PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Does endometriosis affect professional life? – a matched case-control study in Switzerland, Germany and Austria
AUTHORS	Sperschneider, Marita; Hengartner, Michael; Kohl-Schwartz, Alexandra; GEraedts, Kirsten; Rauchfuss, Martina; Woelfler, Monika; Haeberlin, Felix; von Orelli, Stephanie; Eberhard, Markus; Maurer, Franziska; Imthurn, Bruno; Imesch, Patrick; Leeners, Brigitte

VERSION 1 – REVIEW

REVIEWER	Prof. Dr. Tewes Wischmann Institute of Medical Psychology, University Hospital Heidelberg, Heidelberg, Germany
REVIEW RETURNED	05-Oct-2017

GENERAL COMMENTS	This is an excellent study on the very interesting and often neglected topic, how endometriosis influences the daily and professional life of women affected with this chronic disease. The relevant literature is covered in the manuscript, the study design is adequate and the sample size very impressive (>500 patients with confirmed endometriosis and >500 matched controls). The results are presented adequately, the discussion is well considered and the conclusions are clear and of clinical importance. I have only some remarks and suggestions that might help to strengthen the quality of the paper. The response rate of about 64% in the cases is high for a clinical sample, but I do not agree with the authors that a response rate of about 36% in the control group is in the upper level of comparable studies (on page 17). In my opinion this rate is low and this has to be mentioned as one of the few limitations of this study. What I do not understand exactly is what the authors write concerning the matching process of cases and controls. According to the section on recruitment, each woman with endometriosis was matched to a control woman recruited in the same centre (page 7, lines 177-178). How do the authors then explain the divergent distributions in the nationality of the participants (table 1) with about 42% Swiss cases vs. 57% Swiss controls and about 49% German cases vs. about 32% German controls? Some minor remarks: Page 2, line 36: I suggest to write "… is a gynaecologic disease most commonly causing severe ..." Page 7, lines 175-176: The part of the sentence "… and were matched to the patient cohort in respect to age and ethnical background (pair-Matching)." can be skipped because this information is given in the next sentence. Last paragraph on page 10 and first paragraph on page 11: Which of the differences between cases and controls are statistically significant or not significant?

	Page 11, line 282: The pain frequency percentages should be added. Page 17, line 424: Write “surgical records” (instead of “operational records”). Table 1, line 21: A typo, it should be “(79.4%)”. Table 1, line 27: Why were pregnancies >24 weeks listed and not live born children?

REVIEWER	Arnaud Fauconnier CHI Poissy-Saint-Germain, Versailles Saint-Quentin University, France
REVIEW RETURNED	16-Oct-2017

GENERAL COMMENTS	1. Summary of the content: This was a multicenter retrospective case-control study, performed in German-speaking populations, designed to investigate whether endometriosis interferes with professional choices, career development and daily working life. It demonstrate that endometriosis, especially in association with chronic pain, interfered with professional activity. 2. My overall opinion of the manuscript: The authors provide potentially interesting results concerning the occupational consequences of the disease in endometriosis patients: women diagnosed with endometriosis showed a lower likelihood of working in their profession of choice and stronger health-related considerations on their career decisions. They had higher professional experience and had stayed longer in their current employment. However, to be generalized, and thus may be have some implications in the care and social insurance, the results must be checked for several important point: First, the spectrum of the disease, apart from the rASRM measurement, I was not able to find the description of the population of endometriosis case (type of endometriosis, intestinal or urological involvement, type of surgery etc…). Furthermore, as all women were selected by having verification surgery there might be an important referral bias. Control women are also particular while some of them were hospitalized for begnign gynecologic conditions. Second, I am not convinced by the way of the professional impairment was measured. I wonder if some validated instrument does exist for this aim. From this point of view, it would be interesting that the present article to be reviewed by an expert in occupational medicine. Anyway, I would like to be more convinced by the choice of questions and their construct value. Moreover, the bulk presentation of the various measures deserves to be revised in accordance with the main hypothesis of the authors. A principal judgment criterion (and therefore an a priori analysis of power) must be defined in order to avoid any ambiguity in the analysis. 3. My recommendations, with reasons: Although, I found that the authors made important effort to clarify the relation between endometriosis and occupational consequence, I do think that the present manuscript merits important efforts, including re-analyses and rewriting, in order to present clear-cut result and resolve, if they could, the difficulties mentioned above. 4. General comments: This patient-centered question is important in the field of quality of life and endometriosis. Few studies on the impact of professional life have been previously published and the present study is the first that use control group to assess professional life of endometriosis patients. The authors of the present study should highlight this point

	to justify the present study in the introduction of the article. This study provide a high sample of patients (550 cases and 550 control) and the authors adequately followed the STROBE checklist. But in general the manuscript is difficult to read and the writing should be more concise. 5. Specific comments: “the aim of the present study to investigate (i) career development, (ii) current work performance”. The authors raise an important and sound question, however isn’t it to ambitious to test such hypothesis by a case control study and is there proper methodology to bring clear-cut answer of theses questions? Matching: the recruitment of the control group was made in the same hospitals and units which is a strength of the study. However, beyond the age and the ethnic background, it would have been better to match with the incomes of patients’ parents (which could impact the main outcome measure). “A smaller proportion of the study population was recruited through different self-help groups for endometriosis”. It Is unclear to me why the authors decide to use these patient as they were able to recruit numerous hospital patients. As it is presented hereafter, these patient may have very particular features for occupational life that can biases the results in the present case. I would exclude these patient from analyses. “ethnic background”, It is unclear what it does mean. Endometriosis patient were included irrespective of disease symptoms but only in case of surgically and histologically confirmed diagnosis. However it is not true because to have surgery an endometriosis patient must have significant symptoms as chronic pain and or infertility. This may create artefactual difference with control women and should be properly checked. As the authors said, the most frequent reasons reported for not participating were lack of time. However I wonder how the lengths of the questionnaire (about 500 questions!) might affect the participation of women. It might happen that the women who were very busy by their job refuse to participate. This should be investigated more deeply. “The current analysis focused on 26 questions about professional life”. What is the validity of the questionnaire used? As the impact of a disease on professional life might be difficult to measure it may be important to use rigorous instrument. It seems that the authors have developed their own questionnaire, what is therefore the value of their findings. Hard to say. Was the rASRM the only descriptor of the extent of the disease? In the German speaking countries it is usual to use the ENZIAN score sheet during surgery. It may be feasible to get this information. The modeling strategy is rather confusing to me. The authors stated that the endometriosis group was introduced as an “independent” predictor variable. It is unusual to do so as there is numerous different occupational variable to explain. So it would be more convincing to present the adjusted differences in term of occupational consequences between endometriosis women and controls. The result section encompasses numerous results and it is hard to read in the present ful length presentation. The authors should report unadjusted results and focus on important results in the text. Line 258 to 265. Could you provide p-value? Moreover, could you explain why have you specifically focused on this population (>1 child). The associations between a diagnosis of endometriosis and

	reporting a lower likelihood of working in the job of choice, stronger health influences on the selection of the professional activity , a higher experience in the current profession, and a longer duration of the present employment, are important and new results and should be highlighted. The intensity of reported health related limitations in career choice was independent of the rASRM-stage. It would be important to test other relation between occupational limitation and the characteristics of the disease as it would be of interest to demonstrate a relation between the most severe forms of endometriosis and the worst professional impairment. Which cofounders did you use for the adjustment (Table III)? Did you use the nationality as cofounders since there is a significant difference between groups? There is somes errors in table 3 that must be corrected. There is no need to present the results in text and table simultaneously.

REVIEWER	Caroline Law De Montfort University, Leicester, UK
REVIEW RETURNED	16-Oct-2017

GENERAL COMMENTS	As stated to the editors, I am not able to comment on the statistical aspects of the paper and do not have a background in quantitative research. Instead, my review focuses on broader study design, relevance and contribution to the wider literature on endometriosis, and clarity of reporting. - The paper addresses an important issue, and key relevant literature on the topic is reviewed in the introduction and discussed in the discussion. - There is also some interesting discussion provided, e.g. on how age at symptom onset might affect education and qualifications and resultant variance in findings between studies, and the impact of parenthood on working lives, etc. However, the arguments made in the discussion could be clearer and discussion could be better related back to the current study. - Unfortunately, a crucial issue is the lack of detail provided about the control group. It is stated that this group comprises women recruited via regular annual gynaecological consultation or via hospital stays because of benign gynaecological problems other than endometriosis. No detail is provided on how many women form this latter subsection of the control group and what symptoms these women may have experienced, and no discussion is provided about the potential implications of this, i.e. how the presence of such gynaecological problems/symptoms in the control group might have influenced the findings. In particular, this causes problems for the finding that women with endometriosis did not experience higher stress at work than the control group, and the resultant implication that endometriosis does not correlate with work related stress. If the women in the control group experienced symptoms and related stress, the lack of difference between the two groups does not support the idea that endometriosis does not correlate with work related stress. - Overall, there is a lack of clarify in the way the findings are reported, and this runs throughout the paper and makes it difficult to read and comprehend. For example, phrases are used unproblematically or without definition and at times it is difficult to grasp the meaning (e.g. ‘job of choice’ or ‘loss of working power’). The presentation of figures is unclear at times (e.g. 285-289). The

	discussion of psychological symptoms (308) as a variable is problematic as this was not discussed in the 'questionnaire' section and we are not informed what these psychological symptoms are. It is unclear if and how validated questionnaires were incorporated (202-204). The unclear phrasing is also found in other sections of the paper (e.g. 132-133, 147-149, 197-198). Recruitment is described inconsistently (e.g. self help groups are named as a recruitment route in some places and not others) and unclearly (e.g. 'university', 'private offices' are not explained). - It needs to be clear to all audiences (those with quantitative background and those without) whether causation can be identified or only correlation. If causation cannot be claimed, the abstract and line 315 need rewording. - The abstract suggests that most other associations between endometriosis and work were weak. This seems contradicted in lines 273-278. - The main argument in the paper doesn't come across very clearly or consistently – while the conclusion in the abstract emphasises the detrimental impact endometriosis can have on working lives, the conclusion of the paper downplays this. - While the topic of endometriosis and work/professional life is a very important one, the paper could be clearer in explaining how it contributes to the existing literature and to what is already known about the topic. As it stands the contribution comes across as fairly minimal. - The paper requires an English language edit, in conjunction with greater clarity of reporting.

