PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness of interventions for perinatal anxiety and/or depression: a systematic review.
AUTHORS	Camacho , Elizabeth; Shields, Gemma

VERSION 1 – REVIEW

REVIEWER	Siham Sikander Health Services Academy & Human Development Research Foundation, Pakistan
REVIEW RETURNED	01-Mar-2018

GENERAL COMMENTS	It is an important topic, especially the cost effectiveness of perinatal mental health interventions. It would be good to have some details about the dose of these interventions (eg number of sessions spanning over xyz months or pregnancy to postnatal months) as well as some details about the delivery agents. This will be value added addition.

REVIEWER	Jemimah Ride Centre for Health Economics, University of York, UK
REVIEW RETURNED	06-Mar-2018

GENERAL COMMENTS	Review for BMJ Open Paper: Cost-effectiveness of interventions for perinatal anxiety and/or depression: a systematic review. Comments to the authors The authors have clearly described the systematic review undertaken, which looks at interventions for perinatal anxiety and depression. The methods for systematic review appear sound and reproducible. However, the paper would benefit from providing a clear rationale for reviewing such a heterogeneous set of interventions together (prevention, treatment, identification). While this reflects the complex nature of interventions for perinatal mental health problems, it makes it more difficult to see the review as a cohesive whole. The authors

	reflect this in their comments that there is heterogeneity in the studies, making it difficult to draw strong conclusions, but this issue could have been foreseen from the outset because of the choice to draw such wide boundaries for the review. Because of this, I think the authors could be more cautious in drawing comparisons across these very different sets of interventions. The issue of heterogeneity of definitions and methods has been touched upon by the authors, but is particularly relevant in this field, where definitions of perinatal mental health problems differ from paper to paper. The authors could discuss this more clearly in the background section to set the scene for the different approaches taken in the papers they review. Abstract: 1. While the abstract states the objective as 'to systematically review and critically appraise published economic evaluations of interventions for the prevention or treatment of perinatal anxiety and/or depression (PAD)', it would be clearer if a well-defined research question was provided, so that the reader could determine whether and how the review answers the question. 2. The phrase 'complete lack of economic evidence' seems a little subjective, it might be better to state instead that there were no studies that met the criteria for inclusion in this review on those subjects. 3. The abstract could lead the reader to the conclusion that interventions involving identification and treatment have been directly compared to prevention or treatment alone by the use of the phrase 'most likely to be cost-effective', while in fact there are very few studies on any of these types of interventions, and there has been no possibility of pooling data for meta-analysis. It would be better if they stated their findings on the strength of evidence for cost-effectiveness separately for the different types of intervention. Strengths and weaknesses: 4. The first dot point does not connect the first part of the sentence to the latter part 5. Are the authors aware of relevant studies in other languages? This point seems to suggest they do; it would be worth mentioning this if so. Background: 6. Again, it would provide clarity for the reader if the rationale for reviewing such a diverse set of interventions was outlined here, along with a clearly stated research question reflecting this. 7. While it is not the focus of this review paper to explore the

	complexities of definitions in the field of perinatal mental health, it would be helpful to demonstrate more clearly the established basis for the definition of perinatal anxiety and depression used by the authors, and to provide background on the different approaches used in the papers included in the study. For instance, it would be helpful to reflect on the differing definitions used in the literature, some of which apply clinical diagnoses, and some which use a cutoff above a certain level on a screening tool (most often the Edinburgh Postnatal Depression Scale). In relation to the combined focus on anxiety and depression, it could be informative to the reader to mention that 'postnatal depression', especially when measured by the EPDS, is often used as an umbrella term for many different types of mental health problem, and may include anxiety or adjustment disorders. The use of different time horizons might be elucidated by reference to the differing definitions of 'perinatal' that are used in the literature. In addition, reference/s supporting the use of the acronym PAD would be helpful. 8. The associations between maternal perinatal mental health problems and children's problems have not been established to be causal, so the authors could be more cautious in their use of language about 'impacts'. 9. It would be clearer for the reader if instead of using the term 'currently' to refer to number of births per annum, the year of this statistic was provided. 10. The authors state that 'Evidence suggests that the costs of improving perinatal mental health services are likely to be outweighed by the benefits [7,14].'. Such a statement suggests there would be no need for economic evaluations in this area, and does not reflect the weakness of economic evidence found in this review. Does this instead refer to the high estimated societal cost of perinatal mental health problems? If so, such a statement could be misleading if it implies that the whole estimated cost could be averted by intervening in perinatal mental health problems. Such costs do not identify which elements of current practice contributing to those costs are inefficient and where efficiency gains might be made. 11. Rather than stating that it is 'generally accepted that psychological therapy and/or antidepressant medication are effective at treating the symptoms of PAD for many women', could the authors instead make reference to the recommendations of clinical guidelines, or the evidence behind those recommendations? 12. Reference is made to 'vital funds' – might be clearer (and avoid subjective language) if the authors referred to scarce resources or opportunity costs. 13. A description of previous systematic reviews on this topic should be provided in the background section. Later (in the methods section) the authors refer to two prior reviews, both of which were published in 2016, so it would be helpful if the authors could provide a rationale for the need for this review in light of previous evidence. Methods: 14. Studies published prior to 2000 are excluded with the rationale that older references are less useful for decision

