Author’s response to reviews

Title: Cytochrome P450 Family 4 Subfamily F Member 2 (CYP4F2) rs1558139, rs2108622 polymorphisms and susceptibility to several cardiovascular and cerebrovascular diseases

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Author’s response to reviews:

Technical Comments:

1. Please include, at minimum the names, institutions, countries and email addresses of all authors, and the full postal address of the submitting author in the Title page.

Response: Thanks for your comments. According to your suggestion, we have added the information of all authors in the title page.

2. Please provide Declarations heading in Declarations section.

Response: Thanks for your comments. According to your suggestion, we have added the necessary heading information in Declarations section.

3. Please provide only the initials of the authors in the Acknowledgement sub-section of Declarations section.

Response: Thanks for your comments. According to your suggestion, we have revised that point.

Editor Comments:

The three reviewers have identified a number of issues which should be addressed by the authors in a revised version of the manuscript.

In addition I have the following comments:

1. I agree with Reviewer 1, this meta-analysis should be made as accessible as possible to both basic scientists and cardiologists to attract interest from the widest readership. More details on the terminology used if not already defined/explained would help with this.
Also some more detail on the proposed role of 20-HETE in the modulation of blood pressure, renal function, cerebral blood flow and pulmonary circulation would aid the reader in evaluating the relevance of this report to their interests.

Response: Thanks for your very nice comments. According to your useful suggestion, we have rephrased our “Background” section in our revised manuscript. The information on the SNP definition, SNP/CV association, and the role of 20-HETE were provided in details.

2. Include brief details of the search strategy of the Methods section of Abstract and comprehensive details of the search strategy and the rationale for choosing search details in the Methods section of the manuscript.

Response: Thanks for your very nice comments. According to your useful suggestion, we have added the brief details of search strategy in the “abstract” section. In addition, we have performed a new round of database searching up to Jan 2018, as shown in revised Figure 1. We also have added the details of the search strategy based on four databases in Additional file 9: Table S1.

3. Explain explicitly why search terms for specific forms of heart disease (eg. myocardial infarction, hypertension) were not included in the strategy. If the failure to search on these terms has biased the selection of studies analysed, the meta-analysis should be repeated with their inclusion.

Response: Thanks for your very nice comments. Just as the above statement, we performed a new round of database searching up to Jan 2018, as shown in revised Figure 1 and Table S1. According to your useful suggestion, we spared no effort to retrieve the relative articles using the general terms and the specific forms of heart, cardiovascular and cerebrovascular diseases (e.g., myocardial infarction, coronary artery disease, heart failure or hypertension, etc.). We also have added the relative information in the “discussion” section.

4. Explain explicitly why only the SNPs rs1558139 & rs2108622 were included in this meta-analysis and not other SNPs from the CYP4F2 gene.

Response: Thanks for your very nice comments. Adequate data on the genotype frequencies of both case and control studies are necessary to conduct SNP meta-analyses or subgroup analyses. Thus, only two SNPs (rs1558139, rs2108622) were studied in the present meta-analysis based on the available data. We did not examine the role of other variants within the CYP4F2 gene, such as rs3093100, rs3093105, rs3093166, and rs3093135. The “G/G/G/T” haplotype of rs2108622-rs3093100-rs3093105-rs3093135 has been associated with an increased risk of coronary artery disease, however the “G/G/T/A” haplotype was associated with a reduced risk of coronary heart disease. The potential distinct effect of different haplotypes merits further study. In addition, the combined effect of CYP4F2 and other genes, such as CYP4A11 (Cytochrome P450 Family 4 Subfamily A Member 11), should be analyzed upon the publication of sufficient data. We also have explained this point in the “discussion” section, according to your useful suggestion.

5. Explain the rationale for choosing the reference genotypes in subgroup analyses.
Response: Thanks for your very nice comments. Just as the above statement, we have explained this point in the “discussion” section, according to your useful suggestion.

6. Please comment on the possible mechanism for role of rs1558139 in the reduced risk factor of hypertension in the Asian population in the Discussion. Further please comment on the validity of this finding if the search term "hypertension" was not included in the search strategy.

