Author's response to reviews

Title: The relationship between depressive symptoms, health service consumption, and prognosis after acute myocardial infarction: a prospective cohort study.

Authors:

Paul A Kurdyak (paul_kurdyak@camh.net)
William H Gnam (william_gnam@camh.net)
Paula Goering (paula_goering@camh.net)
Alice Chong (alice.chong@ices.on.ca)
David A Alter (david.alter@ices.on.ca)

Version: 2 Date: 18 July 2008

Author's response to reviews: see over
July 17, 2008

Dr. Mark Todd
Assistant Editor
BMC-series journals
Fax: +44 (0)20 7631 9923

Dear Dr. Todd:

Re: MS: 1736068856193442
The relationship between depressive symptoms, health service consumption, prognosis after acute myocardial infarction: a prospective cohort study.

Thank you for the opportunity to respond to the reviewers’ comments and to re-submit this manuscript for consideration as a submission to BMC Health Services. The revised manuscript has a new word count of 3767 words (excluding abstract, references, tables, figures, and appendix). Our original submission included 1 figure, 2 tables and 4 appendices. There are now 2 figures, 4 tables, and 1 appendix.

We are very grateful to the reviewers for the careful review of the manuscript and thoughtful comments provided. We feel that the revisions based on the reviewers’ helpful input have resulted in a substantially improved manuscript.

All reviewers commented on the description of the depression measures. Accordingly, the depression measurement description and limitations section have been significantly revised. Additionally, we have more explicitly described the objective and hypothesis of the paper. We have responded to each of the comments of the reviewers on the enclosed pages and have made suggested changes in the manuscript.

Thank you for your consideration of this manuscript.

Kindest regards,

[Signature]

David A. Alter, M.D., Ph.D., F.R.C.P.C
Senior Scientist, Institute for Clinical Evaluative Sciences
Staff Physician, Division of Cardiology
St. Michael's Hospital, and the Toronto Cardiac Rehabilitation Centre
Associate Professor of Medicine, University of Toronto
G-106, 2075 Bayview Ave,
Toronto, ON M4N 3M5 Canada
Telephone: (416) 480-5838
Fax: (416) 480-6048
A point-by-point response to the 3 Reviewers’ comments is discussed below:

Reviewer 1:

Major Compulsory Revisions

1) A thorough description of inclusion and exclusion criteria were requested.

The following text was added to the Data Source and Study Sample sub-section of the Methods section (page 6, last paragraph):

“Patients were included if they were English-speaking and if 2 of 3 AMI criteria were met: presence of symptoms, abnormal electrocardiographic findings, or elevated serum levels of cardiac enzymes. Patients were excluded if they were younger than 19 years of age or older than 101 years of age, lacking a valid health card number issued by the province of Ontario, and those who were transferred to the recruiting hospital. Eligibility for the study required completion of a self-administered baseline survey; patients who died within 24 hours of admission, who had very severe illness, who had language barriers, or who underwent early discharge or transfer were therefore ineligible.”

2) Points 2, 3 and 4 refer to the incomplete BCDRS (the survey contained only 9 of 12 items), the lack of rationale for the 9-item scale, the use of the GUSTO study measure which has never been validated, and the use of an unpublished imputation method.

All three reviewers requested clarification of the depression symptom measurement section. The SESAMI study included 9 of the 12 items included in the BCDRS. We have revised the depression measure section to be clearer about the absence of 3 items. We have included a table outlining the 9 items of the BCDRS that were included in the survey, as well as a comparison of the 3 items that were missing and 3 items that were included in the SESAMI survey. We conducted our main analyses using the 9-item scale with a cut-off score of 5. We used approximations of the 3 missing items to re-analyze service utilization outcomes to determine the degree to which associations between the 9 items of the BCDRS are concordant with the 3 items that were missing. These three replacement items were taken from the SF-12 (1 item) and the psychological well-being measure used in a quality of life sub-study of the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) trial {Mark et al., 1994, N Engl J Med, 331, 1130-5} (2 items). References to outcome analyses from the GUSTO psychological well-being measure were removed from the main depression measures sub-section of the Methods section and only referred to as a sensitivity analysis. Finally, we revised the limitation section of the discussion to include the BCDRS missing items as a significant limitation of this study. The following section was included in the Depressive Symptom Measure sub-section of the Methods section (page 6, last paragraph):

“The SESAMI survey consisted of psychometric questions that explored various domains related to depression, including low mood, loss of interest, sleep
disturbance, reduced appetite/wt loss, agitation/slowing, low self-esteem/guilt, suicidal thoughts, reduced energy level, loss of concentration (Table 1). The SESAMI surveys were telephone administered by standardized trained health care personnel (nurses).

