## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Depression and Anxiety in Prostate Cancer: A Systematic Review and Meta-Analysis of Prevalence Rates |
| **AUTHORS** | Leydon, Gerry; Birch, Brian; Prescott, Philip; Lai, Lily; Eardley, Susan; Lewith, George; Watts, Sam |

## VERSION 1 - REVIEW

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| **REVIEWER** | Professor Allan Hackshaw<br>University College London<br>UK |
| **REVIEW RETURNED** | 27-Sep-2013 |

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| **GENERAL COMMENTS** | 1. It has long been known that cancer is associated with depression and anxiety, so the findings of this meta-analysis support the evidence base. The need to provide adequate support to patients is already acknowledged by many health care systems. However, depression and anxiety are difficult characteristics to measure and examine, and given that there are several factors that influence them (e.g. disease stage, whether or not local support services are available from the clinic or patient groups, support from relatives, etc) , it is difficult to see the value of estimating a single prevalence over a range of populations.<br><br>2. There was no table (even in an appendix) showing key features of each study where available, such as number of patients, geographical location, years of study, average age of patients, stage of cancer, first diagnosis or treatment for recurrence, etc. Such a table is required in order to get a feel of the studies and data used in the meta-analysis.<br><br>3. Having such details could explain, for example, why there is a prevalence estimate for pre-treatment depression from van Tol-Geerdink, but not for anxiety, even though the HADS questionnaire was used for both.<br><br>4. Importantly, there were no details of how each study defined depression and anxiety; since they each would have used score cut-offs. Different cut-offs applied to the same health questionnaire would result in different prevalence values.<br><br>5. Furthermore, there has been no investigation into the potential reasons for the wide variability in the prevalence estimates seen in the Figures 2-4, and this would be difficult to do using summary data only.<br><br>This paper would be more appropriate for a general cancer journal, |

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| | or urological specialist journal. |

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| **REVIEWER** | Andrea Tavlarides<br>Mayo Clinic Florida, USA |
| **REVIEW RETURNED** | 21-Oct-2013 |

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| **GENERAL COMMENTS** | Overall, the article is a concise report using a large and satisfactory sample size and methodology. I believe the paper addresses important psychological issues that prostate cancer survivors face, and provides findings that may have useful clinical applications. I have several suggestions that may improve the manuscript.<br>1. Consider rewording Introduction sentences on Page 4 lines 20-27 from<br>"In addition to generic QoL issues, current National Cancer Survivorship Initiative (NCSI) guidelines have identified the need for better assessment, diagnosis and treatment of the specific psychological conditions associated with cancer diagnoses and treatment as one of the five key goals of improved, personalised and patient centred cancer care within the UK (3)." to "Additionally, the National Cancer Survivorship Initiative (NCSI) established five key goals of improved, personalised, and patient centred care in the UK. One goal was the need to better address specific psychological concerns associated with the diagnosis and treatment of cancer."<br>2. Page 5 line 3-4. "Were this known, or at least better understood, it would allow health care professionals to be more proactive and aware of what stages of treatment patients are most likely to experience depression and anxiety which would allow the health care team to "risk-adapt" their psychological screening and support processes." Consider changing to ""Were this known, or at least better understood, it would allow health care professionals to be more proactive and aware of what stages of treatment patients are most likely to experience depression and anxiety. This would allow health care teams to "risk-adapt" their psychological screening and support processes."<br>3. Methods, page 5: While your analysis uses quantitative methods, one could argue that qualitative research would provide more in depth knowledge about the psychological experiences of depression and anxiety in PCa patients. This is a limitation to the study. Future studies utilizing qualitative methods might help to identify specific ways to treat PCa depression/anxiety effectively.<br>4. PCa treatments under taken in Table 2, page 9: What made this categorization impossible? Treatment type is often determined by disease stage, particularly in advanced or metastatic disease. Consequently, treatment type may be a factor in depression of anxiety in these patients. Consider further analysis or greater explanation as to why it was impossible to stratify the treatment undertaken.<br>5. It is unclear how you defined "depression" and "anxiety" for the purpose of your study. Under "Number of studies reporting anxiety", page 10: You mention "…9 reported depression in pre-treatment, 4 in on-treatment and 11 in post-treatment." It is unclear if you meant to report depression or anxiety here. If it is your intention to present those patients with co-occurring psychological issues, please alter "number of studies reporting depression" to reflect anxiety prevalence as well. If it is not your intention to combine depression and anxiety, consider changing line 20 of page 10.<br>6. Discussion, line 31 page 12: Please proofread. The phrase in parentheses is unclear "(37order of refs right?)". |