	making. It would be helpful to the reader to have a sense of how many studies are thereby excluded, and how the findings of those older studies compare to newer ones. 15. Could the authors state the proportion of studies reviewed by the second reviewer? Results: 16. Table 3 would benefit from the inclusion of confidence intervals around the point estimates. For instance, the intervention in the study by Morrell et al (2009) is described as highly likely to be cost effective, but it would be helpful to the reader to know that in the main analysis from this study, neither the QALY gains nor cost savings were statistically significant compared to the control group. Discussion: 17. The information on the use of QALYs to measure health benefit and the NICE threshold would be better in the background rather than discussion. 18. Could the authors compare the magnitude of clinical effectiveness found in the included trials to wider studies on clinical effectiveness of that type of intervention? (There are relevant meta-analyses e.g. (Dennis and Hodnett 2007, Dennis and Dowswell 2013)) If the magnitude of clinical effect was similar, this would provide the reader with more assurance that these results were plausible. 19. Strengths and limitations – could discuss that although two tools were used to assess critically assess the included studies, one was developed for this review (and mention if validated in any way). 20. Future research – the word 'massive' referring to burden of disease seems unnecessarily subjective. 21. Again the authors restate the view that costs of improving perinatal mental health are likely to be outweighed by the benefits. The same comments as applied in the background section apply here. 22. The reference to spill overs needs to be described more clearly (e.g. are the authors talking about effects on children, or on time off work?) and to be supported by appropriate references. If the authors are referring to family spillovers, there is a relevant literature to reference (e.g. papers on this topic in general (Davidson and Levin 2010, Bobinac, van Exel et al. 2011, Al-Janabi, van Exel et al. 2016, Al-Janabi, Van Exel et al. 2016), and a paper by Ride (2017) refers to this issue in the context of perinatal mental health specifically), and it would be relevant to discuss the statements of decisions makers (including NICE) that explicitly allow for such effects to be taken into account. Conclusion: 23. If a clearer research question was posed at the outset, the conclusions could reflect that.

	Minor errors: 24. A word ‘is’ seems to be missing from line 16 (…time which likely…) 25. Line 40 – sentence starting with ‘Whereas’ References Al-Janabi, H., J. van Exel, W. Brouwer and J. Coast (2016). "A framework for including family health spillovers in economic evaluation." Medical Decision Making **36**(2): 176-186. Al-Janabi, H., J. Van Exel, W. Brouwer, C. Trotter, L. Glennie, L. Hannigan and J. Coast (2016). "Measuring health spillovers for economic evaluation: a case study in meningitis." Health economics **25**(12): 1529-1544. Bobinac, A., N. J. van Exel, F. F. Rutten and W. B. Brouwer (2011). "Health effects in significant others: separating family and care-giving effects." Medical Decision Making **31**(2): 292-298. Davidson, T. and L.-A. Levin (2010). "Is the societal approach wide enough to include relatives? Incorporating relatives' costs and effects in a cost-effectiveness analysis." Applied Health Economics and Health Policy **8**: 25+. Dennis, C. L. and T. Dowswell (2013). "Psychosocial and psychological interventions for preventing postpartum depression." Cochrane Database of Systematic Reviews(2). Dennis, C. L. and E. Hodnett (2007). "Psychosocial and psychological interventions for treating postpartum depression." Cochrane Database of Systematic Reviews(4): CD006116. Ride, J. (2017). "Setting the Boundaries for Economic Evaluation: Investigating Time Horizon and Family Effects in the Case of Postnatal Depression." Value in Health.

