Author's response to reviews

Title: Impact of briefly-assessed depression on secondary prevention outcomes after acute coronary syndrome: a one-year longitudinal survey

Authors:

Hannah M McGee (hmcgee@rcsi.ie)
Frank Doyle (fdoyle4@rcsi.ie)
Ronan M Conroy (rconroy@rcsi.ie)
Davida De La Harpe (davida.delaharpe@erha.ie)
Emer Shelley (Emer_Shelley@health.irlgov.ie)

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Author's response to reviews:

21st September 2005

RE: MS: 7957293147224256 - Impact of briefly-assessed depression on secondary prevention outcomes after acute coronary syndrome: a one-year longitudinal survey

Dear Editor,

We have addressed each of the reviewers' comments as outlined. We trust that the paper now meets your approval.

Yours sincerely,

Frank Doyle (on behalf of the authors)

Reply to reviewers:

Reviewer 1:

Reviewer's report:
General: In literature several examples show the role of mental depression as primary risk factor for coronary heart disease (CHD). This paper, by an appropriate and replying method, demonstrates that depression may be a risk factor in the secondary prevention of this disease. In general, data concerning the "impact of briefly assessed depression" in the text and abstract are well controlled and written.

Major compulsory revision.
Query 1. It sounds obvious that this study is limited to a specific country and population. Before any general conclusions, it seems necessary to emphasize more deeply the need of similar studies in population of different geographic areas, culture and psychology.

Response:
The reviewer is correct that similar national studies are needed in different cultures, as not only may there
be psychological differences across countries, there may also be significant differences in the secondary prevention profile of the different populations. However, at least two large studies (Braam et al, 2005, Br J Psychiat, 187, 35-42; Ormel et al, 1994, JAMA, 272, 1741-8) have shown that the relative impact of depression on physical health is steady across cultures. Therefore, although specific studies for the impact of depression on secondary prevention profiles are necessary, it is unlikely that a cultural difference would be found. This point has been included in the manuscript:

Discussion:
Survey limitations
Since the present study was based in one country, results may not be generalisable to other countries for two reasons: Firstly, the secondary prevention profile compares favourably to that in other European countries [4-7]. Secondly, depressive symptoms may be experienced differently in different cultures/countries. However, at least two large studies [37, 38] have shown that the impact of depression on physical health is similar across populations and countries. Thus there is some evidence supportive of cross-cultural generalisability.

Query 2. The selected population includes patients with acute coronary syndromes defined as "unstable angina and myocardial infarction". Are these cases at their first episode of CHD? The depression should be investigated in patients "first episode" or chronic.

Response:
The study sample combined participants with a prior positive history of ACS (36%) and those with a first episode. In general, a positive history of ACS had little impact on the secondary prevention profile of the participants. It also had no significant impact on depressive symptoms at one year, when controlling for baseline depression. To address the reviewer's query, we have included the following sentences throughout the Results section, as outlined next:

Results
Paired comparisons of baseline and one-year characteristics
Of the current sample, 36% had a previous history of ACS.

Health advice, smoking and service use
Patients who were depressed at baseline were no more likely to be current smokers at index admission (OR=1.5, 95% CI 0.96-2.3, p=0.073), but were significantly more likely to continue to smoke after hospitalisation (OR=2.3, 95% CI 1.3-4.0, p=0.003), even when controlling for a prior history of ACS (OR=2.4, 95%CI 1.4-4.1, p=0.003).

Depression also predicted frequent users when controlling for prior history of ACS (OR=2.1, 95% CI 1.3-3.4, p=0.005).

Depression did not predict cardiac rehabilitation attendance (OR=0.6, 95% CI 0.4-1.1, p=0.120), and remained non-significant when controlling for prior ACS (OR=0.7, 95% CI 0.4-1.2, p=0.148).

Psychosocial outcomes
Depressed patients were less likely to return to work (OR=0.4, 95% CI 0.2-0.8, p=0.015), even when controlling for prior ACS (OR=0.5, 95% CI 0.2-0.9, p=0.025), or when controlling for age and sex (OR=0.4, 95% CI 0.2-0.7, p=0.004).

