

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:

obgyn@greenjournal.org.

Date: 02/06/2023
To: "Caroline Diguisto" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-23-8

RE: Manuscript Number ONG-23-8

Preventability of cardiac and vascular maternal deaths: a nationwide study

Dear Dr. Diguisto:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 02/27/2023, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

Thank you for your submission to the Green Journal. We are willing to consider a revised version of your manuscript if you are able to adequately address the Reviewers' points below. In particular, please address issues regarding how the groups were assigned and how the preventability of a death was decided.

The manuscript contains table cells with small counts ($n < 10$). Please confirm in writing that you have permission to publish this data in this format and that there are no restrictions on its use or instructions to suppress small cell counts to preserve patient anonymity.

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works or need to be cited:

- Please vary the language used in lines 5-21: "The multiple sources... undetermined)."

* Figure 1: Please check the n values under etiologies for n=49 (total 48).

REVIEWER COMMENTS:

Reviewer #1:

The authors present a descriptive cohort study regarding the rates of maternal cardiac and vascular deaths in France. They describe the number of cases that were due to preventable factors based on French confidential inquiry and

determine that the majority of cases involved preventable factors.

Abstract:

- The objective is not completely clear and can be shortened
- Methods: the confidential enquiry needs more description in the abstract. Also please define the term "death preventability factors"
- Results: line 16 needs to be clarified.

Introduction:

- line 10 can be clarified.
- Line 18- please include a hypothesis and a more succinct objective or aim.

Methods:

- line 1 - why did the authors exclude stroke and thrombosis? Are these not vascular diseases?
- Line 20- does the committee lists specific preventable factors?
- Line 24- how was "cardiac" versus "vascular" disease defined? What diagnoses were included? (this is seen in figure 1 but may be noted in the methods as who met inclusion criteria).

Results:

- Did the authors evaluate if the preventable deaths occurred more frequently in certain diagnosis?
- Line 14- how were the seven women without completed information treated. Did they get excluded?
- Line 9- was the preventable factor among the women advised against pregnancy the pregnancy itself?

Discussion:

- Line 9- the authors note a strength of the study was identifying cardiac and vascular disease as separate causes, why was this a particular strength? How is this clinically useful?
- Line 22- the authors correctly identify the limited external validity of the study as this pertains to the local hospital systems and it is difficult to identify if these differ than other systems globally.
- Line 10- among the women who had a preventable death felt to be due to limited coordination of care, did the authors collect data on access to care?
- Page 13 line 3- the studies that could be ordered may be conjecture, as the authors do no present data to know if these studies would have prevented the death.
- Line 19- how do the findings encourage the use of POC ultrasound by ob anesthesia?

Reviewer #2:

This is a retrospective descriptive paper from a national database. All maternal deaths from a cardiac or vascular disease were identified, and then divided into those for whom the condition was known prior to the acute event and those for whom the condition was not known. The maternal deaths with preventable factors (based on expert analysis) outnumbered maternal deaths that were deemed unpreventable.

Major Revisions:

Fascinating database, and thus the descriptive statistics approach when used in isolation may prove unsatisfying for a largely clinical audience. Could consider an analysis of the data, or could include case reviews. This reviewer remains unconvinced that known versus unknown is the only important stratification, or that this distinction is a categorical variable (suspect that many patients are both known to some providers and not all, or that some extent of their disease is known but not the full extent).

Line Notes:

Intro

8. The cited study does not seem to be related to this statement; or if it is, please elaborate.
9. While usually true, there is some congenital cardiovascular disease that goes unrecognized into adulthood.
14. The distinction between known and unknown conditions is a thoughtful distinction but more evidence is needed to convince that this is a main driver for mortality (and in turn, opportunities for prevention). For example, this reviewer proposes that a major driver in the US may be the timing of the acute event. For example, even an unknown condition that is exacerbated in prenatal care or labor may be more likely to be diagnosed than an acute event that happens at 6 months postpartum when the patient is not under routine care (here in the US also driven by insurance). Consider whether commenting on timing of event is appropriate to your national context. Please comment on other possible variables that could be drivers of mortality and opportunities for prevention.

Info collected

3. How were these characteristics selected? Please elaborate on the socioeconomic determinants of health in your country if they are pertinent to the characteristics selected.

Results

15. Postulate on the 10 women whose information was not available to study. How could it be that this information was

not available? Are these women lost to follow up different than the women in this analysis?

Table 1

- Interesting that women with known vascular disease who died were all P0.
- Please comment on the overrepresentation of Cesarean section in all deaths. Does this C-section rate match your national expected C-section rate?

Table 2

- Postpartum would be more relevant if it was subcategorized into immediate postpartum and late postpartum.

Reviewer #3:

The authors have undertaken a retrospective cohort analysis of the characteristics and preventability of maternal death due to cardiac and vascular causes using a national database approach capturing pregnant people in France between 2007-2015.

General comments:

- 1) It is my understanding that Obstetrics and Gynecology is moving toward more gender neutral language since individuals who can become pregnant do not all identify as women. If the authors have an indication from their data that all included individuals identified as women, that could be stated as well.
- 2) The preventability aspect of this paper can be a unique contribution to the field. However, I think more information on the way that preventability was determined, and in particular, the way the committee deliberated and/or chose opportunities for improvement that could prevent death is needed from the methods standpoint, and more details on exactly the delays or missed diagnoses (e.g. delayed imaging, delayed labs, dismissed symptoms, late transfer of care) that could have improved care will provide the important lessons learned that can be applied across contexts.

Abstract:

- 1) It may help to briefly describe what the "national enquiry" is for readers who are not familiar. It could be construed as either a national database of deaths curated by a central body vs a nation-wide records request of French hospitals prompted by the authors. I would encourage the authors to briefly give the name of the curated registry (as mentioned in Methods).
- 2) It may also be prudent to include in the abstract how the cardiac and vascular cases were initially ascertained for review within the ENCMM database. Did the ENCMM keep this information on each case in a searchable database? Or were the cases to be reviewed identified via discharge or hospital codes? Or via some other review process?
- 3) Was a standardized form or definition used to identify suboptimal care or preventability factors? Given space constraints in the abstract, if a standardized form or definition was used, adding the phrase "using a standard definition" or "using a standard evaluation form" would be sufficient.
- 4) The use of the National Perinatal Survey is not mentioned.

Introduction:

- 1) I appreciate the brevity of the introduction, but I think a bit more detail regarding the separation of cardiac and vascular disease is warranted. It would be helpful to provide examples of cardiac vs vascular diagnoses. On line 10 in particular, "coronaropathy" is not a commonly used word to describe coronary artery disease; it may be more clear to simply state coronary artery disease or coronary artery diseases (and is this the extent of what the authors consider vascular diseases? Or do aortopathies, aneurysms, dissections, and other vascular abnormalities count?). Is coronaropathy a cardiac or a vascular condition?
- 2) A better understanding of the authors' descriptions of cardiac vs vascular disease may also help to better motivate the study. Why is it important to differentiate between these two diagnoses?
- 3) Line 9: Not all pregnant people with congenital cardiac disease are identified prior to pregnancy (e.g., bicuspid aortic valve is not always diagnosed in childhood, and subsequent enlarged root may have pregnancy consequences)
- 4) Line 12: Case series typically do not make the distinction between known and previously un-identified disease? Or do not make the distinction between congenital cardiac disease and acquired coronary artery disease? Perhaps a sentence that combines the ideas in the two sentences on Line 12 and 13 may help to increase clarity of meaning
- 5) Line 16: The authors state that "vascular diseases [causing death] have rarely been described." Could the authors provide examples of the vascular diseases they mean?
- 6) Lines 18-21: Objective is clearly stated, but a little detail in the preceding paragraphs will help to motivate the paper/objective and make it more obvious/urgent why such an analysis is needed.