REVIEWER	Emily Callander Australian Institute of Tropical Health and Medicine, James Cook University, Australia
REVIEW RETURNED	08-Mar-2018

GENERAL COMMENTS	This was an interesting paper on a topical subject, with high policy and practice importance. My overall concern with the paper was that it lacked a clear purpose and a strong justification for the study. The Introduction did not build a strong story, and the aims were for general exploration of the topic, as opposed to aiming to answer a specific question. The methods were excellent and the results were very clearly written. Because there were no clear aims of the study, the discussion was not well structured and left the reader wondering what conclusions could actually be drawn from this paper.

REVIEWER	Robert T. Ammerman Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, USA

REVIEW RETURNED	25-Mar-2018

GENERAL COMMENTS	This article is a systematic review of cost-effectiveness studies of interventions to prevent or treat depression or anxiety during pregnancy or postpartum. It is a thorough and scholarly work. The presentation of all of the steps of the review in incorporated and supplementary tables is a strength and provides an excellent reference point for future efforts. The findings are clearly presented. They support the cost-effectiveness of interventions, but note the heterogeneity and methodological unevenness of the extant literature. This cannot be a definitive review as a result, but limitations in studies are presented in a way that should advance the literature. There are several issues that need attention and some areas that would benefit from expanded discussion, these are presented below. 1. The introduction should provide a more compelling rationale for the review at this point—what does it add relative to prior reviews other than being an update? 2. It is stated that there were no studies on fathers but this term was not found in the list of search words. My knowledge is that there are no studies, but if this is going to be part of the review it should be searched. 3. The introduction should include some mention of prior reviews of economic analyses of interventions and mention of reviews documenting effectiveness of interventions for depression and anxiety in pregnant and postpartum mothers. 4. The discussion should include a more explicit calling out of what studies should report to facilitate future reviews. The authors note that some studies omitted important information that limited their review, and this is an opportunity to lay out what the standards should be going forward. 5. One study was missing that seemed to meet criteria for inclusion: Ammerman, R. T., Mallow, P. J., Rizzo, J. A., Putnam, F. W., & Van Ginkel, J. B. (2017). Cost-effectiveness of In-Home Cognitive Behavioral Therapy for low-income depressed mothers participating in early childhood prevention programs. Journal of affective disorders, 208, 475-482. It is based on a clinical trial of a treatment for postnatal depression that addressed both depression and anxiety, although the cost-effectiveness study focused only on depression.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

It is an important topic, especially the cost effectiveness of perinatal mental health interventions. It would be good to have some details about the dose of these interventions (eg number of sessions spanning over xyz months or pregnancy to postnatal months) as well as some details about the delivery agents. This will be value added addition.

RESPONSE: Where reported in the original study, we have added the suggested details to Table 1.

Reviewer: 2

Abstract:

1. While the abstract states the objective as 'to systematically review and critically appraise published economic evaluations of interventions for the prevention or treatment of perinatal anxiety and/or

depression (PAD)', it would be clearer if a well-defined research question was provided, so that the reader could determine whether and how the review answers the question.
RESPONSE: We have added to the research question in the main paper but are limited by the word count as to what could be added to the abstract so have included the overarching aim of the review to the first section of the abstract.
INSERTED TEXT: Economic evaluations of interventions for the prevention or treatment of perinatal anxiety and/or depression (PAD) were systematically reviewed with the aim of guiding researchers and commissioners of perinatal mental health services towards potentially cost-effective strategies.

2. The phrase 'complete lack of economic evidence' seems a little subjective, it might be better to state instead that there were no studies that met the criteria for inclusion in this review on those subjects.
RESPONSE: We have removed this phrase from the abstract.

3. The abstract could lead the reader to the conclusion that interventions involving identification and treatment have been directly compared to prevention or treatment alone by the use of the phrase 'most likely to be cost-effective', while in fact there are very few studies on any of these types of interventions, and there has been no possibility of pooling data for meta-analysis. It would be better if they stated their findings on the strength of evidence for cost-effectiveness separately for the different types of intervention.
RESPONSE: We have re-phrased this sentence in the abstract.
INSERTED TEXT: Uncertainty and heterogeneity across studies in terms of setting and design make it difficult to make direct comparisons or draw strong conclusions. However the two interventions incorporating identification plus treatment of perinatal depression were both likely to be cost-effective.

Strengths and weaknesses:
4. The first dot point does not connect the first part of the sentence to the latter part
RESPONSE: In response to a comment from the Editor we have revised the Strengths and Weaknesses section; this point is no longer included.
5. Are the authors aware of relevant studies in other languages? This point seems to suggest they do; it would be worth mentioning this if so.
RESPONSE: We are not aware of relevant studies in other languages. This point was made to acknowledge that our search strategy would not have identified any if they did exist.