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| | 7. Page 13: As a limitation, you list the likelihood that those with metastatic disease might present with higher psychological distress, skewing the data interpretation. Therefore, metastatic patients should be described separately from the rest of the patients in the study.<br>8. Page 13: Was there any indication that men had a lifetime diagnosis of depression or anxiety prior to the diagnosis of PCa, or were on treatment for a psychological disorder prior to or concurrently with their treatment of PCa? If so, it could provide a vehicle of prediction for those who may benefit from adjuvant psychological treatment prior to/during/after treatment for PCa.<br>9. Throughout the paper you mention patients being “on-treatment”. For those in chemotherapy or hormonal therapy, this makes sense. However, it’s unclear how you defined “on-treatment” for surgical patients.<br>10. Consider using more recent literature in your references. Reference 26 has an inappropriate year (20000. |

**VERSION 1 – AUTHOR RESPONSE**

All alterations to the manuscript based on the recommendations of Prof. Allan Hackshaw are highlighted in red.
All of the alterations to the manuscript based on the recommendations of Andrea Tavlarides are highlighted in yellow (these were submitted previously as discussed in our email correspondence but for the sake of clarity I have included them again in the attached manuscript).
All of the alterations to the manuscript based on the recommendations of the Editor are highlighted in blue.
Response to Reviewer 1: Prof Allan Hackshaw
Comment 1. It has long been known that cancer is associated with depression and anxiety, so the findings of this meta-analysis support the evidence base. The need to provide adequate support to patients is already acknowledged by many health care systems. However, depression and anxiety are difficult characteristics to measure and examine, and given that there are several factors that influence them (e.g. disease stage, whether or not local support services are available from the clinic or patient groups, support from relatives, etc) , it is difficult to see the value of estimating a single prevalence over a range of populations.
Response: We are in agreement that depression and anxiety are very difficult psychological constructs to measure and examine and ones that are influenced by a wide variety of variables. We understand and acknowledge the limitations that exist in generating a single estimate of depression and anxiety prevalence across a heterogeneous population of PCa patients at varying states of treatment. We believe that we have addressed the most pressing of these limitations in the discussion, namely that large longitudinal rather than cross-sectional studies are now needed to provide a more detailed and accurate portrayal of the changing nature of depression and anxiety in this patient group.
Despite these limitations, we still believe that there is value in estimating depression and anxiety prevalence from the information currently available in this way. This data is a first step and creates the argument for more detailed studies. It is also important that health care professionals are aware of the issues of psychological distress in the patients they treat. For many common cancers very similar meta-analytical estimates of conditions such as depression and anxiety exist as a first step in our understanding of these conditions. These data provide clinicians working with such patients with an important estimate of how prevalent such conditions are in the patients they treat. Data of this nature are currently not available for those working with PCa patients. The novel data generated through this study has gone some way to remedying this situation. It is our hope that this will provide health care professionals working in PCa with an initial estimate of depression and anxiety prevalence in the patients they treat and allow them to become more aware of what stages of treatment patients are most likely to experience these conditions.
Comment 2: There was no table (even in an appendix) showing key features of each study where available, such as number of patients, geographical location, years of study, average age of patients, stage of cancer, first diagnosis or treatment for recurrence, etc. Such a table is required in order to get a feel of the studies and data used in the meta-analysis.