Nine of twelve questions were directly abstracted from the Brief Carroll Depression Rating Scale (BCDRS). These nine questions served as our primary determinant of depressive symptoms. The original 12-item BCDRS is a depression rating scale which has been validated among hospitalized mentally ill populations, and has a sensitivity of 92% and a specificity of 89% using a cut-off scale of 6 {Koenig et al., 1988, J Am Geriatr Soc, 36, 699-706}.

While a score of 6 or more of the original 12-item BCDRS has been used to define depression, affirmative responses to 5 or more of the 9-items administered BCDRS items were used to define patients as having “depressive symptoms” for the purposes of our study. A score of 5 rather than 6 was used because it corresponded most closely with the median score of 6, and because five or more depressive constructs are required to fulfill DSM-IV criteria for depression, and hence is concordant with the diagnostic criterion threshold from DSM-IV.

The three questions comprising the 12-item BCDRS not included in the SESAMI survey, related to sleep disturbance, concentration, and self-esteem, and were as follows: “my sleep is restless and disturbed”; “I can concentrate easily when reading the paper”; and “I feel worthless and ashamed about myself”(Table 1). However, these missing questions were replaced with the following: “During the past week, how much time have you had trouble sleeping for example, having trouble falling asleep or waking up too early and unable to get back to sleep”; and “you are a burden on others”(Table 1). These three items were abstracted from two data sources: The first two replacement items originated from a psychological well-being measure incorporated within the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) trial quality of life substudy [14], whose design served as the foundation for the SESAMI. The GUSTO psychological well-being measure included 10 items[14]. The remaining replacement item originated from the SF-12. For scoring purposes, responses related to the first 2 replacement questions were dichotomized around the median (3+ days per week vs. < 2 days per week). The last replacement question elicited a binary response (Table 1). These three additional replacement questions were analyzed separately from the 9-item BCDRS and reported within the sensitivity analysis section below.

The sensitivity analysis using the three replacement items for the missing items from the BCDRS are described as follows in the Sensitivity and Sub-group Analysis sub-section of the Methods section (page 14, first paragraph):

“First, we examined the relationship between the 3 replacement questions and health service utilization. Second, we examined the use of different cut-off scores
to define “depressive symptoms” for both the 9-item BCDRS and the 3 depressive-symptom replacement items. Third, we explored whether our results were consistent when using the Duke Psychological Well-Being Scale, another psychometric instrument.”

Finally, the following sentence was included in the Discussion section on limitations (page 20, last paragraph):

“Our study has several noteworthy limitations. First, our scale was designed to ascertain depressive symptoms rather than depressive disorders and was missing 3 items from the original, validated depression rating scale. Our health service consumption findings were similar whether the 9 items or 3 replacement items were used to define depression. The comparability of results with these two depression measures suggests that the two scales are measuring the same construct.”

5) The reviewer did not feel the multiple imputation method to impute missing depression measures was not justifiable.

Multiple imputation is a model-based method to impute missing values. This addition to the analysis was seen as a strength by Reviewer 2. We have responded to the Reviewer 2’s request for greater clarification of the variables used to impute values, as well as the number of data sets created for imputation. Please refer to the response to Reviewer 2’s request for clarification on the imputation methods used to impute missing depression values.

6) The reviewer requests an explanation for the higher relative risks for the stratified analysis of health service consumption outcomes based on the GRACE prognostic index.

The relative rates of health service consumption are only higher in the stratified analysis (Table 4) than the entire cohort analyses (Figure 1) for the stratum with lower cardiac illness severity. The stratum with higher illness severity has a point estimate that is consistently lower than the point estimate from the entire cohort. This result is consistent with our interpretation that the increased service consumption following AMI is most pronounced in those with the lowest cardiac illness severity.

