account other migraine features such as frequency of attacks, which have been linked to stroke occurrence, but not for other cardiovascular outcomes. [55] The efficacy of adequate migraine control with triptans and the use of antiplatelet agents or statins for primary prevention are all areas of research which might provide insight on the best therapy for prevention of cardiovascular and cerebrovascular events among migraineurs. [56]"

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Simona Sacco
Institution and Country: Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, Italy
Please state any competing interests: None declared

Please leave your comments for the authors below
Authors performed an updated meta-analysis of cohort studies assessing the association between migraine and vascular events. Authors found that subjects with migraine had a higher risk of stroke and myocardial infarction (MI) compared with non-migraineurs, while migraine with aura was associated with a higher risk of stroke and all-cause mortality.
Overall, the study lacks novelty as it is mostly the update of previous work in which several points have already been discussed.

Please find below my observations.
We would like to thank the reviewer for the constructive feedback and for the time which she devoted to review our manuscript.

- The main flaw of this study is the lack of novelty as several meta-analyses are available on this same topic. Results are confirmatory of what is already known by those meta-analyses.

We agree with the reviewer that there has been several previous meta-analyses which have evaluated the risk of cardiovascular and cerebrovascular events, however we included the extended follow up data for several studies such as the WISE study, the Nurses Health Study, and the ARIC studies. In addition, most of these prior meta-analyses focused on one outcome and included case control studies which are less robust in evidence as compared to cohort studies. In this meta-analysis, we have provided the totality of evidence to date on a wide scale of outcomes, and performed multiple subgroup and meta-regression analyses to explore the heterogeneity.

"To the best of our knowledge, the current meta-analysis represents the largest and most updated meta-analysis of cohort studies evaluating the association between migraine and cardiovascular and cerebrovascular outcomes. The strengths of this study include: the large sample size, the use of adjusted summary estimates which attempted to minimize the risk of confounding, and the wide variety of analyses which were conducted to assess for the reasons of statistical heterogeneity among the included studies. Unlike other meta-analyses which focused on one outcome such as mortality [10], MI and angina [43], ischemic stroke [57], haemorrhagic stroke [58], or any stroke [59], this meta-analysis evaluated a wide range of cardiovascular and cerebrovascular outcomes. In addition, we included only cohort studies, which are considered of higher evidence as compared to case-control studies. By using the totality of evidence to date, this meta-analysis provided more refined estimates for the outcome of stroke and demonstrated a significant association between migraine and the risk of MI as compared with the prior meta-analysis by Schürks et al [10]."

- Authors addressed the association between migraine with different vascular outcomes, performed specific analyses for gender, migraine type and subtypes of vascular events. Consequently, most of the material (even when relevant) of this study is provided as supplement. I do not think this is good as the main results should be available in the published paper.
We would like to thank the reviewer for this suggestion, we have provided the figures for gender, migraine type and subtypes of stroke in the manuscript. Given the journal's limit on the numbers of Figures/Tables, we have included the forest plots for the remainder of the outcomes in the Supplemental data. We would be glad to include these figures in the main paper with the Editors' permission.

- Authors performed a meta-analysis including 1,099,003 subjects, while a previous meta-analysis of cohort studies addressing the risk of stroke in subjects with migraine compared with non-migraineurs (Neurol Sci 2017;38:33-40) included 2,221,888 subjects. I suggest providing reasons for that discrepancy. Besides, I suggest discussing the differences between the previous and the present meta-analysis with regard to the risk of stroke in subjects with migraine.
Thank you for pointing this out. The meta-analysis by Hu et al included the study by Gelfand et al (reference 28) which enrolled ~1.6 million. This study enrolled exclusively a pediatric population which was an exclusion criteria in our meta-analysis. In addition, the meta-analysis by Hu had double counted the subjects for the cohorts which had more than one publication from the same cohort such as the Nurse's Health Study and the Physician's Health Study. These differences explain the difference in the number of included subjects between our meta-analysis and the meta-analysis by Hu et al. Also, this could explain why the meta-analysis by Hu et al, unlike our meta-analysis, did not show a significant effect on haemorrhagic stroke. This has been added to our discussion "Although a recent meta-analysis of cohort studies which included 2,221,888 participants demonstrated that migraine was associated with a higher risk of stroke, particularly ischemic stroke, but there was no difference in the risk of haemorrhagic stroke [59], unlike our meta-analysis. The difference in the inclusion criteria could explain these differences. In our meta-analysis, we excluded the study by Gelfand et al [28], since this study enrolled only pediatric subjects (i.e., ~1.6 million subjects)."