Methods:

- 1) Why were the years 2007-2015 chosen? If data were collected from 1996 to presumably the current time, it would be important to know why these years were chosen by the authors.
- 2) Page 5, Lines 24-25: Were pregnant people with "known cardiovascular disease" those who were known to have disease prior to pregnancy, or prior to the acute event, or both?
- 3) Page 6, Lines 19-22: was a standardized tool used by the committee when they deliberated about contributing factors to possibly or probably preventable deaths?
- 4) Page 6, Line 22: "Non-compliance" with treatment has connotations of blame on the patient rather than acknowledging the structural or system-level features that often drive "poor compliance." I think the category description

is understandable without the parenthetical statement "(non-compliance with treatment)." and I would recommend just removing the parenthetical.

5) Page 7, Line 8-13: I admit I am a bit confused about the inclusion of the 2010 National Perinatal Survey. Could this section be clarified somewhat? Were only the women with available data on timing of diagnoses (the people in the 4 groups described by the authors) compared to the National Perinatal Survey, or were all people with cardiovascular deaths compared to this NPS? What statistical techniques were used to compare the two groups? It also seems odd to have the first mention of this dataset in the Analysis section. Consider moving the description of the NPS data to the beginning of the methods? Perhaps at the end of "population"?

6) Same comment as Abstract - was a standardized review tool for identifying preventability factors used by the committee? Please describe (or consider including as an Appendix?)

Results & Tables:

1) Figure 1 is very helpful for delineating what constitutes cardiac vs vascular disease. The terms cardiopathy and coronaropathy feel a bit odd to this reviewer but may be more commonly used outside the US? It would also be helpful to delineate how individuals with a congenital cardiac anomaly that leads to vascular issues might fit (for instance, how would a person with a bicuspid aortic valve and aortic dissection or aortic rupture be classified?).

2) Table 1 - there are two single asterisks, one after the "Others" subcategory of maternal country/region of birth, and one after fetal death/stillbirth. The foot note matches fetal death/stillbirth, I believe, but the asterisk after Others should be addressed

3) Table 1 - numbers for dyslipidemia and smoking do not appear to align with the category labels (they are shifted up one row)

4) Page 8, Line 23-24. How were the cardiovascular risk factors contained in the National Perinatal Survey obtained? Patient report, chart abstraction, etc? Please add to methods. Improved ascertainment of risk factors would be expected during the mortality review process compared to common methods used by nationally representative population databases (such as discharge codes), which could partially explain the higher rate of risk factors among those who died from cardiovascular disorders.

5) The results seem to be reported somewhat out of order compared to the Tables, particularly for the Vascular maternal deaths section, which references Table 3 before any others. I can see the appeal of going through Cardiac and then Vascular deaths separately, while also having a side-by-side comparison available in the Tables. Perhaps some additional structure to the Results would help - such as subheadings under cardiac deaths and vascular deaths that correspond with the data in each table: Maternal Demographic and Clinical Characteristics; Characteristics of cardiac events; and Preventability of Events. Some additional guideposts will help the results feel more ordered and guide readers through the tables.

6) Table 2 - the onset of symptoms postpartum subcategories (<7 days, etc) are oddly separated from the post-partum category, making it initially difficult to interpret.

7) All tables - I think the relationships between n and % across categories, rows, and tables, would be easier to interpret if either the % or the n were presented in parentheses within the same column - such as 61 (37%) or 37% (61) so that they eye can search across fewer columns of numbers. In addition, the proportions should probably have the % sign next to them so that they are not confused with N. It would just make the tables much easier to read, particularly when each table contains so much data.

8) All tables - some categories have MD for missing data while others do not. Is it true that no individuals were missing data for pregnancy disorders such as hypertensive disorder of pregnancy or gestational diabetes or cardiovascular risk factors such as smoking before pregnancy?

9) Page 8, Lines 17-20. If I understand the Tables correctly, the data provided in these lines also appears in Table 2? It may help to have an overall column on Table 2 similar to that on Table 3 to assist with interpretability, at least for timing of death and gestational age/stillbirths.

10) Page 9, Lines 18-19. Is the citation #16 a guideline document for when IVF could be considered in people with Turners or other aortic root dilation? If so, is the citation better located after the sentence that ends "... contraindicate IVF at the time it was performed"? In addition, Table 3 does not seem to provide any data about the frequency of aortic size monitoring throughout pregnancy for these individuals. Why is Table 3 cited here?

11) Pregnancy-related hypertensive disorders appear to be significantly more frequent among people with cardiac maternal deaths compared to general population, but this is not noted in results prose anywhere. Seems as though it would be interesting to mention, given its relationship with cardiomyopathy.

12) Table 3 - why are subcategories of Content of Care opportunities to prevent death listed (e.g., delayed work up of presenting symptom) but not for organization of care (e.g. delay transfer to ICU) or Patient-care system interaction? Is "women advised not to be pregnant" a subcategory of Patient-care system interaction?

13) Page 10, Lines 3-7 and Page 9 Lines 5-12: Is there a form that the ENCM uses to identify preventability factors? This may be helpful for readers to know which things could be listed as preventability factors, and which ones were actually present in these cases.

14) In general, more detail on the preventability factors will allow for more generalizable lessons learned across contexts.

15) Based on table 3, there appear to be more individuals who had suboptimal care identified than those whose deaths were considered certainly or possibly preventable. Were there instances where suboptimal care was identified but not deemed a sufficient opportunity to intervene/change the outcome?

Discussion:

1) Page 11, Line 20: Consider having separate paragraphs for strengths and limitations so as to break up this long paragraph and to provide additional guideposts for readers.

2) Page 11, Line 22: I believe validation on this line may be a typo/incorrect word, as I believe the authors are

referencing the external validity of the study rather than any external validation of the data.

3) The UK/Ireland Confidential Enquiries for Maternal Deaths recently released updated cardiac death data in 2019 and in 2021. It may be interesting to spend a bit more time in the discussion placing what this report provides within the context of what other Enquiries have identified regarding prevalence and preventability of cardiovascular deaths. In addition, situating these results within other countries' findings can further bolster the authors' claim that separating vascular and cardiac conditions is necessary and helpful.

4) More detail in general is needed on the preventability features in order to create some actionable lessons learned. The list of possible interventions on Page 12 and 13 are the first opportunity we are given to see where opportunities for improvement truly lie (delayed imaging, for instance, which is not mentioned in Table 3).

STATISTICAL EDITOR COMMENTS:

1) Please include a summary diagram or Table of the major causes of death for the cohorts with known vs previously unknown CV disease.

2) Please provide more detail for an example of how the decision was made to classify a particular case as "preventable" death. For many of these diagnoses, "potentially preventable" would seem to be more appropriate. For instance, among women with known aortic dilation, hypertrophic cardiomyopathy, dilated cardiomyopathy, there are certainly treatments and guidelines, but survival is not assured, so death is not entirely preventable.

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Sincerely,
Mark Allen Clapp, MD, MPH
Editorial Fellow

The Editors of Obstetrics & Gynecology

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

February, 22nd 2023

Dear Editor,

Please find attached our revised manuscript entitled “Preventability of cardiac and vascular maternal deaths: a nationwide study” (ONG-23-8) which we hope will be considered for publication in *Obstetrics & Gynecology*.

We would like to thank the editor and the reviewers for their helpful comments and for giving us the opportunity to improve our manuscript.

You will find below, a point-by-point answer to each of their comments or questions.

In the revised version of the manuscript, all corresponding changes are highlighted with “track changes”.

We hope that our revised manuscript meets the standards of *Obstetrics and Gynecology*.

Sincerely,

Catherine Deneux-Tharaux
On behalf of co-authors

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EDITOR COMMENTS:

Please note the following:

1. Thank you for your submission to the Green Journal. We are willing to consider a revised version of your manuscript if you are able to adequately address the Reviewers' points below.

In particular, please address issues regarding how the groups were assigned and how the preventability of a death was decided.

Answer:

We acknowledge that the information provided on the French enhanced surveillance system for maternal mortality, the National Confidential Enquiry into Maternal Deaths (ENCMM), was not very detailed.