REVIEWER	Federica Facchin Faculty of Psychology, Catholic University of Milan, Italy
REVIEW RETURNED	20-Oct-2017

GENERAL COMMENTS	This is an interesting study that I enjoyed reading because I think it addresses a very relevant research question regarding the impact of endometriosis on professional life. Specifically, the study aimed at examining whether endometriosis negatively affects women's career development and current work performance. The association between specific endometriosis symptoms (i.e., chronic pain and fatigue) and work performance was also explored. The importance of such a research question is clearly underlined by the authors in the introduction section. Endometriosis is a chronic painful disease that often involves remarkable limitations in everyday activities, including work. The disruptive impact of the disease on women's lives and plans for the future has been highlighted by several qualitative studies. There is also evidence that impaired work functioning (decreased productivity, absenteeism due to pain as well as to the need for medical visits and treatments…) contributes to the psychosocial and economic burden of the disease. This study examined the association between endometriosis and women's professional life in a systematic fashion (using a case-control research design). The sample was large since it was composed of 505 women with surgically/histologically confirmed endometriosis and 505 matched controls without endometriosis. Inclusion and exclusion criteria for both groups were clearly explained, as well as recruitment procedures (a detailed figure – Figure 1 – was provided to describe the overall recruitment process). Data were derived from a larger research that involved a 390-item

	questionnaire administered to all women, plus 90 questions specifically focused on endometriosis-related issues. I think there is a lack of clarity in the section entitled “Questionnaire” (p. 8). First, the aims of the larger research and the original 390-item questionnaire were not specified. A description of the dimensions addressed by the questionnaire was provided on p. 8, lines 196-204, but I actually don’t understand whether the authors here were describing the 390 questions for all women, or the 90-question set for endometriosis participants, or both sets of questions at the same time. From lines 200-204, the authors explained that chronic pelvic pain (frequency, duration, and intensity) – which is commonly referred to as non-menstrual pelvic pain that lasts at least six months – was assessed using items derived from the Brief Pain Inventory and the Pain Disability Index. I would like to know why the authors did not assess also cyclic pelvic pain (dysmenorrhea), which is a major clinical problem in women with endometriosis and may significantly affect everyday life and work performance. I do not see anything about dysmenorrhea, neither in the text, nor in the table reporting the associations between endometriosis symptoms and sick leave/productivity loss. I think this lack of important information should be motivated and acknowledged as a study limitation. As reported in Table IV, frequency of fatigue and psychological symptoms were also assessed. I think the authors should clarify in the “Questionnaire” section which specific endometriosis symptoms were assessed and how. For instance, how was fatigue defined in the question? I am interested because I think chronic fatigue is an important endometriosis symptom, although understudied, especially as compared with pelvic pain. The category “psychological symptoms” is also vague and I would like to know more about the specific question used in the questionnaire (which seems to be a general dichotomous variable: yes/no): was the question referred to diagnosed psychological disorders? What type of psychological symptoms was assessed? Were psychological symptoms assessed only in women with endometriosis (and why)? It was also mentioned (lines 202-204) that different internationally validated questionnaires investigated aspects of quality of life, including professional life. Were these questionnaires (which questionnaires?) or parts of them included in the study? Based on the subsequent description (lines 206-220), I understand that these validated questionnaires were not analyzed in this study. I invite the authors to increase clarity, for instance by providing example items for the two question sets. Overall, the section should be reorganized in a more systematic manner, with a clear description of the original questionnaire (390 + 90 items) vs. the 26 questions included in the current study for all participants and for women with endometriosis. A precise description of the endometriosis symptoms and the psychological symptoms assessed should be provided. In the Statistical analyses section, p. 10, line 242, I would write “To test associations between study groups and characteristics of professional life” (or to test group differences…). The presentation of the results is also a little confused. For example, in the section entitled “Characteristics of study groups and possible

	confounders", I don't understand – on the basis of Table I – the reason why the authors reported the proportional distribution of having a gainful occupation (full time, part time, no occupation) for women with at least one child by study group. Was the comparison between these subgroups (chi squared test) significant? Was this information relevant according to your research question? Table I is very clear, but I think the authors should clarify in the text that significant between-group differences were found for some socio-epidemiological parameters (please specify whether in these preliminary analyses significance tests were performed at P < 0.05), which were included in subsequent analyses as potential confounders (I hope I understood well). Endometriosis characteristics are reported in Table II. I think that symptom characteristics (presence and frequency of chronic pain, fatigue, presence of psychological symptoms) should be displayed in this Table. Table IV is important because it shows the associations between symptoms and sick leave/productivity loss, but I miss a more comprehensive description of the endometriosis group. There is a similar problem with Table III. On p. 11, lines 268-269, it is written that "characteristics of professional activity in women diagnosed with endometriosis and control women are presented in Table III". Actually, Table III reports the results of the logistic regressions conducted and there are no other tables reporting the characteristics of these work parameters by study group. Perhaps, this material could be included in Table I to avoid the creation of another table. On p. 11, lines 269-272, I don't understand why the sentence ends with "…showed statistical significant differences in both groups". Because study group is the independent variable, these are between-group differences (rather than within-group differences). I am sure the analyses are correct, but the way in which findings are reported in the text should be carefully reviewed. As regards the section "Work impairment and compensatory mechanisms", these percentages are not written correctly: 10,7% (it should be 10.7%), 0,5% (twice), 7,6% (lines 285-288). These are merely descriptive findings that per se don't allow any conclusion about the association between endometriosis and work performance. I don't understand why work performance and sick leave were not evaluated in the control condition in order to address very interesting comparisons. This should be acknowledged as a limitation. Some of the Conclusions should be more cautious and less enthusiastic. For example: "According to the present results women with endometriosis were very successful in their health-related choice of future professions" (lines 338-339). Indeed, findings revealed that these women had higher experience in the current profession and stayed longer in their current employment relative to controls. However, I would not conclude that these can be firmly considered as positive findings. First, these two variables may be associated (did you check?): perceived higher experience in current job may depend on longer practice; second, these findings do not necessarily imply that women with endometriosis feel satisfied and successful, especially if we consider that most of them were NOT doing their work of choice, because their decisions were influenced by health-related issues. This study findings suggest that these

	women struggled to have and keep their job despite endometriosis, to the point that 75.5% of them reported to have gone to work in spite of severe pain in the month prior the study. Moreover, as acknowledged by the authors (lines 343-346), women might stay in their current occupation because the environment is adapted to their endometriosis-related needs. One hand this may be the reason for not seeking another job (as well as fear, of course); on the other hand, the adequate environment characteristics may motivate the absence of group differences with regard to work-related stress. The authors may disagree, but that's how I read their findings. Lines 350-361: these considerations are speculative and not supported by statistical tests. Moreover, I would not introduce new findings in this section. Overall, this study suggests that endometriosis may negatively affect professional life (including women's choices), but there is need for more research to understand this association. Moreover, I wonder why the authors did not control for the potential confounding effect of age (the two groups did not differ, but age may play an important role) and time from diagnosis (it seems like they had this information, see p. 16, line 405). I think there is a lot of work to do here (i.e., major revision), but there is potential for improvement and I do believe that this study with its novelty value may provide interesting suggestions for future research. The association between endometriosis and professional life is an important topic, and studies addressing this issue are more thank welcome to me.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Tewes Wischmann
Institution and Country: Institute of Medical Psychology, University Hospital Heidelberg, Heidelberg, Germany
Please state any competing interests or state 'None declared': no competing interests to declare

Please leave your comments for the authors below
This is an excellent study on the very interesting and often neglected topic, how endometriosis influences the daily and professional life of women affected with this chronic disease. The relevant literature is covered in the manuscript, the study design is adequate and the sample size very impressive (>500 patients with confirmed endometriosis and >500 matched controls). The results are presented adequately, the discussion is well considered and the conclusions are clear and of clinical importance. I have only some remarks and suggestions that might help to strengthen the quality of the paper. The response rate of about 64% in the cases is high for a clinical sample, but I do not agree with the authors that a response rate of about 36% in the control group is in the upper level of comparable studies (on page 17). In my opinion this rate is low and this has to be mentioned as one of the few limitations of this study.

2. RESPONSE: We included the response rate of 36% in the control group as a limitation.

What I do not understand exactly is what the authors write concerning the matching process of cases and controls. According to the section on recruitment, each woman with endometriosis was matched to a control woman recruited in the same centre (page 7, lines 177-178). How do the authors then explain the divergent distributions in the nationality of the participants (table 1) with about 42% Swiss cases vs. 57% Swiss controls and about 49% German cases vs. about 32% German controls?

3. RESPONSE: We fully agree to Dr. Wischmann. Cases and controls were recruited in the same centers, but pair matching was done partly across centers. We reworded the sentence accordingly.

Some minor remarks:
Page 2, line 36: I suggest to write "… is a gynaecologic disease most commonly causing severe ..."

4. RESPONSE: Done.

Page 7, lines 175-176: The part of the sentence "… and were matched to the patient cohort in respect to age and ethnical background (pair-Matching)." can be skipped because this information is given in the next sentence.

5. RESPONSE: Done.

Last paragraph on page 10 and first paragraph on page 11: Which of the differences between cases and controls are statistically significant or not significant?

6. RESPONSE: We now limited this information and related p-values to table I.

Page 11, line 282: The pain frequency percentages should be added.

7. RESPONSE: We added this information to table II.

Page 17, line 424: Write "surgical records" (instead of "operational records").

8. RESPONSE: Done.

Table 1, line 21: A typo, it should be "(79.4%)".

9. RESPONSE: Corrected.

Table 1, line 27: Why were pregnancies >24 weeks listed and not live born children?

10. RESPONSE: The question about motherhood is interesting in our context because of the impact pregnancies and raising children can have on the amount a woman is able to work in a paid occupation and also on questions about career growth. A stillbirth in the later pregnancy leads to a temporarily reduced or interrupted work ability like a pregnancy with a life born child. For this reason we selected pregnancies >24 weeks.