Response: We agree that this was an important omission from the paper and we have now included such a table with this revision (Table 1, page 19).
Comment 3: Having such details could explain, for example, why there is a prevalence estimate for pre-treatment depression from van Tol-Geerdink, but not for anxiety, even though the HADS questionnaire was used for both.
Response: This was an error on our behalf. The original pre-treatment depression and anxiety graph did provide prevalence data for all of the authors measuring pre-treatment depression and anxiety. It seems that the original graph got unintentionally amended during the process of creating the high resolution TIFF files for publication. We have now rectified this error and have attached the updated graph (Figure 2: pre-treatment depression and anxiety prevalence) to this response.
Comment 4: Importantly, there were no details of how each study defined depression and anxiety; since they each would have used score cut-offs. Different cut-offs applied to the same health questionnaire would result in different prevalence values.
Response: We agree that this constitutes important information. As a key inclusion criteria, all of the studies included within this review had to clearly define the clinical cut-off score utilised on the investigators questionnaires of choice. In all cases these were in keeping with the clinical cut-offs recommended in the related research. Seven independent well validated questionnaires for anxiety and depression were utilised in the studies entered into this review, the clinical cut-off scores for each are listed below:
Questionnaires utilised , frequency of use and cut-off scores utilised
Questionnaire Name Frequency of Use Clinical Cut-Off Scores Utilised
Hospital Anxiety and Depression Scale (HADS) 13 HADS-A: ≥8
HADS-D: ≥8
Beck Depression Inventory (BDI) 6 ≥10
Self Rating Anxiety Scale (SAS) 4 ≥36
Self Rating Depression Scale (SDS) 4 ≥40
Centre for Epidemiologic Studies Depression Scale (CES-D) 4 ≥15
Stait-Trait Anxiety Scale (STAI) 4 ≥44
Memorial Anxiety Scale for Prostate Cancer (MAX-PC) 3 ≥27

We have included this amended table into the revised manuscript (Table 4, page 21) along with a brief sentence to define what constituted depression and anxiety caseness in each of the questionnaires utilised.
Comment 5. Furthermore, there has been no investigation into the potential reasons for the wide variability in the prevalence estimates seen in the Figures 2-4, and this would be difficult to do using summary data only.
Response: There is wide variability in both the point prevalence estimates of anxiety and depression and the 95% confidence intervals associated with them. There are likely to be many reasons for this variability which include sample size, selective populations and the differing instruments that have been used to measure depression and anxiety.
Our statistician (Prof Phil Prescott) has reviewed this variability and based on the available data it is not likely that we could formally investigate the properties of the populations to determine whether there were any differences that would explain this variability. We have included a brief paragraph in the limitations section of the discussion to expand on this issue.
Response to Reviewer 2: Andrea Tavlarides
1. Comment: Consider rewording Introduction sentences on Page 4 lines 20-27 from
“In addition to generic QoL issues, current National Cancer Survivorship Initiative (NCSI) guidelines have identified the need for better assessment, diagnosis and treatment of the specific psychological conditions associated with cancer diagnoses and treatment as one of the five key goals of improved, personalised and patient centred cancer care within the UK (3).” to
“Additionally, the National Cancer Survivorship Initiative (NCSI) established five key goals of improved, personalised, and patient centred care in the UK. One goal was the need to better address specific psychological concerns associated with the diagnosis and treatment of cancer.”

Response: We have revised the manuscript to include this recommendation.

2. Comment: Page 5 line 3-4. “Were this known, or at least better understood, it would allow health care professionals to be more proactive and aware of what stages of treatment patients are most likely to experience depression and anxiety which would allow the health care team to “risk-adapt” their psychological screening and support processes.” Consider changing to ““Were this known, or at

least better understood, it would allow health care professionals to be more proactive aware of what stages of treatment patients are most likely to experience depression and anxiety. This would allow health care teams to "risk-adapt" their psychological screening and support processes."

Response: We have revised the manuscript to include this recommendation.

3. Comment: Methods, page 5: While your analysis uses quantitative methods, one could argue that qualitative research would provide more in depth knowledge about the psychological experiences of depression and anxiety in PCa patients. This is a limitation to the study. Future studies utilizing qualitative methods might help to identify specific ways to treat PCa depression/anxiety effectively.