We have now provided further information to explain how the groups were assigned in the revised Methods section, page 8 lines 11-21, as mentioned below; we hope it is now easier to understand.

“For this study, based on the underlying causal condition selected by the national expert committee, we classified maternal deaths caused by cardiac disease (congenital cardiac disease, acquired valvular cardiac disease, acquired pulmonary hypertension, dilated cardiomyopathy, hypertrophic cardiomyopathy, rhythmic, peripartum cardiomyopathy, acute myocardial infarction) or vascular disease (aortic rupture, splenic or renal arterial rupture). Within these two groups we further classified maternal deaths according to a known preexisting disease or not. We used the term “preexisting disease” to characterize women with a cardiac or vascular disease known before the acute event leading to death.”

We also changed the manuscript to explain more precisely how preventability of death was decided. In the Enquête Nationale Confidentielle sur les Morts Maternelles, preventability and preventability factors are determined by the national expert committee. This committee is a permanent group of clinicians and epidemiologists, experts in the domain of obstetrics/maternal health and maternal mortality. Each case of maternal death is assessed in a plenary session by the entire committee based on a review of all available anonymized data collected from interviews and manual review of medical records and autopsy reports. The national expert committee determines, by consensus, whether the death was probably or possibly or not preventable, or if preventability cannot be determined (undetermined), according to the guidelines and scientific literature available at the time of death. Among probably or possibly preventable maternal deaths, contributing factors are classified as related to the care provided (failed or delayed diagnosis and/or inadequate treatment) or to an inappropriate organization of care or to an inadequate interaction between the patient and the care system, non-exclusive categories. The committee’s synthetic conclusion is collected in a standardized form for each case.

These details are provided in the revised Methods section, page 8, lines 1-10, with a reference to the detailed ENCMM’s method in English: “Preventability decision by the expert committee aims to determine whether the death could have been avoided if one or more aspects of the woman's care course had gone differently, based on guidelines and standard of care at the time of the death. Among probably or possibly preventable maternal deaths, contributing factors are classified as related to the care provided (failed or delayed diagnosis and/or inadequate treatment) or to an inappropriate organization of care or to an inadequate interaction between the patient and the care system, non-exclusive categories. The committee’s synthetic conclusion is collected in a standardized form for each death (13).”

2. The manuscript contains table cells with small counts ($n < 10$). Please confirm in writing that you have permission to publish this data in this format and that there are no restrictions on its use or instructions to suppress small cell counts to preserve patient anonymity.

We confirm that we have permission to publish these data in this format.

3. * Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

We have done so.

4. * All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works or need to be cited:

- Please vary the language used in lines 5-21: "The multiple sources... undetermined)."

The ENCMM database used in the current study was used for previous analyses that come from our team, which is why the manuscript matches published works. We would rather keep the manuscript as it is as our study comes from the same authors, concerns analysis using the same methods and using the same data than those whose manuscripts they match. In particular, this is the case for the recently paper we published on maternal mortality in obese women (Saucedo et al, pmid 33093597).

5. Figure 1: Please check the n values under etiologies for $n=49$ (total 48).

Answer: We thank the reviewer for noticing this mistake. The number of women with "undetermined" etiology of cardiac disease is 3 (and not 2 as mistakenly written in the initial flow chart). We have revised Figure 1 accordingly.

REVIEWERS' COMMENTS:

Reviewer #1:

The authors present a descriptive cohort study regarding the rates of maternal cardiac and vascular deaths in France. They describe the number of cases that were due to preventable factors based on French confidential inquiry and determine that the majority of cases involved preventable factors.

Abstract:

1. The objective is not completely clear and can be shortened

Answer: We have shortened the objective to "To describe the clinical profile, management and preventability factors of maternal cardiovascular deaths."

2. Methods: the confidential enquiry needs more description in the abstract.

Answer: The confidential enquiry is now described with more details in the abstract: "We conducted a retrospective study of all maternal deaths from a cardiac or vascular disease during pregnancy or up to 1 year after the end of pregnancy in France from 2007 to 2015, identified via the permanent national enhanced maternal mortality surveillance system (Enquête Nationale Confidentielle sur les Morts Maternelles)".

As we are limited in the number of words for the abstract, we could not provide more details here. However, we have enriched the description of the ENCMM system in the revised Methods section, page 7, lines 4-8: "The ENCMM, the French nationwide enhanced surveillance system for maternal

mortality surveillance, has been set up in 1996 under the authority of the national Public Health Agency (Santé Publique France) and the national institute for health research (Institut National de la Santé et de la Recherche Médicale) to identify and document all maternal deaths in France”.

3. Also please define the term "death preventability factors"

Answer: Again, the words number 's constraint for the abstract does not allow to provide many details on preventability assessment. We still specified in the revised abstract that death preventability and contributing factors were determined by the national expert committee: “Maternal characteristics, clinical features and components of suboptimal care were described, along with the death preventability factors determined by the national experts committee using a standard evaluation form.”

In addition, we provided further details on preventability assessment and classification in the revised Methods section page 8, lines 1-8:” Preventability decision by the expert committee aims to determine whether the death could have been avoided if one or more aspects of the woman's care course had gone differently, based on guidelines and standard of care at the time of the death. Among probably or possibly preventable maternal deaths, contributing factors are classified as related to the care provided (failed or delayed diagnosis and/or inadequate treatment) or to an inappropriate organization of care or to an inadequate interaction between the patient and the care system, non-exclusive categories. The committee’s synthetic conclusion is collected in a standardized form for each death (13).”

4. Results: line 16 needs to be clarified.

Answer: We understand that the reviewer would like clarification on the maternal mortality ratio. The maternal mortality ratio is classically calculated as the number of maternal deaths due to cardiac or vascular condition per 100,000 live births during the same time period. We have rephrased the sentence and hope it is now clear: “During the 9-year period, 103 women died from cardiac or vascular disease, i.e a maternal mortality ratio from these conditions of 1.4 per 100,000 live births (95%CI 1.1-1.7).”

Introduction:

5. Line 10 can be clarified.

Answer: We agree that the initial wording was improvable. We have revised the sentence and hope it is now clear: “Women who die from congenital cardiovascular diseases are usually known to have a cardiac condition; conversely a fatal acute myocardial infarction leading to death may be inaugural or occur in women with a known coronary disease”.

6. P- Line 18- please include a hypothesis and a more succinct objective or aim.

Answer: We thank the reviewer for this advice, which helps clarify the presentation of our objective. We have revised this section to include a hypothesis and a shortened objective: “We hypothesized that preventability factors and lessons to be learned from them may differ according to the cardiac or vascular underlying causal condition and also to whether the acute event occurs in the context of a known pre-existing disease. We aimed to describe the clinical profile, management and preventability factors of maternal cardiovascular deaths, taking into account those characteristics.”

Methods:

7.- line 1 - why did the authors exclude stroke and thrombosis? Are these not vascular diseases?

Answer: We agree that in a way, stroke and venous thrombosis are vascular diseases. Maternal mortality data are classically analyzed according to the usual categories of causes, where pulmonary embolism is distinguished in a separate category, as well as strokes, which makes it possible to have a quantitative and qualitative analysis of these two causes of death separately.

Conversely, maternal deaths due to cardiac or vascular pathologies (excluding pulmonary embolism and stroke) are generally considered together in the same category, although they are heterogeneous. It is this heterogeneity that we seek to subcategorize here, as it hinders the emergence of relevant areas for improvement.

8. Line 20- does the committee lists specific preventable factors?

Answer:

Yes, preventability factors identified by the committee are reported using a standardized form listing specific categories of factors. We have further detailed this in the revised manuscript page 8 lines 3-8: "Among probably or possibly preventable maternal deaths, contributing factors are classified as related to the care provided (failed or delayed diagnosis and/or inadequate treatment) or to an inappropriate organization of care or to an inadequate interaction between the patient and the care system, non-exclusive categories. The committee's synthetic conclusion is collected in a standardized form for each death (13)."