Response: Thanks for your very nice comments. According to your useful suggestion, we have discussed the possible mechanism for role of rs1558139 in the reduced risk factor of hypertension in the Asian population in the “Discussion” section. Also, we have added the “hypertension” term in the our new database search strategy. Moreover, we also discussed the possible mechanism for role of rs2108622 in susceptibility to coronary heart disease in the “Discussion” section.

7. Please ensure the revised version of the manuscript is edited to correct the numerous instances of typographical errors, grammatical errors and lack of clarity, preferably by a reputable copy-editing service.

Response: We are very sorry for our poor English. The manuscript version 2 has been edited for English language usage, grammar, spelling and punctuation by recommended Standard Editing service (#SQSNMHYBD) of American Journal Experts (http://bit.ly/AJE_BS).

Specific Comments

Page 2, Line 43

insistent -> inconsistent

Page 3 Line 40

non-SNP -> non-SNP gene variant

Page 6 Line 24

In our study, we remove two studies, … -> In our study, we removed two studies, …

Response: Sorry for our mistake. We have corrected it in the revised version.

BMC Cardiovascular Disorders operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.
Response: Thanks for your nice work. We tried our best to revise our manuscript, according to the useful suggestions of reviewers.

Reviewer reports:

Rita Pavasini (Reviewer 1):

This is a complex meta-analysis on the relation of some genetic polymorphism and both cerebrovascular and cardiovascular disease. However, some more details on tables and figures are necessary to better understand the message of the paper. Furthermore, I have some major comments:

- There are several grammatical mistakes.
- There are also some punctuation errors and repetitions of words.

Response: We are very sorry for our poor English. The manuscript version 2 has been edited for English language usage, grammar, spelling and punctuation by recommended Standard Editing service (#SQSNMHYBD) of American Journal Experts (http://bit.ly/AJE_BS).

- The introduction is very rough, mainly where authors explain what are cardiovascular and cerebrovascular disease. I suggest to remove it and to better focus the introduction on the role of polymorphisms on CV diseases. For example, define what is SNP, because this a journal for Cardiologist mainly, so the Reader knows what is cardiovascular diseases, maybe a bit less the genetic behind them.

Response: Thanks for your very nice comments. According to your useful suggestions, we have rephrased our “background” section in our revised manuscript. The information on the SNP definition, SNP/CV association, and the role of 20-HETE were provided in details.

- What does it mean that "we did not obtain the meta-analysis regarding the role of CYP4F2 rs2108622 in other cardiovascular and cerebrovascular diseases"? Was something already published that was not available to the Author or there is no meta-analysis on this issue? Please amend this sentence.

Response: We are very sorry for our improper statement. We have revised this sentence. “Additionally, there is no meta-analysis regarding the role of CYP4F2 rs2108622 in the risk other cardiovascular and cerebrovascular diseases.”

- Why did Author not include other important words in the search strategy more specific for cardiovascular disease? e.g. "myocardial infarction" "heart failure" and other CV disease? Because the concept of cardiovascular disease is too wide. It is necessary to describe what was the main aim of Authors regarding the concept of CV disease, which were those in particular object of the meta-analysis and accordingly to update the search strategy.
Response: Thanks for your very nice comments. According to your very useful suggestion, we performed a new round of database searching up to Jan 2018, as shown in revised Figure 1. We spared no effort to retrieve the relative articles using the general terms and the specific forms of heart, cardiovascular and cerebrovascular diseases (e.g., myocardial infarction, coronary artery disease, heart failure or hypertension, etc.). We also have added the details of the search strategy based on four databases in Additional file 9: Table S1. We also have stated this point in the “discussion” section. Considering the conflicting conclusions, we quantitatively measured the genetic correlation between CYP4F2 SNPs and the risk of cardiovascular and cerebrovascular diseases via meta-analysis based on the publicly published data.

- Which statistical test was used for subgroup analysis?

Response: Thanks for your very nice comments. Subgroup meta-analyses by ethnicity (Caucasian/Asian), disease type (hypertension/ CAD / IS/ CI/ MI), source of control (population/ hospital-based), and gender (male/female), were also conducted through Mantel-Haenszel statistics, based on the Stata/SE software version 12.0. We have added this point in the “Statistical analysis” section.