7) The reviewer requests inclusion of systematic reviews on the topic of depression and mortality following AMI.

We are grateful for the reviewers’ comments and have included the systematic review references to the revised manuscript in the following paragraph of the Discussion section (page 18, last paragraph):

“In our sample, depressive symptoms were not associated with increased mortality or recurrent AMI, which is contrary to previous evidence {Frasure-Smith et al., 1995, Circulation, 91, 999-1005} {van Melle et al., 2004, Psychosom Med, 66,}
However, the association between depression and cardiovascular outcomes remains controversial [Lane et al., 2001, Psychosom Med, 63, 221-30] [Sorensenf et al., 2005, Psychother Psychosom, 74, 69-80] and the results of this study are not sufficient to address the controversial prognostic importance of depression definitively, especially given inter-study differences in measurement and timing of depression.”

**Minor Essential Revisions:**

1) The reviewer requested clarification of phrases on page 5 and editing of a reference to an article by Katon.

*The requested changes have been made to the manuscript as follows (page 5, second paragraph):*

“Evidence from utilization patterns of depressed patients in primary care settings suggest that depressed patients use more health care services than non-depressed patients regardless of medical illness severity [Katon, 1996, Gen Hosp Psychiatry, 18, 215-9].”

2) The reviewer requests a modification to the reference to depression prevalence.

*This change has been made in the context of substantial revisions to the depression measures outlined above.*

3) The baseline characteristics in Table 1 do not match those in Appendix 2 for the GRACE index and %PTCA.

*The error was a typo and has been corrected in Table 1. Appendix 2 has been removed in relation to revisions made to the depression measurements.*

**Discretionary Revisions:**

1) Revise wording of objective on page 5.

*The wording has been revised as follows (page 5, last paragraph):*

“Accordingly, the objective of our study was to evaluate the impact of depressive symptoms on health service consumption and cardiovascular prognosis following AMI.”

2) Clarify references to demographic and socioeconomic determinants of service use variation.

*The references in this sentence were included to indicate to the reader that there have been other observed variables related to differences in service utilization pattern.*
Psychosocial measures could be another cause of service utilization gradients following AMI. The sentence has been modified as follows in the final paragraph of page 5:

“Yet, unexplained variations in health service consumption exist across patient populations {Chen et al., 2001, N Engl J Med, 344, 1443-9} {Alter et al., 2004, JAMA, 291, 1100-7}; similar health service consumption variations may be explained by psychosocial factors.”

Reviewer 2

Major Compulsory Revisions

1) The first five points are related to lack of clarity of the depression measures.

The revisions related to the depression measures were described above in Reviewer 1 Major Compulsory Revisions, 2).

2) Please provide discrimination of GRACE and DASI in the SESAMI cohort.

The GRACE prognostic index is a cardiac illness severity rating scale that generates a prognostic probability derived from baseline cardiac parameters. As indicated in the manuscript, the GRACE has been validated as a prognostic tool using SESAMI data. The predicted 6-month mortality as derived using GRACE closely mirrored observed mortality rates with strong accuracy and precision (c-statistic = 0.80 for the overall cohort and within each income and education strata).

The DASI is a self-report rating instrument that was administered in the one-month follow-up survey. The DASI was validated against treadmill stress test and is a measure of cardiac functional status {Hlatky et al., 1989, Am J Cardiol, 64, 651-4}. The validity of the DASI as a prognostic measure has also been replicated {Shaw et al., 2006, J Am Coll Cardiol, 47, S36-43}.

Both instruments are described in the first paragraph of the Cardiac Risk Severity subsection of the Methods section of the manuscript. If the editor wishes, we can elaborate on our two measures of cardiac illness severity.

3) The reviewer recommends the use of hierarchical modeling or GEE to account for clustering of patients within hospitals.

