PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort Profile: The Mayo Clinic Cohort Study of Oophorectomy and Aging-2 (MOA-2) in Olmsted County, Minnesota (USA)
AUTHORS	Rocca, Walter; Gazzuola Rocca, Liliana; Smith, Carin; Grossardt, Brandon; Faubion, Stephanie; Shuster, Lynne; Stewart, Elizabeth A.; Mielke, Michelle; Kantarci, Kejal; Miller, Virginia

VERSION 1 – REVIEW

REVIEWER	Martha Hickey The University of Melbourne, Australia
REVIEW RETURNED	07-Aug-2017

GENERAL COMMENTS	Thank you for asking me to review this manuscript. Whilst the practice of removing normal ovaries at the time of hysterectomy has become less common in recent decades, oophorectomy without clear medical indications still occurs (as the authors have indicated). High quality evidence indicating the potential risks and benefits of surgical menopause (pre-menopausal bilateral oophorectomy) is needed for clinical practice and informed consent. Data from the previous cohort (MOA-1) published by these authors has been highly cited and (in my experience) has directly influenced clinical practice. I am delighted to hear that a more recent and carefully evaluated cohort is being established. However, I have several concerns about the study design and planned outcomes that I hope the authors might consider addressing: The stated purpose is to study the effects of USO and BSO on the "ageing process". What exactly does this mean and how exactly will this be measured? The underlying assumption seem to be that BSO will accelerate ageing and this assumption is echoed in the comment that "the abrupt and extreme hormonal changes caused by BSO will have a major effect on the ageing process across the full body". This sounds like the authors have already decided that there will be extensive adverse outcomes from BSO. How will the ageing process be measured? The authors mention multimorbidity as a marker of ageing, can they be more specific about exactly what conditions they are referring to and what they mean by MM in this context? The published literature on menopause and biological ageing (eg PMID: 27457926) measures epigenetic signatures for ageing that are not being collected in this study. The authors refer in several places to the “abrupt and extreme hormonal change" associated with BSO. What exactly does this mean? I don’t think hormonal measures are included in the protocol.

	Women experience cyclic changes in sex hormones regularly, and the natural transition from peri to postmenopause is marked by substantial changes in circulating estradiol concentrations (PMID: 18574431). One could also say that starting a postmenopausal woman on HT leads to an “abrupt and extreme hormonal change”. I am not a methodologist, but central to this cohort study is the assumption that adverse health outcomes observed more frequently in the BSO group compared to the age-matched control population are attributable to the BSO. This is problematic and does not consider likely confounders such as SES. As the authors have previously published: "the association between bilateral oophorectomy and cardiovascular mortality may be confounded by socioeconomic status. In particular, lower socioeconomic status may increase the probability of undergoing a bilateral oophorectomy,[49] decrease the probability of receiving adequate estrogen treatment after the oophorectomy,[50] and independently increase cardiovascular mortality.[51]Women undergoing BSO are likely to differ" (PMID: 19034050). Since SES is likely to influence the likelihood of undergoing BSO and the outcomes of interest, what measures of SES do the authors have (apart from years of education)? How will they account for the likely effect of SES on their outcome measures? There is additional evidence in this manuscript that the intervention group may differ from controls regarding important risk factors for the outcomes to be studied. Whilst the specific outcomes to be measured in MOA-2 are not entirely clear, they include neurological and psychiatric disease. On page 14, the authors comment that women having BSO before aged 46 were more likely to have suffered emotional and physical abuse in childhood, and those having BSO under 40 were more likely to have experienced physical abuse as adults (previously published). Clearly this is highly likely to impact on the risk of current and later psychiatric and potentially neurological disease. How will this be considered in data analysis? Is the study powered to address its primary outcome having controlled for childhood and adult abuse? It would be helpful for the authors to clearly state the primary and secondary outcomes of interest, why these outcomes have been chosen and the power of the study to determine the association between the intervention and outcomes. Also, I am puzzled why only negative outcomes are of interest. It is very likely that BSO will substantially reduce ovarian cancer risk, and may also reduce breast (and total cancer) risk (PMID: 24807324). Chronic pelvic pain affects up to 26% of women (PMID: 24658485) and around 30% of those who underwent BSO has endometriosis. What is the long-term effect of BSO on pelvic pain? This information would be useful clinical practice and help women and HCP making informed choices. Data from the MOA-2 cohort is likely to influence decision making around BSO and this study has the potential to provide new information about both the risks and benefits of this procedure. Establishing menopausal status at the time of oophorectomy, current chronic disease and risk factors for chronic disease such as tobacco use and obesity, is critical to the interpretation of long-term health outcomes and the attribution of these outcomes to BSO.