Background:
6. Again, it would provide clarity for the reader if the rationale for reviewing such a diverse set of interventions was outlined here, along with a clearly stated research question reflecting this.
RESPONSE: In response to this comment and others we have better described the rationale for the review in the Background section and have stated our research questions within the Methods.
INSERTED TEXT (Background): Different perinatal mental health conditions often co-occur (Letourneau et al 2012, Roomruangwong et al 2016) and in the UK there has been a move towards commissioning the healthcare services for conditions under this umbrella together. Furthermore, widely used screening instruments such as the Edinburgh Postnatal Depression Scale (Cox et al 1987) were not designed to differentiate between different perinatal mental health conditions which may mean that people with different (albeit related) conditions are treated with the same interventions. As such it is likely to be more relevant and useful to commissioners and researchers to present synthesised evidence from a broad range of interventions for PAD. There has not been a recent review which aimed to bring all of the economic evidence on prevention and treatment interventions for PAD into a single narrative.

This review sought to produce an up-to-date synthesis of current knowledge about the cost-effectiveness of interventions for the prevention or treatment of PAD. Particular objectives were to

identify characteristics of potentially cost-effective interventions, gaps in current knowledge, and important avenues for future research.

INSERTED TEXT (Background): The aim of this review is to provide an evidence-base that could potentially inform these decisions by bringing information from different sources together into a comprehensive and critically-appraised summary with recommendations for commissioners and researchers.

INSERTED TEXT (Methods): The research questions addressed by this review were:
1) What are the characteristics of existing interventions for PAD that are likely to be cost-effective?
2) Where do the evidence and knowledge gaps indicate future research should be focussed?

7. While it is not the focus of this review paper to explore the complexities of definitions in the field of perinatal mental health, it would be helpful to demonstrate more clearly the established basis for the definition of perinatal anxiety and depression used by the authors, and to provide background on the different approaches used in the papers included in the study. For instance, it would be helpful to reflect on the differing definitions used in the literature, some of which apply clinical diagnoses, and some which use a cutoff above a certain level on a screening tool (most often the Edinburgh Postnatal Depression Scale). In relation to the combined focus on anxiety and depression, it could be informative to the reader to mention that 'postnatal depression', especially when measured by the EPDS, is often used as an umbrella term for many different types of mental health problem, and may include anxiety or adjustment disorders. The use of different time horizons might be elucidated by reference to the differing definitions of 'perinatal' that are used in the literature. In addition, reference/s supporting the use of the acronym PAD would be helpful.
RESPONSE: In response to this and other comments we have added to the Background section, clarifying the decision to conduct a broad literature search (see response to comment 6) and additional details about the identification of PAD. We have also now noted in the Discussion about differing definitions of the perinatal period. The acronym PAD was generated as short-hand for the purpose of this paper and is defined in the abstract and upon first use in the main text.
INSERTED TEXT (Background): The gold standard for clinical diagnosis of PAD is a structured interview (Spitzer et al 1992), typically conducted by a psychiatrist. The current recommendation in the UK is that at first contact with maternity services and in the weeks following childbirth healthcare professionals consider asking women the Whooley and Generalised Anxiety Disorder scale (GAD-2) case-finding questions (NICE, 2014). However the Edinburgh Postnatal Depression Scale (EPDS) is the most frequently used instrument used to detect PAD in research settings (Hewitt et al 2009), which has validated cut-off scores to identify antenatal and postnatal women experiencing PAD (Matthey et al 2006).
INSERTED TEXT (Discussion): For example, the definition of the perinatal period adopted by researchers (up to 4 weeks (DSM-V), 6 weeks (ICD-10), or 12 months postpartum (NICE))...

8. The associations between maternal perinatal mental health problems and children's problems have not been established to be causal, so the authors could be more cautious in their use of language about 'impacts'.
RESPONSE: We have rephrased all uses of the word 'impact'.
INSERTED TEXT: Background, page 3, paragraphs 1 and 2; Discussion, page 14, paragraphs 1-3.

