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

TITLE (PROVISIONAL)	DEPRESSION FOLLOWING FRACTURE IN WOMEN: A STUDY OF AGE-MATCHED COHORTS
AUTHORS	Williams, Lana; Berk, Michael; Henry, Margaret; Stuart, Amanda; Brennan, Sharon; Jacka, Felice; Pasco, Julie

VERSION 1 - REVIEW

REVIEWER	Yea-Ing Lotus Shyu Chang Gung University, Taiwan
REVIEW RETURNED	01-Nov-2013

GENERAL COMMENTS	This is a well-written paper on an important clinical phenomenon and the results can contribute to the current knowledge based and benefit future studies. Especially, the use of population-based sample is the strength of this study. Several areas would need to be further clarified and explained: 1. In the introduction, the rationale for combining different types of fracture, focusing on women, and the differentiation of old and young age, need to be further strengthened. The clinical significance of this study needs to be explicitly stated. 2. In the method section, how the sample of fracture and also control narrowed down from those received initial assessment to those participated in 6-year follow-up? What are the differences between those who returned the questionnaire and those who did not at the final sample? 3. In the method section, for the self-report questionnaire based on the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV) criteria, in addition to the internal reliability, what is the sensitivity and specificity of this scale, since it was used to identify those with likelihood of depression? 4. In the result section, the association of depression and fracture is not significant for younger women needs to be explicitly stated. 5. In the result section, the statistic results of the logistic regression needs to be presented in a table. Why the analysis on younger women and older women were independent and separated? Why not treating the sample as a whole and see if there were interaction between age (young and old) and fracture for predicting likelihood of depression? 6. In the discussion, the generalizability of the study results can be discussed based on comparison of the sample characteristics of initial assessment with sample of 6-year follow-up, and comparison of those who returned the questionnaire with those did not. 7. In the discussion, on page 15, a reference to support the point that "compared to older women, younger women may have more access to social networks .... and be able to fulfill ongoing work and social commitments during recovery" is suggested to be added.

REVIEWER	Morris, Julie
	South Manchester NHS Trust, Medical Statistics Department
REVIEW RETURNED	04-Nov-2013

GENERAL COMMENTS	This study identifies fracture cases during the period 1994-1996 and non-fracture controls and compares rates of depression 6 years onwards.
	In general, the statistical analysis of the data is appropriate but there are a few points relating to the design, analysis, presentation and interpretation of the results that need to be addressed.
	1. The design is described as a case-control study, but the selected groups are not defined by the outcome (depression). The groups have been selected on the basis of 'exposure' ie fracture. Therefore the study is really a cohort study (with two cohorts – fracture and non-fracture) and references to case-control in the paper should be corrected.
	2. Background section. "….was to investigate whether fracture is associated with depressive symptoms". Presumably, this should read, "….was to investigate whether fracture is associated with subsequent depressive symptoms"?
	3. Methods section. "Those who participated in the 6-year follow-up (n=439) were sent a depression questionnaire, with a total of 296 returned...". Does this mean that only just over half of those who participated in the initial part of the study agreed to be part of the 6-year follow-up (439/832)? The potential for response bias is mentioned in the Discussion section, but I believe should be emphasised more.
	4. A power calculation should be included.
	5. Statistical Analysis section. "Associations between fracture and depression differed for younger and older women, thus all analyses were stratified by age (≤65 and >65 years)". How was this split decided? What analyses were carried out to identify this cut-off point?
	6. Results section – younger women (Page 12). "…more likely to smoke and less likely to have depression (Table 1)". Actually Table 1 shows that there is no difference in depression rates between the two groups (p=0.074). "The relationship was attenuated after adjusting for age and weight…". But the OR values slightly increased ie were not 'weakened' (ie. not attenuated). The associated p-value increased due to the increase in the number of predictors/confounders in the regression model.
	7. Only a limited number of confounders were considered (see Table 1). Some discussion of potential bias due to unmeasured confounders should be added. It is unfortunate that no measure of depression is available for the time of fracture.
	8. Conclusion section (and Abstract). "…this study demonstrated that…….depression is a persistent health burden, likely to affect long-term recovery in the elderly". But evidence for this has not been provided by this study.

Reviewer 1:

1. In the introduction, the rationale for combining different types of fracture, focusing on women, and the differentiation of old and young age, need to be further strengthened. The clinical significance of this study needs to be explicitly stated.

