PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Support for mid-life anxiety diagnosis as an independent risk factor for dementia: a systematic review.
AUTHORS	Gimson, Amy; Schlosser, Marco; Huntley, Jonathan; Marchant, Natalie

VERSION 1 – REVIEW

REVIEWER	Dr Claire Burton Keele University, UK
REVIEW RETURNED	05-Sep-2017

GENERAL COMMENTS	A very well written systematic review exploring a potentially modifiable risk factor of future dementia diagnosis; this study contributes important information to the evidence base surrounding dementia aetiology. The methods, results and conclusion are presented in a thorough and systematic way. Potential neurochemical pathways are alluded to in the discussion and references made to potential clinical implications. When describing inclusion criteria, specifically case definition, I wonder if the methodology used by Zilken's et al could be expanded on a little? The author may wish to mention some of the issues surrounding the use of Read codes to identify cases and controls.

REVIEWER	Andrew Petkus, Ph.D. University of Southern California Department of Neurology Los Angeles, CA United States
REVIEW RETURNED	22-Sep-2017

GENERAL COMMENTS	The following is a review of the article "Support for mid-life anxiety diagnosis as an independent risk factor for dementia: a systematic review". The article presents an important topic of anxiety and its association with dementia. This topic is also understudied compared to other psychiatric symptoms. The paper is generally well-written. My biggest criticism of the paper is that the authors develop the rationale that length of follow-up time is really important when examining the association between anxiety symptoms and risk of dementia. This is based on the depression literature. Despite developing this rationale, they actually never test this hypothesis in the paper. The authors choose papers where there are follow-up periods of greater than 10 years. I think the paper could be improved if they found a method to test this hypothesis that length of follow-up

	is important. Can the authors compare the effect size between studies with long and short follow-up periods to determine if the effect size is in fact larger for follow-up studies? Without directly making this comparison I think there claim that the longer follow-up period is important is not entirely supported. I also have some notes and comments on specific sections of the paper which are included below. Thank you for the opportunity to review this very interesting review paper. Introduction Page 4 line 27 – the authors state that a recent study opposes the finding that a stronger association over shorter intervals would have been more indicative of prodromal symptoms. Can you elaborate on this? The authors cite the Gulpers et al. 2016 review and discuss how they concluded that anxiety was likely a prodromal symptom of dementia. Can you review the mean follow-up time between anxiety assessment and dementia diagnosis? Was this only 5-10 years' follow-up? It would be helpful to state this as you make the argument that they were incorrect in their conclusion because they only focused on studies with short follow-up periods. Methods: Can you state the number of occurrences that there was disagreement between reviewer 1 (AG) and reviewer 2 (MS) which the third reviewer (NM) had to resolve? Results: The statement that the STAI is the gold standard assessment of anxiety symptoms is debatable. There is a fairly large body of literature that shows the STAI is highly correlated with depressive symptoms. Other geriatric specific measures of anxiety symptoms have better psychometric properties than the STAI. I would recommend removing this statement. The Petkus et al. (2016) study did use a cutscore of 25 or higher to represent high anxiety. This cutoff represented one SD above the mean anxiety symptoms. The statement that this cutoff indicated clinically significant anxiety symptoms is not supported. There is no research examining what clinical cutoff has best sensitivity/specificity to represent clinically significant anxiety with the version of the STPI that they used. Therefore, although the cutoff included individuals 1 SD over the mean anxiety symptoms it is not clear if this cutoff best represents clinically significant anxiety. It is confusing why the authors did not compare studies with less than 10 years of follow-up to studies with more than 10 years of follow-up. The authors should highlight the fact that the Petkus et al., 2016 study was with a twin sample. Also although the diagnosis of dementia was primary achieved through ongoing assessment via the study, they did use health registry diagnoses of dementia for participants who were lost to follow-up. The article from Petkus et

	al., 2016 also found that when excluding individuals who developed dementia within 5 years of baseline they still found an association between higher anxiety and risk of dementia. This also provides evidence for the argument that anxiety is not just a prodrome of dementia. Discussion: The first paragraph of the discussion could be clearer. The authors just remake the same statements from the introduction. The authors should highlight the possibility of a publication bias in the limitations. The likelihood of a study being published with positive findings between anxiety and dementia is greater than the likelihood that either authors will pursue publication (or a study will be published) if anxiety was not associated with dementia.

VERSION 1 – AUTHOR RESPONSE

We are grateful to both reviewers and the editor for their helpful and constructive comments on our systematic review article. We have addressed all the comments, which we detail below, and have revised the manuscript accordingly. We believe that our manuscript has been substantially improved as a result.