9. It would be clearer for the reader if instead of using the term 'currently' to refer to number of births per annum, the year of this statistic was provided.
RESPONSE: We have made this change as suggested.
INSERTED TEXT: All the babies born in a single year in the United Kingdom (almost 700,000 in 2016)

10. The authors state that ‘Evidence suggests that the costs of improving perinatal mental health services are likely to be outweighed by the benefits [7,14].’. Such a statement suggests there would be no need for economic evaluations in this area, and does not reflect the weakness of economic evidence found in this review. Does this instead refer to the high estimated societal cost of perinatal mental health problems? If so, such a statement could be misleading if it implies that the whole estimated cost could be averted by intervening in perinatal mental health problems. Such costs do not identify which elements of current practice contributing to those costs are inefficient and where efficiency gains might be made.
RESPONSE: We have clarified this statement to reflect the need for high quality economic evidence.
INSERTED TEXT: Evidence suggests that the costs of improving perinatal mental health outcomes are likely to be outweighed by the benefits [7,14]; high quality economic evidence is needed to identify the most efficient ways of doing so.

11. Rather than stating that it is ‘generally accepted that psychological therapy and/or antidepressant medication are effective at treating the symptoms of PAD for many women’, could the authors instead make reference to the recommendations of clinical guidelines, or the evidence behind those recommendations?
RESPONSE: We have now referred to the NICE guidance for perinatal mental health and Cochrane reviews as evidence/support and rephrased this sentence.
INSERTED TEXT: Systematic reviews of the evidence (Cochrane reviews) suggest that psychological therapy and/or antidepressant medication are effective at treating the symptoms of PAD for many women which is reflected in current clinical guidance (NICE guidance).

12. Reference is made to ‘vital funds’ – might be clearer (and avoid subjective language) if the authors referred to scarce resources or opportunity costs.
RESPONSE: We have changed this to scarce resources as we are aware of the wide readership of the journal and feel that this is more accessible to people unfamiliar with health economics terminology.

13. A description of previous systematic reviews on this topic should be provided in the background section. Later (in the methods section) the authors refer to two prior reviews, both of which were published in 2016, so it would be helpful if the authors could provide a rationale for the need for this review in light of previous evidence.
RESPONSE: We have added references to existing reviews in the Background section and noted the need for this review.
INSERTED TEXT: A systematic review of literature published before July 2013 and relating to *preventative* interventions for perinatal depression concluded that midwifery redesigned postnatal care, a person-centred approach-based intervention, and an interpersonal therapy-based intervention showed some evidence of cost-effectiveness but with considerable uncertainty (Morrell et al 2016). A recent report on the long-term cost-effectiveness of perinatal mental health interventions included a selective review of interventions which had previously been found to be cost-effective and concluded that all of the interventions led to a long-term net monetary benefit from a societal perspective (Bauer et al 2014)...There has not been a recent review which brings all of the economic evidence on preventative *and* treatment interventions for PAD into a single narrative.

Methods:
14. Studies published prior to 2000 are excluded with the rationale that older references are less useful for decision making. It would be helpful to the reader to have a sense of how many studies are thereby excluded, and how the findings of those older studies compare to newer ones.
RESPONSE: We feel that it is contrary to the methods of this paper to comment on the findings of studies which did not meet the inclusion criteria but have noted in the Discussion that a search for relevant studies prior to 2000 in the NHS EED database returned no results.

INSERTED TEXT: The exclusion of studies published prior to the year 2000 may have introduced bias, however a post hoc search of the NHS EED database returned no relevant studies from before this time.

15. Could the authors state the proportion of studies reviewed by the second reviewer?
RESPONSE: The second reviewer reviewed all abstracts and full texts and reviewed the data extracted from half (n=4) of the studies included in the review. We have changed the text to reflect this.
INSERTED TEXT: One reviewer (EMC) completed the data extraction process with half reviewed by the second reviewer (GES). No issues were identified that suggested that the second reviewer needed to review all data extracted.

Results:
16. Table 3 would benefit from the inclusion of confidence intervals around the point estimates. For instance, the intervention in the study by Morrell et al (2009) is described as highly likely to be cost effective, but it would be helpful to the reader to know that in the main analysis from this study, neither the QALY gains nor cost savings were statistically significant compared to the control group.
RESPONSE: We have added confidence intervals or p-values for the net costs and benefits where reported in the original studies.

Discussion:
17. The information on the use of QALYs to measure health benefit and the NICE threshold would be better in the background rather than discussion.
RESPONSE: We have reviewed this section of the discussion and felt that as the literature search was not restricted to cost-utility analyses the discussion of QALYs was more relevant to the discussion than the background and may make the rationale for the review less clear if moved.