Patients who were depressed at baseline were less likely to feel better one year later (OR=0.6, 95% CI 0.3-1.0, p=0.05), but this effect became marginal when controlling for prior ACS (OR=0.6, 95% CI 0.4-1.04, p=0.068), or when controlling for age and sex (OR=0.6, 95% CI 0.4-1.04, p=0.071).

Depression status
Those depressed at baseline were more likely to be depressed at one year (OR=6.6, 95% CI 3.7-11.8, p<0.001). Controlling for baseline depression, age (OR=0.97 for 1 year, 95% CI 0.94-0.996, p=0.025) was a significant predictor of one-year depression, but sex (OR=1.1, 95% CI 0.6-2.2, p=0.734), and prior ACS (OR=1.5, 95% CI 0.8-2.7, p=0.186) were not. Participants with a discharge diagnosis of confirmed myocardial infarction were less likely to be depressed at one year (OR=0.5, 95% CI 0.3-0.9, p=0.014), when controlling for baseline depression.

Discussion
Impact of depression
Importantly, a prior history of ACS had little impact on secondary prevention outcomes in the current sample. This indicates that the depression scales were robust in predicting outcomes, regardless of previous cardiovascular history.

Also of note in the current sample was that younger patients were more likely to be depressed at one year, but women were not. That younger patients were more likely to be depressed supports previous findings [22, 32], but the absence of a relationship between depression and sex contradicts previous research [16]. Sex was not related to baseline depression (data not shown). It may be that in the present survey women did not find the acute cardiac event any more stressful than men, therefore this relationship remained non-significant at one year.

Those discharged with confirmed myocardial infarction (vs. unstable angina) were less likely to be depressed at one year. This is surprising, given that myocardial infarction would be considered a more stressful event. However, previous research has also found a higher prevalence of depression in unstable angina patients than in myocardial infarction patients [10, 11]. It may be that frequent episodes of recurrent angina contribute to higher rates of stress and subsequent depression.

Query 3. The questionable "unifying theory" in the acute coronary syndromes includes "sudden death". Mental depression has been considered a primary risk factor of the latter as shown in many examples. In the one-year follow-up of this study 59 deaths are reported. In the discussion a unique sentence "...depressed patients have worse outcomes in terms of mortality (manuscript submitted for publication..." is mentioned. My opinion is that data concerning these dead patients belong to the present text. The reader must know if depression is or not associated with death and its type (sudden, re-infarction, other?) in this paper. No reason for another one.

Response: We disagree with the reviewer on this point. The focus of this paper is the secondary prevention profile of the surviving patients, and the predictive validity of briefly-assessed depression. The mortality data was submitted as a different paper as it includes an in-depth analysis of mortality when controlling for standard medical variables, and provides a theoretical discussion of these findings in terms of other studies and the diagnosis of major depressive disorder. It is therefore a very different paper, with a minimal focus on health services research. Several previous studies also adopt the approach of using mortality data only (e.g. Frasure-Smith and colleagues). In order for the present paper to focus properly on the surviving patients we feel it is important to initially profile the patients in comparison to other studies, and then show that depression predicts this profile. The current manuscript therefore addresses the usefulness for health services of these brief depression scales. Also, to include mortality in the detail necessary in the current manuscript would lead to a very long, unwieldy and insufficiently focused paper. The mortality data has since been accepted for publication, and the reference number is included instead of the text "manuscript submitted for publication". We can now cite the hazard ratio for mortality and the journal reference:

Discussion
Impact of depression
Overall, these results imply that not only do depressed patients have worse outcomes in terms of mortality (hazard ratio=2.8 for one-year mortality (REFERENCE)) and health service use, but that the surviving depressed patients also perceive their general health outcomes to be worse.

Query 4. Even if the baseline methodology has been already published, the selection of patients should be reported in more exhaustive way. The reader needs also to know whether or not the patients were treated by invasive methods (PTCA, bypass surgery). In results, the rehabilitation attendance was more frequent in young people having a "private health insurance and receiving reperfusion at baseline" What means reperfusion? Fibrinolytic or invasive therapy and how reperfusion demonstrated?

