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Identifying Symptom Profiles of Depression and Anxiety in Patients with an Acute Coronary Syndrome Using Latent Class and Latent Transition Analysis

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Abstract

Objective—To identify symptom profiles of depression and anxiety in patients with an acute coronary syndrome (ACS), to examine changes in symptom profiles over time and finally, to examine the effects of age and sex on patients' symptom profiles.

Methods—100 ACS patients with mild to severe symptoms of depression and/or anxiety at one month posthospital discharge were enrolled in a randomized trial of cognitive behavioral therapy. Latent class and latent transition analyses were used to identify symptom profiles and describe change over the time in profile membership.

Results—A two-class solution was selected to describe depression and anxiety symptom profiles. Class I (76% of patients at baseline) was labeled "depression and some anxiety symptoms". Class II (24% of patients at baseline) was labeled "anxiety and some depression symptoms". Approximately 25% of patients in the treatment condition transitioned from the depression and some anxiety symptoms class to the anxiety and some depression symptoms class at follow-up compared to 10% of patients in the control condition at follow-up; nearly 50% of patients in the control condition showed worsening of symptoms as compared to 28% in the treatment condition. Results suggested age differences in the probabilities of transitioning between the classes; older patients were more likely to continue having depression and some anxiety symptoms at the time of follow-up.

Conclusions—Identifying symptom profiles of depression and anxiety in patients with an ACS may improve diagnostic practices and help to design tailored interventions.

Keywords

depression; anxiety; latent class analysis; acute coronary syndrome; latent transition analysis

Introduction

Patients with an acute coronary syndrome (ACS) experience considerable stress adjusting to living with their illness. Thus, it is not surprising that depression and anxiety are more prevalent in this group of patients than in the general population [1], [2], [3], [4], [5], [6]. A

recent meta-analysis reported that the proportion of ACS patients with depressive symptoms or depressive disorder at baseline ranged from 8% to 47% [7]. Anxiety is a highly prevalent disorder affecting approximately 20% to 50% of patients following an ACS [8]. Moreover, it has been reported that approximately 60% of depressed patients may have concomitant anxiety [6]. Patients with an ACS and symptoms of depression and anxiety not only experience higher rates of long-term morbidity and mortality but also report a worse quality of life than patients without symptoms of these psychiatric disorders [3], [4], [5]. Due to the clinical and public health significance, as well as the economic burden of depression and anxiety in ACS patients, identifying symptom profiles of these psychiatric disorders will not only better inform clinical management by improving diagnostic practices but will help to design tailored interventions aimed to improve quality of life and other clinical outcomes in these high risk patients.

The primary objective of the current study was to characterize symptom profiles of depression and anxiety in patients with an ACS using the hospital anxiety and depression scale (HADS), and to examine changes over time in symptom profiles. An advantage of using the HADS is that this scale excludes the somatic aspects of depression, preventing the potential confounding of symptoms of depression and ACS such as insomnia and fatigue. A secondary study objective was to examine the effects of age and sex on these symptom profiles.

This study employed latent class and latent transition analysis (LCA/LTA) to identify classes (i.e., profiles) of depression and anxiety symptoms in patients after an ACS. An advantage of using LCA/LTA is that these methods can be used to model multidimensional variables. In the current study, multiple dimensions of depression and anxiety, as represented by the symptoms of each disorder, were modeled simultaneously. The goal of modeling depression and anxiety symptoms in this way is to improve the diagnosis of symptomatic individuals and better represent the relative severity of diagnostic categories [9]. The underlying idea of this study is that patient symptomatology is better represented by a multidimensional combination of the HADS items than by considering each item separately.

Methods

The study sample consisted of 100 patients hospitalized with an ACS in two coronary care units at a university hospital in Boston, MA, between September, 2001 and August, 2003 [10], [11]. Patients were 35 years and older at the time of trial entry and had symptoms corresponding to mild to moderate levels of symptoms of depression and/or anxiety as indicated by a score of seven or higher on either subscale of the HADS. Most of the patients included in this study presented unstable angina and non-ST-segment elevation myocardial infarction, these being the most common manifestations of this disease. Exclusion criteria included mental health care in the prior 3 months, psychoactive drug use during the past year, and diagnosis of substance abuse during the past year [10], [11]. Potentially eligible patients were identified by a research nurse through the review of hospital records and hospital census information. Patients were screened approximately one month after hospital discharge for an ACS, and those meeting the predefined study inclusion criteria were randomly assigned to either cognitive behavioral therapy (CBT) or a usual-care control group [10], [11].