- Authors state in the Introduction that they evaluated the association of migraine with "a wide range of outcomes"; however, they only assessed the association of migraine with cardiac and cerebral events. The present study does not evaluate the association of migraine with other vascular events, including peripheral arterial events and venous thrombosis. That should be pointed out.
We have amended the Introduction to "We aimed to conduct a comprehensive meta-analysis evaluating the association of migraine on cardiovascular and cerebrovascular outcomes." We also highlighted in the limitations that we did not assess the association between migraine and peripheral arterial events and venous thrombosis "Ninth, we did not assess the association between migraine and other vascular disorders such as peripheral arterial disease and venous thrombosis, which has been suggested in some studies [47]."

- Authors included cohort studies with a migraine arm and a non-migraine one. Among non-migraineurs, a proportion of subjects with non-migraine headache may have been included depending on the study design. The comparison between subjects with migraine and subjects with non-migraine headaches may have affected results and may have increased the clinical heterogeneity of studies. I suggest discussing that point.

We agree with the reviewer that this might have results in some degree of clinical heterogeneity among the studies, we have acknowledged this in the limitations "Finally, we could not exclude the possibility that some subjects in the control arm might have had non-migraine headache, this comparison might contribute to the increased the clinical heterogeneity between the studies."

- Authors state in the Methods that they preferred the evaluation of all-cause over vascular mortality because all-cause mortality "is considered a preferable outcome in the evaluation of cardiovascular disease". Was all-cause mortality preferred to vascular mortality also because of a stronger statistical effect due to higher numbers?

As we have stated some researchers have suggested that all-cause mortality is a better end point when assessing mortality, rather than cardiovascular mortality. We agree with the reviewer that by evaluating all-cause mortality we had more events and a more likelihood to detect a potential statistical difference, we have amended this statement to "All-cause mortality was evaluated, rather than cardiovascular mortality, as all-cause mortality is considered a preferable outcome in the evaluation of cardiovascular disease; [16] this would additionally increase the number of events and statistical power to detect any potential difference." We hope that the reviewer finds this acceptable.

- At the end of page 5, the abbreviations RR and HR should be explained. Do Authors think that the difference between RR and HR among the included studies may be a source of methodological heterogeneity? If so, I suggest discussing that point.

We apologize for this overlook, we have provided these abbreviations "risk ratio (RR) or hazards ratio (HR)". We agree with the reviewer that including studies which assessed either RR or HR could be a source of methodological heterogeneity, however some prior meta-analyses on this topic have adopted a similar strategy by using HR and RR interchangeably. This has been added to the limitations "In addition, some of the included studies used HRs and others used RR; this approach of using RR and HR interchangeably has been adopted in prior meta-analyses on this topic [43], however, this approach could have resulted in methodological heterogeneity."

- Authors state in the Methods (page 6) that they used the I2 statistic to evaluate the degree of heterogeneity. According to the Cochrane Handbook for Systematic Reviews of Interventions, heterogeneity in meta-analyses has three components, namely statistical, clinical, and methodological. The I2 only assesses statistical heterogeneity. Therefore, I suggest using the term "statistical heterogeneity" each time the I2 results are shown. Besides, I suggest adding to the Discussion some considerations about clinical and methodological heterogeneity.