We have now amended the introduction as follows. These points have also been highlighted in the discussion.

Amendments to the text read as follows:

"Independently, depression and fracture are both increasingly prevalent public health concerns, particularly in women, and are associated with high levels of disability, functional impairment and early mortality." (page 7, paragraph 1)

"Declines in quality of life are typical following a fracture, regardless of the site of fracture, and impose substantial medical and social costs [9]." (page 7, paragraph 1)

"Moreover, depression has been shown to be a common response to chronic medical conditions that can, in turn, impact on symptom burden and treatment adherence and increase the risk of complications [14]." (page 7, paragraph 1)

"Given the high prevalence of both depression and fracture in women, as well as the previously reported associations showing depression to precede fracture, the aim of this study was to investigate whether fracture is associated with subsequent depressive symptoms in an age-matched fracture vs. non-fracture cohorts." (page 7, paragraph 1)

"Understanding such an association is important in providing integrated and effective treatment." (page 7, paragraph 1)

2. In the method section, how the sample of fracture and also control narrowed down from those received initial assessment to those participated in 6-year follow-up? What are the differences between those who returned the questionnaire and those who did not at the final sample?

We do not have this information for the fracture cohort, however it is noteworthy that the participation rate was over 60%. For the non-fracture cohort we have previously reported that there is no difference in SES status between participants and non-participants. Furthermore, characteristics of the non-fractured population have been shown to be comparable with the national level in regards to age, country of birth, marital status and weekly income (Pasco, 2012). We have acknowledged the associated limitations in the manuscript.

3. In the method section, for the self-report questionnaire based on the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV) criteria, in addition to the internal reliability, what is the sensitivity and specificity of this scale, since it was used to identify those with likelihood of depression?

Sensitivity and specificity of this scale was not determined and this has now has been included as a limitation.

Amendments to the text read as follows:

"The use of a self-report instrument, rather than a clinical diagnostic interview must also be acknowledged, also sensitivity and specificity of this scale was not determined." (page 16, paragraph 1)

4. In the result section, the association of depression and fracture is not significant for younger women needs to be explicitly stated.

We have now amended as suggested.

Amendments to the text read as follows:

"The association between fracture and depression among younger women was not significant." (page 12, paragraph 2)

"Adjustment for age and weight did not affect the relationship (OR=0.62, 95% CI 0.35-1.11, p=0.12), nor did further adjustment for height, physical activity, smoking and alcohol consumption." (page 12, paragraph 3)

5. In the result section, the statistic results of the logistic regression needs to be presented in a table. Why the analysis on younger women and older women were independent and separated? Why not treating the sample as a whole and see if there were interaction between age (young and old) and fracture for predicting likelihood of depression?

Results were presented in text due to size of the results section. However, we are happy to be guided by the editor on this matter. Age was identified as an effect modifier in the relationship between depression and fracture; 65 years is the age at which the direction of the relationship between depression and fracture changed according to visual inspection of the scatterplot, thus the dataset was split at this point.

6. In the discussion, the generalizability of the study results can be discussed based on comparison of the sample characteristics of initial assessment with sample of 6-year follow-up, and comparison of those who returned the questionnaire with those did not.

This has been further highlighted in the limitation section.

Amendments to the text read as follows:

"Last, as with all observational studies, our results could be biased by unrecognised confounders and may not be generalizable to other populations of women, men, or those with other medical conditions" (page 16, paragraph 1)

7. In the discussion, on page 15, a reference to support the point that "compared to older women, younger women may have more access to social networks .... and be able to fulfill ongoing work and social commitments during recovery" is suggested to be added.

References have now been added (numbers 29-31).

Reviewer 2:

1. The design is described as a case-control study, but the selected groups are not defined by the outcome (depression). The groups have been selected on the basis of 'exposure' ie fracture.

Therefore the study is really a cohort study (with two cohorts – fracture and non-fracture) and references to case-control in the paper should be corrected.

We have amended our manuscript to identify this study as one involving fracture vs. non-fracture cohorts.