- What about the quality analysis of the paper?

Response: Thanks for your very nice comments. According to your very useful suggestion, we have added the new data of Newcastle-Ottawa Scale (NOS) system for paper quality assessment. The NOS system data suggested that no included studies showed poor quality, as all NOS scores were larger than five (Table S2).

- How were summarized data?

Response: Thanks for your very nice comments. We have introduced the relative information in our revised “Statistical analysis” section.

- Which was the definition of cardio- or cerebro-vascular disease in each included study? Please add this information in a table.

Response: Thanks for your very nice comments. Considering the conflicting conclusions, we quantitatively measured the genetic correlation between CYP4F2 SNPs and the risk of cardiovascular and cerebrovascular diseases via meta-analysis based on the publicly published data. We spared no effort to retrieve the relative articles using the general terms and the specific forms of heart, cardiovascular and cerebrovascular diseases (e.g., myocardial infarction, coronary artery disease, heart failure or hypertension, etc.). However, limited data of the above relative factors were obtained. Adequate data on the genotype frequencies of both case and control studies are necessary to conduct SNP meta-analyses or subgroup analyses. Based on the reported data, only hypertension, CAD, IS, CI and MI were focused. It is hard for us to list all cardio- or cerebro-vascular diseases in a table. Thus, we have added the relative information of the main analyzed diseases in the revised manuscript. We also discussed this limitation point in the “Discussion” section.
- Please add the number of patients included for each analysis.

Response: Thanks for your very nice comments. According to your very useful suggestion, we have added the data of sample size, number of case/control groups in Table 1, Table2, Table S5, Table S6.

- Please provide a description of the meaning of supplemental online tables. I would probably add a unique supplemental online file with an index and a description of the figures and tables.

Response: Thanks for your very nice comments. According to your very useful suggestion, we have added the information regarding the necessary supplemental data in “Methods” section. In addition, according to the requirement of Journal style, we have added the index and description in the “Additional files” section.

- Please add also data regarding comorbidities, cardiovascular risk factors, mean age of the population of each study included and if possible it should be useful to perform a metaregression on these data.

Response: Thanks for your very nice comments. According to your very useful suggestion, we have added the characteristics of the participants, including age and gender information of case and control groups (shown in Additional file 10: Table S2 Basic information of the eligible studies in the meta-analysis.). We also added the new data of subgroup analysis by gender of the association between the CYP4AF2 rs1558139, rs2108622 polymorphism and the risk of cardiovascular and cerebrovascular diseases (data shown in Table S3, Table S4, Table S5, Table S6, Figure S3 and Figure S8).

Although no high degree of heterogeneity was observed in all meta-analyses of the CYP4AF2 rs1558139 polymorphism, high heterogeneity was observed in most of the overall meta-analyses of CYP4AF2 rs2108622. Apart from coronary heart disease and hypertension subgroup analyses, high heterogeneity still existed in other “Asian”, “ischemic stroke” and “population-based” subgroups. The complexity of disease feature might be the source of the large publication bias. In addition, unpublished data or articles in other languages may bias the selection of the studies analyzed. In addition, given the complicated etiologies in different types of cardiovascular and cerebrovascular diseases, additional relative factors, such as obesity, age, comorbidities, smoking, and drinking should be assessed. We have fully discussed this point in the “Discussion” section.

Sanaz Sedaghat (Reviewer 2): Zhang et al. evaluated the association between two variants in CYP4F2 with cardiovascular disorders.

- If the selected SNPs are common, they are probably present in large GWA studies, did the authors checked the publicly available data for the P-value and effect estimate of the variants?
Response: Thanks for your very nice comment. According to your very useful suggestion, we have added the relative information in the “Background” section.

- It is not clear why authors chose rs1558139 variant among the other variants in the intron region, was it because there were no study on other variants?