	It would be helpful to have more information about ascertainment of these baseline details. Are the authors relying solely on what the treating surgeon (presumably the gynaecologist) has written in the patient notes? As a gynaecologist, I would not be confident that these details would systematically be collected or that menopausal status would be accurately recorded. If there was no standardised collection of data at baseline (including clarification of how menopausal status was defined), the information from clinical records is likely to be scanty and may be unreliable. Can the authors clarify whether a clinical checklist or standardised data collection was used during the consultation prior to BSO? The sample size includes 1653 women who underwent BSO and 570 who underwent USO. Although the authors plan to investigate a wide range of (adverse) health outcomes, there are no power calculations. Can the authors please specify and justify the primary and secondary outcomes to be studied and provide power calculations to indicate whether this sample size can demonstrate whether these outcomes differ between BSO, USO and control participants? This is particularly important for the 20% who underwent BSO prior to age 40 years, since the authors previous publications suggest that this group may be at greatest risk of adverse long-term outcomes. Data on use of HT following BSO will be collected. Data from MOA-1 have previously been utilised to demonstrate that HT use may reduce some of the adverse long-term health outcomes associated with surgical menopause. The current absence of prospective data on surgical menopause means that cohort studies like MOA-1 play an important role in directly clinical practice. Several other factors are likely to influence use of HT following surgical menopause. For example, history of endometriosis (recorded in 35% of BSO participants), obesity, personal or family history of VTE, poorly controlled hypertension etc. In addition, symptoms (particularly VMS) are likely to influence prescription and uptake of HT. This is directly relevant to the outcomes of interest. For example, an obese woman undergoing BSO with hypertension is less likely to be prescribed HT and more likely to have later CVD. Without knowledge of the key variables affecting both CVD and use of HT, it is not possible to conclude (as previously) that use of HT may reduce long-term adverse outcomes following BSO. How will factors likely to influence the prescribing and uptake of HT following BSO be ascertained and accounted for in the analysis? Finally, the population sampled are 94% white. Whilst this may be locally representative, it is not representative of the US population overall (or many other countries), and the findings cannot necessarily be generalised to more diverse populations. Ethnicity may independently impact on the likelihood of BSO, on menopausal symptoms and on the long-term outcomes of interest to this study and it would be helpful to include this in limitations of the study. In summary, more information is urgently needed about the risks and benefits of surgical menopause and the impact of subsequent HT use. This cohort presents a valuable opportunity to better understand the consequences of BSO, but requires further clarification of primary and secondary end points and statistical power.

REVIEWER	Louise Wilson MEpi The University of Queensland, Brisbane, Australia
REVIEW RETURNED	10-Aug-2017