Reviewer: 2
Reviewer Name: Arnaud Fauconnier
Institution and Country: CHI Poissy-Saint-Germain, Versailles Saint-Quentin University, France
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

1. Summary of the content:
This was a multicenter retrospective case-control study, performed in German-speaking populations, designed to investigate whether endometriosis interferes with professional choices, career development and daily working life. It demonstrate that endometriosis, especially in association with chronic pain, interfered with professional activity.
2. My overall opinion of the manuscript:
The authors provide potentially interesting results concerning the occupational consequences of the disease in endometriosis patients: women diagnosed with endometriosis showed a lower likelihood of working in their profession of choice and stronger health-related considerations on their career decisions. They had higher professional experience and had stayed longer in their current employment.
However, to be generalized, and thus may be have some implications in the care and social insurance, the results must be checked for several important point:
First, the spectrum of the disease, apart from the rASRM measurement, I was not able to find the description of the population of endometriosis case (type of endometriosis, intestinal or urological involvement, type of surgery etc…).

11. RESPONSE: We added additional information about the disease – including localizations of endometriosis lesions - in table II. Correlations between disease locations and professional life have been included in the results section.

Furthermore, as all women were selected by having verification surgery there might be an important referral bias. Control women are also particular while some of them were hospitalized for begnign gynecologic conditions.

12. RESPONSE: As surgical confirmation of diagnosis is the golden standard for a diagnosis of endometriosis, we considered this approach as most appropriate to define our case group. We now included these selection criteria for cases and controls within the limitations. We also specified that we did not include women with chronic benign gynecological diseases in the control group, e.g. a mid- or longterm effect of these diseases on professional activity is unlikely.

Second, I am not convinced by the way of the professional impairment was measured. I wonder if some validated instrument does exist for this aim. From this point of view, it would be interesting that the present article to be reviewed by an expert in occupational medicine. Anyway, I would like to be more convinced by the choice of questions and their construct value.

13. RESPONSE: Yes, we fully agree to this comment and would have appreciated to use a validated questionnaire. However, when designing our study, there was no validated questionnaire focused on the specific associations between endometriosis and working ability. According to our clinical experience endometriosis has a very specific effect on working ability as women may be pain-free in some day but experience intensive pain, which seriously interferes with working ability on other days. To choose the methodologically best possible way to approach the research question, we designed a questionnaire in close cooperation with the head of the German self-help group society.

Moreover, the bulk presentation of the various measures deserves to be revised in accordance with the main hypothesis of the authors. A principal judgment criterion (and therefore an a priori analysis of power) must be defined in order to avoid any ambiguity in the analysis.
14. RESPONSE: The methods section has been carefully revised to restructure different outcome measures. We also added a power analysis to underline reliability of our findings. As the total study included also outcome measures where we expected smaller differences than those found for associations between endometriosis and profession, the study group was much larger than would have been needed to gain adequate power for the present analysis.

3. My recommendations, with reasons:
Although, I found that the authors made important effort to clarify the relation between endometriosis and occupational consequence, I do think that the present manuscript merits important efforts, including re-analyses and rewriting, in order to present clear-cut result and resolve, if they could, the difficulties mentioned above.

15. RESPONSE: We thank the reviewer for his meticulous revision of our manuscript and the opportunity to improve our analysis and interpretation of the findings.

4. General comments:
This patient-centered question is important in the field of quality of life and endometriosis. Few studies on the impact of professional life have been previously published and the present study is the first that use control group to assess professional life of endometriosis patients. The authors of the present study should highlight this point to justify the present study in the introduction of the article.

16. RESPONSE: Thank you for emphasizing these qualities of our study design, which now have been added to the introduction and the “strength passage” in the discussion.

This study provide a high sample of patients (550 cases and 550 control) and the authors adequately followed the STROBE checklist. But in general the manuscript is difficult to read and the writing should be more concise.

17. RESPONSE: We revised the whole presentation of the results as well as several phrasings in the Discussion. We improved the linguistic quality of the whole manuscript by proofreading from a professional native-speaking corrector.

5. Specific comments:
“the aim of the present study to investigate (i) career development, (ii) current work performance”. The authors raise an important and sound question, however isn’t it to ambitious to test such hypothesis by a case control study and is there proper methodology to bring clear-cut answer of theses questions?

18. RESPONSE: We replaced this sentence with a more precise description of the measured outcomes, which also emphasizes the personal experience of the women investigated.

Matching: the recruitment of the control group was made in the same hospitals and units which is a strength of the study. However, beyond the age and the ethnic background, it would have been better to match with the incomes of patients’ parents (which could impact the main outcome measure).

19. RESPONSE: We unfortunately have no information on the incomes of the participants parents. But in fact, this is an interesting point. It is probable that incomes between participants correlate with those of their parents in both groups. But, while there are countries where education is prohibitively expensive for people of low income, in the three countries where our study was conducted, the educational system is financed by governments and accessible to persons from all socioeconomic groups, as well as vertically open, i.e., vocational education can be continued towards higher levels. For these reasons, we think that educational or income level of parents has no essential impact on our main outcome measures “desired profession”, “health related limitations in career choice” and “professional experience”.

“A smaller proportion of the study population was recruited through different self-help groups for endometriosis”. It Is unclear to me why the authors decide to use these patient as they were able to

recruit numerous hospital patients. As it is presented hereafter, these patient may have very particular features for occupational life that can biases the results in the present case. I would exclude these patient from analyses.

20. RESPONSE: Thank you very much for this very helpful comment. We now performed an analysis without these women, which did not alter most of the results, except for two results: On the one hand the association between endometriosis and experience in the current profession was attenuated and even more important, the correlation with the duration working with the same employer was no longer significant. These findings were added to the results section and the discussion was adapted accordingly. The abstract was also modified.

“ethnic background”, It is unclear what it does mean.

21. RESPONSE: Within this study ethnic background includes the information whether a study participant was Caucasian or not. This criterion was used as endometriosis prevalences vary between different ethnicities. A specification has been included within the methods section.

Endometriosis patient were included irrespective of disease symptoms but only in case of surgically and histologically confirmed diagnosis. However it is not true because to have surgery an endometriosis patient must have significant symptoms as chronic pain and or infertility. This may create artefactual difference with control women and should be properly checked.

22. RESPONSE: We included also patients with coincidentally diagnosed endometriosis (e.g. during appendectomy) even if these constitute a small minority. But in fact, as a reliable diagnosis of endometriosis can only be made by surgery, patients with endometriosis but not a single symptom and no surgery for other reasons as well as symptomatic women who do not have access to or do refuse surgery remain undiagnosed and unstudied. This is a fundamental problem of all research about endometriosis.
To be clearer we rewrote the concerning sentence: „Endometriosis patients were included irrespective of the stage and type of disease as well as of severity and profile of symptoms.
Also, we added a comment on these concerns to the limitation section.

As the authors said, the most frequent reasons reported for not participating were lack of time. However I wonder how the lengths of the questionnaire (about 500 questions!) might affect the participation of women. It might happen that the women who were very busy by their job refuse to participate. This should be investigated more deeply.

23. RESPONSE: We agree. Very likely such circumstances are relevant in the case and the control group. As our response rate in the endometriosis group was higher than in the control group, we assume that endometriosis related problems were not a particular reason to refrain from study participation. A statement on women neglecting study participation because a very heavy work-load is now included within the discussion.

“The current analysis focused on 26 questions about professional life”. What is the validity of the questionnaire used? As the impact of a disease on professional life might be difficult to measure it may be important to use rigorous instrument. It seems that the authors have developed their own questionnaire, what is therefore the value of their findings. Hard to say.

24. RESPONSE: Please see our comment in response 13.

Was the rASRM the only descriptor of the extent of the disease? In the German speaking countries it is usual to use the ENZIAN score sheet during surgery. It may be feasible to get this information.

25. RESPONSE: We did not use the ENZIAN score, but we registered several localizations of endometriosis and surgical findings: adhesions, endometrioma, obliteration of Douglas, involvement of ligamentum sacrouterinum/ vaginal fornix/ wall of pelvis. We now present this information in table II. Additionally, we investigated the association of localization of endometriosis to health-related limitations in career choice as well as to stress on the job, sick leave and productivity loss and added this information to the results and within the discussion.

The modeling strategy is rather confusing to me. The authors stated that the endometriosis group was introduced as an "independent" predictor variable. It is unusual to do so as there is numerous different occupational variable to explain. So it would be more convincing to present the adjusted differences in term of occupational consequences between endometriosis women and controls.

26. RESPONSE: Testing associations between study groups and characteristics of professional life by conducting a series of either multinomial logistic regression for nominal-scaled outcomes or ordinal logistic regression for ordinal-scaled outcomes allowed us not only to define significant group differences but to also provide information on the effect size of the investigated associations (Nagelkerke's pseudo R2). To evaluate whether either endometriosis or another predictor variable showed stronger associations with outcome measures we decided to include endometriosis as an independent variable.

The result section encompasses numerous results and it is hard to read in the present ful length presentation. The authors should report unadjusted results and focus on important results in the text.

27. RESPONSE: We revised the whole presentation of the results in order to make it more reader-friendly, better point out important results and avoid redundancy between tables and text.

Line 258 to 265. Could you provide p-value? Moreover, could you explain why have you specifically focused on this population (>1 child).

28. RESPONSE: These results and related p-values are now shown in table I and were deleted from the text. As children strongly influence women's decisions to work full- or part-time we integrated this factor as a confounder in the multivariate analysis of associations between endometriosis and professional life.

The associations between a diagnosis of endometriosis and reporting a lower likelihood of working in the job of choice, stronger health influences on the selection of the professional activity , a higher experience in the current profession, and a longer duration of the present employment, are important and new results and should be highlighted.

29. RESPONSE: Thank you very much for this helpful comment. We revised the whole chapter „Results", and reported these main results clearer and more prominent.

The intensity of reported health related limitations in career choice was independent of the rASRM-stage. It would be important to test other relation between occupational limitation and the characteristics of the disease as it would be of interest to demonstrate a relation between the most severe forms of endometriosis and the worst professional impairment.

30. RESPONSE: We now additionally tested the association of different localizations of endometriosis to health-related limitations in career choice as well as to stress on the job, sick leave and productivity loss and added this information in the different sections of the manuscript.