Response: Thanks for your very nice comment. In the revised manuscript, we have performed a new round of database searching up to Jan 2018, as shown in revised Figure 1. We also have added the details of the search strategy based on four databases in Table S1. However, adequate data on the genotype frequencies of both case and control studies are necessary to conduct SNP meta-analyses or subgroup analyses. Thus, only two SNPs (rs1558139, rs2108622) were studied in the present meta-analysis based on the available data. We did not examine the role of other variants within the CYP4F2 gene, such as rs3093100, rs3093105, rs3093166, and rs3093135. The “G/G/G/T” haplotype of rs2108622-rs3093100-rs3093105-rs3093135 has been associated with an increased risk of coronary artery disease, however the “G/G/T/A” haplotype was associated with a reduced risk of coronary heart disease. The potential distinct effect of different haplotypes merits further study. In addition, the combined effect of CYP4F2 and other genes, such as CYP4A11 (Cytochrome P450 Family 4 Subfamily A Member 11), should be analyzed upon the publication of sufficient data. We have fully discussed this point in the “Discussion” section.

- It would be informative if authors provide some characteristics of the participants of the included studies like age, gender, ...

Response: Thanks for your very nice comment. According to your very useful suggestion, we have added the characteristics of the participants, including age and gender information of case and control groups (shown in Additional file 10: Table S2 Basic information of the eligible studies in the meta-analysis.). We also added the new data of subgroup analysis by gender of the association between the CYP4AF2 rs1558139, rs2108622 polymorphism and the risk of cardiovascular and cerebrovascular diseases (data shown in Table S3, Table S4, Table S5, Table S6, Figure S3 and Figure S8).

Minor

- It is better to add further information to the methods of the abstract like type of meta-analyses and tests used for heterogeneity and publication bias rather than the software used.

Response: Thanks for your very nice comment. According to your very useful suggestion, we have revised that point in the “Abstract” section.

- Abbreviation PB is not well known, please change to population-based

Response: Thanks for your very nice comment. According to your very useful suggestion, we have revised that point in the entire manuscript.
Page 2 line 53, "we also did not obtain…" do the authors mean there was no meta-analysis on the role of rs2108622 and CVD in the literature? If yes, maybe revise it so it is clear.

Response: Thanks for your very nice comment. According to your very useful suggestion, we have corrected that point. “Additionally, there is no meta-analysis regarding the role of CYP4F2 rs2108622 in the risk other cardiovascular and cerebrovascular diseases.”

- It would be informative to know the total sample size and number of cases in the figure or beginning of the results.

Response: Thanks for your very nice comments. According to your very useful suggestion, we have added the data of sample size, number of case/control groups in Table 1, Table2, Table S5, Table S6. In addition, we have added the new data of Newcastle-Ottawa Scale (NOS) system for paper quality assessment. The NOS system data suggested that no included studies showed poor quality, as all NOS scores were larger than five (Table S2).

Steven Jones (Reviewer 3):

This is a meta analysis of 2 SNPs in the CYP4F2 gene locus vs. cardiovascular outcomes. The analysis follows standard PRISMA methodology for meta analysis. Statistics and methods are clearly described as well as search methodology and results. The findings are discussed adequately and conclusions drawn appropriately given results of analysis.

The paper suffers from numerous difficulties in awkward wording and difficulties with formation of plurals, word choice and phrasing which would benefit from stylistic editing by a native English speaker or similar editor/co-author.

This is an interesting result that may have significant implications in guiding additional mechanistic investigation or quide further epidemiologic investigation of risk predictors in similar Asian populations.

Response: Thanks for your very nice comments. We are very sorry for our poor English. The manuscript version 2 has been edited for English language usage, grammar, spelling and punctuation by recommended Standard Editing service (#SQSNMHYBD) of American Journal Experts (http://bit.ly/AJE_BS). In addition, according the requirement of BMC Cardiovascular Disorders style, we have tried our best to revise it. The expression styles of Table, Figure, Declarations have been revised carefully.

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with
English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.

Response: Thanks for your very nice comments. We are very sorry for our poor English. The manuscript version 2 has been edited for English language usage, grammar, spelling and punctuation by recommended Standard Editing service (#SQSNMHYBD) of American Journal Experts (http://bit.ly/AJE_BS).

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Declarations

- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
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Response: Thanks for your very nice comments. According to the requirement of BMC Cardiovascular Disorders style, we have tried our best to revise it. The expression styles of Table, Figure, Declarations have been revised carefully. Please check it.