9. Line 24- how was "cardiac" versus "vascular" disease defined? What diagnoses were included? (this is seen in figure 1 but may be noted in the methods as who met inclusion criteria).

Answer: We have further explained those aspects in the revised Methods section page 8 lines 11-18:

"For this study, we selected all maternal deaths from cardiac or vascular disease (not including deaths from stroke, venous thrombosis or thromboembolism) from 2007 to 2015. Based on the underlying causal condition selected by the national expert committee, we classified those maternal deaths caused by cardiac disease (congenital cardiac disease, acquired valvular cardiac disease, acquired pulmonary hypertension, dilated cardiomyopathy, hypertrophic cardiomyopathy, rhythmic, peripartum cardiomyopathy, acute myocardial infarction) or vascular disease (aortic rupture, splenic or renal arterial rupture). "

Results:

10. Did the authors evaluate if the preventable deaths occurred more frequently in certain diagnosis?

Answer: We agree with the reviewer that this is an interesting question. However, as maternal deaths remain rare events, the number of cases for each causal condition was too small to conduct an analysis of preventability by condition.

11. Line 14- how were the seven women without completed information treated. Did they get excluded?

Answer:

The seven (5 with a cardiac disease and 2 with a vascular disease) women for whom the timing of diagnosis was missing were excluded. The details on women excluded have been clarified

- **In the manuscript page 11, line 14: "The timing of diagnosis of the causal condition was missing for 7 women (5 with a cardiac disease and 2 with a vascular disease, Figure 1)."**
- **And in the Figure's footnote:**
 - "- Among the 78 maternal deaths by cardiac disease, 8 occurred in women with no information from the confidential enquiry including five with missing timing of diagnosis.**
 - Among the 25 maternal deaths by vascular disease, 2 occurred in women with no information from the confidential enquiry including and missing timing of diagnosis."**

12. Line 9- was the preventable factor among the women advised against pregnancy the pregnancy itself?

Answer: We thank the reviewer for this comment. Indeed, in these women, the high risks associated with pregnancy, given their pre-existing condition, had been explained but perhaps inadequately; that is why death was considered possible preventable because of an inadequate

patient-care system interaction assessed by the expert committee. We have rephrased the sentence page 12 line 14: “...were also related to inadequate patient-care system interaction (n=11), including seven women in whom the high risks associated with pregnancy had been explained but perhaps inadequately.” We also changed the corresponding wording in Table 3.

Discussion:

13. Line 9- the authors note a strength of the study was identifying cardiac and vascular disease as separate causes, why was this a particular strength? How is this clinically useful?

Answer: We hypothesized that preventability factors and lessons to be learned from them could vary between cardiac and vascular causes of maternal death. As suggested by this reviewer (comment 6.), we have formulated this hypothesis at the end of the revised Introduction.

Our findings of preventability factors which do vary according to this classification justifies our classification which becomes a strength of the study. Following our results, we wish to deliver prevention messages to clinicians specific of each of those different situations.

14. Line 22- the authors correctly identify the limited external validity of the study as this pertains to the local hospital systems and it is difficult to identify if these differ than other systems globally.

Answer: Yes, we have mentioned this limitation. However, as mentioned in the text, we believe the lessons learned to improve care from our study are valuable for other high-income countries.

15. Line 10- among the women who had a preventable death felt to be due to limited coordination of care, did the authors collect data on access to care?

Answer: We agree with the reviewer that information on access to care would be interesting.

However, given the design of the data collection, and the compelling fact that all women are deceased and cannot be interviewed, relevant data on access to care cannot be reliably collected and are thus not available.

16. Page 13 line 3- the studies that could be ordered may be conjecture, as the authors do not present data to know if these studies would have prevented the death.

Answer : We are not sure what studies the Reviewer refers to. If you would like to clarify the precise phrase referred to, we will be happy to respond to your comment.

17. Line 19- how do the findings encourage the use of POC ultrasound by ob anesthesia?

Answer: Anesthetists, in charge of anesthetic care in the maternity unit, are trained for POC ultrasound, notably in the context of the management of trauma patients at their admission to provide quick diagnoses. Thus, the performance of fast echography by obstetric anesthetists in obstetric patients with acute decompensation would help to reduce delays in the diagnosis of cardiac failure or of intra-abdominal bleeding.

This idea was not clearly explained in the first version of the manuscript, we reformulated the section page 16 lines 12-21: “In addition, measuring the level of N-terminal pro-hormone brain natriuretic peptide and troponin, as also suggested by the experts from the MBRRACE (r19), performing ultrasounds to identify cardiac failure or intraperitoneal bleeding, and injected CT scan to diagnose an aneurysmal process may have saved some of these women’s lives by avoiding delay in their care. Anesthetists are more and more trained for point-of-care ultrasound, notably in the context of the management of trauma patients at their admission to provide quick diagnosis. The use of fast cardiac or abdominal ultrasounds in obstetrics patients with acute decompensation by obstetric anesthetics would help to reduce delay in the diagnosis of cardiac failure or of intra-abdominal bleeding (20)”.

Reviewer #2:

This is a retrospective descriptive paper from a national database. All maternal deaths from a cardiac or vascular disease were identified, and then divided into those for whom the condition was known prior to the acute event and those for whom the condition was not known. The maternal deaths with preventable factors (based on expert analysis) outnumbered maternal deaths that were deemed unpreventable.

Major Revisions:

1. Fascinating database, and thus the descriptive statistics approach when used in isolation may prove unsatisfying for a largely clinical audience.

Could consider an analysis of the data, or could include case reviews.

Answer: We unfortunately cannot include or describe individual case reports in our study. Because of the rarity of maternal death and the specificities of each woman's story, some women could be easily be identified by doing so. As the key principle of the survey is its confidentiality, which is the basis of clinicians' confidence in the system and their involvement, we want each death to remain anonymous, without the possibility of identifying the institutions and practitioners involved. This also makes it possible to avoid the families of a deceased woman recognizing the case that concerns them.

2. This reviewer remains unconvinced that known versus unknown is the only important stratification, or that this distinction is a categorical variable (suspect that many patients are both known to some providers and not all, or that some extent of their disease is known but not the full extent).

Answer: We agree that the unknown versus known status may not be the only relevant stratification and that others could have been used. But this approach is pragmatic and corresponds to clinical reality. We believe that the lessons learned from the analysis perspective we chose provide useful information to improve the management of such situations.

We have added a section to the revised discussion recognizing that this assumed choice of categorization is not the only one possible, page 14 lines24: "Our approach using a stratification according to known and unknown causal diseases may not be the only relevant one; for example, the timing of the event could have been another stratification; yet our approach was a pragmatic one for clinicians based on the information they have in a given clinical context."

Regarding the classification of the known versus unknown in 2 categories, we agree with the reviewer that more nuances on the degree of known information would be possible; nevertheless, given the small number of cases, this somewhat schematic categorization allows for comparison of groups.

Intro

3. The cited study does not seem to be related to this statement; or if it is, please elaborate.

Answer: Thank you for noticing this mistake, we have removed this reference.

4. L9. While usually true, there is some congenital cardiovascular disease that goes unrecognized into adulthood.

Answer: We agree and have added the word "usually" to acknowledge some congenital cardiovascular disease may be unrecognized into adulthood: "Women who die from congenital cardiovascular diseases are usually known to have a cardiac condition"

5. L14. The distinction between known and unknown conditions is a thoughtful distinction but more evidence is needed to convince that this is a main driver for mortality (and in turn, opportunities for prevention). For example, this reviewer proposes that a major driver in the US may

be the timing of the acute event. For example, even an unknown condition that is exacerbated in prenatal care or labor may be more likely to be diagnosed than an acute event that happens at 6 months postpartum when the patient is not under routine care (here in the US also driven by insurance). Consider whether commenting on timing of event is appropriate to your national context. Please comment on other possible variables that could be drivers of mortality and opportunities for prevention.