Amendments to the text read as follows:

"Depression following fracture in women: a study of age-matched cohorts" (page 1)

"Design: A study of age-matched fracture vs. non fracture cohorts of women" (page 3, paragraph 2)

"Differences in characteristics between those with fracture and those without fracture according to age group..." (page 10, paragraph 3)

"A total of 296 women with fracture (12 hip, 48 vertebral, 92 wrist/forearm, 17 upper arm, 7 pelvis, 12 rib, 64 lower leg and 48 other fractures) and 590 women without fracture were included in the analyses. Characteristics of the women with fracture vs. those without fracture according to age are shown in Table 1." (page 12, paragraph 1)

"Among the younger women (n=552), there were no differences in weight, height, depression, physical activity or alcohol consumption between those with and those without fracture, however women with fracture were older and more likely to smoke (Table 1)." (page 12, paragraph 2)

"Among the older women (n=334), no differences in weight, height, physical activity, alcohol or smoking status were evident between those without or without fracture; however women with fracture were younger and more likely to have depression (Table 1)." (page 13, paragraph 1)

2. Background section. "….was to investigate whether fracture is associated with depressive symptoms". Presumably, this should read, "….was to investigate whether fracture is associated with subsequent depressive symptoms"?

We have now adjusted the manuscript to reflect this request in both the abstract and background section.

Amendments to the text read as follows:

"The aim of this study was to investigate whether fracture is associated with subsequent depressive symptoms in a population-based sample of women." (page 3, paragraph 1)

"...the aim of this study was to investigate whether fracture is associated with subsequent depressive symptoms in a study of age-matched fracture vs. non-fracture cohorts." (page 7, paragraph 1)

3. Methods section. "Those who participated in the 6-year follow-up (n=439) were sent a depression questionnaire, with a total of 296 returned...". Does this mean that only just over half of those who participated in the initial part of the study agreed to be part of the 6-year follow-up (439/832)? The potential for response bias is mentioned in the Discussion section, but I believe should be emphasised more.

We have addressed this matter further in the discussion, as per response to previous comment.

4. A power calculation should be included.

With our number of women with and without fracture, and data suggesting the prevalence of fracture is 10%, we were powered to detect an odds ratio for depression of at least 1.5 in exposed relative to unexposed subjects with 80% power. We have not included this information in the manuscript but are happy to be guided by the editor on this matter.

5. Statistical Analysis section. "Associations between fracture and depression differed for younger and older women, thus all analyses were stratified by age (≤65 and >65 years)". How was this split decided? What analyses were carried out to identify this cut-off point?

See question above.

6. Results section – younger women (Page 12). "…more likely to smoke and less likely to have depression (Table 1)". Actually Table 1 shows that there is no difference in depression rates between the two groups (p=0.074).
"The relationship was attenuated after adjusting for age and weight…". But the OR values slightly increased ie were not 'weakened' (ie. not attenuated). The associated p-value increased due to the increase in the number of predictors/confounders in the regression model.

We have now adjusted the manuscript accordingly.

Amendments to the text read as follows:

"Among the younger women (n=552), there were no differences in weight, height, depression, physical activity or alcohol consumption between those with and those without fracture, however women with fracture were older and more likely to smoke (Table 1)." (page 12, paragraph 2)

"Adjustment for age and weight did not affect the relationship (OR=0.62, 95% CI 0.35-1.11, p=0.12), nor did further adjustment for height, physical activity, smoking and alcohol consumption." (page 12, paragraph 3)

7. Only a limited number of confounders were considered (see Table 1). Some discussion of potential bias due to unmeasured confounders should be added. It is unfortunate that no measure of depression is available for the time of fracture.

We agree and have now added this suggestion to the limitation section

Amendments to the text read as follows:

"Last, as with all observational studies, our results could be biased by unrecognised confounders." (page 16, paragraph 1)

8. Conclusion section (and Abstract). "…this study demonstrated that…….depression is a persistent health burden, likely to affect long-term recovery in the elderly". But evidence for this has not been provided by this study.

We have amended these sections accordingly.

Amendments to the text read as follows:

"This study demonstrated that differences in mood status exist between older and younger women following fracture and that fracture is associated with increased depression in older women." (page 4, paragraph 1)

"In conclusion, this study demonstrated that differences in mood status exist between older and younger women following fracture and that fracture is associated with increased depression in older women." (page 16, paragraph 2)

VERSION 2 – REVIEW

REVIEWER	Yea-Ing Lotus Shyu Chang Gung University, Taiwan
REVIEW RETURNED	31-Dec-2013

GENERAL COMMENTS	The comments have been responded satisfactory.