GENERAL COMMENTS	General comments: The aim of this paper is to describe The Mayo Clinic Cohort Study of Oophorectomy and Aging-2 (MOA-2), established to study the long-term effects of unilateral and bilateral oophorectomy on the ageing process in women who had these surgeries before they are 50 years of age and during the period 1988 through 2007. This study replicates a prior cohort study that has followed women who had unilateral/bilateral oophorectomies during the period 1950 through 1987. This study will make an important contribution to knowledge about the longer-term outcomes of these surgeries, and as the authors note, provides access to more complete information than MOA-1 and reflect more recent surgical practices. A description of this cohort is a useful contribution to the literature. Specific comments in relation to the manuscript follow. Dot-pointed Strengths and Limitations of the Study It would be preferable if these dot-points were more concise. 1st dot-point: This point starts with “our four cohorts of women”; there should be more context provided in this sentence e.g. “The four cohorts of women in the Mayo Clinic Cohort Study of Oophorectomy and Aging-2 are population-based and nested within a medical records-linkage system, with median follow-up already longer than 14 years”. 2nd dot-point: This point could be reworked into one, shorter sentence. 3rd dot-point: Rather than just saying that the participation was high because almost all women gave general authorization to use their medical records, it would be good to give the actual percentage. The second sentence of this dot-point is covering a different topic and could be omitted. In addition, the choice of referent population is not necessarily either a strength or a limitation as it really depends upon the research questions that are being asked. Introduction The Introduction would benefit from the inclusion of the overall aim of the paper, making it clear that the intention is to describe the MOA-2 cohort. Page 6; line 52: The sentence: “Analyses related to some outcomes in the four cohorts have been reported elsewhere” is confusing. Although, the four cohorts are described in the Abstract, the main body of the manuscript and the Abstract are designed to stand alone, and the four cohorts have not been mentioned previously at this point in the main body of the paper. In addition, MOA-1 also has four cohorts, further adding to the confusion. The sentence could easily be amended to read: “Analyses related to some outcomes of the study have been reported elsewhere”.

	Cohort description Page 7, Line 41: Although the references to the Rochester Epidemiology Project are provided, it would be useful to include a brief description of the project, including, for example, the geographic coverage of the project, the length of time it has been operating and the size of the dynamic cohort. Unilateral oophorectomy study Page 8, Line 29: I am curious to know how women with a high genetic risk of ovarian cancer were identified (e.g. through genetic testing or response to questions about family history), and whether this information would have been complete for all women with oophorectomy. Page 8, Line 46/P9, Line 38: It is interesting that referent women who underwent unilateral oophorectomy or bilateral oophorectomy after the index date were included in the cohort. I am interested to know how these women would be treated in any analyses of outcomes. Are they censored at the time they have the surgery for oophorectomy? Or do they become part of the relevant oophorectomy group? How many women in the referent groups have had subsequent oophorectomies to date? Page 9, Line 12: A comment is made that women with prior hysterectomy are included in the bilateral oophorectomy group because "hysterectomy was not considered a cause of ovarian sufficiency". This statement should be referenced, as the results from studies are conflicting in this regard (see: Trabuco et al (2016) PMID: 27054925; Nahas et al (2003) PMID: 12737673 and Lee et al PMID: 20211514). Page 11, Line 52 and Page 12, Line 24: In the unilateral oophorectomy group, 11 women were found to have ovarian cancer at pathological examination and 25 women in the bilateral oophorectomy group. Could you please clarify whether or not these women were then excluded from the study? Page 17, Line 45: Please turn the bracketed phrase "passive surveillance via medical records: recall bias was minimized" into a proper sentence. Out of curiosity, are there future plans to compare results from MOA-1 and MOA-2 to try to discern period and/or cohort differences?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 – Dr. M. Hickey

Comment 1. "Thank you for asking me to review this manuscript. Whilst the practice of removing normal ovaries at the time of hysterectomy has become less common in recent decades, oophorectomy without clear medical indications still occurs (as the authors have indicated). High quality evidence indicating the potential risks and benefits of surgical menopause (pre-menopausal bilateral oophorectomy) is needed for clinical practice and informed consent.

Data from the previous cohort (MOA-1) published by these authors has been highly cited and (in my experience) has directly influenced clinical practice. I am delighted to hear that a more recent and carefully evaluated cohort is being established. However, I have several concerns about the study design and planned outcomes that I hope the authors might consider addressing."

Response: Many thanks for the positive remarks and for recognizing our contribution to the controversy about bilateral oophorectomy. Unfortunately, bilateral oophorectomies without a clear medical indication continue to be performed. We added three new references on the controversy (new references 25-27).