Thank you for pointing this out, we have used the term "statistical heterogeneity" throughout. We provided some discussion in the limitations regarding the considerations for clinical and methodological heterogeneity "Fourth, although we performed several subgroup and meta-regression analyses to further explore the statistical heterogeneity, some considerations of clinical and methodological heterogeneity are worth mentioning. For example, the studies included several races and ethnicities, with some only including Asians and others done in Europe or the United States. Due to the lack of patient level data, further stratification for race and ethnicity could not be performed. In addition, some of the included studies used HRs and others used RR; this approach of using RR and HR interchangeably has been adopted in prior meta-analyses on this topic [43], however, this approach could have resulted in methodological heterogeneity."

- Authors presented the results of both adjusted and unadjusted analyses. I suggest adding in the Discussion section some considerations about the different (or similar) results of the adjusted and the unadjusted results.

In the first paragraph of the discussion, we provided some discussion for the results of both adjusted and unadjusted analyses "These associations were demonstrated on both the unadjusted analysis as well as the adjusted analysis (this was seen for all of the outcomes assessed except for MACCE). This was performed in an attempt to minimize the effect of confounding, given the observational nature of the included studies".

- Authors found that the risk of MI and all-cause mortality, but not that of stroke, increased with increasing length of follow-up. A previous meta-analysis already found that the risk of MI increases with follow-up length in migraineurs compared with non-migraineurs (Eur J Neurol 2015;22:1001-1011), while the risk of stroke appeared stable over time. That difference between the risk of stroke and that of MI is an important point that can be better discussed.

We would like to thank the reviewer for this suggestion and for providing us with this reference. We have provided some further discussion to elaborate on the difference in the risk of stroke and MI with follow-up time "These findings are also in agreement with prior studies that followed migraineurs for a longer duration and found a significant association of migraine (especially those with aura) with higher risk of MI and cardiovascular mortality [42,43]. The difference in the duration of follow up could explain why this association was not demonstrated for the outcome of stroke. In our study, the mean follow up for MI was 8.8 years, as opposed to 5.8 years for stroke. This effect was also noted in some studies such as the Women's Ischaemia Syndrome Evaluation study, where there was no association between migraine and cardiovascular events, including stroke, at a median of 4.4 years [23], but there was an increased risk of cardiovascular events, driven by a higher risk of stroke, at a median of 6.5 years [6]."

- Authors should also clarify what this study adds considering the available meta-analysis addressing the association between migraine and hemorrhagic stroke.

We have compared our results to the meta-analysis by Hu et al which showed no association between migraine and the risk of haemorrhagic stroke "Although a recent meta-analysis of cohort studies which included 2,221,888 participants demonstrated that migraine was associated with a higher risk of stroke, particularly ischemic stroke, but there was no difference in the risk of haemorrhagic stroke [59], unlike our meta-analysis. The difference in the inclusion criteria could explain these differences. In our meta-analysis, we excluded the study by Gelfand et al [28], since this study enrolled only pediatric subjects (i.e., ~1.6 million subjects)", as well as the meta-analysis by Sacco et al (reference 54).

- An important source of between-study clinical heterogeneity is race/ethnicity.

We agree with the reviewer, and have provided some further discussion on this point in the limitations "Fourth, although we performed several subgroup and meta-regression analyses to further explore the statistical heterogeneity, some considerations of clinical and methodological heterogeneity are worth mentioning. For example, the studies included several races and ethnicities, with some only including Asians and others done in Europe or the United States. Due to the lack of patient level data, further stratification for race and ethnicity could not be performed."

- I suggest replacing the term "gender" with "sex" throughout the manuscript, as "sex" is related to biological characteristics, while "gender" is related to cultural characteristics.

Thank you for this suggestion, we have changed to "sex" throughout.

- I suggest mentioning the results of case-control studies assessing the association between migraine and vascular diseases, in order to point out whether the results of the more robust cohort studies are comparable or different.