Editor
1. Please include the names of the databases searched in the abstract.
We have included names of the databases searched in the abstract:

P2Ln8: “MEDLINE, PSYCINFO, and EMBASE were searched for peer-reviewed journals up until 8 March 2017.”

2. Please state the start date for the search in your methods section - was this from inception?
We have added search start date into methods:

P6Ln2: “A systematic literature search of MEDLINE, PSYCINFO and EMBASE databases was conducted of articles published from inception up until 8th March 2017 to identify articles reporting analyses of the association between anxiety”

3. Please provide an example of a complete search strategy for at least one database, as a supplementary file.
We have now included a supplementary file containing the complete search strategy, which has been referenced in the main text.

Reviewer 1

1. When describing inclusion criteria, specifically case definition, I wonder if the methodology used by Zilken's et al could be expanded on a little?
We agree that a more detailed description of the methodology would help the reader, and have now expanded the descriptions for both the Zilkens and Boot studies:

P9Ln5: “Zilkens et al. (2014) and Boot et al. (2013) conducted matched case-control studies, which retrospectively analysed community and hospital records of individuals with dementia or case-matched controls for anxiety diagnosis, and therefore did not include a cognitive assessment at baseline to exclude dementia. Zilkens et al. (2014) drew controls from the electoral roll, whereas Boot et al. (2013) drew them from the community-dwellling persons included in the Mayo Clinic Study of Aging.”

2. The author may wish to mention some of the issues surrounding the use of Read codes to identify cases and controls.
We thank the author for this valuable suggestion, and have added the following to address this point:

P14Ln1 : “The use of read codes in retrospective studies may have resulted in lower identification of individuals with clinically significant anxiety as a result of inconsistent entry of read codes during evaluations, or of absence of clinical record for non-help seekers [33].”

Reviewer 2

1. My biggest criticism of the paper is that the authors develop the rationale that length of follow-up time is really important when examining the association between anxiety symptoms and risk of dementia. This is based on the depression literature. Despite developing this rationale, they actually never test this hypothesis in the paper. The authors choose papers where there are follow-up periods of greater than 10 years. I think the paper could be improved if they found a method to test this hypothesis that length of follow-up is important. Can the authors compare the effect size between studies with long and short follow-up periods to determine if the effect size is in fact larger for follow-up studies? Without directly making this comparison I think there claim that the longer follow-up period is important is not entirely supported. It is confusing why the authors did not compare studies with less than 10 years of follow-up to studies with more than 10 years of follow-up

Thank you to the reviewer for this thoughtful comment. We have used the minimum follow up length of 10 years in order to assess the correlation between anxiety in mid-life as opposed to anxiety that presents as a prodromal symptom of dementia. There is an established association between common mental illnesses, such as anxiety, in pre-clinical dementia, as well as in dementia itself. To ensure we were correlating anxiety independent of any dementia prodrome, with dementia later in life, we decided not to include studies that may be assessing anxiety in the years close to dementia diagnosis, as these may be symptoms of a prodromal state. We therefore agree with the reviewer that including studies with shorter follow up times may produce different associations between anxiety and dementia due to this potentially confounding effect of prodromal anxiety. However we did not think that it would add to the paper to explicitly examine this by comparing the association between anxiety and dementia between studies with greater than 10 year follow up to studies with shorter follow up times, as this has been reviewed recently elsewhere (Gulpers et al 2016). Our main aim in this review is to examine whether anxiety is independently associated with risk of developing dementia, rather than to examine prodromal anxiety. We therefore deliberately wanted to avoid the confounding effect of prodromal anxiety and judged that a 10 year follow up period was an appropriate length of follow up to remove this confounder. We have changed the text in these ways in order to minimize the ambiguity of the purpose of our review:

P2Ln3: “Often believed to be a prodromal feature of neurodegenerative disease, anxiety may also be an independent risk factor for dementia, operationally defined here as preceding dementia diagnosis by >10 years.”

P2Ln21: “These findings indicate that anxiety may be a risk factor for late-life dementia, excluding anxiety that is related to prodromal cognitive decline.”

P3Ln6: “to investigate a life-course association between a potentially modifiable risk factor, anxiety, and dementia, whilst excluding anxiety related to pre-clinical dementia.”

P5Ln5: “The association between anxiety symptoms (independent of the dementia-prodrome) and dementia in later life could more easily be investigated with longer intervals between anxiety assessment and dementia diagnosis, as the studies that have investigated this association within a 5-10 year interval have reported variable results [12,13].”