18. Could the authors compare the magnitude of clinical effectiveness found in the included trials to wider studies on clinical effectiveness of that type of intervention? (There are relevant meta-analyses e.g. (Dennis and Hodnett 2007, Dennis and Dowswell 2013)) If the magnitude of clinical effect was similar, this would provide the reader with more assurance that these results were plausible.
RESPONSE: We agree that this may be interesting and in response to comment 17 we have added confidence intervals/p-values to net differences reported in Table 3, however further exploration of clinical effectiveness is beyond the scope of this review which intentionally focuses on the evidence available in the economic publications.

19. Strengths and limitations – could discuss that although two tools were used to assess critically assess the included studies, one was developed for this review (and mention if validated in any way).
RESPONSE: We have noted in the discussion that the second tool was developed for this review, although agreement was reached between both authors there was no formal validation process.
INSERTED TEXT: Two separate tools were used to critically appraise the studies which included more criteria and gave a broader perspective than a single approach, although one was developed specifically for this review and not formally validated.

20. Future research – the word ‘massive’ referring to burden of disease seems unnecessarily subjective.
RESPONSE: We have changed the word 'massive' to 'considerable'.

21. Again the authors restate the view that costs of improving perinatal mental health are likely to be outweighed by the benefits. The same comments as applied in the background section apply here.
RESPONSE: We have deleted this statement in the Discussion as it was felt that it added nothing further to the point made earlier in the paper.

22. The reference to spill overs needs to be described more clearly (e.g. are the authors talking about effects on children, or on time off work?) and to be supported by appropriate references. If the authors are referring to family spillovers, there is a relevant literature to reference (e.g. papers on this topic in general (Davidson and Levin 2010, Bobinac, van Exel et al. 2011, Al-Janabi, van Exel et al. 2016, Al-Janabi, Van Exel et al. 2016), and a paper by Ride (2017) refers to this issue in the context of perinatal mental health specifically), and it would be relevant to discuss the statements of decisions makers (including NICE) that explicitly allow for such effects to be taken into account.
RESPONSE: In response to other comments we have endeavoured to make the Discussion clearer and more in line with the research objectives. It was felt that introducing the literature on spillover effects may have detracted from the messages therefore we have removed this section from the paper.

Conclusion:
23. If a clearer research question was posed at the outset, the conclusions could reflect that.
RESPONSE: We have restructured the conclusion to reflect the research questions and aims of the review.

Minor errors:
24. A word 'is' seems to be missing from line 16 (…time which likely…)
INSERTED TEXT: time which is likely
25. Line 40 – sentence starting with 'Whereas'
RESPONSE: We have corrected this.

References
Al-Janabi, H., J. van Exel, W. Brouwer and J. Coast (2016). "A framework for including family health spillovers in economic evaluation." Medical Decision Making 36(2): 176-186. Al-Janabi, H., J. Van Exel, W. Brouwer, C. Trotter, L. Glennie, L. Hannigan and J. Coast (2016). "Measuring health spillovers for economic evaluation: a case study in meningitis." Health economics 25(12): 1529-1544. Bobinac, A., N. J. van Exel, F. F. Rutten and W. B. Brouwer (2011). "Health effects in significant others: separating family and care-giving effects." Medical Decision Making 31(2): 292-298. Davidson, T. and L.-A. Levin (2010). "Is the societal approach wide enough to include relatives? Incorporating relatives' costs and effects in a cost-effectiveness analysis." Applied Health Economics and Health Policy 8: 25+. Dennis, C. L. and T. Dowswell (2013). "Psychosocial and psychological interventions for preventing postpartum depression." Cochrane Database of Systematic Reviews(2). Dennis, C. L. and E. Hodnett (2007). "Psychosocial and psychological interventions for treating postpartum depression." Cochrane Database of Systematic Reviews(4): CD006116. Ride, J. (2017). "Setting the Boundaries for Economic Evaluation: Investigating Time Horizon and Family Effects in the Case of Postnatal Depression." Value in Health.

Reviewer: 3
This was an interesting paper on a topical subject, with high policy and practice importance. My overall concern with the paper was that it lacked a clear purpose and a strong justification for the study. The Introduction did not build a strong story, and the aims were for general exploration of the topic, as opposed to aiming to answer a specific question. The methods were excellent and the results were very clearly written. Because there were no clear aims of the study, the discussion was not well structured and left the reader wondering what conclusions could actually be drawn from this paper.
RESPONSE: In response to this comment and those from other reviewers, we have added to the Background section to clarify the rationale for the review and have defined the research question in

the Methods section. The structure of the discussion has been reviewed in light of this and amended to reflect how the review addresses the research question.
INSERTED TEXT (Background): Different perinatal mental health conditions often co-occur (Letourneau et al 2012, Roomruangwong et al 2016) and in the UK there has been a move towards commissioning the healthcare services for conditions under this umbrella together. Furthermore, widely used screening instruments such as the Edinburgh Postnatal Depression Scale (Cox et al 1987) were not designed to differentiate between different perinatal mental health conditions which may mean that people with different (albeit related) conditions are treated with the same interventions. As such it is likely to be more relevant and useful to commissioners and researchers to present synthesised evidence from a broad range of interventions for PAD. There has not been a recent review which aimed to bring all of the economic evidence on prevention and treatment interventions for PAD into a single narrative.

