PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Mental health status and risk of new cardiovascular events or death in patients with myocardial infarction: a population-based cohort study
AUTHORS	Nielsen, Tine; Vestergaard, Mogens; Christensen, Bo; Christensen, Kaj; Larsen, Karen

VERSION 1 - REVIEW

REVIEWER	Prof.Dr. Adriaan Honig MD, PhD, MRC Psych. Dept. of Psychiatry Head Psychiatric Consultation-Liaison Service St.Lucas Andreas Hospital/ Dept of Psychiatry VUmc
REVIEW RETURNED	28-May-2013

THE STUDY	Using a population-based cohort design (n=880) this paper focussed on a possible association between morbidity and mortality after a first MI and the mental health subscale of a well estab-lished quality of life scale (SF12) along with a depression and anxiety symptom checklist (HADS). They found a strong association between low mental health status and risk of new cardiovascular events over and above other risk factors such as depressive and anxiety symptoms, physical activ-ity, and severity of cardiovascular disease. The paper is clearly written, and data discussed in a balanced manner. The cohort is well stratified on MI related information using a National Patient Register. As far as I can evaluate adequate and recent statistical procedures were applied. Their conclusions add up to current literature on possible psychological, social and functional risk factors for an adverse course of first MI patients. Minor comment: 1.they state that MI is followed by depression and anxiety. However in about 1/3 of cases symptoms of depression and anxiety precede a first MI. 2. only 68% of the cohort participated and 3. psychosocial data were based on questionnaires filled out at home without supervisoin by a research team member. This leaves open the question who filled out the questionnaires.

REVIEWER	Sylvie Cossette, RN. PhD Full professor, Faculty of Nursing University of Montreal, Regular researcher, Montreal Heart Institute Research Center

	No competing interests to declare
REVIEW RETURNED	27-Jun-2013

THE STUDY	describe how multicollinearity was handle in including depression, anxiety, and mental health status
GENERAL COMMENTS	The study by Larsen et al aims to describe the association between mental health status after a first myocardial infarction, and new cardiovascular events or all-cause mortality. This is a large, population-based, cohort study of 880 new MI patients recruited during 2009 in central Denmark. Mental health data were collected at 12-14 weeks after hospital discharge, and major mental health variables were assessed using the SF-12, which includes six mental health items and six physical items. Depression and anxiety, were assessed with the HAD, a well-known tool, but with unstable sensitivity and specificity for both measures (65% sensitivity and 91% specificity for depression; 90% sensitivity and 61% specificity for anxiety as reported in the paper). Co-morbidities were assessed with database data on diagnosis and prescribed medication, and measures of health behaviour were also assessed, including rehab participation, which is also a factor related to decreased mortality in MI patients. The results showed that cardiac events (a composite measure of MI, heart failure, and stroke-transient ischaemic attack) were two times more likely among patients in the lowest mental health quartile compared to those in the highest mental health quartile after adjustment for critical variables. The strength and originality of the paper is that it controlled for anxiety and depression which are known factors related to cardiac re-events, in addition to clinical and sociodemographic factors. Other strengths of the study include its large population, and the homogeneity of the MI sample (i.e., first time MI). Additionally, the data are mostly database-derived, which reduces the potential of self-reporting bias. The statistical model controlled for anxiety and depression in demonstrating the link between mental health and cardiac events. However, there is usually a high correlation between anxiety, depression and mental health, and thus an overlap in these measures. How was this multicollinearity dealt with in the analysis? From a theoretical point of view, while there have been several attempts in the literature to disentangle the effects of various mental health measures in predicting cardiac events (including type D personality and negative affect), there remains a knowledge gap in this area, and, as the authors acknowledge, it is important to evaluate the patient's mental health more broadly in a clinical setting rather than just assessing depression and anxiety. In the future, it is likely that other mental health status measures will be linked to cardiac events and this emphasizes the need to examine possible mechanisms for this deleterious effect. In the present paper, no information is provided on possible mechanisms by which the observed results may be explained. For instance, a potential explanation linking anxiety or depression and cardiac re-events includes arrhythmia and coagulation mechanisms, as well as behavioural risk factors in depressed or anxious patients (e.g., inactivity, smoking). Not all interventions succeed in improving these specific mental health measures and cardiac mortality. In sum, this is an interesting paper which adds to the literature describing the link between mental health and cardiac mortality. It remains to be seen which types of interventions will ultimately

	improve these mental health measures, thereby reducing cardiac mortality.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Prof.Dr. Adriaan Honig MD, PhD, MRC Psych.
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Minor comment:
1.they state that MI is followed by depression and anxiety. However in about 1/3 of cases symptoms of depression and anxiety precede a first MI.
REPLY: MI patients may have had symptoms of depression and anxiety prior to the MI, and the ongoing discussion about the direction of the association is very interesting. It may be bidirectional. We believe that this discussion is beyond the scope of the present paper, but we can add a sentence about it, if the editor would like us to.

2. only 68% of the cohort participated and
REPLY: We have addressed possible selection bias in the “Strengths and limitations of the study” section of the paper. In order to address the potential risk of selection bias, we used antidepressant consumption as a proxy for depression and calculated hazard ratios (HRs) for the association between antidepressant consumption and new cardiovascular events or death for both participants and non-participants. The estimates of this association were similar for both participants and non-participants.

3. psychosocial data were based on questionnaires filled out at home without supervision by a research team member. This leaves open the question who filled out the questionnaires.
REPLY: In the questionnaire we asked for informed consent and all the questionnaires were signed by the participating patients. We have no reason to doubt whether the participating patients should have filled the questionnaire.

Reviewer: Sylvie Cossette, RN. PhD
Full professor, Faculty of Nursing
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The statistical model controlled for anxiety and depression in demonstrating the link between mental health and cardiac events. However, there is usually a high correlation between anxiety, depression and mental health, and thus an overlap in these measures. How was this multicollinearity dealt with in the analysis?
REPLY: We have calculated the variance inflation factor (VIF) to check for multicollinearity between the depression/anxiety variable and the mental health status variable. As a rule of thumb, a variable whose VIF values are greater than 10 may merit further investigation of multicollinearity. The VIF in our case was 1.5. We have added information about this in the “Statistical analysis” section.

In the present paper, no information is provided on possible mechanisms by which the observed results may be explained. For instance, a potential explanation linking anxiety or depression and cardiac re-events includes arrhythmia and coagulation mechanisms, as well as behavioural risk factors in depressed or anxious patients (e.g., inactivity, smoking). Not all interventions succeed in

improving these specific mental health measures and cardiac mortality.

REPLY: There is an ongoing discussion about the possible mechanisms behind the association between mental health problems after MI and adverse outcome. Our results have no final explanation on this issue, but we discuss possible mechanisms in the “Possible explanations and future research” section. Several mechanisms have been suggested in the association between depression and anxiety symptoms and adverse outcome, and we believe that it may be some of the same mechanisms that are at stake with mental health status. In addition, we explored the association between mental health status and outcome in subgroups, but we identified no factors that modified the risk. However, the sample size was low in some of the subgroups.