Answer: We agree that the unknown versus known status may not be the only relevant stratification to classify maternal deaths and that others could have been used.

Indeed, the timing of the acute event is also an important information which was available in Table2. It turns out that none of the maternal deaths due to vascular diseases are late deaths i.e they all occurred before 42 days post-partum.

Our approach is pragmatic and corresponds to clinical reality. We believe that the lessons learned from the analysis perspective we chose provide useful information to improve the management of such situations. We have added a section to the revised discussion recognizing that this assumed choice of categorization is not the only one possible, page 14 lines24: “Our approach using a stratification according to known and unknown causal diseases may not be the only relevant one; for example, the timing of the event could have been another stratification; yet our approach was a pragmatic one for clinicians based on the information they have in a given clinical context.”

6. Info collected

L3. How were these characteristics selected? Please elaborate on the socioeconomic determinants of health in your country if they are pertinent to the characteristics selected.

Answer:

The characteristics collected were selected according to their relevance to the subject and their availability in the database. As explained in the description of the ENCM system, the information is collected from the medical records and is therefore limited by them.

This is particularly true for social characteristics, which are generally not very detailed in the medical records.

As documented in a recent article, the characterization of vulnerable subgroups for maternal death varies from country to country and, in France, the main social inequalities in maternal mortality described are those related to the maternal age and country of birth (1) In France, ethnic statistics are not possible. For these reasons, we collected maternal age and country of birth in our analysis.

Results

7. L15. Postulate on the 10 women whose information was not available to study. How could it be that this information was not available? Are these women lost to follow up different than the women in this analysis?

Answer: It happens that the confidential enquiry may not be conducted. The medical files may be unavailable for several reasons: a court case may be ongoing, or the medical files may have gone missing, or the caregivers may be reluctant to give access to the files.

Noteworthy, all women without a confidential enquiry are from the 2007-2009 period which shows the number of maternal deaths that do not have available data for the confidential enquiry tends to reduce. This time period is likely to be the main driver of these missing data.

Among these ten women without confidential enquiry, 4 had valvular cardiac disease, a larger proportion than among women with complete data; this was already described in Figure 1.

Apart from this, the few available characteristics of women (age, country of birth) were not different.

8. Table 1

Interesting that women with known vascular disease who died were all P0.

Please comment on the overrepresentation of Cesarean section in all deaths. Does this C-section rate match your national expected C-section rate?

Answer: We thank the reviewer for this comment pointing an important result. As described in Table 1 (revised presentation to express the % of cesarean among women who delivered), the 50 to 79% cesarean rate among the various subgroups of women who died is much higher than the 21% reference rate for France at this time period, as mentioned in the last column of Table 1. We have further analyzed the context of cesarean in women who died to test the hypothesis that the high rate reflects the need for emergency delivery because of the acute cardiac or vascular condition. We found that a majority of these cesareans were emergency ones: 6/11; among women who died from cardiac disease diagnosed before the acute event; 16/19 among those with cardiac disease undiagnosed before the acute event; 2/3 among those with vascular disease diagnosed before the acute event 2/3 ; and 10/10 in women with vascular disease undiagnosed before the acute event.

We have revised the presentation of the mode of delivery in Table 1; and added information on emergency cesarean.

In addition, we have commented these results on cesarean in the revised Results section page 12 lines 2-3: “One fourth died while pregnant; among those who gave birth, the majority had a caesarean, most often performed in emergency (Table 1).”

9. Table 2

Postpartum would be more relevant if it was subcategorized into immediate postpartum and late postpartum.

Answer: The postpartum is subcategorized into <7 days, 7-42 days, > 42 days, making it possible to differentiate immediate and late postpartum. This was already mentioned in table 2 but was unclear due to inappropriate settings of the table. We have reformatted this information in Table 2 and hope it is now clear.

Reviewer #3:

The authors have undertaken a retrospective cohort analysis of the characteristics and preventability of maternal death due to cardiac and vascular causes using a national database approach capturing pregnant people in France between 2007-2015.

General comments:

1) It is my understanding that Obstetrics and Gynecology is moving toward more gender neutral language since individuals who can become pregnant do not all identify as women. If the authors have an indication from their data that all included individuals identified as women, that could be stated as well.

Answer: We agree that we cannot ascertain that all the included patients would have identified themselves as women. However, we have used the term “women” throughout the text to describe patients as it is the word usually used for studies conducted on maternal mortality. We will leave the editor to decide whether or not we should change women to a more gender neutral term.

2) The preventability aspect of this paper can be a unique contribution to the field. However, I think more information on the way that preventability was determined, and in particular, the way the committee deliberated and/or chose opportunities for improvement that could prevent death is needed from the methods standpoint, and more details on exactly the delays or missed diagnoses (e.g. delayed imaging, delayed labs, dismissed symptoms, late transfer of care) that could have improved care will provide the important lessons learned that can be applied across contexts.

Answer: We acknowledge that more details on preventability assessment are useful and we have changed the manuscript to explain more precisely how preventability of death was decided, as it was also suggested by Reviewer 1.

In the *Enquête Nationale Confidentielle sur les Morts Maternelles*, preventability and preventability factors are determined by the national expert committee. This committee is a permanent group of clinicians and epidemiologists, experts in the domain of obstetrics/maternal health and maternal mortality. Each case of maternal death is assessed in a plenary session by the entire committee based on a review of all available anonymized data collected from interviews and manual review of medical records and autopsy reports. The national expert committee determines, by consensus, whether the death was probably or possibly or not preventable, or if preventability cannot be determined (undetermined), according to the guidelines and scientific literature available at the time of death. Among probably or possibly preventable maternal deaths, contributing factors are classified as related to the care provided (failed or delayed diagnosis and/or inadequate treatment) or to an inappropriate organization of care or to an inadequate interaction between the patient and the care system, non-exclusive categories. The committee's synthetic conclusion is collected in a standardized form for each case.

These details are provided in the revised Methods section, page 8, lines 1-10, with a reference to the detailed ENCMM's method in English: "Preventability decision by the expert committee aims to determine whether the death could have been avoided if one or more aspects of the woman's care course had gone differently, based on guidelines and standard of care at the time of the death. Among probably or possibly preventable maternal deaths, contributing factors are classified as related to the care provided (failed or delayed diagnosis and/or inadequate treatment) or to an inappropriate organization of care or to an inadequate interaction between the patient and the care system, non-exclusive categories. The committee's synthetic conclusion is collected in a standardized form for each death (13)."

Abstract:

1) It may help to briefly describe what the "national enquiry" is for readers who are not familiar. It could be construed as either a national database of deaths curated by a central body vs a nation-wide records request of French hospitals prompted by the authors. I would encourage the authors to briefly give the name of the curated registry (as mentioned in Methods).

Answer: We thanks the reviewer for this comment which will help clarify the data source.

Although the term "Confidential Enquiry" is classic in the field of maternal mortality surveillance and refers to a specific system for studying these deaths, it is important that all readers understand from the abstract that this is a nationwide established permanent surveillance system coordinated centrally.

The confidential enquiry is now described with more details in the abstract: ".....identified via the nationwide permanent enhanced surveillance system of maternal mortality (*Enquête Nationale Confidentielle sur les Morts Maternelles*)". As we are limited in the number of words for the abstract we have also given more details in the methods section: "The ENCMM, the French nationwide enhanced surveillance system for maternal mortality surveillance, has been set up in 1996 under the authority of the national Public Health Agency (*Santé Publique France*) and the national institute for health research (*Institut National de la Santé et de la Recherche Médicale*) to identify and document all maternal deaths in France (10,11)."

2) It may also be prudent to include in the abstract how the cardiac and vascular cases were initially ascertained for review within the ENCMM database. Did the ENCMM keep this information on each case in a searchable database? Or were the cases to be reviewed identified via discharge or hospital codes? Or via some other review process?