Although we agree with the reviewer that comparing the association between migraine and cardiovascular outcomes in case-control studies versus cohort studies would be of interest. However, we designed this meta-analysis to include only cohort studies (which have a higher level of evidence as compared to case-control studies) to add to the robustness of the results. Thus, we have not analysed the outcomes for the case-control studies since this was beyond the scope of our meta-analysis. We hope that the reviewer finds this acceptable.

Reviewer: 2
Reviewer Name: Hemang Panchal
Institution and Country: East Tennessee State University, Johnson City, TN, USA
Please state any competing interests: Interventional Cardiology

Please leave your comments for the authors below
This is a well performed meta-analysis study. My comments are as below.
We would like to thank the reviewer for the constructive feedback and for the time which he devoted to review our manuscript.

- How was the adjusted and unadjusted analysis performed? Did you have patient level data? What variables were adjusted?
For the purpose of the adjusted analyses, we used the adjusted hazards ration or relative risk which was reported for the outcome, while we used the crude or unadjusted events for the purpose of the unadjusted analysis. One example, from the study by Ramparat et al [reference 6], we used the "raw events" in Table 2 for the "unadjusted analysis" while we used the adjusted HR for the adjusted analysis:

The variables which have been adjusted for in each study is already reported in Supplemental Table 3:

Study [Ref.]	Age	HTN	DM	BMI	Smoking	Alcohol	Exercise	Post-menopausal	OCP	HPL	FH of premature CAD	Aspirin
Waters et al [8]												
X			X									
Sternfeld et al [40]												
X	X	X	X				X					
Merikangas et al [38]												
X	X	X										
Hall et al [34]												
X	X	X	X	X			X	X				
Velentgas et al [37]												
X	X	X	X				X	X				
Kurth et al (WHS) [21,22]												
X	X	X	X	X	X	X	X	X	X	X	X	
Kurth et al (PHS) [7,39]												
X	X	X	X	X	X	X		X	X			
Gudmundsson et al [33]												
X	X	X	X	X			X	X				
Kuo et al [35]												
X	X	X	X					X			X	
Wang et al [32]												
X	X	X	X					X				
Åsberg et al [5]												
X	X	X	X	X	X	X		X				

Peng et al [36]
X X X X X
Kurth et al (NHS) [12]
X X X X X X X X X X X X
Androulakis et al [11]
X X X X X X X X
Rambarat et al [6]
X X X X X X X X
Lantz et al [41] X X X X X X

- In addition to definition of migraine and aura, I believe the definitions of outcomes also varied between studies which is not unusual for any meta-analysis study. However, it will be worth mentioning the outcomes definitions provided in original studies. How was the stroke diagnosed? How was MI diagnosed?
We agree with the reviewer that reporting the definition for each of the outcomes is important, we have already reported the definition for MACCE and MI in Supplemental Tables 6 & 8 in the prior submission. In this submission, we also added how each study assessed the outcome of stroke as Supplemental Table 7.

Supplemental Table 6: Major adverse cardiac and cerebrovascular event definitions in included studies

Study [Ref.]	Non-fatal stroke	Non-fatal myocardial infarction	Congestive heart failure	Death due to cardiovascular disease
Kurth et al (WHS) [21,22]	X	X		X
Kurth et al (PHS) [7,39]	X	X	X	
Kurth et al (NHS) [12]	X	X	X	
Rambarat et al [6]	X	X	X	X

WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study

Supplemental Table 7: Assessment of the outcome of stroke among the included studies