Which cofounders did you use for the adjustment (Table III)? Did you use the nationality as cofounders since there is a significant difference between groups?

31. RESPONSE: We adjusted for nationality, number of pregnancies, and occupation, please see the footnote in table IIIb. We now repeated this analysis and integrated age as an additional confounder.

There is somes errors in table 3 that must be corrected.

32. RESPONSE: Done.

There is no need to present the results in text and table simultaneously.

33. RESPONSE: We now critically revised the whole presentation of the results and controlled for redundancy.

Reviewer: 3
Reviewer Name: Caroline Law
Institution and Country: De Montfort University, Leicester, UK
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
As stated to the editors, I am not able to comment on the statistical aspects of the paper and do not have a background in quantitative research. Instead, my review focuses on broader study design, relevance and contribution to the wider literature on endometriosis, and clarity of reporting.

- The paper addresses an important issue, and key relevant literature on the topic is reviewed in the introduction and discussed in the discussion.
- There is also some interesting discussion provided, e.g. on how age at symptom onset might affect education and qualifications and resultant variance in findings between studies, and the impact of parenthood on working lives, etc. However, the arguments made in the discussion could be clearer and discussion could be better related back to the current study.

34. RESPONSE: We revised and shortened the chapter “Discussion” in order to make it more concise. We also checked carefully that the discussion focused more strictly on the results of the current study.

- Unfortunately, a crucial issue is the lack of detail provided about the control group. It is stated that this group comprises women recruited via regular annual gynaecological consultation or via hospital stays because of benign gynaecological problems other than endometriosis. No detail is provided on how many women form this latter subsection of the control group and what symptoms these women may have experienced, and no discussion is provided about the potential implications of this, i.e. how the presence of such gynaecological problems/symptoms in the control group might have influenced the findings.

35. RESPONSE: We fully agree to the reviewer that more differentiated information on the control group would have been beneficial. We carefully checked that these women had no chronic gynecological diseases and specified this detail in the description of the recruitment. We acknowledge that symptoms from other diseases might interfere with adequate working performance, however, such further diagnoses would also occur in the endometriosis group ie influence professional activity

in both groups. This important limitation was added in the initial strength and limitation section as well as in the discussion to make it transparent and explain potential consequences to the readers.

In particular, this causes problems for the finding that women with endometriosis did not experience higher stress at work than the control group, and the resultant implication that endometriosis does not correlate with work related stress. If the women in the control group experienced symptoms and related stress, the lack of difference between the two groups does not support the idea that endometriosis does not correlate with work related stress.

36. RESPONSE: As we did not control for symptoms from diseases other than endometriosis in both groups, it is likely that some women diagnosed with endometriosis as well as some of the control group will have suffered from other symptoms. However control women for the present analysis were either recruited during routine gynecological care or within hospital stays for non-chronic mild disease. This information has been added to the methods section. Also endometriosis is associated with a variety of other pain syndromes, for example migraine, ie the probability that women with endometriosis experience pain due to other diseases is more likely than in control women. On this background we assume that disease symptoms in the control group are unlikely to be responsible for the lack of differences between stress levels. A comment on lack of differentiated data on this association has been added to the limitations.

- Overall, there is a lack of clarify in the way the findings are reported, and this runs throughout the paper and makes it difficult to read and comprehend. For example, phrases are used unproblematically or without definition and at times it is difficult to grasp the meaning (e.g. ‘job of choice’ or ‘loss of working power’).

37. RESPONSE: We revised the manuscript for unprecise wordings as well as the clarity the way findings are reported.
The words “job of choice” and “loss of working power” have been replaced. We asked a professional native proofreader to check the text for inadequate wording.

The presentation of figures is unclear at times (e.g. 285-289).

38. RESPONSE: We reformulated this paragraph and now show the total sick leave in the last month without differentiation regarding medical certificates. We think that this version of the paragraph is more convincing without any loss of relevant information.

The discussion of psychological symptoms (308) as a variable is problematic as this was not discussed in the ‘questionnaire’ section and we are not informed what these psychological symptoms are.

39. RESPONSE: We now described this question in the part “Questionnaire” of the chapter “Material and Method”. It asks participants of the case group if they had psychological symptoms related to endometriosis of more than three months like depressive mood/ anxiety or reduced resilience. Possible answers were yes or no.

It is unclear if and how validated questionnaires were incorporated (202-204).

40. RESPONSE: We specified questions, which were incorporated for the present analysis. To provide further details but avoid confusing readers we now added a reference where further details of the whole “Quality of life in endometriosis” project can be seen.

The unclear phrasing is also found in other sections of the paper (e.g. 132-133, 147-149, 197-198).

41./ 42./ 43. RESPONSE: We tried to be more specific and corrected the concerning sentences:
Lines 132-133: "Therefore, medical professionals need to know about possible difficulties symptoms of endometriosis can bring on daily working life and professional development; notably as endometriosis affected women repeatedly emphasize their wish for comprehensive information[20,22,23] and advice in managing their disease in daily life[22,23], instead of isolated treatment of endometriosis symptoms.[20,22,23]

Lines 147-149: "Main outcome measures are health limitations in career choice as well as quality and stability of the current work situation. Secondary outcome measures investigate the gradual impact of different symptoms as well as localisation of endometriosis on sick leave and loss of productivity."

Lines 197-198: We revised the whole section about the questionnaire and provide a more precise description of the collected data.

Recruitment is described inconsistently (e.g. self help groups are named as a recruitment route in some places and not others) and unclearly (e.g. 'university', 'private offices' are not explained).

44. RESPONSE: We revised the section "recruitment" and tried to be more precise. We replaced "private practice" with "doctors' practice" as a more common term and explained it as well as the term "university hospital".
Germany was the only country where recruitment of study participants took place in self-help groups.

It needs to be clear to all audiences (those with quantitative background and those without) whether causation can be identified or only correlation. If causation cannot be claimed, the abstract and line 315 need rewording.

45. RESPONSE: The design of the study does not allow proofing causation. We corrected wording in the abstract, results and discussion.

The abstract suggests that most other associations between endometriosis and work were weak. This seems contradicted in lines 273-278.

46. RESPONSE: The main outcome measures "health related limitations in career choice", "desired profession" and "professional experience" showed highly significant results in the group comparison. However, except for health influences on career choice ($R2 = 0.062$), the proportion of variance explained by each factor was small (all $R2 < 0.027$).
We revised the abstract as well as the whole section "Results" in order to present the findings of our study more consistently and to be clearer.

The main argument in the paper doesn't come across very clearly or consistently – while the conclusion in the abstract emphasises the detrimental impact endometriosis can have on working lives, the conclusion of the paper downplays this.

47. RESPONSE: We revised the different sections of the manuscript to improve clarity as well as consistency of findings and conclusions.

While the topic of endometriosis and work/professional life is a very important one, the paper could be clearer in explaining how it contributes to the existing literature and to what is already known about the topic. As it stands the contribution comes across as fairly minimal.

48. RESPONSE: Two sentences to specify which information is currently lacking on the association between endometriosis and professional life and which are addressed in the current study have been added to the Introduction. The new findings were emphasized in the discussion.

The paper requires an English language edit, in conjunction with greater clarity of reporting.

49. RESPONSE: We extensively revised the manuscript in order to improve clarity and comprehensibility. Additionally, a professional native speaking proofreader improved the linguistic quality of the manuscript.

Reviewer: 4
Reviewer Name: Federica Facchin
Institution and Country: Faculty of Psychology, Catholic University of Milan, Italy
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
This is an interesting study that I enjoyed reading because I think it addresses a very relevant research question regarding the impact of endometriosis on professional life. Specifically, the study aimed at examining whether endometriosis negatively affects women's career development and current work performance. The association between specific endometriosis symptoms (i.e., chronic pain and fatigue) and work performance was also explored.

The importance of such a research question is clearly underlined by the authors in the introduction section. Endometriosis is a chronic painful disease that often involves remarkable limitations in everyday activities, including work. The disruptive impact of the disease on women's lives and plans for the future has been highlighted by several qualitative studies. There is also evidence that impaired work functioning (decreased productivity, absenteeism due to pain as well as to the need for medical visits and treatments…) contributes to the psychosocial and economic burden of the disease.

This study examined the association between endometriosis and women's professional life in a systematic fashion (using a case-control research design). The sample was large since it was composed of 505 women with surgically/histologically confirmed endometriosis and 505 matched controls without endometriosis. Inclusion and exclusion criteria for both groups were clearly explained, as well as recruitment procedures (a detailed figure – Figure 1 – was provided to describe the overall recruitment process).

Data were derived from a larger research that involved a 390-item questionnaire administered to all women, plus 90 questions specifically focused on endometriosis-related issues. I think there is a lack of clarity in the section entitled "Questionnaire" (p. 8).

First, the aims of the larger research and the original 390-item questionnaire were not specified.

50./ 51. RESPONSE: The aims of the larger research was specified within the methods section with the following sentence: Study participants were prospectively recruited for a larger research project on quality of life of endometriosis….
We now provide very detailed information on the content of the questionnaire.

A description of the dimensions addressed by the questionnaire was provided on p. 8, lines 196-204, but I actually don't understand whether the authors here were describing the 390 questions for all

women, or the 90-question set for endometriosis participants, or both sets of questions at the same time.

52. RESPONSE: We differentiated clearer between the description of the main questionnaire and questions which were evaluated for the present manuscript. The revised version contains information on which questions were addressed to which group.

From lines 200-204, the authors explained that chronic pelvic pain (frequency, duration, and intensity) – which is commonly referred to as non-menstrual pelvic pain that lasts at least six months – was assessed using items derived from the Brief Pain Inventory and the Pain Disability Index. I would like to know why the authors did not assess also cyclic pelvic pain (dysmenorrhea), which is a major clinical problem in women with endometriosis and may significantly affect everyday life and work performance. I do not see anything about dysmenorrhea, neither in the text, nor in the table reporting the associations between endometriosis symptoms and sick leave/productivity loss. I think this lack of important information should be motivated and acknowledged as a study limitation.