Comment 2. “The stated purpose is to study the effects of USO and BSO on the "ageing process". What exactly does this mean and how exactly will this be measured? The underlying assumption seems to be that BSO will accelerate ageing and this assumption is echoed in the comment that "the abrupt and extreme hormonal changes caused by BSO will have a major effect on the ageing process across the full body". This sounds like the authors have already decided that there will be extensive adverse outcomes from BSO. How will the ageing process be measured? The authors mention multimorbidity as a marker of ageing, can they be more specific about exactly what conditions they are referring to and what they mean by MM in this context? The published literature on menopause and biological ageing (eg PMID: 27457926) measures epigenetic signatures for ageing that are not being collected in this study.”

Response: Our analyses for accelerated aging measured by the rate of accumulation of multiple chronic conditions have already been published (Rocca et al., 2016, new reference 8; Rocca et al., 2017, new reference 9). In our two papers we provide extensive details about the conditions considered and the methodology. A summary of our methods and findings concerning multimorbidity is provided in the revised manuscript (lines 265-295). We plan to study epigenetic signatures for aging (e.g., DNA methylation) as part of the in-person follow-up of the bilateral oophorectomy cohort. This plan was more directly described in the revised manuscript (lines 326-331). The paper by Levine et al., 2016, was already cited in our initial submission (new reference 24).

Comment 3. “The authors refer in several places to the “abrupt and extreme hormonal change" associated with BSO. What exactly does this mean? I don’t think hormonal measures are included in the protocol. Women experience cyclic changes in sex hormones regularly, and the natural transition from peri to postmenopause is marked by substantial changes in circulating estradiol concentrations (PMID: 18574431). One could also say that starting a postmenopausal woman on HT leads to an “abrupt and extreme hormonal change”.”

Response: Our intention was to emphasize that the surgical removal of an endocrine organ (in this case the ovaries) is a particularly abrupt and extreme event, as compared to naturally occurring cyclic changes, naturally occurring menopause, or to pharmacological interventions that supplement the hormones produced by the endocrine organ. Nevertheless, we removed the word “extreme” throughout the manuscript.

Comment 4. “I am not a methodologist, but central to this cohort study is the assumption that adverse health outcomes observed more frequently in the BSO group compared to the age-matched control population are attributable to the BSO. This is problematic and does not consider likely confounders such as SES. As the authors have previously published: "the association between bilateral oophorectomy and cardiovascular mortality may be confounded by socioeconomic status. In particular, lower socioeconomic status may increase the probability of undergoing a bilateral oophorectomy,[49] decrease the probability of receiving adequate estrogen treatment after the oophorectomy,[50] and independently increase cardiovascular mortality.[51] Women undergoing BSO are likely to differ" (PMID: 19034050). Since SES is likely to influence the likelihood of undergoing BSO and the outcomes of interest, what measures of SES do the authors have (apart from years of education)? How will they account for the likely effect of SES on their outcome measures?”

Response: In our two publications that used the MOA-2 to investigate the effect of bilateral oophorectomy on the accumulation of multimorbidity, we addressed the possible confounding effect of socioeconomic status (SES) by including race and education in our inverse probability weights (new references 8 and 9). In addition, we included smoking, body mass index, age at baseline, and calendar year at baseline. Finally, we included 18 chronic conditions present at baseline. As shown in Supplemental Figure 1 in Rocca et al., 2016, education was not very different before adjustment (standardized difference of means of 0.06), and the rebalancing was successful. Race had a greater imbalance (standard difference of means of 0.13), but the rebalancing was successful. We believe that our complex method of inverse probability weighting has removed most of the potential confounding for SES. However, to address any potential residual confounding, we plan to link women in our cohorts with income at the census block group level. This information is available from the 2000 US Census. Our plan for future analyses was added to the Limitations section (lines 415-424). We also provided a new reference on the methods (new reference 36).