The full sample multivariate analyses have now been repeated using GEE to account for clustering within hospitals. The results of these analyses were revised in Fig. 1 to reflect the new results (which do not differ substantially from the original results). The Statistical Analysis sub-section of the Methods section has been modified to reflect this change with the following sentence (first paragraph, page 13):

“Finally, for the health service utilization multivariate models, we used
generalized estimating equations (GEE) to adjust for hospital-level variations in patient care.”

4) Clarify the use of regression models for specific outcomes.

*The statistical analysis sub-section of the Methods section has been revised to address this lack of clarity. The change is reflected in the following sentence (first paragraph, page 13):

“We estimated Poisson regression models for rates of service utilization, as well as Cox proportional hazard models for mortality, recurrent AMI, and time to first angina hospitalization, adjusting for age, sex, income, cardiac risk factors, total medical comorbidities, prognostic index (GRACE score {Granger et al., 2003, Arch Intern Med, 163, 2345-53} and DASI {Hlatky et al., 1989, Am J Cardiol, 64, 651-4}), drugs at discharge, and peri-infarction procedures using non-parsimonious modeling.”

5) Specify variables used and number of imputed data sets used in multiple imputation.

*These revisions were included in the Sensitivity and Sub-group Analysis sub-section of the Methods section as follows (first paragraph, page 14):

“Finally, multiple imputation was used to impute depression measures for the 888 missing depression values due to non-response {Little RJA, 2002, Statistical Analysis with Missing Data, second edition} to test whether our outcomes were affected by systematic differences between survey responders and non-responders. Variables used to model the missing data included demographic variables (age, sex, SES), cardiac risk factors and illness severity (GRACE prognostic index and DASI), revascularization procedures, drugs prescribed at discharge, and the 9-item depression scale. There was no difference between aggregated results from 5 and 10 imputed data sets; results from 5 imputed data sets are reported.”

**Discretionary Revisions**

1) The reviewer questions the lack of association between our depressive symptom measure and ER visit rates given that depression is associated with health-seeking behaviour.

*Patients with significant depressive symptoms had significantly more ER visits based on univariate comparisons (mean of 1.7 visits vs. 1.3; P<0.001)(Table 3). After adjustment for all variables, the relationship between depressive symptoms and ER visits following AMI were still elevated (Relative Rate (95% CI) – 1.08 (0.99-1.18); P = 0.06). This result is not statistically significant after adjustment, but the point estimate and confidence interval suggest that the relationship between depressive symptoms and ER
visits is similar to other health service consumption outcomes. Furthermore, the relationship between ER visits and depressive symptoms in a sample stratum with lower cardiac illness severity is highly significant (low GRACE stratum – 1.21 (1.07-1.37); low DASI stratum – 1.49 (1.24-1.79))(Table 4). These results all suggest that the high ER visit rate observed in patients with depressive symptoms, particularly in those with low cardiac illness severity, is suggestive of health seeking behaviour.

2) The reviewer questions the validity of the GUSTO psychological well-being scale.

GUSTO scale items have been included as a comparison of the relationship between the 3 replacement items for the missing BCDRS items. Outcomes related to the entire GUSTO trial depression scale have been removed from the manuscript.

3) The reviewer questions the long retrospective time frame for ascertaining cardiac risk factors.

There is recent evidence to suggest that cross-sectional chart review and patient self-report are not reliable estimates of the presence of cardiac risk factors {Gravell-Witte et al., J Clin Epidemiol, in press}. As such, the retrospective chart review allowed for more comprehensive detection of cardiac risk factors as well as the presence of comorbid medical illnesses. Furthermore, there is evidence that increasing the retrospective ascertainment of comorbidities improves prediction of mortality {Zhang et al., 1999, Med Care, 37, 1128-39}. The following sentences have been included in the Preexisting Noncardiovascular Comorbid Conditions sub-section of the Methods section (last paragraph, page 10):

This method has been used and demonstrated to increase the prevalence of chronic conditions, which historically are known to be under-coded using single data sources alone {Gravell-Witte et al., 2008, Journal of Clinical Epidemiology, In press} {Alter et al., 2006, Ann Intern Med, 144, 82-93}. Furthermore, a longer retrospective ascertainment of comorbidities using administrative data has been shown to improve accuracy {Zhang et al., 1999, Med Care, 37, 1128-39}.

4) The reviewer questions why race was not included as a covariate.