53. RESPONSE: The term chronic pelvic pain includes cyclic as well as non-cyclic pain e.g. focusses on the chronicity of the pain and not on its occurrence in relation to the menstrual cycle. We choose this approach as some of the women had a natural cycle and others experienced chronic pain despite a hormonal treatment e.g. no natural cycle or no cycle at all. This information was added to the methods section.

As reported in Table IV, frequency of fatigue and psychological symptoms were also assessed. I think the authors should clarify in the “Questionnaire” section which specific endometriosis symptoms were assessed and how. For instance, how was fatigue defined in the question? I am interested because I think chronic fatigue is an important endometriosis symptom, although understudied, especially as compared with pelvic pain. The category “psychological symptoms” is also vague and I would like to know more about the specific question used in the questionnaire (which seems to be a general dichotomous variable: yes/no): was the question referred to diagnosed psychological disorders? What type of psychological symptoms was assessed? Were psychological symptoms assessed only in women with endometriosis (and why)?

54. RESPONSE: In the section “questionnaire”, we now describe all questions about endometriosis symptoms that were relevant for this study as they are presented in the questionnaire. We also specified to whom these questions were addressed.
To better understand why women diagnosed with endometriosis might experience impaired working performance, we focused on symptoms the women subjectively experienced as related to endometriosis.

It was also mentioned (lines 202-204) that different internationally validated questionnaires investigated aspects of quality of life, including professional life. Were these questionnaires (which questionnaires?) or parts of them included in the study? Based on the subsequent description (lines 206-220), I understand that these validated questionnaires were not analyzed in this study.

55. RESPONSE: Yes, except the pain questionnaires, data from other validated questionnaires were excluded to focus on the present research question. Please see also our comment RESPONSE 40.

I invite the authors to increase clarity, for instance by providing example items for the two question sets.
Overall, the section should be reorganized in a more systematic manner, with a clear description of the original questionnaire (390 + 90 items) vs. the 26 questions included in the current study for all

participants and for women with endometriosis. A precise description of the endometriosis symptoms and the psychological symptoms assessed should be provided.

56. RESPONSE: We revised the section “questionnaire” extensively and describe the questions asked to women diagnosed with endometriosis and to control women in a more systematic and concrete way.

In the Statistical analyses section, p. 10, line 242, I would write “To test associations between study groups and characteristics of professional life” (or to test group differences…).

57. RESPONSE: Done (specified).

The presentation of the results is also a little confused.

58. RESPONSE: Thank you for this feed-back. We restructured the presentation of the results after adding the suggested information. We checked the tables and text for redundancy, made it more reader-friendly and emphasized important results.

For example, in the section entitled “Characteristics of study groups and possible confounders”, I don’t understand – on the basis of Table I – the reason why the authors reported the proportional distribution of having a gainful occupation (full time, part time, no occupation) for women with at least one child by study group. Was the comparison between these subgroups (chi squared test) significant? Was this information relevant according to your research question?

59. RESPONSE: Results and related p-values can be seen in table I and were deleted from the text. As having children likely influences the decision for a full- or part-time profession we included parity as a confounder in subsequent analysis. The discussion of this point has been condensed.

Table I is very clear, but I think the authors should clarify in the text that significant between-group differences were found for some socio-epidemiological parameters (please specify whether in these preliminary analyses significance tests were performed at $P < 0.05$), which were included in subsequent analyses as potential confounders (I hope I understood well).

60. RESPONSE: The significance level was added within the methods. We also added that significant factors were added to subsequent analysis.

Endometriosis characteristics are reported in Table II. I think that symptom characteristics (presence and frequency of chronic pain, fatigue, presence of psychological symptoms) should be displayed in this Table. Table IV is important because it shows the associations between symptoms and sick leave/productivity loss, but I miss a more comprehensive description of the endometriosis group.

61. RESPONSE: The tables have been adjusted according to the suggestion of the reviewer.

There is a similar problem with Table III. On p. 11, lines 268-269, it is written that “characteristics of professional activity in women diagnosed with endometriosis and control women are presented in Table III”. Actually, Table III reports the results of the logistic regressions conducted and there are no other tables reporting the characteristics of these work parameters by study group. Perhaps, this material could be included in Table I to avoid the creation of another table.

62. RESPONSE: We now show the descriptive statistics of parameters of working life by study group in table IIIa. This is a new table. The former table III is now named IIIb.

On p. 11, lines 269-272, I don’t understand why the sentence ends with “…showed statistical significant differences in both groups”. Because study group is the independent variable, these are between-group differences (rather than within-group differences). I am sure the analyses are correct, but the way in which findings are reported in the text should be carefully reviewed.

63. RESPONSE: Yes, you are absolutely correct, we adjusted the presentation of the findings.

As regards the section “Work impairment and compensatory mechanisms”, these percentages are not written correctly: 10,7% (it should be 10.7%), 0,5% (twice), 7,6% (lines 285-288).

64. RESPONSE: Has been corrected accordingly.

These are merely descriptive findings that per se don’t allow any conclusion about the association between endometriosis and work performance. I don’t understand why work performance and sick leave were not evaluated in the control condition in order to address very interesting comparisons. This should be acknowledged as a limitation.

65. RESPONSE: In fact, the lack of a reference group for these questions is a limitation, which we added to the discussion.

Some of the Conclusions should be more cautious and less enthusiastic. For example: “According to the present results women with endometriosis were very successful in their health-related choice of future professions” (lines 338-339). Indeed, findings revealed that these women had higher experience in the current profession and stayed longer in their current employment relative to controls. However, I would not conclude that these can be firmly considered as positive findings. First, these two variables may be associated (did you check?): perceived higher experience in current job may depend on longer practice;

66. RESPONSE: Spearman correlation was added to the results and a comment on this finding was integrated into the discussion.

second, these findings do not necessarily imply that women with endometriosis feel satisfied and successful, especially if we consider that most of them were NOT doing their work of choice, because their decisions were influenced by health-related issues. This study findings suggest that these women struggled to have and keep their job despite endometriosis, to the point that 75.5% of them reported to have gone to work in spite of severe pain in the month prior the study.
Moreover, as acknowledged by the authors (lines 343-346), women might stay in their current occupation because the environment is adapted to their endometriosis-related needs. One hand this may be the reason for not seeking another job (as well as fear, of course); on the other hand, the adequate environment characteristics may motivate the absence of group differences with regard to work-related stress. The authors may disagree, but that’s how I read their findings.

67. RESPONSE: Thank you for these interesting and very helpful remarks. We included them with pleasure in the revised discussion.

Lines 350-361: these considerations are speculative and not supported by statistical tests. Moreover, I would not introduce new findings in this section.

68. RESPONSE The discussion has been reduced to findings in our study.

Overall, this study suggests that endometriosis may negatively affect professional life (including women’s choices), but there is need for more research to understand this association. Moreover, I

wonder why the authors did not control for the potential confounding effect of age (the two groups did not differ, but age may play an important role) and time from diagnosis (it seems like they had this information, see p. 16, line 405).

69. RESPONSE: We now included age as well as time since initial diagnosis into our analysis, however this did not influence our results. The manuscript was adapted accordingly.

I think there is a lot of work to do here (i.e., major revision), but there is potential for improvement and I do believe that this study with its novelty value may provide interesting suggestions for future research. The association between endometriosis and professional life is an important topic, and studies addressing this issue are more thank welcome to me.

VERSION 2 – REVIEW

REVIEWER	Prof. Dr. Tewes Wischmann Institute of Medical Psychology, University Hospital Heidelberg, Heidelberg, Germany
REVIEW RETURNED	13-Dec-2017

GENERAL COMMENTS	The paper has improved very much in the revision process, and the findings are presented very clear now, as well as the limitations of the study, so I can recommend the paper for publication now. I have only three minor remarks: The two sentences in lines 161 to 165 exist twice so one of them can be omitted. Lines 219 to 220: square brackets should be inserted :"...nationality [German, Swiss, Austrian, other (with the possibility of entering nationality)], age ..." Line 524: I suggest to add "psychological" in the sentence: "Therefore, medical and psychological support should address such issues ..."

REVIEWER	Fauconnier Arnaud CHI Poissy-Saint-Germain Hospital, Poissy, France
REVIEW RETURNED	13-Dec-2017

GENERAL COMMENTS	The authors have performed several modification to respond to my comment, although II do recognize that important rewriting has been done, I do regret that to of my major comments were not satisfactorily responded and raise question about the validity of the conclusions presented here. First, although the authors have made transparent responses on the questions that have been used to attempt to measure professional impairment and other important outcome to explain the relation between endometriosis and working life. I was definitely not convinced by the way these very important outcomes were measured and also which of the many questions that were asked to the women, were used in the analyses. No validated questionnaire (as I can check) does not mean that a questionnaire may be developed ex nihilo, as many studies on various chronic or malignant disease have already focused on professional impairment.

	I was not able to find among the long recitation of the outcomes used (two page !) convincing explanation of the manner the authors aimed to measure the professional impairment. I will be ready to trust the different outcomes presented in the results at the very condition that the authors explain the reasons for these choices, if possible in relation to published data in other pathologies (for example chronic painful disease or malignant disease). Conversely, the jumbled presentation of these results that seem to demonstrate the link between endometriosis and professional impairment, could instead be a post-hoc statistic construction (see also my second concern). There is many other thinks to say about this very important point, i. e. how outcomes were measured: for example how were analyzed the numerous questions about work impairment that were asked only to endometriosis case (see line 245 – 257); no use of HrQol questionnaires (some are greatly validated in endometriosis); painful symptoms not satisfactorily measured… Secondly, the modeling strategy remain unclear to me. As I already wrote, the case versus control group was introduced as an "independent" predictor variable (together with several other variables) in a logistic regression model to explain different occupational variable to explain, that mean that numerous logistic models were built each one to explain one of the 7 variables that measure professional impairment . Reading the table 3 one may conclude that among 7, 4 are independently associated with endometriosis case. However it is quit unlikely to be the case while many of these 7 variables measuring the same construct may be closely associated. So it would be more convincing to present the adjusted differences in term of occupational consequences between endometriosis women and controls. This is the usual way to analyses outcomes and or exposure difference in case control study. The modelling strategy presented here insidiously suggests a matched follow-up design the exposure factor being the fact of having endometriosis and the outcome being the occupational status parameters. However the present study is a matched case control study without any follow-up, endometriosis case and control having there occupational status parameters measured while they have been included in the study.