Study [Ref.]	Assessment of the outcome of stroke
Merikangas et al [38]	Self-reported physician diagnosis of the condition
Hall et al [34]	Identification with ICD-9 codes
Velentgas et al [37]	Identification with ICD-9 codes
Kurth et al (WHS) [21,22]	Self-reported on follow up questionnaires then confirmed by medical record review by physician
Kurth et al (PHS) [7,39]	Follow up questionnaires then confirmed by medical records review
Gudmundsson et al [33]	Identification with ICD-9 and 10 codes
Kuo et al [35]	Identification with ICD-9 codes
Wang et al [32]	Identification with ICD-9 codes
Åsberg et al [5]	Identification with ICD-10 codes
Peng et al [36]	Hospitalizations claims (accuracy validated prior study to be 94%)

Kurth et al (NHS) [12]
Self-reported on follow up questionnaires then confirmed by medical record review by physician
Androulakis et al [11]
Reviewing reports of CT or MRI brain imaging
Rambarat et al [6]
Follow up phone interviews, and confirmed by reaching the referring physician.
Lantz et al [41] Identification with ICD-9 codes
ICD: International Classification of Disease, WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study

Supplemental Table 8: Myocardial infarction definitions in included studies.
Study [Ref.] Definition of myocardial infarction
Sternfeld et al [40]
Identification with ICD-9 codes
Hall et al [34] Identification with ICD-9 codes
Velentgas et al [37]
Identification with ICD-9 codes
Kurth et al (WHS) [21,22]
Occurrence of typical symptoms by World Health Organization definition, in addition to diagnostic electrocardiographic or cardiac enzymes elevation.
Kurth et al (PHS) [7,39]
Occurrence of typical symptoms by World Health Organization definition, in addition to diagnostic electrocardiographic or cardiac enzymes elevation.
Kurth et al (NHS) [12] Occurrence of typical symptoms by World Health Organization definition, in addition to diagnostic electrocardiographic or cardiac enzymes elevation.
Rambarat et al [6] Asking patients about MI diagnosis, then confirming by contacting the referring physician or obtaining health records
ICD: International Classification of Disease, WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study

Reviewer: 3
Reviewer Name: Giuseppe Biondi-Zoccai
Institution and Country: Sapienza University of Rome, Italy
Please state any competing interests: I have consulted for Abbott Vascular and Bayer

Please leave your comments for the authors below

The authors report an interesting systematic review on the risk of migraine, pooling adjusted risk estimates from published studies. The authors have registered their protocol, followed appropriate methodological guidelines, searched extensively, abstracted and appraised appropriately the primary studies, and used extensive and validated analytical methods. Accordingly, their results are solid and valid within the realms of the primary data feeded in.
I have no major comments.
We would like to thank the reviewer for the constructive feedback and for the time which he devoted to review our manuscript.

I would only suggest to explore other potential moderators (eg drug therapy) and discuss them in detail (for instance, NSAIDs could be the cause of adverse events, at least in part).

Unfortunately the data on drug therapy such as NSAIDs was not reported among the studies, thus we could not explore the effect modification of NSAIDs. We have listed this as a limitation “Sixth, we could not comment on the potential impact of some therapies such as non-steroidal anti-inflammatory drugs as this information was not reported by the studies”

Also, it would be interesting to provide stratified analyses by publication or enrolment year, to check whether the effects are more or less pronounced in recent cohorts.
Thank you for this suggestion. We have performed a meta-regression analysis with the mid enrolment period for all the outcomes, and reported these results.

Reviewer: 4
Reviewer Name: James Brophy
Institution and Country: McGill University
Please state any competing interests: None declared

Please leave your comments for the authors below
Title: Migraine and the risk of cardiovascular and cerebrovascular events: A meta-analysis of 15 cohort studies including 1,099,003 subjects

Summary: A systematic review and meta-analysis of cohort studies showing an association between migraine headaches and a long-term increased risk of cardiovascular and cerebrovascular events.

Main comments: I found this is to be a well-organized, well performed and well written paper. The authors have appropriately followed and used all the conventional quality metrics including PRIMSA, MOOSE and Newcastle-Ottawa checklists.