Race was not included as a covariate in our models for two reasons. First, the measurement of race in Canada is complicated by whether or not an individual is an immigrant. Canada’s immigration policies impose a selection bias for healthier individuals. As such, it is unclear whether reduced utilization, which is frequently observed amongst minorities, is due to reduced access or because immigrants are healthier {Chen and Kazanjian, 2005, Can J Public Health 96:49-51}. The determination of race in SESAMI does not allow for discrimination of race vs. immigrant effect.

Minor Essential Revisions
1) Typo in reference 14 of original submission.

This reference has been removed from the manuscript.

2) The reviewer requested modifications to forest plots.

The forest plots in Figures 1 and 2 have been modified as requested. The grid lines and plot fill colour have been removed. The plots centre around 1 and a dashed line has been included to mark a Relative Rate of 1 throughout the plot area.

3) Change multivariable to multivariate.

The document was searched and the only reference to models was “multivariate” rather than multivariable.

Reviewer 3

Major Compulsory Revisions

1) The reviewer feels that we only assessed the relationship between depressive symptoms, health service utilization and not prognosis.

We included two types of outcome in our study. One type of outcome was health care utilization as measured by hospitalizations and physician visits. The other type was prognosis, as measured by mortality and recurrent AMI. These outcomes are described in detail in the Methods section. However, we will provide further clarification if the editor requests it. The Background section of the Abstract was modified as follows (first paragraph, page 3):

“The use of cardiovascular health services is greater among patients with depressive symptoms than among patients without. However, the extent to which such associations between depressive symptoms and health service utilization are attributable to variations in comorbidity and prognostic disease severity is unknown. This paper explores the relationship between depressive symptoms, health service cardiovascular consumption, and prognosis following acute myocardial infarction (AMI).”

2) The reviewer requests the inclusion of our negative mortality result in the abstract.

The following sentence has been included at the end of the Results section of the abstract (last paragraph, page 3):

“Depressive symptoms were not associated with increased mortality after adjusting for baseline patient characteristics.”
3) The reviewer requests that a research hypothesis be included in the **Introduction**.

*A research hypothesis has been included in the Introduction as follows (first paragraph, page 6):*

“We hypothesized that health service consumption following AMI would be increased among patients with depressive symptoms as compared to those without and would be independent of comorbidity and cardiac illness severity.”

4) The first 4 points following “Methods:” relate to previous reviewers’ comments about our depression measures.

*The description of our depression measures has been substantially revised to address all the reviewers’ concerns. Please refer to the revisions related to the depression measures described above in Reviewer 1 Major Compulsory Revisions, 2)*

5) The reviewer requests clarification that demographic measures were based on patient self-report.

*The text has been changed to reflect the self-report nature of our demographic measures in the following sentence from the Demographics sub-section of the Methods section (second paragraph, page 9):*

“Demographic factors such as age, sex, and income tertile were acquired from the baseline survey and were based on patient self-report.”

6) The reviewer questions our use of co-morbidities rather than Charlson or Elixhauser.

*We elected to use a count measure of comorbidities rather than the Charlson or Elixhauser indexes because noncardiac comorbidities are a powerful predictor of health service consumption in patients with cardiovascular illnesses [Braunstein et al., 2003, J Am Coll Cardiol, 42, 1226-33]. The type of comorbidity is important to include in analyses as different comorbidities have differing impacts on prognosis and service utilization [Kerr et al., 2007, J Gen Intern Med, 22, 1635-40]. Consequently, we have used both type of comorbidity and number of comorbidities to measure burden of noncardiac comorbidities; this approach has been used previously as an effective measure of disease burden [Alter et al., 2006, Ann Intern Med, 144, 82-93] [Parker et al., 2006, Can J Cardiol, 22, 131-9].*

*These issues have been clarified in the Preexisting Noncardiovascular Comorbid Conditions sub-section of the Methods section as follows (last paragraph, page 10):*