Comment 5. “There is additional evidence in this manuscript that the intervention group may differ from controls regarding important risk factors for the outcomes to be studied. Whilst the specific outcomes to be measured in MOA-2 are not entirely clear, they include neurological and psychiatric disease. On page 14, the authors comment that women having BSO before aged 46 were more likely to have suffered emotional and physical abuse in childhood, and those having BSO under 40 were more likely to have experienced physical abuse as adults (previously published). Clearly this is highly likely to impact on the risk of current and later psychiatric and potentially neurological disease. How will this be considered in data analysis? Is the study powered to address its primary outcome having controlled for childhood and adult abuse?”

Response: Our case-control study of adverse childhood and adult experiences was restricted to the 128 case-control pairs in which both women had medical record information dating back to age 15 years or earlier. Therefore, the information about adverse childhood and adult experiences has not been collected for the full cohort. Based on the results of our study, we plan to expand the data collection to the full cohort. We added a description of the plan for new data collection to the manuscript (lines 333-337). Statistical power was addressed in our response to comment 6 of Reviewer 1 below. We also added a new reference on our case-control study (new reference 23).

Comment 6. “It would be helpful for the authors to clearly state the primary and secondary outcomes of interest, why these outcomes have been chosen and the power of the study to determine the association between the intervention and outcomes.”

Response: A statement about primary and secondary outcomes and about statistical power was added to the manuscript (lines 348-358).

Comment 7. “Also, I am puzzled why only negative outcomes are of interest. It is very likely that BSO will substantially reduce ovarian cancer risk, and may also reduce breast (and total cancer) risk (PMID: 24807324). Chronic pelvic pain affects up to 26% of women (PMID: 24658485) and around 30% of those who underwent BSO has endometriosis. What is the long-term effect of BSO on pelvic pain? This information would be useful for clinical practice and help women and HCP making informed choices. Data from the MOA-2 cohort is likely to influence decision making around BSO and this study has the potential to provide new information about both the risks and benefits of this procedure.”

Response: Although a risk versus benefit approach is normally optimal in evaluating a medical practice, in the case of bilateral oophorectomy, we are confronted with the need to emphasize the risks in order to modify a practice that has become rooted in the minds of physicians and persists despite the lack of scientific evidence. The authors that continue to endorse the practice, use the risk versus benefit approach to present the decision to remove or not remove the ovaries as a matter of preference or choice. We believe that in a premenopausal woman who does not have ovarian cancer, does not carry a high risk genetic variant, and does not meet the criteria for definite family history of ovarian cancer, bilateral oophorectomy should not be offered as an "option". A recent example of the perspective of gynecologists who continue to support the practice is given by Evans et al., Obstet Gynecol, 2016. We responded to that publication with a letter explaining our position (Rocca et al., Obstet Gynecol, 2017). We added three new references on this controversy (new references 25-27). Nevertheless, as requested, we added a discussion of possible beneficial outcomes to the revised manuscript (lines 313-321).

Comment 8. "Establishing menopausal status at the time of oophorectomy, current chronic disease and risk factors for chronic disease such as tobacco use and obesity, is critical to the interpretation of long-term health outcomes and the attribution of these outcomes to BSO. It would be helpful to have more information about ascertainment of these baseline details. Are the authors relying solely on what the treating surgeon (presumably the gynaecologist) has written in the patient notes? As a gynaecologist, I would not be confident that these details would systematically be collected or that menopausal status would be accurately recorded. If there was no standardised collection of data at baseline (including clarification of how menopausal status was defined), the information from clinical records is likely to be scanty and may be unreliable. Can the authors clarify whether a clinical checklist or standardised data collection was used during the consultation prior to BSO?"