I have been asked to particularly review the statistical aspects of the paper. Hera again I found the work to be of high quality and have only a few queries/comments/suggestions.
We would like to thank the reviewer for the constructive feedback and for the time which he devoted to review our manuscript.
1. In the abstract and throughout the paper, the authors refer to mean follow-up. Although I haven’t looked at the distribution of the individual 15 studies, I suspect that they should be using the median with IQR.
We would like to point out to the reviewer that we calculated a weighted mean of follow-up across the studies. While each study reported a median follow-up time, we calculated the weighted mean of these medians.

2. The abstract conclusion is succinct as desired but perhaps too much so. I think there should be a mention of the limitations, especially given the heterogeneity that is seen with the abstract results (I2 >60%).
We have added the following statement to the abstract conclusion “This effect was due to an increased risk of stroke and MI. There was a moderate to severe degree of heterogeneity for the outcomes, which was partly explained by the presence of aura.”

3. Page 7 MACCE the authors report adjusted RR 1.42, 95% CI 1.26-1.60 and 1.39, 95% CI 1.24-1.57, for high quality studies. Given that there are forcibly less studies in the high quality sensitivity analysis how can the 95% CI be narrower?
4. The same issue occurs on page 8 line 15 where the restricted sensitivity analysis gives adjusted HR 1.39, 95% CI 1.21-1.60 compared to the unrestricted adjusted analysis gives HR 1.45, 95% CI 1.26-1.66.
By excluding the low quality studies, we believe that this had resulted in a more refined CI since those low quality studies had a higher hazards ratio and wider CI (like stroke in Rambarat et al).

5. Although PHS and WHI reported hemorrhagic and ischemic strokes separately they come from the same study and I think they should appear within the subsection of total strokes. Studies that reported only 1 type of stroke are obviously suspect from a quality viewpoint and this should be stated.
We agree with the reviewer, in the revised Figure 2 we reported data for these 2 studies for total stroke as well as ischemic and haemorrhagic stroke.

6. Page 8 line 53 "Subgroup analysis according to gender did not illustrate any differences according to gender (Supplemental Figure 3)." I think this is a significant negative finding and that the quantitative result should be reported in the main text.
We have included this Figure in the main text.

7. Page 8 line 55 "The heterogeneity of MI risk was improved by meta-regression by follow-up duration, with evidence of higher risk of MI as the duration of follow-up was increased (P=0.02)" I don't think simply reporting p values is helpful in assessing the strength of the evidence, the actual effect size and associated uncertainty should be reported.
We have provided the coefficient and the corresponding confidence interval for the meta-regression analysis for MI and all-cause mortality with follow up.

8. Page 9 line 41 Discussion "we demonstrated that migraine might be associated…" I think the data says it is associated. Although I do accept and respect the authors' concern about what is its implication, the statement as written is unclear.
We have changed this statement to ", we demonstrated that migraine is associated with a higher risk of MACCE".

9. The authors should mention as a limitation that the power of the funnel plot to detect publication bias is limited in the scenarios where there are few studies.
We have added to the limitations the following statement "Seventh, the power of the funnel plot to detect publication bias is limited in the scenarios where there are few studies included in the analysis.

VERSION 2 – REVIEW

REVIEWER	Simona Sacco University of L'Aquila, Italy
REVIEW RETURNED	27-Dec-2017

GENERAL COMMENTS	No further comments.

REVIEWER	James Brophy McGill University Montreal, CANADA
REVIEW RETURNED	27-Dec-2017

GENERAL COMMENTS	my previous comments have been adequately addressed

REVIEWER	Giuseppe Biondi-Zoccai Sapienza University of Rome, Latina, Italy
REVIEW RETURNED	31-Dec-2017

GENERAL COMMENTS	All my comments have been satisfactorily addressed.

REVIEWER	Hemang Panchal East Tennessee State University, Johnson City, TN, USA
REVIEW RETURNED	03-Jan-2018

GENERAL COMMENTS	Revision looks good to me. No more concern.