Noncardiovascular risk factors consisted of all co-morbid diseases that were captured through primary and secondary diagnostic fields of hospital discharge abstracts (Canadian Institute for Health Information) from 1 April 1988 to the
presenting hospitalization. This method has been used and demonstrated to increase the prevalence of chronic conditions, which historically are known to be under-coded using single data sources alone[19] [20]. Furthermore, supplementing clinical data sources with longer retrospective ascertainment of comorbidities using administrative data has been shown to improve accuracy [21]. Non-cardiovascular conditions were categorized as cancer and as diseases of the central nervous system, endocrine system, hematologic system, musculoskeletal system, respiratory system, gastrointestinal system, and genitourinary system. We categorized diabetes, secondary hypertension, and hyperlipidemia as cardiovascular risk factors, not as diseases of the endocrine system[22]. Available evidence has demonstrated that the number of non-cardiac comorbidities have independent prognostic significance in patients with cardiovascular illness[23]. For the purposes of our study, non-cardiac comorbidities were analyzed as a count variable (0, 1, 2 or 3 or more). However, a re-analysis of our data in which we incorporated both the count, and the type of non-cardiac comorbidity did not alter our results.

7) The reviewer requests that we describe why these outcomes were chosen.

The Outcomes sub-section of the Methods section has been modified to include a rationale for choosing these outcomes (last paragraph, page 12):

“These outcomes were chosen because they reflect health care consumption measures that can be accurately measured in the linked administrative health data sets.”

8) The reviewer requests clarification of “adverse prognostic events” in the Statistical analysis section.

We agree with the reviewer that this sentence lacked clarity and was unnecessary for the text. As such, it was removed from the re-submission.

9) The reviewer requests clarification of the Cox proportional hazard models for angina hospitalization.

The reviewer is referring to analysis reported in the Results section (first paragraph of page 16) and discussed in the Conclusion section (last paragraph of page 18). This analysis was an attempt to indirectly determine whether the increased likelihood to be admitted for angina following the index AMI attributable to depression was based on a physician-based bias to admit depressed patients for angina vs. a patient factor. Our argument is that if the likelihood to be admitted for angina was based on physician factors, then adjusting for the number of ER visits between index AMI and angina hospitalization should not affect the hazard ratio for angina hospitalizations. However, if the likelihood to be admitted for angina is related to patient factors, and more
specifically to an increased likelihood to visit ERs more frequently, then the association between depression and angina hospitalization will be negated by adjustment for ER visits which is what we found.

We will await feedback from the reviewers and editor regarding whether or not to include this section of the manuscript.

10) The reviewer raises the issue of the depression measure again.

As stated above, the description of our depression measure has been extensively revised to reflect comments from all the reviewers.

11) The reviewer requests including somatization and untreated depression as possible causes of increased health service consumption.

The prior manuscript included a reference to a study showing a link between increased health service utilization and somatization. The reference to this study as a somatization study was made more explicit in the following sentence from paragraph 4 of the Discussion section:

“Some have hypothesized that mental illness and/or psychological phenomena such as somatization promote health seeking behaviors (Katon, 1996, Gen Hosp Psychiatry, 18, 215-9), (Barsky et al., 2005, Arch Gen Psychiatry, 62, 903-10).”

The fifth paragraph of the Discussion, starting with the sentence “Our study has several important clinical and policy implications.” describes a rationale for increasing the detection of depression as a possible way to decrease health service utilization. This paragraphs also refers to a study showing that depression is unlikely to be detected in a cardiovascular illness patient population. In making the case for systematic depression detection and treatment following AMI, we agree with the reviewer that untreated depression is a possible cause for the increased health service consumption and feel our Discussion reflects this opinion.

Minor Essential Revisions

1) The reviewer requests a clarification of the Canadian health care system as one with no financial barriers to equal health care access.

The text from the Health Care System Context sub-section of the Methods section has been changed to reflect the precise wording of Canada’s health care act as follows (second paragraph, page 6):

“Canada's universal health insurance system provides comprehensive coverage for most medical and hospital services without user fees at point of service. Under such provisions, patients are entitled to equitable access to health care
services based on medical need, regardless of age, financial status, or financial circumstances (Canada Health Act, Chapter C-6).”

2) The reviewer requests % and raw numbers for deaths and refusals.

The % has been included in the text from the Data Source and Study Sample subsection of the Methods section.