Patient recruitment began during the index hospitalization for an ACS. Once patients consented to trial enrollment, the study coordinator administered the 14-item HADS by phone to assess symptoms of anxiety and depression. Subjects with scores between 7 and 15 on either the anxiety or depression subscale were enrolled into the trial and randomized into

the intervention or control groups [10], [11]. Almost 30% of the patients that screened positive for depression or anxiety during hospitalization showed spontaneous remission of symptoms within a month after release from the hospital, thus they were excluded from the study. Non- significant differences were found in the demographic characteristics of patients that were enrolled and those excluded from the study.

The trial intervention consisted of a series of CBT sessions that helped patients identify and manage the challenges of living with a chronic condition [10]. The intervention extended for an 8-week period. Each 30 minute-session was conducted by doctoral-level clinicians (a psychiatrist, or clinical psychologist). During the first session, patient and counselor reviewed 8 fears commonly experienced by those living with chronic medical conditions: loss of control, loss of self-image, dependency, stigma, abandonment, anger, isolation, and fear of death [10]. In sessions 2 to 6, they identified strategies to address possible barriers to achieve patient's goals [10]. Patients were expected to complete 6 sessions but allowed to participate in as few as 4 if the therapist and patient agreed that all 8 issues set forth during treatment were reviewed, and that treatment goals were reached. At weekly meetings the counselors reviewed cases and notes with the research team to monitor fidelity to the intervention. Control patients received a booklet on coping with cardiac illness typical of those given at hospital discharge and were instructed to contact their primary care physician if they experienced any warning signs of depression [10]. Baseline survey assessments (within 30 days of hospital discharge) included the Primary Care Evaluation of Mental Disorders (PRIME-MD), the Work and Social Adjustment Scale (WSAS) and the HADS, the primary outcome measure [10]. The study protocol was reviewed and approved by the institutional review board of the participating hospital.

Data Collection Protocols

Data were collected at the time of baseline enrollment for the HADS using interactive voice recognition (IVR). Patients completed the HADS at two, three, and six month follow-up visits. An aggressive follow-up system was used to enhance survey response rates, which consisted of reminder postcards, telephone call reminders, and re-mailing of questionnaires. Data reported for the present study were collected at baseline and the two-month follow-up visit. Additional analysis of data from the four- and six-month follow-ups did not differ substantively from those at the two-month follow-up.

Assessment Instrument

The HADS contains seven questions to assess depression and seven to assess anxiety symptoms. Each scale is scored from 0 to 21; scores between four and seven represent subclinical symptoms of depression whereas scores of eight or higher represent a clinically significant level of symptoms of depression. The same criteria and scores are used for diagnosing significant symptoms of anxiety. One important advantage of using the HADS is that this scale focuses on cognitive rather than somatic constructs which minimizes the likelihood that somatic symptoms of ACS will be attributed to depression.

Data Analysis

Descriptive analyses of patient baseline characteristics at the time of trial entry were performed; t-tests and chi-square tests, as appropriate, were used to examine possible differences in baseline continuous and categorical variables between patients randomly assigned to the intervention and control groups.

LCA and LTA were used to identify subgroups of patients with similar patterns of depression and anxiety symptoms and to describe changes over time in subgroup membership. LCA identifies a set of mutually exclusive and exhaustive latent classes (i.e.,

subgroups) characterized by similar patterns of responses to the HADS items [12], [13]. LTA is a longitudinal extension of LCA that additionally models change over time in latent class membership [12], [13]. LCA and LTA are measurement models that separate measurement error from other aspects of the model. LCA estimates two sets of parameters. Item-response probabilities estimate the probabilities of responding positively and negatively to the HADS items given class membership. These probabilities are used to interpret and name the classes. Latent class membership probabilities estimate the distribution of the classes. LTA additional estimates transition probabilities, which estimate the probability of latent class membership at time t+*1* conditional on latent class membership at time t. These probabilities are used to describe change over time in class membership. LTA with a grouping variable [14] was used to examine the effects of treatment group, sex and age.

The 14 items of the HADS were used as indicators of depression and anxiety symptoms and were recoded such that 1 represented never or rarely ever experiencing the symptom and 2 represented experiencing the symptom sometimes or most of the time. First, models with different numbers of latent classes were fit and compared using LCA to select one that optimally balanced fit and parsimony in its identification and characterization of depression and anxiety symptoms. Statistical indices of goodness-of-fit used to select the optimal model included: the Akaike information criterion (AIC), Bayesian information criterion (BIC) and G2 fit statistic. Second, this optimal model was extended longitudinally using LTA to examine change in symptom profiles from baseline to the two-month follow-up visit. Third, grouping variables for treatment group, sex and age were added to the LTA to examine their effects on symptom profiles at baseline and change over time. To ensure that the maximum likelihood solution was identified for all LCA and LTA models, 100 sets of random starting values were used to examine potential solutions and solution stability.