REVIEWER	Caroline Law De Montfort University, UK
REVIEW RETURNED	07-Dec-2017

GENERAL COMMENTS	As stated to the editors, I am not able to comment on the statistical aspects of the paper and do not have a background in quantitative research. Instead, my review focuses on broader study design, relevance and contribution to the wider literature on endometriosis, and clarity of reporting. This revised version of the manuscript is very much improved. The findings are reported much more clearly and consistently, and the contribution to what is known about this topic, and how and why the study is important, are much more explicit. The further description of the control group containing women with only mild, temporary gynaecological problems enables the reader to be much more assured that the control group were not simply experiencing different but comparable conditions to endometriosis, which allows for much greater confidence in the results. The inclusion of questions asked and responses allowed allows for a much improved understanding of what the study investigated. Overall it is significantly improved from the initial manuscript.

	Some minor suggestions are made: Line 46 as qualitative data is not included in the paper, could this reference be removed? Line 96 is missing the word 'experience' Lines 124-125 suggest change 'they' to 'some women may' Line 126 suggest change 'they' to 'women' Lines 127-131 and 534-526 I think the findings have important implications for others beyond medical professionals who may have a role in supporting women, e.g. support groups, policy makers etc. The potential broader application of findings could be articulated. Line 134 suggest substitute 'counselling' for 'support and interventions' Line 150 and 515 the word 'gradual' seems in accurate here as it suggests changes across time which the study didn't investigate. It may help to remove it. Figure 1 is missing The section on recruitment, and different routes for case and control women, is still a little unclear to the reader. It may help to describe firstly how ALL women (case and control) were recruited; then describe any additional/different procedures for case women; then describe any additional/different procedures for control women. Line 172 suggest ';' instead of ','. Line 173 suggest remove parenthesis and text within them. Line 183 suggest change 'the questionnaire was explained' to 'the study was explained' - if indeed this is what you mean? The current phrasing sounds like the questionnaire was talked through, e.g. a face-to-face questionnaire completion. Line 219 suggest amend to 'the analysis presented in this paper was based…' Line 220 end parenthesis missing. Line 224 suggest change '/' to 'to'. Line 225-6 suggest change to 'women were asked to…' Line 240 is the soecification of first diagnosis necessary? Surely they are only diagnosed once? Do you mean initial diagnosis? Lines 219-257 the spacing in between dashes, figures and symbols needs to be consistent. Line 256-257 is unclear and would benefit from amending. Line 296, table I 'single' and the associated figures need to be on the same line. Line 324, table II can the N values be added in where missing (last 4 rows)? Line 329-331, this implies the impact on desired profession was not a key finding, which elsewhere you suggest it is. Can this text be amended, and still be statistically accurate? Lines 358-359 what time period does this statement cover? Line 361-362 is this all women with endometriosis? Line 366-367 is this all women with endometriosis? Line 53-56 and 383-394 – these sections deal with whether presence of chronic pain, frequency of chronic pain, frequency of fatigue and psychological symptoms were associated with sick leave and productivity loss. It still seems a little unclear which of these potential 8 correlations were found, can this be made explicit and consistent, in both places? Lines 405-417 – this section still reads unclearly and could be better related back to the current study, being explicit about the ages of the sample at the time of the study and the ages of the sample at diagnosis, in both this and other studies, and how exactly that might account for contrasting findings regarding education level. The general idea is in the paragraph but it needs to be fully explained. Line 421 suggest substitute 'higher quality' for 'greater length'

	Lines 425-428 a more negative interpretation could be added here to more fully consider what the findings might mean, e.g. women felt less able to change profession, and stuck in their undesired profession because of endometriosis. Line 481 suggest change ‘exhaustion’ to ‘fatigue’ to be consistent with rest of paper Line 483-485 – this seems like a big speculation, and I am not convinced your results enable you to know what women want and what they might be willing to sacrifice to have this. If it is retained, perhaps you could substitute ‘In summary,’ to ‘It may be that’ so as to indicate this is speculative.

REVIEWER	Federica Facchin Faculty of Psychology, Catholic University of Milan, Italy
REVIEW RETURNED	09-Dec-2017

GENERAL COMMENTS	I appreciate the remarkable effort the authors have made to address the issues raised by the reviewers. The authors did their best to increase clarity, especially in the Methods and Results sections; the discussion is also better organized, with more reasonable (and less enthusiastic) conclusions derived from their findings. I still see a general difficulty in providing a systematic picture of the huge amount of information collected, but I think the current version of the manuscript can be accepted for publication. I only suggest a final round of editing (for example, make sure that British English was used throughout the manuscript). This is an interesting study: The association between endometriosis and work functioning is an important topic, with clinical and social implications, and - on a personal note - I would like to thank the authors for the new insights they gave me into my own work.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 3
Reviewer Name: Caroline Law

Institution and Country: De Montfort University, UK

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

Please leave your comments for the authors below
As stated to the editors, I am not able to comment on the statistical aspects of the paper and do not have a background in quantitative research. Instead, my review focuses on broader study design, relevance and contribution to the wider literature on endometriosis, and clarity of reporting.
This revised version of the manuscript is very much improved. The findings are reported much more clearly and consistently, and the contribution to what is known about this topic, and how and why the study is important, are much more explicit. The further description of the control group containing women with only mild, temporary gynaecological problems enables the reader to be much more assured that the control group were not simply experiencing different but comparable conditions to endometriosis, which allows for much greater confidence in the results. The inclusion of questions asked and responses allowed allows for a much improved understanding of what the study investigated. Overall it is significantly improved from the initial manuscript.

1. Response: Thank you very much for these compliments. We are happy that we were able to satisfy your suggestions for improvement of the manuscript.

Some minor suggestions are made:
Line 46 as qualitative data is not included in the paper, could this reference be removed?

2. Response: We specified the main outcome measures to remove the term “qualitative”.

Line 96 is missing the word ‘experience’

3. Response: Thank you for this remark. We now added the word experience to this sentence.

Lines 124-125 suggest change ‘they’ to ’some women may’

4. Response: Done.

Line 126 suggest change ‘they’ to ‘women’

5. Response: Done.

Lines 127-131 and 534-526 I think the findings have important implications for others beyond medical professionals who may have a role in supporting women, e.g. support groups, policy makers etc. The potential broader application of findings could be articulated.

6. Response: Thank you for this input. We added this information at both suggested paragraphs.

Line 134 suggest substitute ‘counselling’ for ‘support and interventions’

7. Response: Done.

Line 150 and 515 the word ‘gradual’ seems in accurate here as it suggests changes across time which the study didn’t investigate. It may help to remove it.

8. Response: Done.

Figure 1 is missing

9. Response: Thank you for this remark. Figure 1 was uploaded in a separate document, we are sorry that you did not receive this file and hope you have now access to the full version of our manuscript.

The section on recruitment, and different routes for case and control women, is still a little unclear to the reader. It may help to describe firstly how ALL women (case and control) were recruited; then describe any additional/different procedures for case women; then describe any additional/different procedures for control women.

10. Response: We reorganised this section following your suggestions.

Line 172 suggest ‘;’ instead of ‘,’.

11. Response: Done.

Line 173 suggest remove parenthesis and text within them.

12. Response: Done.

Line 183 suggest change ‘the questionnaire was explained’ to ‘the study was explained’ - if indeed this is what you mean? The current phrasing sounds like the questionnaire was talked through, e.g. a face-to-face questionnaire completion.

13. Response: The sentence has been reworded as suggested.

Line 219 suggest amend to ‘the analysis presented in this paper was based…’

14. Response: Has been modified accordingly.

Line 220 end parenthesis missing.

15. Response: Parenthesis have been added.

Line 224 suggest change ‘/’ to ‘to’.

16. Response: To make it clearer we now present the two different ranges of income for the different countries study participants were recruited: “… (six choices for responses ranging from none to >2500 Euros for participants in Germany and Austria and from none to >6000 Swiss francs for participants in Switzerland), …”

Line 225-6 suggest change to ‘women were asked to…’

Response: Has been reworded as suggested. Line 240 is the specification of first diagnosis necessary? Surely they are only diagnosed once? Do you mean initial diagnosis?

17. Response: Yes, initial diagnosis was meant; the sentence was rephrased following your remark.

Lines 219-257 the spacing in between dashes, figures and symbols needs to be consistent.

18. Response: Has been corrected.

Line 256-257 is unclear and would benefit from amending.

19. Response: We formulated this sentence more precisely and changed to the following wording: “Chronic pelvic pain included cyclic as well as non-cyclic pelvic pain.”

Line 296, table I ‘single’ and the associated figures need to be on the same line.

20. Response: Done.

Line 324, table II can the N values be added in where missing (last 4 rows)?

21. Response: We do not understand why these numbers were missing in the version you received. We verified our documents and can only explain this by some technical problems. We hope that you can now see the complete table with all numbers.

Line 329-331, this implies the impact on desired profession was not a key finding, which elsewhere you suggest it is. Can this text be amended, and still be statistically accurate?

22. Response: The association of endometriosis and desired profession is a key finding with a significant difference between the case and the control group. But nevertheless we wanted to be transparent in the fact that the Naegelkes Pseudo-R-Square for desired profession and for professional experience is not very high. We modified the concerning text in the following way: "Results of the main outcome measures "health influences on career choice", "desired profession" and "professional experience" are highly significant; even if the proportion of variance explained by the last two factors was rather small. "

Lines 358-359 what time period does this statement cover?

23. Response: Thank you for this helpful comment. The sentence refers to the last year. We now added this essential information.

Line 361-362 is this all women with endometriosis?

24. Response: Yes, we now specified this information in order to be very clear.

Line 366-367 is this all women with endometriosis?

25. Response: Yes, this information has been added in the sentence.

Line 53-56 and 383-394 – these sections deal with whether presence of chronic pain, frequency of chronic pain, frequency of fatigue and psychological symptoms were associated with sick leave and productivity loss. It still seems a little unclear which of these potential 8 correlations were found, can this be made explicit and consistent, in both places?