Answer : Identification of maternal deaths is performed via multiple sources, as explained in the Methods section page 7 lines 8-14; the hospital discharge database is used as a complementary source for this step as part of the exhaustivity checking. Then, for each woman, the cause of death

is selected by the expert committee based on the whole information collected by the assessors (as explained page 7 lines 19-21), and is not derived for pre-coded information in an existing database. Finally, for each maternal death, the main characteristics of the woman, her pregnancy and care pathway, as well as the conclusions of the expert committee, are entered in a electronic permanent searchable database. In addition, all information collected for each death is kept as electronic and paper files.

We have rephrased the sentence in the abstract as: **"We conducted a retrospective study of all maternal deaths from a cardiac or vascular disease during pregnancy or up to 1 year after the end of pregnancy in France from 2007 to 2015, identified via the database of the nationwide permanent enhanced maternal mortality surveillance system (Enquête Nationale Confidentielle sur les Morts Maternelles)".**

We also provided more information on the ENCMM system in the Methods section.

3) Was a standardized form or definition used to identify suboptimal care or preventability factors? Given space constraints in the abstract, if a standardized form or definition was used, adding the phrase "using a standard definition" or "using a standard evaluation form" would be sufficient.

Answer: yes, the conclusion of the expert committee on suboptimal care and preventability is collected for each case using a standardized form.

We have added the suggested phrase in the abstract.

We also provided further information on the process in the Methods section (page 8 lines 1-10).

4) The use of the National Perinatal Survey is not mentioned.

Answer:

We used the published aggregate results of the National perinatal Survey only as a reference to compare the baseline characteristics of our population to those of the general pregnant population in France. We did not conduct any analysis on these data. In consequence, we believe it is appropriate not to mention this survey in the Abstract, but only in the main text.

Introduction:

1) I appreciate the brevity of the introduction, but I think a bit more detail regarding the separation of cardiac and vascular disease is warranted. It would be helpful to provide examples of cardiac vs vascular diagnoses. On line 10 in particular, "coronaropathy" is not a commonly used word to describe coronary artery disease; it may be more clear to simply state coronary artery disease or coronary artery diseases (and is this the extent of what the authors consider vascular diseases? Or do aortopathies, aneurysms, dissections, and other vascular abnormalities count?). Is coronaropathy a cardiac or a vascular condition?

Answer: We have provided more details in the revised Methods section on which disease were considered as cardiac and which were considered as vascular, page 8, lines 13-18: "Based on the underlying causal condition selected by the national expert committee, we classified those maternal deaths caused by cardiac disease (congenital cardiac disease, acquired valvular cardiac disease, acquired pulmonary hypertension, dilated cardiomyopathy, hypertrophic cardiomyopathy, rhythmic, peripartum cardiomyopathy, acute myocardial infarction) or vascular disease (aortic rupture, splenic or renal arterial rupture)."

We have changed coronaropathy to acute myocardial infarction throughout the manuscript and the tables.

We chose to consider coronaropathy as a cardiac disease as what leads to death during an acute myocardial infarction is not the obstruction of the coronary artery but the impact this obstruction has on the whole heart.

2) A better understanding of the authors' descriptions of cardiac vs vascular disease may also help to better motivate the study. Why is it important to differentiate between these two diagnoses?

Answer: Cardiac and vascular disease are always considered as one subcategory of disease but pathophysiologic pathways leading to maternal deaths, symptoms, strategies for diagnosis and management as well as opportunities for improvement in various aspects of care clearly differ according to those two categories of disease. We hypothesized that preventability factors and lessons to be learned from them may differ according to the cardiac or vascular underlying causal condition.

We have explicitly formulated this hypothesis at the end of the revised introduction : “We hypothesized that preventability factors and lessons to be learned from them may differ according to the cardiac or vascular underlying causal condition and also to whether the acute event occurs in the context of a known preexisting disease.”

3) Line 9: Not all pregnant people with congenital cardiac disease are identified prior to pregnancy (e.g., bicuspid aortic valve is not always diagnosed in childhood, and subsequent enlarged root may have pregnancy consequences)

Answer: We agree and have added the word “usually”: “Women who die from congenital cardiovascular diseases are usually known to have a cardiac condition”.

4) Line 12: Case series typically do not make the distinction between known and previously unidentified disease? Or do not make the distinction between congenital cardiac disease and acquired coronary artery disease? Perhaps a sentence that combines the ideas in the two sentences on Line 12 and 13 may help to increase clarity of meaning

Answer: We thank the reviewer for the advice; we have combined these two sentences in one: “Strategies for diagnosis and management as well as opportunities for improvement in various aspects of care clearly differ according to whether a condition is already known before the acute event, yet case series of maternal deaths have rarely made this distinction (6-8).”

5) Line 16: The authors state that "vascular diseases [causing death] have rarely been described." Could the authors provide examples of the vascular diseases they mean?

Answer: Again, we thank the reviewer for this advice which helps clarifying our introduction. We have revised the sentence to: “In particular, vascular diseases responsible for maternal deaths including aortic rupture or splenic or renal arterial rupture, have rarely been described, although they may have their own preventability factors”.

6) Lines 18-21: Objective is clearly stated, but a little detail in the preceding paragraphs will help to motivate the paper/objective and make it more obvious/urgent why such an analysis is needed.

Answer: We have included a hypothesis and shortened the objective to make the text more obvious: “We hypothesized that preventability factors and lessons to be learned from them may differ according to the cardiac or vascular underlying causal condition of maternal deaths and also to whether the acute event occurs in the context of a known pre-existing disease. We aimed to describe the clinical profile, management and preventability factors of maternal cardiovascular deaths, taking into account those characteristics.”

Methods:

1) Why were the years 2007-2015 chosen? If data were collected from 1996 to presumably the current time, it would be important to know why these years were chosen by the authors.

Answer: 2015 was the most recent year of complete data available when the study was conducted; we have added this information in the revised Methods section.

We preferred to include cases from 2007 and not earlier ones, to analyze a time period in which practices can be considered homogeneous and still to inform the current ones. In addition, the ENCMM method was less standardized and there were more missing data in later years.

2) Page 5, Lines 24-25: Were pregnant people with "known cardiovascular disease" those who were known to have disease prior to pregnancy, or prior to the acute event, or both?

Answer: As mentioned page 8 lines 19-21: "We used the term "pre-existing disease" to characterize women with a cardiac or vascular disease known before the acute event leading to death". This is also specified in each column of the tables.

3) Page 6, Lines 19-22: Was a standardized tool used by the committee when they deliberated about contributing factors to possibly or probably preventable deaths?

Answer: Yes a standardized form is used to assess preventability and contributing factors. We have provided further details in the Methods section page 8 lines 1-10, and also added the reference to the ENCMM website where the complete method's description is available in English (ref 13).

4) Page 6, Line 22: "Non-compliance" with treatment has connotations of blame on the patient rather than acknowledging the structural or system-level features that often drive "poor compliance." I think the category description is understandable without the parenthetical statement "(non-compliance with treatment)." and I would recommend just removing the parenthetical.

Answer: We thank the reviewer for this comment and agree. We have removed this statement accordingly.

5) Page 7, Line 8-13: I admit I am a bit confused about the inclusion of the 2010 National Perinatal Survey. Could this section be clarified somewhat? Were only the women with available data on timing of diagnoses (the people in the 4 groups described by the authors) compared to the National Perinatal Survey, or were all people with cardiovascular deaths compared to this NPS? What statistical techniques were used to compare the two groups? It also seems odd to have the first mention of this dataset in the Analysis section. Consider moving the description of the NPS data to the beginning of the methods? Perhaps at the end of "population"?

Answer: We acknowledge that the mention of the National Perinatal Survey was confusing. Indeed, we used the published aggregate results of the National perinatal Survey only as a reference to compare the baseline characteristics of our population to those of the general pregnant population in France. We did not conduct any analysis on these data. We have rephrased this section to clarify this, page 10 lines 3-6: "These characteristics were compared to the published aggregate data from the reference population of women included in the 2010 National Perinatal Survey a contemporary national representative sample of pregnant women including all those who gave birth at gestational age ≥ 22 weeks in every maternity unit in France for a complete 1-week period (15). "

6) Same comment as Abstract - was a standardized review tool for identifying preventability factors used by the committee? Please describe (or consider including as an Appendix?)