Results

Details about the study cohort selection are presented in Fig. 1. The control and intervention groups were well-balanced with respect to a variety of baseline patient characteristics; both groups were predominantly comprised of white, older males. Average depression and anxiety scores were slightly higher for the intervention group at baseline but the differences were not statistically significant.

LCA: Identification and Description of the Classes

LCA was used to identify the most common anxiety and depression symptom profiles in patients after an ACS. Models with two and three latent classes were fit and compared at baseline; selection of the optimal model considered solution stability, goodness-of-fit and parsimony using various statistical fit indices. Based on the fit indices and stability of the models, a 2-class solution was selected. Although the AIC was somewhat lower in the three-class model, it was less stable than the two-class model. In addition, the BIC was higher for the 3-class model than the 2-class model.

Table 3 presents the item-response probabilities, conditional on class membership, for the 14 items assessed by the HADS. In the selected 2-class solution, Class I (76% of patients at baseline) was termed “depression and some anxiety symptoms”. This class was characterized by a pattern of item-response probabilities that indicated high probabilities of endorsing symptoms of depression and a few symptoms of anxiety for class members. Class II (24% of patients at baseline) was termed “anxiety and some depression symptoms”. This class was characterized by a pattern of item-response probabilities that indicated high probabilities of endorsing almost all symptoms of anxiety and a few milder symptoms of depression. Class I had higher probabilities of experiencing negative anticipation, panic,

lack of enjoyment, and general symptoms of anhedonia. Class II, on the other hand, had higher probabilities of experiencing worrying thoughts but class members could still sit and relax, and they did not refer any symptoms related to anhedonia. Due to the interpretation of the classes, Class II is considered the less severe class.

LCA was also used to examine the structure of the classes at the time of the two-month follow-up contact (the analysis was also performed for month three and six of follow up with identical results). The class structure appeared to be similar, but the distribution of the classes was different, as patients changed class membership over time. Patient change over time is discussed below in the context of the LTA model.

LTA: Identification and Description of the Classes

LTA was used to examine change over time from baseline to follow-up. Two- and 3-class models were fit and compared to confirm that the two classes identified with LCA at baseline were adequate. Model comparison and confirmation was based on the log-likelihood. The G2 fit statistic was not computed for these models because the number of possible response patterns was very large (i.e., 14 items measured at two times=2ˆ28 possible response patterns). The 2-class solution with a log-likelihood of -1032.01 was identified 88% of the time. Estimation of the three-class model was less stable, and the solution with a log-likelihood of -999.74 was identified only 24 % of the time. The instability of the three-class solution, combined with the results of the LCA discussed above, led to the selection of the 2-class solution as the best at balancing model fit and parsimony in its description of the data.

Class I (55% of patients at baseline and 64% of patients at follow-up) was characterized by a similar pattern of item-response probabilities to the one from the LCA. It was again labeled “depression and some anxiety symptoms”. Class II (45% of patients at baseline and 36% of patients at follow-up) was also characterized by a similar pattern of item-response probabilities to the one from the LCA. It was again labeled “anxiety and some depression symptoms”. It should be noted that differences between the LCA and LTA results may be due to a variety of reasons, including different amounts of power in the two models and high standard errors of the parameter estimates with the small sample size of the current study.

LTA: Transitions Between Latent Classes

To examine change over time in class membership, LTA was used to estimate the probabilities of transitioning between classes. About 86% of patients with depression and some anxiety symptoms at baseline continued to have similar symptoms at the two-month follow-up contact. Among patients with anxiety and some depression symptoms at baseline, 41% reported a worsening of symptoms by transitioning to the depression and some anxiety symptoms class at the two-month follow-up contact.

LTA: Examining Treatment-Related Effects

Treatment group was included in the LTA as a grouping variable in follow-up analyses to determine the effects of treatment on latent class membership. Patients who received the intervention showed some improvement in their symptom profile, as approximately 26% of treated patients transitioned to the anxiety and some depression symptoms class. In comparison, less than 10% of patients in the control group made the transition to the anxiety some depression symptoms class. In addition, 72% of patients in the treatment group remained in the anxiety and some depression symptoms class over time, compared to 51% of patients in the control group.