Response: Information about menopausal status, chronic diseases, and risk factors before the index date was collected from historical medical records accumulated over time in a records-linkage system. To strengthen our data quality, we used a manual of instructions to define the variables collected by the two abstractors (lines 182-184). Therefore, these data rely neither on the documentation produced by the treating surgeon at the time of the surgery (very often inadequate) nor on the ability of a woman to recall and self-report past events at an interview. We emphasized this unique strength of our study in the revised manuscript (lines 363-373). We also reported that women had a median of 22.8 years of medical record information before the index date (lines 186-187).

Comment 9. "The sample size includes 1653 women who underwent BSO and 570 who underwent USO. Although the authors plan to investigate a wide range of (adverse) health outcomes, there are no power calculations. Can the authors please specify and justify the primary and secondary outcomes to be studied and provide power calculations to indicate whether this sample size can demonstrate whether these outcomes differ between BSO, USO and control participants? This is particularly important for the 20% who underwent BSO prior to age 40 years, since the authors previous publications suggest that this group may be at greatest risk of adverse long-term outcomes."

Response: See our response to comment 6 above.

Comment 10. "Data on use of HT following BSO will be collected. Data from MOA-1 have previously been utilised to demonstrate that HT use may reduce some of the adverse long-term health outcomes associated with surgical menopause. The current absence of prospective data on surgical menopause means that cohort studies like MOA-1 play an important role in directing clinical practice. Several other factors are likely to influence use of HT following surgical menopause. For example, history of endometriosis (recorded in 35% of BSO participants), obesity, personal or family history of VTE, poorly controlled hypertension etc. In addition, symptoms (particularly VMS) are likely to influence prescription and uptake of HT. This is directly relevant to the outcomes of interest.

For example, an obese woman undergoing BSO with hypertension is less likely to be prescribed HT and more likely to have later CVD. Without knowledge of the key variables affecting both CVD and use of HT, it is not possible to conclude (as previously) that use of HT may reduce long-term adverse outcomes following BSO. How will factors likely to influence the prescribing and uptake of HT following BSO be ascertained and accounted for in the analysis?"

Response: We added a discussion of the possible confounding by indication for the effects of estrogen and other sex steroid hormones in women who underwent bilateral oophorectomy (lines 425-429). Outside of a randomized clinical trial, we can only reduce the possible confounding effects using statistical methods, primarily multivariable models.

Comment 11. "Finally, the population sampled is 94% white. Whilst this may be locally representative, it is not representative of the US population overall (or many other countries), and the findings cannot necessarily be generalised to more diverse populations. Ethnicity may independently impact on the likelihood of BSO, on menopausal symptoms and on the long-term outcomes of interest to this study and it would be helpful to include this in limitations of the study."

Response: This limitation was discussed in the revised manuscript (lines 46-48 and lines 399-404).

Comment 12. "In summary, more information is urgently needed about the risks and benefits of surgical menopause and the impact of subsequent HT use. This cohort presents a valuable opportunity to better understand the consequences of BSO, but requires further clarification of primary and secondary end points and statistical power."

Response: Many thanks for recognizing the significance of the study. See our response to comment 6 above for a discussion of statistical power.

Reviewer 2 – Dr. L. Wilson

Comment 1. "Dot-pointed Strengths and Limitations of the Study. It would be preferable if these dot-points were more concise.

1st dot-point: This point starts with "our four cohorts of women"; there should be more context provided in this sentence e.g. "The four cohorts of women in the Mayo Clinic Cohort Study of Oophorectomy and Aging-2 are population-based and nested within a medical records-linkage system, with median follow-up already longer than 14 years".

2nd dot-point: This point could be reworked into one, shorter sentence.

3rd dot-point: Rather than just saying that the participation was high because almost all women gave general authorization to use their medical records, it would be good to give the actual percentage. The second sentence of this dot-point is covering a different topic and could be omitted. In addition, the choice of referent population is not necessarily either a strength or a limitation as it really depends upon the research questions that are being asked."

Response: The corrections requested were implemented (lines 30-43).

Comment 2. "Introduction. The Introduction would benefit from the inclusion of the overall aim of the paper, making it clear that the intention is to describe the MOA-2 cohort."

The introduction was modified as requested (lines 68-71).