We agree that it would be informative to compare effect sizes based on length of follow-up. We have altered our manuscript to qualitatively clarify the differences in effect sizes for papers of different follow up length that we have cited in the review. Unfortunately we cannot quantitatively compare the effect sizes of these included studies (or those not included in this review that had shorter follow-up periods) because the heterogeneity of the study methodologies prohibited us from conducting reliable statistical comparisons between them. In order to make an indirect assessment, we have compared the effect sizes of the studies reviewed in Gulpers et al (2016), who had a follow up of <10 years, to the studies included in our review. The alterations we have made are detailed below:

P9Ln17: “Zilkens et al. (2014): OR = 1.61 (95% CI 1.28-2.02), Boot et al. (2013): OR = 7.4 (95% CI 3.5-16), Gallacher et al. (2009): OR = 1.62 (95% CI 0.59-4.41) and Petkus et al. (2016): OR = 1.48 (95% CI 1.01-2.18), respectively. On the whole, retrospective studies that looked back for life-long diagnoses of anxiety found a stronger association between mid-life anxiety and later dementia diagnosis, than prospective studies investigating an association over a shorter time period.”

P12Ln7: “Given the short time interval between assessments, Gulpers et al. were unable to determine whether anxiety could also serve as an independent risk for dementia. This review reports solely articles that were not included Gulpers et al.’s analyses, and therefore furthers their work by providing an independent assessment of the anxiety-dementia association. Effect sizes of the studies included in this review (1.48 - 7.4) were comparable to the overall effect size found by Gulpers et al. (2016) of 1.61, suggesting that the association between clinically significant mid-life anxiety and later-life dementia is as strong as that between late-life anxiety symptoms and dementia.”

4. Page 4 line 27 – the authors state that a recent study opposes the finding that a stronger association over shorter intervals would have been more indicative of prodromal symptoms. Can you elaborate on this?
We agree with the reviewer that this statement warrants elaboration. We have added a statement as follows:

P4Ln10: This substantiates interpretations of depression as a risk factor for developing dementia, whereas a stronger association over shorter intervals would have been more indicative of prodromal symptoms [2]. Conversely, a recent study found no association between dementia and depressive symptoms experienced more than 22 years before dementia diagnosis, however a positive association between dementia and depressive symptoms experienced on average 11 years prior to diagnosis of dementia was reported [5].

5. The authors cite the Gulpers et al. 2016 review and discuss how they concluded that anxiety was likely a prodromal symptom of dementia. Can you review the mean follow-up time between anxiety assessment and dementia diagnosis? Was this only 5-10 years’ follow-up? It would be helpful to state this as you make the argument that they were incorrect in their conclusion because they only focused on studies with short follow-up periods.
Thank you for highlighting this ambiguity in the manuscript. We have now added a sentence to explain the follow up length of studies reviewed in Gulpers et al. as follows:

P11Ln21: “A recent systematic review reported a positive association between anxiety symptoms and dementia diagnosis over a short time interval. In that review the majority of studies reported follow up periods between 2-3.8 years. A single study had a follow up time of up to 11.8 years, however the average interval between anxiety and dementia diagnosis may have been less than 10 years therefore it was not included in the current review”

6. Can you state the number of occurrences that there was disagreement between reviewer 1 (AG) and reviewer 2 (MS) which the third reviewer (NM) had to resolve?
Thank you for highlighting this omission. We have now included this information:. We have not provided information in the manuscript about which studies were discussed for conciseness. These studies were De Brujn et al. (2014), which was excluded due to ambiguity of follow-up length, and Petkus et al. (2016) which was included.

P6Ln12: “Any disagreement was resolved by consensus with a third reviewer (NM), which occurred in two cases.”

7. The statement that the STAI is the gold standard assessment of anxiety symptoms is debatable. There is a fairly large body of literature that shows the STAI is highly correlated with depressive symptoms. Other geriatric specific measures of anxiety symptoms have better psychometric properties than the STAI. I would recommend removing this statement.
We agree with the reviewer that no consensus has been reached regarding anxiety assessments, and have removed this statement. It now reads as follows:

P8Ln6: “Gallacher et al. (2009) measured anxiety using the STAI, which has a range from 20 to 80 [17], and is a validated measure for assessing anxiety symptoms.”

8. The Petkus et al. (2016) study did use a cutscore of 25 or higher to represent high anxiety. This cutoff represented one SD above the mean anxiety symptoms. The statement that this cutoff indicated clinically significant anxiety symptoms is not supported. There is no research examining what clinical cutoff has best sensitivity/specificity to represent clinically significant anxiety with the version of the STPI that they used. Therefore, although the cutoff included individuals 1 SD over the mean anxiety symptoms it is not clear if this cutoff best represents clinically significant anxiety.