LTA: Examining the Effects of Sex and Age

The effects of sex and age on patient symptom profiles of depression and anxiety after an ACS were also examined in follow-up analyses. The effect of sex was investigated by including sex in the LTA as a grouping variable to compare class membership probabilities and transitions for women and men. The gender differences in the probabilities of class membership at baseline were non-significant (p-value=0.77); the intervention was not hypothesized to work differently for men and women.

Similarly, the effect of age was investigated by including age in the LTA as a grouping variable. Patients were split into two groups, younger (< 60 years old) and older (60 years and older). Table 5 reports the latent class membership probabilities by age group. Baseline differences in the probabilities of latent class membership for younger versus older patients were borderline significant (p-value=0.07).

Of the younger patients who reported depression and some anxiety symptoms at baseline, 59% remained in the same class at the time of follow-up. In comparison, about 70% of older patients remained in the depression and some anxiety symptoms class. In addition, 31% of younger patients with anxiety and some depression symptoms transitioned to the depression and some anxiety symptoms class whereas almost 60% of older patients made that transition.

Discussion

Identifying Prevalent Symptoms of Depression and Anxiety

The results of the present study suggest that two clinically relevant classes of symptoms of depression and anxiety in patients with an ACS can be identified. Class I, labeled “depression and some anxiety symptoms” had a higher prevalence at baseline and month two of follow-up (55% and 64% respectively) than Class II, labeled “anxiety and some depression symptoms”. Moreover, more than 40% of patients who reported “anxiety and some depression symptoms” at baseline transitioned to the “depression and some anxiety symptoms” class at the time of the two-month follow-up visit. These results emphasize the importance of the assessment of depression and anxiety in patients after an ACS not only at the time of their acute event but over a more extended follow-up period.

Regarding the particular items assessed by the HADS, it is important to highlight the presence of anhedonia as a key factor differentiating the two symptom profile classes. Patients that endorsed the “depression and some anxiety symptoms” class gave a positive response to all questions that assessed anhedonia in the HADS, whereas patients that endorsed the “anxiety and some depression symptoms” class did not report any major signs of anhedonia.

Other researchers have stressed the importance of anhedonia in patients after an ACS as a predictor of cardiac mortality [15]. The results of one study conducted in 40 hospitals in Ireland investigated the use of the HADS and the Beck depression scale in assessing one-year mortality risk in a national sample of patients after an ACS. Depression, as measured by the HADS, but not by the Beck scale, was associated with an increased risk of dying within one-year [15]. The HADS concentrates on anhedonia, whereas the Beck scale focuses on psychiatric criteria for a major depressive disorder. Another group of researchers investigate the effects of anhedonia on prognosis at 3-year follow-up in patients hospitalized for ACS. 291 patients completed the Chapman Physical Anhedonia Scale (PAS) and the HADS depression subscale at baseline (1-4 days after their admission) [16]. Patients were followed during 3 years for adverse clinical events divided into severe cardiac events (mortality or myocardial infarction and clinical events (mortality, MI, recurrence of ACS,

hospital readmission, and onset or deterioration of heart failure). Researchers reported that dimensional anhedonia and depression were associated with poor prognosis, but anhedonia was the only predictor of severe cardiac events and clinical events after adjusting for demographic and clinical variables [16]. These findings underline the importance on detecting specific symptoms that are key items, such as anhedonia, in the diagnosis of depression and anxiety in patients after an ACS. Early diagnosis and subsequent treatment of these symptoms may improve morbidity and mortality in this group of high-risk patients [15], [16].

Effects of Treatment on Determining Symptom Profiles of Depression and Anxiety

The inclusion of treatment as a grouping variable supplied important information for the determination of the effect of treatment on patients' symptom profiles. Patients receiving the intervention showed improvement in their symptom profiles of depression and anxiety at month two of follow-up; a higher percentage of patients in the treatment group transitioned to the anxiety and some depression symptoms class as compared to the control group. These findings demonstrate the effect of the intervention not only in the improvement of symptoms of depression and anxiety after an ACS but also in the prevention of these symptoms later on in the follow-up period. Considering the important association of depression and anxiety and higher morbidity and mortality in patients after an ACS, CBT should be considered as an important treatment option to improve clinical management in patients after an ACS.