26. Response: Given the limit of 300 words for the abstract, we are forced to concentrate on the main outcome measures and the most important of the secondary outcome measures. Therefore, we are not able to name all eight associations of this theme in the first place. But in the second place we revised the table as well as the text in order to be clear: "Corrected for multiple testing, all four predictor variables were significantly associated with sick leave during the previous four weeks. The occurrence of chronic pain as well as the frequency of fatigue and concomitant psychological symptoms were associated with significantly higher degrees of perceived productivity loss."
In the table we marked the parameters, which remain significant after correction for multiple testing with #.

Lines 405-417 – this section still reads unclearly and could be better related back to the current study, being explicit about the ages of the sample at the time of the study and the ages of the sample at diagnosis, in both this and other studies, and how exactly that might account for contrasting findings regarding education level. The general idea is in the paragraph but it needs to be fully explained.

27. Response: We added more information on the age at diagnosis to this section in order to be more explicit in our argumentation.

Line 421 suggest substitute 'higher quality' for 'greater length'

28. Response: Done.

Lines 425-428 a more negative interpretation could be added here to more fully consider what the findings might mean, e.g. women felt less able to change profession, and stuck in their undesired profession because of endometriosis.

29. Response: Thank you very much for this helpful comment, which we gratefully added to our discussion.

Line 481 suggest change 'exhaustion' to 'fatigue' to be consistent with rest of paper

30. Response: Done.

Line 483-485 – this seems like a big speculation, and I am not convinced your results enable you to know what women want and what they might be willing to sacrifice to have this. If it is retained, perhaps you could substitute 'In summary,' to 'It may be that' so as to indicate this is speculative.

31. Response: You are right; we don't know what women want. In this sentence we give our interpretation of the aggregate results. We added "it may be that" as you suggest, in order to formulate it more modestly.

Reviewer: 4
Reviewer Name: Federica Facchin

Institution and Country: Faculty of Psychology, Catholic University of Milan, Italy

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

Please leave your comments for the authors below
I appreciate the remarkable effort the authors have made to address the issues raised by the reviewers. The authors did their best to increase clarity, especially in the Methods and Results sections; the discussion is also better organized, with more reasonable (and less enthusiastic) conclusions derived from their findings.

Response: We are happy that you share our estimation, that your comments as well as those of the other reviewers helped to present a clearer more convincing version of our manuscript. I still see a general difficulty in providing a systematic picture of the huge amount of information collected, but I think the current version of the manuscript can be accepted for publication. I only suggest a final round of editing (for example, make sure that British English was used throughout the manuscript).

32. Response: Following the additional remarks and aiming for the best way to present our findings, we carefully checked the structure of our manuscript. The manuscript has been revised by a professional proofreader and we did our best to have a sound English editing.

This is an interesting study: The association between endometriosis and work functioning is an important topic, with clinical and social implications, and - on a personal note - I would like to thank the authors for the new insights they gave me into my own work.

33. Response: Thank you for this positive comment! We are very happy to inspire your daily work, this is exactly our motivation to share these findings with everybody directly or indirectly involved in support of women with endometriosis. After many conversations with endometriosis patients, we hope that this study will help to better understand the type and dimension of some of the difficulties affected women are forced to deal with and to use this understanding to improve patients' care.

Reviewer: 1
Reviewer Name: Prof. Dr. Tewes Wischmann

Institution and Country: Institute of Medical Psychology, University Hospital Heidelberg, Heidelberg, Germany

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

Please leave your comments for the authors below

The paper has improved very much in the revision process, and the findings are presented very clear now, as well as the limitations of the study, so I can recommend the paper for publication now. I have only three minor remarks:

The two sentences in lines 161 to 165 exist twice so one of them can be omitted.

34. Response: Sorry, for this mistake, which has now been corrected.

Lines 219 to 220: square brackets should be inserted :"...nationality [German, Swiss, Austrian, other (with the possibility of entering nationality)], age ..."

35. Response: The brackets have been added, however, to be coherent with the rest of the manuscript we permitted us to modify the order of the round and square brackets.

Line 524: I suggest to add "psychological" in the sentence: "Therefore, medical and psychological support should address such issues ..."

36. Response: Yes, we fully agree that psychologists can play an important role in patients' care and added "psychological" to the sentence.

Reviewer: 2

Reviewer Name: Fauconnier Arnaud

Institution and Country: CHI Poissy-Saint-Germain Hospital, Poissy, France

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

Please leave your comments for the authors below

The authors have performed several modification to respond to my comment, although II do recognize that important rewriting has been done, I do regret that to of my major comments were not satisfactorily responded and raise question about the validity of the conclusions presented here.

First, although the authors have made transparent responses on the questions that have been used to attempt to measure professional impairment and other important outcome to explain the relation between endometriosis and working life. I was definitely not convinced by the way these very important outcomes were measured and also which of the many questions that were asked to the women, were used in the analyses.

41 Response: We now describe the structure of the questionnaire and the way questions were selected more precisely and tried to distinguish clearer between the main questionnaire about quality of life and the chapter of professional life, which was analysed in this paper; please see line 209-235 and our answer to your next comment. All questions about work life, which were asked to the study participants, were analysed for this paper.

No validated questionnaire (as I can check) does not mean that a questionnaire may be developed ex nihilo, as many studies on various chronic or malignant disease have already focused on professional impairment. I was not able to find among the long recitation of the outcomes used (two page !) convincing explanation of the manner the authors aimed to measure the professional impairment. I will be ready to trust the different outcomes presented in the results at the very condition that the authors explain the reasons for these choices, if possible in relation to published data in other pathologies (for example chronic painful disease or malignant disease).

42 Response: Wherever possible internationally recognized questionnaires and questions were used. The strategy to develop our questionnaire – and especially the chapter about professional life - has now been described more in detail in the methods section. Further details on the complete questionnaire about quality of life are available at clinicaltrials.gov (NCT 02511626).
Questions on professional activity were based on approaches used in other studies investigating professional activity in the context of chronic diseases. The following instruments were revised to evaluate their appropriateness to collect the informa-tion we aimed for: We revised the broadly used Work Productivity and Activity Impairment Questionnaire (WPAI) developed by Reilly et al. [Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impair-ment instrument. Pharmacoeconomics 1993;4:353-65]. We also evaluated the WPAI:SHP (Specific Health Problem) for questions to be used within our study. We selected the content of question 2 and 5 for the present study but

estimated a time frame of seven days as too short for the context of endometriosis. Therefore, we evaluated productivity loss and sick leave in relation to the last month, as it is suggested for sick leave in The World Health Organization Health and Work Perfor-mance Questionnaire (HPQ) [Kessler RC, Barber C, Beck A et al. The World Health Organization Health and Work Performance Questionnaire (HPQ). Journal of Occu-pational and Environmental Medicine / American College of Occupational and Envi-ronmental Medicine 2003;45,156–174] as well as in the last year. Although the HPQ has very differentiated questions on work performance and self-perception with regard to this performance, unfortunately most of the questions did not meet the specific information we wanted to collect.

Therefore, we evaluated several further instruments, as for example the Work Limi-tations Questionnaire (WLQ), which also investigates many qualitative aspects of work, but did unfortunately not meet the focus of our interest [Lerner D, Amick BC, Rogers WH et al. The Work Limitations Questionnaire. Medical Care 2001;39:72–85]. The Sickness Impact Profile (SIP), published in 1981 and later refined, does not focus on professional activity but evaluates the general impact of sickness on everyday life [**Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: develop-** ment and final revision of a health status measure. Med Care 1981;19:787-805]. The questions of the Work Ability Index (WAI) were not sufficiently differentiated to capture our specific interests with regard to endometriosis [Tuomi K, Ilmarinen J, Jahkola A et al. Work Ability Index. Occupational Health Care 19. Helsinki: Institute of Occupational Health 1994].
Chronic pain was investigated with selected questions from the validated Brief Pain Inventory and Pain Disability Index. Level of education was measured with defined categories following the recommendation of the book “Measuring poverty and socioeconomic status in studies of health and well-being” of Hauser et al. [CDE Work Pap 1995;94-24].

When designing our study, we carefully evaluated existing instruments to investigate the impact of a health problem on professional life and used validated questions wherever possible. However, the aim of the present study was to report the very specific difficulties of living with endometriosis; thus, it was essential to ask the right questions. With this intention an interdisciplinary research team including specialists for minimally invasive endometriosis-surgery, for gynaecological endocrinology and for gynaeco-psychosomatic medicine was built to add their clinical experience to also evaluate systematically what they had learned from individual patients. On this background questions on working despite pain, on using overtime or holidays to compensate for sick leave and on health-related limitations in professional choices were added to the questionnaire. The first version of our questions on professional activity was then revised by the governing body of the German self-help groups in order to map the questions to the experiences reported by women with endome-triosis.

Conversely, the jumbled presentation of these results that seem to demonstrate the link between endometriosis and professional impairment, could instead be a post-hoc statistic construction (see also my second concern).

43 Response: Following your comment, we carefully re-checked the structure of our presentation of results: We first present the characteristics of the study population (table I and II). Secondly, we present the work parameters of the case and the control group in a descriptive manner as it was claimed in the first reviewing process (table IIIa). These first three tables are necessary to understand and evaluate the following results of group comparison of the main outcomes (table

IIIb). In the following text we report additional analyses of associations between disease characteristics and the main outcome measures. This section covers also analyses, which were specifically demanded in the first reviewing process.
With the distinct title “Work impairment and compensatory mechanisms” we move on to analyses of the questions that were asked only to the case group. Results of these parameters are firstly reported descriptively in text form. Secondly, table IV presents associations between endometriosis symptoms and sick leave as well as productivity loss (secondary outcome measures).
With the described structure we tried to present results in a logical sequence. We agree, that the chapter of results is long and full of complex information. But we wanted to analyse all of the asked questions and offer the full picture of investigated relations to the reader in order to avoid selective reporting.