Thank you for raising this important point. We agree with the reviewer that there is no literature examining a clinically significant cutoff score for the version of the STPI, and have clarified this description in the text to make this more reasoned:

P8Ln13: “Participants scoring at least one standard deviation above the population mean, equating to a score of ≥25 out of 40, were categorised having ‘high anxiety’. Although there is no established cut-off for clinically significant anxiety using this scale, scores greater than 1 SD above the population mean are likely to represent a group with a high anxiety symptom burden. After discussion amongst the reviewers (AG, MS, NLM) we reached a consensus judgement that the study was suitable for inclusion in this review.”

9. The authors should highlight the fact that the Petkus et al., 2016 study was with a twin sample. Also although the diagnosis of dementia was primary achieved through ongoing assessment via the study, they did use health registry diagnoses of dementia for participants who were lost to follow-up. The article from Petkus et al., 2016 also found that when excluding individuals who developed dementia within 5 years of baseline they still found an association between higher anxiety and risk of dementia. This also provides evidence for the argument that anxiety is not just a prodrome of dementia.

We thank the reviewer for this insightful comment, and have included this in our article as follows:

P9Ln3: “Petkus et al. (2016) conducted prospective cohort studies using a community twin-population that excluded dementia at baseline.”

P9Ln23: “Additionally, Petkus et al. (2016) demonstrated that the association between high anxiety and dementia diagnosis remained when they excluded participants who developed dementia within 5 years of the baseline assessment. This subsample had an average interval between baseline and dementia diagnosis of 14.7 years (SD 6.7 years). Both lend support that the associations found were independent of prodromal dementia symptoms.”

10. The first paragraph of the discussion could be clearer. The authors just remake the same statements from the introduction.

Thank you for highlighting this repetition. We have improved the clarity of this paragraph as below:

P11Ln15: “This systematic review found four high quality studies that all showed a positive association between clinically significant anxiety and risk of late-onset dementia over a mean interval of at least 10 years from anxiety assessment to dementia diagnosis, even after accounting for potential confounders. This important finding provides further evidence that a common mental health condition in mid-life is associated with later life neurodegenerative disorders.”

11. The authors should highlight the possibility of a publication bias in the limitations. The likelihood of a study being published with positive findings between anxiety and dementia is greater than the likelihood that either authors will pursue publication (or a study will be published) if anxiety was not associated with dementia.
Thank you for this suggestion. To address this important comment, we have added a further sentence in the discussion:

P14Ln4: “Publication bias may also have influenced the studies included, as positive findings may be more likely to have been published than studies finding no association.”

VERSION 2 – REVIEW

REVIEWER	Andrew Petkus University of Southern California Department of Neurology United States
REVIEW RETURNED	30-Nov-2017

GENERAL COMMENTS	The authors were mostly responsive to my comments. This is a well written manuscript on an important topic and modest contribution to the literature. I have two additional comments: First is regarding the statement that the STAI is the gold standard assessment of anxiety symptoms. I still think this is a debatable statement. In the response to reviewer document the authors agree with me that no consensus has been made regarding the assessment of late life anxiety. They also state that they are removing this statement regarding the STAI being the gold standard assessment. However, the statement that the STAI is the gold

	standard assessment was not removed. Can the authors clarify the statement in the second to last paragraph regarding Benzodiazepines. Benzodiazepines have a lot of negative outcomes in the elderly especially mortality (as stated) but also higher rates of dementia. I think the authors are implying that Benzodiazepines should not be considered but this point can be made more explicit. Thank you for the opportunity to review this interesting and important review.

VERSION 2 – AUTHOR RESPONSE

We are grateful to our reviewer for their further comments on our systemic review article. We detail our comments to these 2 points below, and have revised the manuscript accordingly.

Reviewer 2

1. First is regarding the statement that the STAI is the gold standard assessment of anxiety symptoms. I still think this is a debatable statement. In the response to reviewer document the authors agree with me that no consensus has been made regarding the assessment of late life anxiety. They also state that they are removing this statement regarding the STAI being the gold standard assessment. However, the statement that the STAI is the gold standard assessment was not removed.

Thank you for identifying a mistake in the revision including track changes. We have now removed this statement from the with track changes copy.
P8Ln7: "This questionnaire is arguable the gold standard for assessing anxiety symptoms."

2. Can the authors clarify the statement in the second to last paragraph regarding Benzodiazepines. Benzodiazepines have a lot of negative outcomes in the elderly especially mortality (as stated) but also higher rates of dementia. I think the authors are implying that Benzodiazepines should not be considered but this point can be made more explicit.

Many thanks for this suggestion, we have clarified the second to last paragraph to include:
P14Ln14: "Benzodiazepines, commonly used in the treatment of anxiety, have been shown to increase risk of mortality in some groups [35], and therefore cannot be considered a measure to reduce dementia incidence in those with clinical anxiety."