Answer: Yes a standardized tool was used to identify preventability factors. We have provided further details in the Methods section page 8 lines 1-10, and also added the reference to the ENCMM website where the complete method's description is available in English, with forms in French as appendices.

Results & Tables:

1) Figure 1 is very helpful for delineating what constitutes cardiac vs vascular disease. The terms cardiopathy and coronaropathy feel a bit odd to this reviewer but may be more commonly used outside the US? It would also be helpful to delineate how individuals with a congenital cardiac

anomaly that leads to vascular issues might fit (for instance, how would a person with a bicuspid aortic valve and aortic dissection or aortic rupture be classified?).

Answer: We have changed the term coronaropathy to acute myocardial infarction throughout the text and figure.

We agree that the choice of the category of death might not be obvious in some cases. We classified women based on the main causal condition, selected by the national expert committee. For cases where there are multiple contributing conditions, the one who was the main driver to the death is selected as the underlying causal condition.

In the specific mentioned case of a person with a bicuspid aortic valve and aortic dissection or aortic rupture, the cause of death would be the aortic rupture.

2) Table 1 - there are two single asterisks, one after the "Others" subcategory of maternal country/region of birth, and one after fetal death/stillbirth. The foot note matches fetal death/stillbirth, I believe, but the asterisk after Others should be addressed

Answer: We removed the asterisk which was next to "others".

3) Table 1 - numbers for dyslipidemia and smoking do not appear to align with the category labels (they are shifted up one row)

Answer: Thanks for noticing. We have made the needed correction.

4) Page 8, Line 23-24. How were the cardiovascular risk factors contained in the National Perinatal Survey obtained? Patient report, chart abstraction, etc? Please add to methods. Improved ascertainment of risk factors would be expected during the mortality review process compared to common methods used by nationally representative population databases (such as discharge codes), which could partially explain the higher rate of risk factors among those who died from cardiovascular disorders.

Answer: Cardiovascular risk factors in the National Perinatal Survey are obtained through manual chart abstraction, and not through discharge codes; in consequence it is expected to be very accurate. In addition, as this data collection method is the same as the one used for maternal deaths in the ENCM (manual extraction from medical charts), the comparison of the cardiovascular risk profile in the two populations is not likely to be biased by measurement differences. The methodology of the National Perinatal Survey is available in the cited reference 14. As we used the published aggregate results of the National perinatal Survey only as a reference to compare the baseline characteristics of our population to those of the general pregnant population in France and we did not conduct any analysis on these data, we don't think it is necessary to provide more details on this survey.

5) The results seem to be reported somewhat out of order compared to the Tables, particularly for the Vascular maternal deaths section, which references Table 3 before any others. I can see the appeal of going through Cardiac and then Vascular deaths separately, while also having a side-by-side comparison available in the Tables. Perhaps some additional structure to the Results would help - such as subheadings under cardiac deaths and vascular deaths that correspond with the data in each table: Maternal Demographic and Clinical Characteristics; Characteristics of cardiac events; and Preventability of Events. Some additional guideposts will help the results feel more ordered and guide readers through the tables.

Answer: We thank the reviewer for this advice. We have added subheadings to the results section accordingly and hope this makes the manuscript clearer. Subheadings are: "Maternal characteristics", "Characteristics of cardiac/ vascular events" and "Preventability".

6) Table 2 - the onset of symptoms postpartum subcategories (<7 days, etc) are oddly separated from the post-partum category, making it initially difficult to interpret.

Answer: Thanks for noticing. We have made the needed correction.

7) All tables - I think the relationships between n and % across categories, rows, and tables, would be easier to interpret if either the % or the n were presented in parentheses within the same column - such as 61 (37%) or 37% (61) so that they eye can search across fewer columns of numbers. In addition, the proportions should probably have the % sign next to them so that they are not confused with N. It would just make the tables much easier to read, particularly when each table contains so much data.

Answer: We have followed this advice and revised the tables accordingly.

8) All tables - some categories have MD for missing data while others do not. Is it true that no individuals were missing data for pregnancy disorders such as hypertensive disorder of pregnancy or gestational diabetes or cardiovascular risk factors such as smoking before pregnancy?

Answer: There were no missing data on these items. However, we cannot exclude the fact that some conditions were not reported in the medical charts, and considered absent.

9) Page 8, Lines 17-20. If I understand the Tables correctly, the data provided in these lines also appears in Table 2? It may help to have an overall column on Table 2 similar to that on Table 3 to assist with interpretability, at least for timing of death and gestational age/stillbirths.

Answer: As our aim was to show differences in the clinical features between the 4 groups, which suggest the need to not study all these conditions as a single group, we feel that adding a "overall" column would not be in line with our approach.

10) Page 9, Lines 18-19. Is the citation #16 a guideline document for when IVF could be considered in people with Turners or other aortic root dilation? If so, is the citation better located after the sentence that ends "... contraindicate IVF at the time it was performed"?

Answer: We thank the reviewer for this advice and have made the corresponding change.

In addition, Table 3 does not seem to provide any data about the frequency of aortic size monitoring throughout pregnancy for these individuals. Why is Table 3 cited here?

Answer: This was a mistake, thanks for noticing. We have removed the mention.

11) Pregnancy-related hypertensive disorders appear to be significantly more frequent among people with cardiac maternal deaths compared to general population, but this is not noted in results prose anywhere. Seems as though it would be interesting to mention, given its relationship with cardiomyopathy.

Answer: We agree and have mentioned this feature in the revised results section, page 12 line 1.

12) Table 3 - why are subcategories of Content of Care opportunities to prevent death listed (e.g., delayed work up of presenting symptom) but not for organization of care (e.g. delay transfer to ICU) or Patient-care system interaction?

Answer: Beyond the frequency of preventability factors in the 3 pre-specified categories of contributing factors, we provided more detail in Table 3 for the categories contributing most to preventability, i.e those related to the content of care and to the patient-care system interaction. However, we agree with the reviewer that it is also interesting to provide more details on the factors related to the organization of care. That is why we have enriched the Results section page 12 lines 11-20: "For women with a known preexisting cardiac condition, preventability factors were mostly a lack of multidisciplinary management as early as in the preconception period and during pregnancy follow-up (n=12). They were also related to inadequate patient-care system interaction (n=11), including seven women in whom the high risks associated with pregnancy had been explained but likely inadequately; and to inadequate organization of care (n= 7), the most frequent factor in this category being a place of care inappropriate to the condition. Among the 23 women whose deaths were preventable and who had no preexisting cardiac disease, the main preventability factor was

missed or delayed diagnosis of cardiac failure in the context of acute dyspnea (n=15). Inadequate organisation of care was present in 8, most often related with a delay in transfer to intensive care unit."

Is "women advised not to be pregnant" a subcategory of Patient-care system interaction?

Answer: Yes it is, but the phrasing was misleading. Indeed, in these women, the high risks associated with pregnancy, given their pre-existing condition, had been explained but perhaps inadequately; that is why death was considered possible preventable because of an inadequate patient-care system interaction assessed by the expert committee. We have rephrased the sentence page 12 lines 13-15: "...were also related to inadequate patient-care system interaction (n=11), including seven women in whom the high risks associated with pregnancy had been explained but likely inadequately." We also changed the corresponding wording in Table 3.

13) Page 10, Lines 3-7 and Page 9 Lines 5-12: Is there a form that the ENCMM uses to identify preventability factors? This may be helpful for readers to know which things could be listed as preventability factors, and which ones were actually present in these cases.