Response: We agree that utilising qualitative research would allow us to better understand the subjective and "lived" experiences of men with PCa and how this relates to their depression and anxiety. We also agree that information of this kind would be extremely helpful in identifying effective ways of managing these conditions. However, the aim of this paper was simply to provide an initial quantification of the prevalence of depression and anxiety in a men with PCa and not necessarily to address how best to manage these conditions. Thus whilst we agree that this does represent a limitation to this study, we felt it was beyond its scope to also include a narrative synthesis of qualitative research.

4. Comment: PCa treatments under taken in Table 2, page 9: What made this categorization impossible? Treatment type is often determined by disease stage, particularly in advanced or metastatic disease. Consequently, treatment type may be a factor in depression of anxiety in these patients. Consider further analysis or greater explanation as to why it was impossible to stratify the treatment undertaken.

Response: We agree that treatment type may be an important factor in relation to the onset of depression and anxiety in PCa. As such it would have been very helpful if we had been able to stratify treatments undertaken as a function of disease stage or treatment stage. As we stated in the manuscript, this unfortunately was not possible.

The reason that we were not able to stratify the treatments undertaken as a function of disease stage (localised, advanced or metastatic) was because in many instances the authors recruited patients with mixed disease stage and listed which types of treatment had been undertaken generically. They failed however to break down these results to highlight which patients from each stage (localised, advanced or metastatic) had completed each specific treatment. Therefore we were unable to tease apart these data, despite contacting many of the authors, to determine how treatments undertaken varied as a function of disease stage.

Likewise, it was also not possible to determine how the types of treatments undertaken varied as a function of treatment stage (on-treatment and post-treatment). This was again due to the fact that in many studies the authors recruited mixed samples of PCa patients who were either on-treatment or had completed treatment (post-treatment). Whilst the authors listed what types of treatments had or were being undertaken by the patients, they failed to break these results down to show which treatment were being undertaken by those patients who were on-treatment and which has been undertaken by those who were post-treatment. As a result it was not possible to stratify the types of treatments undertaken by treatment stage. As advised, we have explained this issue in greater depth in the manuscript.

5. Comment: It is unclear how you defined "depression" and "anxiety" for the purpose of your study. Under "Number of studies reporting anxiety", page 10: You mention "…9 reported depression in pre-treatment, 4 in on-treatment and 11 in post-treatment." It is unclear if you meant to report depression or anxiety here. If it is your intention to present those patients with co-occurring psychological issues, please alter "number of studies reporting depression" to reflect anxiety prevalence as well. If it is not your intention to combine depression and anxiety, consider changing line 20 of page 10.

Response: This was a typing error and we meant to report anxiety here and not depression. This error has been corrected in the text.

6. Comment: Discussion, line 31 page 12: Please proofread. The phrase in parentheses is unclear

"(35order of refs right?)".

Response: This was a proofreading omission and has been corrected.

7. Comment: Page 13: As a limitation, you list the likelihood that those with metastatic disease might present with higher psychological distress, skewing the data interpretation. Therefore, metastatic patients should be described separately from the rest of the patients in the study.

Response: We agree that it would be beneficial to describe and present data for PCa patients with metastatic disease as a separate sample. However, this was unfortunately not possible. The studies that recruited PCa patients with metastatic disease did so as part of larger collective samples of patients that included those with localised and/or advanced PCa. In the majority of cases, no individual depression and anxiety data was provided specifically for those with metastatic disease. Consequently it was not possible to describe these patients separately. We have expanded upon this issue in the manuscript.

8. Comment: Page 13: Was there any indication that men had a lifetime diagnosis of depression or anxiety prior to the diagnosis of PCa, or were on treatment for a psychological disorder prior to or concurrently with their treatment of PCa? If so, it could provide a vehicle of prediction for those who may benefit from adjuvant psychological treatment prior to/during/after treatment for PCa.

Response: Unfortunately none of the included studies provided any form of data relating to the patients past history of depression and anxiety so it was not possible for us to comment on this.

9. Comment: Throughout the paper you mention patients being "on-treatment". For those in chemotherapy or hormonal therapy, this makes sense. However, it's unclear how you defined "on-treatment" for surgical patients.