This review sought to produce an up-to-date synthesis of current knowledge about the cost-effectiveness of interventions for the prevention or treatment of PAD. Particular objectives were to identify characteristics of potentially cost-effective interventions, gaps in current knowledge, and important avenues for future research.

INSERTED TEXT (Background): The aim of this review is to provide an evidence-base that could potentially inform these decisions by bringing information from different sources together into a comprehensive and critically-appraised summary with recommendations for commissioners and researchers.

INSERTED TEXT (Methods): The research questions addressed by this review were:
1) What are the characteristics of existing interventions for PAD that are likely to be cost-effective?
2) Where do the evidence and knowledge gaps indicate future research should be focussed?

Reviewer: 4
This article is a systematic review of cost-effectiveness studies of interventions to prevent or treat depression or anxiety during pregnancy or postpartum. It is a thorough and scholarly work. The presentation of all of the steps of the review in incorporated and supplementary tables is a strength and provides an excellent reference point for future efforts. The findings are clearly presented. They support the cost-effectiveness of interventions, but note the heterogeneity and methodological unevenness of the extant literature. This cannot be a definitive review as a result, but limitations in studies are presented in a way that should advance the literature. There are several issues that need attention and some areas that would benefit from expanded discussion, these are presented below.

1. The introduction should provide a more compelling rationale for the review at this point—what does it add relative to prior reviews other than being an update?
RESPONSE: In response to this and other comments we have amended the Background to clarify the rationale and contribution this review aims to make.
INSERTED TEXT (Background): Different perinatal mental health conditions often co-occur (Letourneau et al 2012, Roomruangwong et al 2016) and in the UK there has been a move towards commissioning the healthcare services for conditions under this umbrella together. Furthermore, widely used screening instruments such as the Edinburgh Postnatal Depression Scale (Cox et al 1987) were not designed to differentiate between different perinatal mental health conditions which may mean that people with different (albeit related) conditions are treated with the same interventions. As such it is likely to be more relevant and useful to commissioners and researchers to present synthesised evidence from a broad range of interventions for PAD. There has not been a recent review which aimed to bring all of the economic evidence on prevention and treatment interventions for PAD into a single narrative.

This review sought to produce an up-to-date synthesis of current knowledge about the cost-effectiveness of interventions for the prevention or treatment of PAD. Particular objectives were to identify characteristics of potentially cost-effective interventions, gaps in current knowledge, and important avenues for future research.

INSERTED TEXT (Background): The aim of this review is to provide an evidence-base that could potentially inform these decisions by bringing information from different sources together into a comprehensive and critically-appraised summary with recommendations for commissioners and researchers.

2. It is stated that there were no studies on fathers but this term was not found in the list of search words. My knowledge is that there are no studies, but if this is going to be part of the review it should be searched.
RESPONSE: The search terms were not restricted to mothers and did not include the term 'mothers' so that studies involving either parent would be captured as part of the search. For example, a study estimating healthcare costs associated with paternal postnatal depression was identified in the search but it was not included in the review as it did not evaluate an intervention (Edoka IP, Petrou S, Ramchandani PG. Healthcare costs of paternal depression in the postnatal period. Journal of affective disorders. 2011 Sep 1;133(1):356-60.).

3. The introduction should include some mention of prior reviews of economic analyses of interventions and mention of reviews documenting effectiveness of interventions for depression and anxiety in pregnant and postpartum mothers.
RESPONSE: We have added reference to prior Cochrane reviews of effectiveness and economic reviews and in the Background section.
INSERTED TEXT: Systematic reviews of the evidence (Denis et al 2007, Denis et al 2008, Molyneaux et al 2014) suggest that psychological therapy and/or antidepressant medication are effective at treating the symptoms of PAD for many women.
INSERTED TEXT: A systematic review of literature published before July 2013 and relating to *preventative* interventions for perinatal depression concluded that midwifery redesigned postnatal care, a person-centred approach-based intervention, and an interpersonal therapy-based intervention showed some evidence of cost-effectiveness but with considerable uncertainty (Morrell et al 2016). A recent report on the long-term net monetary benefits of perinatal mental health interventions included a selective review of interventions which had previously been found to be cost-effective and concluded that all of the interventions led to a long-term net monetary benefit from a societal perspective (Bauer et al, 2016).