Answer: Yes a standardized form is used to identify preventability factors. This form lists the 3 categories with subcategories of potential preventability factors and the committee decides whether each factor is present or not. Then the committee provides a complementary free text description of the precise preventability factors for the case examined. We have provided further details in the Methods section page 8 lines 1-10, and also added the reference to the ENCMM website where the complete method's description is available in English, with forms in French as appendices (ref 13).

14) In general, more detail on the preventability factors will allow for more generalizable lessons learned across contexts.

Answer:

Thanks for this comment. In that sense we have added the box below summarizing the main lessons learned concerning preventability factors, and introduced it in the revised discussion section page 14 line 8: "Box 1 synthesises the main actionable lessons learned."

"

Box1: Actionable lessons learned

- Apply the same diagnosis strategy in front of acute cardiac or vascular symptoms for women pregnant or recently pregnant as for non-pregnant person.
- Women with acute dyspnea or chest pain should have cardiac evaluation with N-terminal pro-hormone brain natriuretic peptide and troponin levels measurements and cardiac ultrasound.
- Eliminate vascular rupture in pregnant women with unexplained intense abdominal pain, using POC ultrasound and injected CT scan.
- Women with pre-existing cardiac conditions should be managed:
 - by multidisciplinary personalized care
 - in settings with resources for specialized cardiovascular and obstetrical care

15) Based on table 3, there appear to be more individuals who had suboptimal care identified than those whose deaths were considered certainly or possibly preventable. Were there instances where suboptimal care was identified but not deemed a sufficient opportunity to intervene/change the outcome?

Answer: Yes, those two dimensions are different and assessed separately, although most often concordant. However, as the Reviewer anticipated, some women have received suboptimal care, but their death was still considered not preventable because of the severity of the symptoms. The two types of information are complementary. For example, death of a woman who died from splenic arterial rupture was considered unpreventable because she arrived at hospital with refractory hemorrhagic shock, and experts considered that any better care would not have changed the fatal outcome.

Discussion:

1) Page 11, Line 20: Consider having separate paragraphs for strengths and limitations so as to break up this long paragraph and to provide additional guideposts for readers.

Answer: We thank the reviewer for this advice, and have revised this section accordingly.

2) Page 11, Line 22: I believe validation on this line may be a typo/incorrect word, as I believe the authors are referencing the external validity of the study rather than any external validation of the data.

Answer: Yes, this was a mistake, thanks for noticing. We have made the corresponding change.

3) The UK/Ireland Confidential Enquiries for Maternal Deaths recently released updated cardiac death data in 2019 and in 2021. It may be interesting to spend a bit more time in the discussion placing what this report provides within the context of what other Enquiries have identified regarding prevalence and preventability of cardiovascular deaths. In addition, situating these results within other countries' findings can further bolster the authors' claim that separating vascular and cardiac conditions is necessary and helpful.

Answer: You are right.

First, maternal mortality due to cardiovascular deaths in UK is cited in the manuscript page 15 lines 3-7.

Second, some messages and lessons on preventability factors for cardiac and vascular maternal death provided in the last report on maternal deaths from MBRACCE 2022 are quite similar to those we proposed indeed. Notably, they insist on the importance of making a diagnosis in front of acute symptoms of cardiac disease, on the necessity to develop guidance for the use of BNP measurement during pregnancy and finally to think of the aorta in front of acute abdominal pain in pregnant women. Thus, even if they don't clearly mention that cardiac and vascular conditions should be analyzed separately, they do it in their messages.

Similarities in preventive factors between the French and UK/Ireland Confidential Enquiries for Maternal Deaths are now mentioned in the revised manuscript (page 16 lines 2-17): "We found frequent wrong or delayed diagnosis in women with cardiac or vascular symptoms, which emphasizes the need to properly and rapidly explore any acute dyspnea, chest or abdominal pain during pregnancy or in the post-partum period because these were often underestimated and wrongly attributed to pregnancy. Such missed diagnosis concerned general practitioners as much as the obstetric teams and the emergency department. Hence, care providers should be trained in the non-obstetric dimensions of maternal health in order to recognize cardiovascular symptoms and apply the same diagnostic strategy for women who are pregnant or who have recently been pregnant as for a non-pregnant person. These messages are also proposed as lessons to learn to prevent maternal deaths from cardiac disease in the last report by the MBRRACE-UK-Saving Lives, Improving Mothers' Care 2022 (19). In addition, measuring the level of N-terminal pro-hormone

brain natriuretic peptide and troponin, as also suggested by the experts from the MBRRACE (19), performing ultrasounds to identify cardiac failure or intraperitoneal bleeding, and injected CT scan to diagnose an aneurysmal process may have saved some of these women's lives by avoiding delay in their care."

4) More detail in general is needed on the preventability features in order to create some actionable lessons learned. The list of possible interventions on Page 12 and 13 are the first opportunity we are given to see where opportunities for improvement truly lie (delayed imaging, for instance, which is not mentioned in Table 3).

Answer: Thank you for this comment which led us to improve the manuscript. As suggested, we have added in the revised manuscript a box summarizing some actionable lessons learned from our results, and introduced it in the revised discussion section page 12 line 8: "Box 1 synthesises the main actionable lessons learned."

Box1: Actionable lessons learned

- Apply the same diagnosis strategy in front of acute cardiac or vascular symptoms for women pregnant or recently pregnant as for non-pregnant person.
- Women with acute dyspnea or chest pain should have cardiac evaluation with N-terminal pro-hormone brain natriuretic peptide and troponin levels measurements and cardiac ultrasound.
- Eliminate vascular rupture in pregnant women with unexplained intense abdominal pain, using POC ultrasound and injected CT scan.
- Women with pre-existing cardiac conditions should be managed:
 - by multidisciplinary personalized care
 - in settings with resources for specialized cardiovascular and obstetrical care

STATISTICAL EDITOR COMMENTS:

1) Please include a summary diagram or Table of the major causes of death for the cohorts with known vs previously unknown CV disease.

Answer: This information is provided in Figure 1.

2) Please provide more detail for an example of how the decision was made to classify a particular case as "preventable" death. For many calculated over the number of cases for which the national committee could formulate a conclusion on preventability of the death of these diagnoses, "potentially preventable" would seem to be more appropriate. For instance, among women with known aortic dilation, hypertrophic cardiomyopathy, dilated cardiomyopathy, there are certainly treatments and guidelines, but survival is not assured, so death is not entirely preventable.

Answer: We acknowledge that more details on preventability assessment are useful and we have changed the manuscript to explain more precisely how preventability of death was decided.

In the Enquête Nationale Confidentielle sur les Morts Maternelles, preventability and preventability factors are determined by the national expert committee. This committee is a permanent group of

clinicians and epidemiologists, experts in the domain of obstetrics/maternal health and maternal mortality. Each case of maternal death is assessed in a plenary session by the entire committee based on a review of all available anonymized data collected from interviews and manual review of medical records and autopsy reports. The national expert committee determines, by consensus, whether the death was probably or possibly or not preventable, or if preventability cannot be determined (undetermined), according to the guidelines and scientific literature available at the time of death. Among probably or possibly preventable maternal deaths, contributing factors are classified as related to the care provided (failed or delayed diagnosis and/or inadequate treatment) or to an inappropriate organization of care or to an inadequate interaction between the patient and the care system, non-exclusive categories. The committee's synthetic conclusion is collected in a standardized form for each case.

These details are provided in the revised Methods section, page 8, lines 1-8: "Preventability decision by the expert committee aims to determine whether the death could have been avoided if one or more aspects of the woman's care course had gone differently, based on guidelines and standard of care at the time of the death. Among probably or possibly preventable maternal deaths, contributing factors are classified as related to the care provided (failed or delayed diagnosis and/or inadequate treatment) or to an inappropriate organization of care or to an inadequate interaction between the patient and the care system, non-exclusive categories. The committee's synthetic conclusion is collected in a standardized form for each death (13)."

It is absolutely right, as the Reviewer suggests, that some deaths will remain non-preventable, even with the best care provided. This clearly appears with a 53% rate of not preventable deaths in women who died from vascular disease (Table 3).