Response: For surgical patients, on-treatment was defined as measures of depression and anxiety recorded during the 2-weeks before and the first 4-weeks after the completion of surgery when the psychological dysfunction, physical side effects and complications experienced are most acute. This definition was selected for two reasons: 1) this is the approach utilising in other related research and 2) based upon the advice and consensus of the urological surgeons and clinicians involved in this study.

10. Comment: Reference 26 has an inappropriate year (20000).

Response: The typing error identified in reference 26 has been rectified.

Response to Editor's Comments:
Comment 1: We certainly need the table showing characteristics of the studies as mentioned by reviewer Hackshaw.
Response: As discussed in our response to reviewer Allan Hackshaw above, we have now created this table and have attached it to this revision.
Comment 2: Did you look at study quality? You say 'The research base evaluating the prevalence of depression and anxiety within PCa is growing steadily and a sizeable body of clinically relevant research currently exists. Unfortunately much of this data is very heterogeneous and of poor methodological quality and has yet to be subjected to rigorous systematic review and meta-analysis.' but we weren't clear that you assessed the quality.
Response: The quality of each paper entered into this review was assessed and determined through the application of the inclusion criteria. Specifically, for a study to be entered into the review, it had to provide valid and reliable measures of depression and anxiety, include only biopsy confirmed PCa patients, specifically stipulate what stage of treatment the patients were at during the time of assessment for depression and anxiety and be published in peer reviewed journals. Through the application of these criteria we were able to objectively ensure that each of the studies provided high quality data that would allow us to address our research aim (i.e. the meta-analytical assessment of depression and anxiety prevalence specifically in a PCa) in a valid and reliable manner.
Comment 3: We need dates of the search and details of who did what.
Response: We agree that this constitutes important information and have updated the manuscript to include this.

Comment 4: Did you only assess consistency of data extraction for 6 articles?
Response: That is correct. We only assessed consistency of data extraction for 6 randomly selected articles as we believe this would provide a robust enough account of the accuracy of our extraction processes. We erroneously failed to state that the study selection was random in the original manuscript. We have now rectified this. This is also the approach our research team has utilised in several other published systematic reviews and meta-analyses.
Comment 5: We didn't feel that your conclusions support the findings that prevalence is "relatively high and in keeping with that observed in other cancer sites" as you didn't look at other cancer sites.
Response: We agree that this concluding statement is the abstract is ambiguous and confusing. We meant that many other published reviews into the prevalence of psychological distress in common cancers have revealed prevalence data similar to that produced in this study. However, as this confusing statement was from the abstract we feel that it would be best to remove it to prevent any possible confusion. This statement has now been deleted from the revised manuscript.
Comment 6: We also need more information on anxiety and depression by disease stage and by treatment; the most important factor causing anxiety must be cancer disease stage, and type of treatment- with watchful waiting /active surveillance possibly the most stressful.
Response: We agree that treatment type and disease stage may be an important factor in relation to the onset of depression and anxiety in PCa. We have addressed this issue in response to the same point from reviewer Andrea Tavlarides and have replicated this response again below.
The reason that we were not able to stratify the treatments undertaken as a function of disease stage (localised, advanced or metastatic) was because in many instances the authors recruited patients with mixed disease stage and listed which types of treatment had been undertaken generically. They failed however to break down these results to highlight which patients from each stage (localised, advanced or metastatic) had completed which specific treatment. Therefore we were unable to tease apart these data, despite contacting many of the authors, to determine how treatments undertaken varied as a function of disease stage.
Likewise, it was also not possible to determine how the types of treatments undertaken varied as a function of treatment stage (on-treatment and post-treatment). This was again due to the fact that in many studies the authors recruited mixed samples of PCa patients who were either on-treatment or had completed treatment (post-treatment). Whilst the authors listed what types of treatments had or were being undertaken by the patients, the failed to break these results down to show which treatment were being undertaken by those patients who were on-treatment and which has been undertaken by those who were post-treatment. As a result it was not possible to stratify the types of treatments undertaken by treatment stage. As advised, we have explained this issue in greater depth in the manuscript.