4. The discussion should include a more explicit calling out of what studies should report to facilitate future reviews. The authors note that some studies omitted important information that limited their review, and this is an opportunity to lay out what the standards should be going forward.
RESPONSE: We have now reflected this in the Discussion.
INSERTED TEXT: The use of a standardised checklist, such as the commonly used CHEERS checklist for the reporting of economic evaluations (Husereau et al, 2013) would facilitate the synthesis of data in future reviews. In order to meaningfully compare studies, the most critical information is: a full description of the intervention and comparator, inclusion/exclusion criteria, time horizon and perspective of the evaluation, the net outcome, the net cost, ICER, and cost-effectiveness acceptability (reported as the likelihood an intervention is cost-effective at appropriate willingness to pay thresholds), and summary of uncertainty.

5. One study was missing that seemed to meet criteria for inclusion: Ammerman, R. T., Mallow, P. J., Rizzo, J. A., Putnam, F. W., & Van Ginkel, J. B. (2017). Cost-effectiveness of In-Home Cognitive Behavioral Therapy for low-income depressed mothers participating in early childhood prevention

programs. Journal of affective disorders, 208, 475-482. It is based on a clinical trial of a treatment for postnatal depression that addressed both depression and anxiety, although the cost-effectiveness study focused only on depression.
RESPONSE: We have noted in the discussion that despite a robust search strategy there may be papers that were not identified and reported this as one of them.
INSERTED TEXT: Despite a robust search strategy there may be relevant studies that were not identified by this review. For example, the definition of the perinatal period adopted by researchers (up to 4 weeks (DSM-V), 6 weeks (ICD-10), or 12 months postpartum (NICE)) will influence whether interventions for PAD are described as 'perinatal' or 'early childhood'. After this review was completed a paper was brought to the authors' attention which involved an intervention for depression in mothers in the first year postpartum. However, as it was described as an 'early childhood program' and was not explicitly referred to as an intervention for postnatal or postpartum depression it was not identified in this search (Ammerman et al, 2017). The intervention (in-home CBT) was nested within a complex home-visiting support program which aimed to improve the health and wellbeing of low-income parents and babies which was the 'standard care' comparator in the economic evaluation. The study reported the results of an economic model which extrapolated the results from an RCT and concluded that in-home CBT was likely to be cost-effective compared to this standard care as a treatment for depression.

VERSION 2 – REVIEW

REVIEWER	Emily Callander James Cook University, Australia
REVIEW RETURNED	30-Apr-2018

GENERAL COMMENTS	The reviewers have addressed my concerns.

REVIEWER	Jemimah Ride Centre for Health Economics, University of York, UK
REVIEW RETURNED	14-May-2018

GENERAL COMMENTS	New text in the background section states that the EPDS "has validated cut-off scores to identify antenatal and postnatal women experiencing PAD". The EPDS is a screening tool, and these cut-off scores do not identify women experiencing anxiety or depression, they are used to identify high- and low-scoring women, who are at correspondingly higher and lower likelihood of being a 'case' of anxiety or depression. It would be helpful to use clearer language to reflect the status of the EPDS (e.g. "to identify antenatal and postnatal women likely to be experiencing PAD").

REVIEWER	Robert T. Ammerman Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio USA
REVIEW RETURNED	18-May-2018

GENERAL COMMENTS	This is a thorough revision of a strong paper. A number of issues have been clarified, and the paper will be a valuable addition to the literature.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2 comment:

New text in the background section states that the EPDS "has validated cut-off scores to identify antenatal and postnatal women experiencing PAD". The EPDS is a screening tool, and these cut-off scores do not identify women experiencing anxiety or depression, they are used to identify high- and low-scoring women, who are at correspondingly higher and lower likelihood of being a 'case' of anxiety or depression. It would be helpful to use clearer language to reflect the status of the EPDS (e.g. "to identify antenatal and postnatal women likely to be experiencing PAD").

RESPONSE: As suggested we have re-phrased the sentence which now reads "has validated cut-off scores to identify antenatal and postnatal women likely to be experiencing PAD"