Comment 3. “Page 6; line 52: The sentence: “Analyses related to some outcomes in the four cohorts have been reported elsewhere” is confusing. Although the four cohorts are described in the Abstract, the main body of the manuscript and the Abstract are designed to stand alone, and the four cohorts have not been mentioned previously at this point in the main body of the paper. In addition, MOA-1 also has four cohorts, further adding to the confusion. The sentence could easily be amended to read: “Analyses related to some outcomes of the study have been reported elsewhere”.”

Response: The sentence was revised as suggested (lines 71-72).

Comment 4. “Cohort description. Page 7, Line 41: Although the references to the Rochester Epidemiology Project are provided, it would be useful to include a brief description of the project, including, for example, the geographic coverage of the project, the length of time is has been operating and the size of the dynamic cohort.”

Response: We added the specific details requested (lines 91-92).

Comment 5. “Unilateral oophorectomy study. Page 8, Line 29: I am curious to know how women with a high genetic risk of ovarian cancer were identified (e.g. through genetic testing or response to questions about family history), and whether this information would have been complete for all women with oophorectomy.”

Response: We added a discussion of the incomplete genetic testing in the Limitations section (lines 430-435).

Comment 6. “Page 8, Line 46/P9, Line 38: It is interesting that referent women who underwent unilateral oophorectomy or bilateral oophorectomy after the index date were included in the cohort. I am interested to know how these women would be treated in any analyses of outcomes. Are they censored at the time they have the surgery for oophorectomy? Or do they become part of the relevant oophorectomy group? How many women in the referent groups have had subsequent oophorectomies to date?”

Response: Our approach for analyses of outcomes was clarified (lines 119-123 and 144-149).

Comment 7. “Page 9, Line 12: A comment is made that women with prior hysterectomy are included in the bilateral oophorectomy group because “hysterectomy was not considered a cause of ovarian insufficiency”. This statement should be referenced, as the results from studies are conflicting in this regard (see: Trabuco et al (2016) PMID: 27054925; Nahas et al (2003) PMID: 12737673 and Lee et al PMID: 20211514).”

Response: We added the three references and clarified the sentence (see lines 131-134 and new references 14-16).

Comment 8. “Page 11, Line 52 and Page 12, Line 24: In the unilateral oophorectomy group, 11 women were found to have ovarian cancer at pathological examination and 25 women in the bilateral oophorectomy group. Could you please clarify whether or not these women were then excluded from the study?”

Response: We clarified that these women were included in the study (lines 110-112 and 137-140). In addition, we discussed the justification for the inclusion in the revised Discussion (lines 413-415).

Comment 9. “Page 17, Line 45: Please turn the bracketed phrase “passive surveillance via medical records: recall bias was minimized” into a proper sentence.”

Response: The sentence was re-written (lines 369-373).

Comment 10. “Out of curiosity, are there future plans to compare results from MOA-1 and MOA-2 to try to discern period and/or cohort differences?”

Response: Comparative analyses across the two studies are possible, and we will perform them if specific hypotheses arise. We added a comment about these possible analyses in the Strengths section (lines 391-394).

We believe that the manuscript has substantially improved in response to the comments of the reviewers, and we hope that it is now acceptable for publication. To address the extensive requests for additional details, the word count went a bit over the recommended word limit. We hope that this is acceptable.

VERSION 2 – REVIEW

REVIEWER	Martha Hickey University of Melbourne, Australia
REVIEW RETURNED	14-Sep-2017

GENERAL COMMENTS	Thanks Dr Rocca and colleagues for revising this manuscript so thoroughly.

REVIEWER	Louise Wilson The University of Queensland Australia
REVIEW RETURNED	22-Sep-2017

GENERAL COMMENTS	The authors have provided comprehensive responses to the comments made by reviewers and the manuscript has been well-revised. As noted in my original review, this study will make an important contribution to the body of evidence on oophorectomy, and a description of this cohort is a useful contribution to the literature.