## VERSION 2 – REVIEW

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| **REVIEWER** | Alexander Parker<br>Mayo Clinic, USA |
| **REVIEW RETURNED** | 04-Jan-2014 |

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| **GENERAL COMMENTS** | This is a well written paper but to be honest it is a little light on data and ability to make hard conclusions. I'm a little concerned that the scope is not appropriate for this journal.<br><br>Overall, the authors should be commended for a well-written and interesting manuscript. There are a few items that could be addressed that would make the paper more acceptable for consideration for publication. These are listed below.<br><br>1. The authors should help underscore to the reader how this paper adds to the current literature. By saying that describing the prevalence of anxiety and depression at three stages of PCa draws more attention to the need to examine how anxiety and depression affect issues of PCA survivorship is a little shallow and could be |

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| | deepened a bit more. Indeed, there are already papers in the literature directly addressing the affect of these metrics on survivorship issues (e.g. our group published one recently, see Parker et al, Psychooncology, 2013, Jun;22(6):1328-35. doi: 10.1002/pon.3138). Moreover, there are interventions already being studied to lower anxiety and depression in men with PCa. There is even a specific survey tool for measuring cancer-specific anxiety in men with PCa (MAX-PC). Taken together, this emphasizes the need to explain a little deeper how this meta-analysis moves the field forward.<br><br>2. On page 6, the authors use the term “incidence” when their estimates are better described as being of the prevalence of anxiety and depression (as they use in the remainder of the paper).<br><br>3. The introduction is a little lengthy and could be shortened by removing the first paragraph and then focusing the reader on the purpose of this paper and how it significantly adds to the literature.<br><br>4. Without any comparison group of healthy men or men with other cancers at varying stages of treatment, this paper is relegated to being a really nice descriptive paper (i.e. no real hypotheses being tested) regarding the observed prevalence of anxiety and depression in men with PCa. This should be mentioned as a weakness of the study. (Still a good study just a little limited in what we can glean from it)<br><br>5. Another weakness of the study is a lack of data on PCa aggressiveness as it is difficult to accept that a man with Gleason 6 disease should be included in an anxiety and depression analysis with a man with Gleason 8. The same goes for results of the surgery regarding margin status (a man with positive margins will most likely have high anxiety and depression than a man with negative margins). It is understandable that these data are not available (or difficult to get) but again, this lessens the impact of this study. This was alluded to in the second paragraph of page 14 but needs to stated more explicitly (i.e. not pathology data).<br><br>6. Including the metastatic patients with those with localized disease seems inappropriate. The authors need to justify this a bit more as to why men diagnosed and treated for localized disease should be lumped in with men with a diagnosis and treatment for metastatic disease.<br><br>7. It is a little unclear if there were any restrictions on years for the studies included in the meta-analysis. They are all from the 2000s except for one study form 1999.<br><br>Minor revisions:<br><br>1. There is miswording in the abstract in conclusions section “relatively high relatively high…”<br>2. On page 5 is reads “data is” and it should be “data are”. |

## VERSION 2 – AUTHOR RESPONSE

Comment 1: We weren't sure you really addressed Hackshaw's question 2 on assessing study quality, in the sense that this is usually meant in the context of performing systematic reviews. You mention poor methodological quality so how this was assessed for the included studies should be clear in the methods.

Response: We see that our previous response was somewhat vague and agree with this comment. However, as such there is no consistent mechanism or gold standard for assessing quality in the predominately cross-sectional studies making up this review that is equivalent to the Cochrane grading system that is largely used for clinical trials. As a consequence it is very difficult to have any consistent and consensus-based quality assessments in these papers. However, it was fundamental for us to ensure that each of the papers entered into the review were methodological robust in terms of what and who they were measuring. More specifically, for a study to be entered into the review, it had to provide valid and reliable measures of depression and anxiety, include only biopsy confirmed PCa patients, specifically stipulate what stage of treatment the patients were at during the time of assessment for depression and anxiety and be published in peer reviewed journals. Through the application of these criteria we were able to objectively ensure that each of the studies provided high quality data that would allow us to address our research aim (i.e. the meta-analytical assessment of depression and anxiety prevalence specifically in a PCa) in a valid and reliable manner. We understand this concern and if the editor would like us to further elaborate on this in the text we would be happy to do so.

