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)	Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: a 38 year longitudinal population study
AUTHORS	Johansson, Lena; Guo, Xinxin; Hällström, Tore; Norton, Maria; Waern, Margda; Östling, Svante; Skoog, Ingmar; Bengtsson, Calle

VERSION 1 - REVIEW

REVIEWER	Robert Stewart Professor of Psychiatric Epidemiology and Clinical Informatics King's College London UK COI statement: I have co-authored papers in the past with some of the authors.
REVIEW RETURNED	16-May-2013

GENERAL COMMENTS	This paper reports a relatively straightforward analysis from a well-characterised and widely published cohort study in which the authors investigated associations between levels of mid-life stress/distress and later incidence of dementia. The methodology appears appropriate to me and the strengths and limitations are appropriately highlighted. Perhaps the authors ought to be a little more careful about the wording around the lack of association with vascular dementia in the Results, as statistical power is limited. Other than this, I have no comments and I think the manuscript is acceptable in its current form.

REVIEWER	Han, Ling Yale University, Internal medicine
REVIEW RETURNED	07-Jun-2013

GENERAL COMMENTS	**General comments**: This paper presents data from a secondary analysis of a follow up study of a group of middle aged women. After adjusting for long-lasting distress and baseline confounders, it found an independent association between psychosocial stressors and risk of dementia over a 37-year period. While the role of psychosocial stress in natural history of dementia is an interesting topic,

there are several methodological issues that need to be addressed. First and foremost, the stressors were assessed at baseline only whereas the presumed outcome, dementia incidence, was ascertained decades later. Over such an extended long time period, many known risk factors could contribute to the development of dementia, such as functional disability and chronic medical conditions etc. It would be difficult to establish causality without considering these important intermediating confounders. Second, the authors suggested possible biological mechanism via longstanding distress and cumulative burden to brain dysregulation. However, the cited literatures were based on serious or traumatic psychological, rather than common life, stressors; in addition, the psychosocial stressors and long-lasting distress in this study were measured by self-report only. They may represent the same underlying psychological construct— personal tendency to perceive of and react to the environmental stimuli, rather than cause and (mediating) outcome. Some external, objective measures of the distress or physiological reactions to the stressors, may help clarify the confusion. Third, the study sample seems a highly selective subset of the (presumably representative) original cohort, i.e., attendees of a psychiatric examination, with very unique demographic profile (esp., as high as 32% with 1st degree family history of mental illnesses). As a result, the generalizability of the study may be limited.

Specific comments/questions:

Title page (Page 1): indicates a “37”-year f/up study. But in the text (e.g., page 11, Discussion) , it is referred to as “38” year study.
Please keep consistency.

Introduction:

Page 4, Line 50: “… to examine whether experience of psychosocial stressors mediate the previously reported association between longstanding distress …”
I guess the word “mediate” should be “modify”? Because the stressors (in 1968) preceded the distress (1968-1980) in the hypothesized causal pathway to dementia, it can not mediate (or intermediate) the distress-dementia association.
Please also see my recommendation on this below.

Abstract-Conclusion (Page 2, Lines 52-56) and Discussion (pages 11-14)

I think the conclusion and inference from the current study should be made with caution. More evidence from valid observational studies and RCT is needed before recommending “intensive interventions” on middle life psychosocial stressors. The methodological issues raised above should be cited as limitations, if not amenable to address due to lack of data.

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Suggestions/recommendations for revisions:

1) As stated in page 9, lines 64-66, “mental illness in 1st degree

	relatives…" is the most common stressor, accounting for more than 1 third of the sample. This raised two serious concerns: A) Psychiatric family history is actually a maker of genetic predisposition to dementia (and other mental problems), which cannot be viewed as a purely extrinsic, environmental stressor; B) Because the generic predisposition for sure has life time impact on many disease risks, it may fully or partially explain the observed distant effects of the stressors on dementia risk, currently attributed to longstanding distress in the paper. Therefore, I'd suggest to separate this "stressor" from other 17 as an independent covariate. 2) To address the above concerns, I think the following additional analyses are necessary: For Tables 4 and 5, Models a-c: A) Add psychiatric family history as a covariate, either dichotomous or a count of all 1º family members with mental illness. It is inadequate to only exclude people whose parents had mental illness. B) If possible, consider redefining key confounders (esp., hypertension, CHD, stroke, diabetes etc comorbidity) as time-dependent covariates, e.g., based on the time of longstanding distress assessment (i.e., year 1980) and of initial dementia diagnosis. 3) The study aim 2, examining effect modification (or mediation), is set forth in Introduction, but no data was presented. I'd suggest: A) Provide tables showing dementia rate/proportion by quartiles of 17 stressors (eliminating 1° family psychiatric history), stratified by longstanding distress (yes vs no) B) Repeat A according to 1° family psychiatric history (yes vs no) C) Test "effect modification" by adding interaction terms between stressor quartiles, 1° family psychiatric history (yes vs no) , and longstanding distress (yes vs no). I suggest the authors revise the manuscript based on above comments and resubmit for further consideration.

VERSION 1 – AUTHOR RESPONSE

REFEREE: 1

1. Perhaps the authors ought to be a little more careful about the wording around the lack of association with vascular dementia in the Results, as statistical power is limited.

Response: We have now changed the wording in the Result (page 12, paragraph 1, line 2).

RERÉREE: 2

General comments:

1. The stressors were assessed at baseline only whereas the presumed outcome, dementia incidence, was ascertained decades later. Over such an extended long time period, many known risk factors could contribute to the development of dementia, such as functional disability and chronic medical conditions etc. It would be difficult to establish causality without considering these important intermediating confounders.

Response: We agree that there are a number of risk factors occurring between baseline and development of dementia and that these might potentially modify the association between common psychosocial stressors in midlife and dementia. However, these competing risk factors would most likely decrease the possibility to find associations in a study with long follow-up, as may exert competing risk. In case that new factor occurring during follow-up, there is also a risk of over-adjustment. We have now included a passage in the Discussion about this (page 14, paragraph 1, line 10). Furthermore, the progression of dementia is often a subtle process where the seeding for the pathology occurs long before the mildest symptom. Therefore it is desirably to measure possible risk factors long time before the disease becomes clinically manifested. We have now taken into account possible confounders and intermediating factors until 1980, and adjusted for several medical and lifestyle related factors, such as; age, education, socioeconomic status, marital status, work status, hypertension, coronary heart diseases, stroke, diabetes mellitus, waist-to-hip ratio, smoking, wine consumption and longstanding distress. The findings remained after adjusting for all those factors (page 9).

2. The authors suggested possible biological mechanism via longstanding distress and cumulative burden to brain dysregulation. However, the cited literatures were based on serious or traumatic psychological, rather than common life, stressors; in addition, the psychosocial stressors and long-lasting distress in this study were measured by self-report only. They may represent the same underlying psychological construct— personal tendency to perceive of and react to the environmental stimuli, rather than cause and (mediating) outcome. Some external, objective measures of the distress or physiological reactions to the stressors, may help clarify the confusion.

Response:
a) We have now also added references on biological stress mechanism in association to ‘common life stressors’, such as in bereavement of a beloved one (see page 12, paragraph 4, line 24).
b) We did not have external objective measure of distress or physiological reactions to the stressors.

However, perceived stress in 1968 was associated with abdominal symptoms, headache/migraine, infection and muskoloskeletal symptom in 1968, as well from 1968 to 1974 (ref: Hange D, International journal of general medicine 2013). However, we have now included in the Discussion that distress in our study was based on self-report, and that we did not include an objective measure of stress reactions (page 14, paragraph 1, line 8).

3. The study sample seems a highly selective subset of the (presumably representative) original cohort, i.e., attendees of a psychiatric examination, with very unique demographic profile (esp., as high as 32% with 1st degree family history of mental illnesses). As a result, the generalizability of the study may be limited.

Response: The study sample is based on a representative sample from the general population and is not a selected subsample (see page 6, paragraph 1, line 3-18). The proportion of first-degree relatives with a history of mental illness is not surprisingly high, considering that each year 38.2% of the EU population suffers from a mental disorder. (ref: Wittchen HU. Eur Neuropsychopharmacol 2011).

Specific comments/questions:

4. Title page (Page 1): indicates a “37”-year f/up study. But in the text (e.g., page 11, Discussion), it is referred to as “38” year study.