Response: The baseline methodology was as follows (from Doyle et al, 2005, 5,5):

“All Irish centres admitting suspected ACS patients to I/CCU (N=39) agreed to participate following relevant ethics approval. Data collection was conducted from January to October 2003. Four hospitals had not recruited 25 suspected AMI patients by the study cut-off date. Suspected acute coronary syndrome (ACS) patients admitted to I/CCU were recruited. Staff were provided with the consensus definition of ACS as agreed in 2000 by the Joint European Society of Cardiology/American College of Cardiology Committee.
This definition uses enzyme (troponin) change as a marker of myocardial necrosis. The survey was of suspected ACS and the main focus was on how patients with suspected ACS are treated in the early phase of their hospital admission. Therefore the admission diagnosis was used to categorise patients (e.g. if a patient was admitted to I/CCU with a diagnosis of 'chest pain - query AMI', they were listed as suspected AMI for the purposes of this study; if patients were admitted with suspected ACS or suspected unstable angina, they were categorised as 'other ACS'). Data on successive admissions were audited anonymously from hospital charts. Participating hospitals recruited all consecutive suspected ACS patients, until 25 suspected cases of AMI had been admitted to I/CCU. Data on a total of 1365 episodes were collected (935 suspected AMI and 430 suspected other ACS admitted contemporaneously). Data collected assessed demographic details, clinical history, risk factors, presentation and management profile. Eligible patients were also approached to participate in a follow-up survey (results to be reported elsewhere)."

However, we contend that a lot of this is superfluous to the current survey methodology. In accordance with query 7 we have deleted the results regarding attendance at cardiac rehabilitation. It is necessary to keep the Method brief, as the paper is already quite long. To avoid repetition of previous papers, but to address the reviewer's comments, we have changed the following sentences in the Method section:

Method:
Briefly, after receiving ethical approval [25], all Irish centres admitting ACS patients to intensive/coronary care were invited and agreed to participate in a survey focusing on time-to-treatment and reperfusion (thrombolysis and/or direct infarct angioplasty) for eligible patients. Consecutive suspected ACS patients were recruited by staff to participate in the survey, until 25 suspected acute myocardial infarction patients were recruited.

Query 5. No attempt is has been done to investigate depression versus the two considered types of acute coronary syndrome. Unstable angina and myocardial infarction have a totally different clinical patterns in term of morphopathology, myocardial dysfunction, complications, outcome, symptoms and therapeutical approaches, possibly leading to different psychological reaction. Any difference in relation to depression between this two patterns?

Response:
We thank the reviewer for this suggestion. This point is related to queries 2 and 8. It is correct to state that the different clinical profile may have an influence on depression. Confirmed MI was not associated with the outcomes listed in the paper (i.e. continuation of smoking, frequent GP attendance, return to work, feeling better), and therefore we did not differentiate throughout the paper. Baseline depression was not associated with a confirmed discharge diagnosis of MI (OR=0.8, 95% CI 0.5-1.1, p=0.176), but depression at one year was influenced by diagnosis, with confirmed MI patients being less likely to be depressed than confirmed unstable angina patients (OR=0.5, 95% CI 0.3-0.9, p=0.015). A more in-depth analysis of this has been included in both the Results and Discussion sections (also see query 2).

Results
Depression status
Participants with a discharge diagnosis of confirmed myocardial infarction (vs unstable angina) were less likely to be depressed at one year (OR=0.5, 95% CI 0.3-0.9, p=0.014), when controlling for baseline depression.

Discussion:
Those discharged with confirmed myocardial infarction (vs unstable angina) were less likely to be depressed at one year. This is surprising, given that myocardial infarction would be considered a more stressful event. However, previous research has also found a higher prevalence of depression in unstable angina patients than in myocardial infarction patients [10, 11]. It may be that frequent episodes of recurrent angina contribute to higher rates of stress and subsequent depression.

Query 6. Heart and brain relationship is one topic particularly important in the etiopathogenesis of acute coronary syndromes. In this paper almost no mention and no suggestion how depression may act.