Comment 2: The authors should help underscore to the reader how this paper adds to the current literature. By saying that describing the prevalence of anxiety and depression at three stages of PCa draws more attention to the need to examine how anxiety and depression affect issues of PCA survivorship is a little shallow and could be deepened a bit more. Indeed, there are already papers in the literature directly addressing the affect of these metrics on survivorship issues (e.g. our group published one recently, see Parker et al, Psychooncology, 2013, Jun;22(6):1328-35. doi: 10.1002/pon.3138). Moreover, there are interventions already being studied to lower anxiety and depression in men with PCa. There is even a specific survey tool for measuring cancer-specific anxiety in men with PCa (MAX-PC). Taken together, this emphasizes the need to explain a little deeper how this meta-analysis moves the field forward.

Response: We agree that the issue of how the presence of depression and anxiety negatively impacts upon survivorship needed further iteration. We have addressed this in the text (page 13, blue highlighting). We have also added a sentence to emphasise how the prevalence data generated through this meta-analysis has moved this field forward.

Comment 3: On page 6, the authors use the term “incidence” when their estimates are better described as being of the prevalence of anxiety and depression (as they use in the remainder of the paper).

Response: This error has been amended.

Comment 4: The introduction is a little lengthy and could be shortened by removing the first paragraph and then focusing the reader on the purpose of this paper and how it significantly adds to the literature.

Response: We felt, after discussion among the authors, that the first paragraph was needed to set the scene for this paper by underpinning the significance of the issues. If the editor feels that he would like us to remove the first paragraph, we would be happy to do so but hope that he would allow us to keep it in.

Comment 5: Without any comparison group of healthy men or men with other cancers at varying stages of treatment, this paper is relegated to being a really nice descriptive paper (i.e. no real hypotheses being tested) regarding the observed prevalence of anxiety and depression in men with PCa. This should be mentioned as a weakness of the study. (Still a good study just a little limited in what we can glean from it).

Response: We agree that this represents an important limitation of the study and have added a paragraph into the discussion to address this point (page 13, blue highlighter).

Comment 6: Another weakness of the study is a lack of data on PCa aggressiveness as it is difficult to accept that a man with Gleason 6 disease should be included in an anxiety and depression analysis with a man with Gleason 8. The same goes for results of the surgery regarding margin status (a man with positive margins will most likely have high anxiety and depression than a man with negative margins). It is understandable that these data are not available (or difficult to get) but again, this lessens the impact of this study. This was alluded to in the second paragraph of page 14 but needs to stated more explicitly (i.e. not pathology data).

Response: We agree that this represents an important limitation of the study and have amended the appropriate paragraph to address this point (page 14, blue highlighter).

Comment 7: Including the metastatic patients with those with localized disease seems inappropriate. The authors need to justify this a bit more as to why men diagnosed and treated for localized disease should be lumped in with men with a diagnosis and treatment for metastatic disease.

Response: We are in agreement that it is inappropriate to group men with metastatic disease with those with localised disease. Unfortunately however we were not able to separate out the depression and anxiety prevalence date for men with differing disease stage simply because this information was not available in the original data. This issue was raised in the first round of review and we responded to this in the revised manuscript with the following paragraph:
“Unfortunately it was not possible to generate depression and anxiety prevalence data specifically for men with metastatic disease as the studies that recruited PCa patients with metastatic disease did so as part of larger collective samples of patients that included those with localized and/or advanced PCa. In the majority of cases, no individual depression and anxiety data were provided specifically for those with metastatic disease. Consequently it was not possible to describe these patients separately”.
We hope that the editor feel this adequately addresses this important limitation.

Comment 8: It is a little unclear if there were any restrictions on years for the studies included in the meta-analysis. They are all from the 2000s except for one study form 1999.

Response: No date restrictions were imposed upon the included studies. The fact that all but one of the studies were from 2000 onwards was simply due to the fact that no papers pre-1999 were identified during the data searching process. We have included a brief sentence in the methodology section to clarify this issue (page 6, blue highlighter).

Minor revisions:

1. There is miswording in the abstract in conclusions section “relatively high relatively high…”
2. On page 5 is reads “data is” and it should be “data are”.

Response: Both of these errors on our behalf have been rectified.