Response: We have now written “38 years” constantly through the text.

5. Introduction: Page 4, Line 50: “… to examine whether experience of psychosocial stressors mediate the previously reported association between longstanding distress …” I guess the word “mediate” should be “modify”?

Response: We have now changed “mediate” to “modify” (see page 5, paragraph 3, line 22).

6. Abstract-Conclusion (Page 2, Lines 52-56) and Discussion (pages 11-14): I think the conclusion and inference from the current study should be made with caution. More evidence from valid observational studies and RCT is needed before recommending “intensive interventions” on middle life psychosocial stressors. The methodological issues raised above should be cited as limitations, if not amenable to address due to lack of data.

Response: We have now changed the wording in the Abstract (page 2, paragraph 1, line 23) and in the Discussion: page 15, paragraph 2, line 8).

Suggestions/recommendations for revisions:

7. As stated in page 9, lines 64-66, “mental illness in 1st degree relatives…” is the most common stressor, accounting for more than 1 third of the sample. This raised two serious concerns: A) Psychiatric family history is actually a maker of genetic predisposition to dementia (and other mental problems), which cannot be viewed as a purely extrinsic, environmental stressor; B) Because the generic predisposition for sure has life time impact on many disease risks, it may fully or partially explain the observed distant effects of the stressors on dementia risk, currently attributed to longstanding distress in the paper. Therefore, I’d suggest to separate this “stressor” from other 17 as an independent covariate.

Add psychiatric family history as a covariate, either dichotomous or a count of all 1º family members with mental illness. It is inadequate to only exclude people whose parents had mental illness

Response: We agree that family history of psychiatric disorders may be both a stressor and a genetic predisposition. We have now discussed this in the Discussion 4 (see page 14, paragraph 1, line 15) and added ‘psychiatric family history’ as a covariate in Table 3 and Table 4.

8. If possible, consider redefining key confounders (esp., hypertension, CHD, stroke, diabetes etc comorbidity) as time-dependent covariates, e.g., based on the time of longstanding distress assessment (i.e., year 1980) and of initial dementia diagnosis.

Response: We have now taken into account some of the covariates (e.g. hypertension, coronary heart disease, stroke, diabetes mellitus, waist-to-hip ratio, smoking and wine consumption) as possible confounders and intermediating factors until 1980 (see Potential confounders and mediators, Statistics and Table 1-4). The other covariates; education, socioeconomic status, marital status and work status were used from the baseline examination (1968).

9. Provide tables showing dementia rate/proportion by quartiles of 17 stressors (eliminating 1° family psychiatric history), stratified by longstanding distress (yes vs. no). Repeat according to 1° family psychiatric history (yes vs. no). Test “effect modification” by adding interaction terms between stressor quartiles, 1° family psychiatric history (yes vs no), and longstanding distress (yes vs. no).

Response: We have now created a table showing dementia rates/proportions stratified by longstanding distress and psychiatric family history (see below). Maybe it can be too much information in the paper, when also include similar analyses on interaction terms and confounding effects (see Result page 11, paragraph 2, line 10, 18 and 22). However, if Editor find it desirably, we will include this information/table in the paper.

Table X Proportion of dementia in relation to number of psychosocial stressors a, stratified by ‘longstanding distress’ and ’psychiatric family history’.
Longstanding distress Psychiatric family history
No
n=407 Yes
n=244 No
n=370 Yes
n=430
0 psychosocial stressor, n (%) 25 (19.2) 7 (17.9) 23 (15.4) 28 (20.9)

1 psychosocial stressor, n (%) 25 (18.0) 16 (24.2) 16 (13.2) 31 (23.8)
2 psychosocial stressors, n (%) 12 (16.7) 13 (21.7) 8 (16.3) 19 (21.1)
>3 psychosocial stressors, n (%) 17 (25.8) 16 (27.1) 11 (21.6) 17 (22.4)
a 'Psychiatric family history' are not included in number of psychosocial stressors

We have now also done interaction terms between stressor and 'psychiatric family history' in relation to incidence of dementia and between stressors and longstanding stress in relation to dementia. This information is added in the results section (page 11, paragraph 2, line 22).

IMPORTANT: Please also see uploadad PDF file, where the Table in Respons 9 is appropriate.