Response:
The reviewer correctly states the importance of the heart-brain relationship for the etiopathogenesis of ACS. Among many postulated mechanisms for the heart-brain relationship and interaction of depression and cardiovascular disease are increased sympathetic activity, cerebral arteriosclerosis, dysregulation of
serotonin transporter, immune activation or reduced omega-3 fatty acids (Malach & Imperato, 2004, Prev Cardiol, 7, 83-92). This is a very interesting line of research, but unfortunately we do not have measurements of any of these variables. Therefore, we do not think that we can comment on our results or how they relate to this research. However, we do comment on how a reduction in adherence to medications may impact on outcomes (paragraph 1 in Discussion section - Impact of depression). We have also inserted the following text in the Discussion:

**Discussion**

**Impact of depression**

A number of mechanisms have been postulated over time to explain the relationship between cardiovascular disease and depression [35] but coverage is beyond the scope of this paper. However, more recently some researchers have postulated that depression may simply be a marker of disease severity [36]. The finding in the present study that 'depressed' patients were more frequent visitors to general practitioners may provide some support for this hypothesis. Alternatively, it may be that depressed patients have other ailments which require more frequent visits or that depression per se induces professional help-seeking behaviour. The data in the present study cannot clarify this point further.

Query 7. The data of some variables (for instance, antiplatelet or lipid-lowering therapy) are compared with findings in other studies. A too extensive literature exist and my suggestion is to strictly focus on depression in relation to the other variables, without enter in a very complex and debated field.

Response:

We thank the reviewer for this suggestion. We have deleted some of the secondary prevention results as suggested (data in the following sections have been deleted: Health advice, smoking and service use - smoking advice, cardiac rehabilitation attendance predictors; Psychosocial outcomes - age and sex predictors of return to work and feeling better). The Discussion section on the "Secondary prevention profile and psychosocial outcomes" has also been substantially reduced, with discussion of these previously mentioned results deleted. However, we feel it is important to initially profile the patients in comparison to other studies, and therefore some of this data remains (e.g. Table 1, Discussion section). If the profile was not compared to other studies, it would not be clear whether depression predicts secondary prevention activities only in patients with a relatively 'good' profile, or only in those with a relatively 'bad' profile. This would then lead to the question of how useful these brief scales are in the general acute setting.

Query 8. Fluctuation of depression is mentioned without any correlation to other findings. The authors mention that further investigation is needed. Nevertheless can they state that any correlative attempt with findings at baseline was negative?

Response:

Similar to queries 2 and 5, we have now expanded the section on depression status at one-year in line with the reviewer's request. This section now provides a more detailed examination of predictors of depression at one year.

**Results:**

Those depressed at baseline were more likely to be depressed at one year (OR=6.6, 95% CI 3.7-11.8, p<0.001). Controlling for baseline depression, age (OR=0.97 for 1 year, 95% CI 0.94-0.996, p=0.025) was a significant predictor of one-year depression, but sex (OR=1.1, 95% CI 0.6-2.2, p=0.734), and prior ACS (OR=1.5, 95% CI 0.8-2.7, p=0.186) were not. Participants with a discharge diagnosis of confirmed acute myocardial infarction (vs. unstable angina) were less likely to be depressed at one year (OR=0.5, 95% CI 0.3-0.9, p=0.014), when controlling for baseline depression.

**Discussion**

**Impact of depression**

Also of note in the current sample was that younger patients were more likely to be depressed at one year, but women were not. That younger patients were more likely to be depressed supports previous findings [22, 32], but the absence of a relationship between depression and sex contradicts previous research [16]. Sex was not related to baseline depression (data not shown). It may be that in the present survey women did not find the acute cardiac event any more stressful than men, therefore this relationship remained non-significant at one year.

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depressed at one year. This is surprising, given that myocardial infarction would be considered a more stressful event. However, previous research has also found a higher prevalence of depression in unstable angina patients than in myocardial infarction patients [10, 11]. It may be that frequent episodes of recurrent angina contribute to higher rates of stress and subsequent depression.