There is many other thinks to say about this very important point, i. e. how outcomes were measured: for example how were analyzed the numerous questions about work impairment that were asked only to endometriosis case (see line 245 – 257);

44 Response: We tried to explain exactly, which answers were collected and how they were evaluated. Please see our answer number 42 and the methods section of the manuscript. Descriptive results of the named questions are presented in table II as well as in the text under the title “work impairment and compensatory mechanisms” (line 362-381). To test associations between symptoms of endometriosis and sick leave/ productivity loss we conducted a series of ordinal logistic regression, entering work outcomes (namely sick leave and productivity loss) as the dependent variable. These results are presented in table IV.

no use of HrQol questionnaires (some are greatly validated in endometriosis);

45 Response: We fully agree that the Endometriosis Health Profile-30 (EHP-30) from Jones et al, is a valuable, validated questionnaire to investigate quality of life in endometriosis. Unfortunately, it is designed to be used in women diagnosed with endometriosis only and is inappropriate for the evaluation in control women. The aim of our “Quality of life in Endometriosis”- project was a comparison between a case and a control group in order to investigate where and how strong women with endometriosis differ from the “normal” female population. To make evident, how intensively and widely quality of life may be impaired on the background of endometriosis, we wanted to go far more in detail and include more aspects of quality of life than was possible with the 30 questions offered by the EHP-30. Therefore, we used our clinical experiences and discussions with women diagnosed with endometriosis to define different topics of interest and then checked published, internationally validated questionnaires to design a questionnaire adapted to the aims of our study. The current version of the questionnaire represents the result of the best possible compromise between available validated questionnaires and our focus of interest/ the aspects we estimated necessary to better understand the situation of women with endometriosis.

Especially at the time we designed the study (luckily there has been some improvement since then), even congresses specialized on endometriosis only very marginally covered such quality of life aspects. Therefore, our main motivation for the present study was to present reliable data on

different aspects of quality of life in a large cohort of women with endometriosis. Although a fully validated questionnaire would of course have been beneficial, we think that our findings will help to sensitize specialists towards the fact that endometriosis has a major impact on daily life, which should be recognized by health care providers.

painful symptoms not satisfactorily measured…

46 Response: For the questions about pain we used selected questions from the Brief pain inventory and the Pain disability index, two validated, internationally recognized questionnaires. We added this information to the manuscript.

Secondly, the modeling strategy remain unclear to me. As I already wrote, the case versus control group was introduced as an "independent" predictor variable (together with several other variables) in a logistic regression model to explain different occupational variable to explain, that mean that numerous logistic models were built each one to explain one of the 7 variables that measure professional impairment . Reading the table 3 one may conclude that among 7, 4 are independently associated with endometriosis case. However it is quit unlikely to be the case while many of these 7 variables measuring the same construct may be closely associated. So it would be more convincing to present the adjusted differences in term of occupational consequences between endometriosis women and controls. This is the usual way to analyses outcomes and or exposure difference in case control study. The modelling strategy presented here insidiously suggests a matched follow-up design the exposure factor being the fact of having endometriosis and the outcome being the occupational status parameters. However the present study is a matched case control study without any follow-up, endometriosis case and control having there occupational status parameters measured while they have been included in the study.

47 Response: We re-ran all analyses following your suggestions, that is, we entered endometriosis vs. controls as the dependent variable. This allowed us to enter all predictor variables simultaneously in the multivariate adjusted analysis. However, please note that this alternative modelling approach did not alter our main results.

We hope that our modifications meet your expectations and hope that out manuscript is now acceptable for publication in BMJ open.

VERSION 3 – REVIEW

REVIEWER	Xavier Fritel Université de Poitiers, France
REVIEW RETURNED	24-May-2018

GENERAL COMMENTS	A good paper about the impact of endometriosis related chronic pelvic pain in professional life. For the best of my knowledge, there is a lack of survey in the general population about endometriosis prevalence. Because endometriosis may be underdiagnosed, no definitive conclusion about endometriosis prevalence can be made (see CNGOF guidelines: B. Borghese, P. Santulli, L. Marcellin, C. Chapron. Définition, description, formes anatomo-cliniques, pathogenèse et histoire naturelle de l'endométriose, RPC endométriose CNGOF-HAS [Definition, description, clinicopathological features, pathogenesis and natural history of endometriosis: CNGOF-HAS

	Endometriosis Guidelines]. Gynecol Obstet Fertil Senol (2018), 10.1016/j.gofs.2018.02.017). English version arriving soon … A limitation of the work is in the constitution of the groups. Because endometriosis is a profound disease, it is difficult to diagnose. It is therefore difficult to say that the control group was free of endometriosis. The consequences of this bias should be discussed. It is unclear how the control group was recruited, and why they were followed at hospital (if that's where they were recruited). From my point of view, performing an annual gynecological check with a hospital specialist rather than with his GP induced a selection bias, the consequences of which must be discussed. Concerning the cases, they were all, by definition, sufficiently symptomatic to require hospital care, which limits results interpretation. This selection bias, of course inevitable, deserves to be discussed. Please specify what was the definition used for « Caucasian », I do not know a scientific definition for this term expect a geographic one. To my knowledge, the Caucasus is a European region including Georgia, Armenia, Chechen territory. I will be amazed that women from the Caucasus represent o significant part of the sample. In what language were the questionnaires written, in German only or in German and French? Were these German and French versions validated? The authors showed an association between endometriosis related chronic pain and impaired professional life. This link could be mediated by an alteration in perceived health, including occupational health. A woman suffering from chronic pelvic pain has a greater risk of reporting a professional impact because of the cognitive impact of chronic pain that alters all scales that measure health, quality of life, or well-being. It should be noted that this professional impact remains very limited ($R^2 < 0.10$) which is not in favour of a causal link (Hill criteria). I find that the last 2 sentences of the conclusion are not well supported by the results. It seems to me an exaggeration to conclude that endometriosis is a handicap at work.

VERSION 3 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 5
Reviewer Name: Xavier Fritel

1. A good paper about the impact of endometriosis related chronic pelvic pain in professional life.
Response: We are glad you appreciated our work and thank you for your valuable comments.

2. For the best of my knowledge, there is a lack of survey in the general population about endometriosis prevalence. Because endometriosis may be underdiagnosed, no definitive conclusion about endometriosis prevalence can be made (see CNGOF guidelines: B. Borghese, P. Santulli, L. Marcellin, C. Chapron. Définition, description, formes anatomo-cliniques, pathogenèse et histoire naturelle de l’endométriose, RPC endométriose CNGOF-HAS [Definition, description, clinicopathological features, pathogenesis and natural history of endometriosis: CNGOF-HAS Endometriosis Guidelines]. Gynecol Obstet Fertil Senol (2018), 10.1016/j.gofs.2018.02.017). English version arriving soon …
Response: We fully agree to this point and added an according explanation as well as your proposed citation in the introduction section.

3. A limitation of the work is in the constitution of the groups. Because endometriosis is a profound disease, it is difficult to diagnose. It is therefore difficult to say that the control group was free of endometriosis. The consequences of this bias should be discussed.
Response: In addition to the discussion of different types of referral bias in the endometriosis as well as the control group we now described the consequences of such false classification more in detail.

4. It is unclear how the control group was recruited, and why they were followed at hospital (if that's where they were recruited). From my point of view, performing an annual gynecological check with a hospital specialist rather than with his GP induced a selection bias, the consequences of which must be discussed.
Response: In the countries where study participants were recruited most clinics also have an out-patient clinic where they offer annual check-ups also for healthy women. We added this information to the methods section.

5. Concerning the cases, they were all, by definition, sufficiently symptomatic to require hospital care, which limits results interpretation. This selection bias, of course inevitable, deserves to be discussed.
Response: We discussed the impact of eventual false classification of women within the limitation section as part of the discussion. As women with endometriosis were also included when they presented for routine controls e.g. not in the context of a surgical intervention or particularly severe symptoms, our results do not represent findings in only symptomatic women. However, selection bias cannot be excluded so we added a comment within the limitations.

6. Please specify what was the definition used for «Caucasian », I do not know a scientific definition for this term expect a geographic one. To my knowledge, the Caucasus is a European region including Georgia, Armenia, Chechen territory. I will be amazed that women from the Caucasus represent o significant part of the sample.
Response: The term “Caucasians” stands for the ethnic background of our study population and represents a commonly (not geographic) term for the ancestors of the Europeans (“Europides”). It is the classical used term in the English-speaking countries, which – according to my native speaker colleagues - is the adequate word to use in this context (and has been used in all other manuscripts resulting from this project). So we absolutely agree that our study group does not come from the geographic Caucasus, but estimate this expression to be correct.

7. In what language were the questionnaires written, in German only or in German and French? Were these German and French versions validated?
Response: The questionnaire was distributed only in Germany, Austria and the German speaking part of Switzerland and was therefore in German. Wherever possible validated versions of international questionnaires were used. In addition, questions resulting from our clinical experience were added to the questionnaire. The detailed questions are described in the methods section.

8. The authors showed an association between endometriosis related chronic pain and impaired professional life. This link could be mediated by an alteration in perceived health, including occupational health. A woman suffering from chronic pelvic pain has a greater risk of reporting a professional impact because of the cognitive impact of chronic pain that alters all scales that measure health, quality of life, or well-being.
Response: Yes, this is exactly why we evaluated pain as an influencing factor on the association between endometriosis and professional activity. Our results indicate that pain symptoms only show a weak association with the amount of sick leave and productivity loss. Other outcome measures however, like the question of having the desired profession or not, were indeed answered more negatively by endometriosis affected women suffering from severe chronic pain than from those without. These findings are put into context within the discussion.

9. It should be noted that this professional impact remains very limited ($R^2 < 0.10$) which is not in favour of a causal link (Hill criteria).
Response: Yes, we absolutely share this opinion. To make the findings clear we point out the rather small R^2 several times in our manuscript (i.e. line 353, 421, 479, 505) and emphasize the weak associations. We now additionally formulated the conclusion more modestly.

10. I find that the last 2 sentences of the conclusion are not well supported by the results. It seems to me an exaggeration to conclude that endometriosis is a handicap at work.
Response: We now modified this section and formulated a more careful message.

VERSION 4 – REVIEW

REVIEWER	Xavier Fritel Université de Poitiers, France
REVIEW RETURNED	19-Jun-2018

GENERAL COMMENTS	Thanks for the changes

VERSION 4 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 5
Reviewer Name: Xavier Fritel

Institution and Country: Université de Poitiers, France

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

Please leave your comments for the authors below Thanks for the changes

Response: We are happy that our modifications have met your expectations.