Effects of Age and Sex on Determining Symptom Profiles of Depression and Anxiety

The inclusion of these demographic characteristics as grouping variables provided valuable information for the identification of the two classes of symptom profiles. An important association was observed between the "depression and some anxiety symptoms" class and patients' age. Older patients were more likely to report more severe symptoms of depression and anxiety than younger patients both at baseline and over the two-month follow-up. Other researchers have stressed the importance of assessing depression in older patients after an ACS [17]. In a study of more than 100 patients 65 years and older who were released from the hospital a month after an ACS, the Beck and the Standard Clinical Interview for the Diagnostic Statistical Manual of Mental Disorders, Third Edition, Revised (SCID) were completed at the time of baseline enrollment [17]. Older patients with depression were more likely to die during the first four months than older patients without depression [17]. This finding has important implications in terms of allocation of resources for the assessment and treatment of depression and anxiety in ACS patients. Older patients with symptoms of depression and anxiety after an ACS may benefit from more specified diagnostic and treatment programs. Further research should examine the association of depression and anxiety after an ACS and patient's age to determine whether these psychiatric disorders affect subsequent morbidity and mortality in older as compared to younger patients.

There were no significant differences between the symptoms of depression and anxiety in men and women. A note of caution should be taken here in the interpretation of these results because the sample was fairly small. Future studies would benefit from an increase in the number and variety of sites, and a larger and more representative sample.

The overarching goal of this study was to determine symptom profiles of depression and anxiety in ACS patients. Identifying these profiles will not only better inform clinical management by improving diagnostic practices but will help to design tailored interventions aimed to improve quality of life and other clinical outcomes in these high risk patients. A tailored intervention will offer a more specific approach for patients with certain symptoms/characteristics that can predict a better or more rapid response to treatment. As an example if

younger patients have a better response to CBT in this study, then it will necessary to find a different tailored intervention aimed to the older patients group.

Even though other researchers have reported important findings on detecting predictors of response to an intervention to improve mortality, morbidity and quality of life in ACS patients, there are still some inconsistencies in those findings that need further research. As an example, investigators from the Montreal Heart Attack Readjustment Trial (M-HART) reported that patients' coping style is an important predictor of response to psychosocial treatments and it should be considered when tailoring interventions [18]. Findings of this study showed a significant long-term survival benefit of treatment in highly anxious men, for whom reductions in somatic symptoms of depression mediated program impact [18].

Other investigators have also emphasized the importance of including gender when designing and implementing an intervention. A recent meta-analysis review pointed out the effectiveness of different psychological treatments for cardiac patients. Researchers reviewed more than 20 randomized controlled trials in cardiac patients with psychological distress [19]. Investigators reported that mortality benefits only applied to men. They reported that trials initiating treatment at least 2 months after a cardiac event showed greater mortality benefits than those initiating treatment right after the event. In summary, these investigators highlight not only the importance of gender when designing an intervention but also the time of the initiation of treatment, both as predictors of reduction of mortality in cardiac patients [19].

As in the previous study, researchers from the ENRICHD also emphasize gender as predictor of response to CBT. These investigators reported that there was a trend in the direction of treatment efficacy for white men for total mortality or recurrent nonfatal MI and cardiac mortality or recurrent nonfatal MI [20]. Finally, the EXhaustion Intervention Trial investigated the effect of a behavioral intervention program on exhaustion, health-related quality of life (HRQL), depression, anxiety, hostility, and anginal complaints in angioplasty patients who felt exhausted after percutaneous coronary intervention (PCI) [21]. Researchers found that the intervention had a significant beneficial effect on all psychological factors except hostility and on the presence of angina complaints. Gender, again, modified the effect of the intervention on exhaustion and on anxiety. But contrarily with the findings of the previous researchers, the strongest effect being reported in this study was found in women [21].

In summary, based on our findings we recommend a stepped care model or tailored intervention that can improve current practice in the treatment of anxiety and depression in ACS patients. Tailored strategies will prevent unnecessary treatment for most of the patients who will recover spontaneously or with minimal interventions. Specific symptoms should be monitored carefully and patients who fail to respond or exhibit insufficient signs of recovery will be easily detected and given appropriate treatment.

Another point that this study emphasizes is the utility of LCA and LTA in elucidating symptom profiles of depression and anxiety in patients after an ACS. The results demonstrate that depression and anxiety after an ACS tend to occur together, thus treatment of this group of high-risk patients needs to take into account the interplay of these two disorders [15]. The findings also stress the importance of assessment and follow-up of patients after an ACS. An important challenge in clinical practice is to improve the quality of life of patients with a chronic illness such as an ACS. In as much, developing strategies for rapidly detecting and tailored managing those at increased risk is an essential step in overcoming this challenge.

Study Strengths and Limitations

This study has several limitations that must be kept in mind in interpreting the results. Patients with very severe symptoms of depression/anxiety, patients who had received mental health care in the prior three months and those who had a diagnosis of substance abuse during the past year were excluded from this study. Thus, the findings may not apply to these high-risk individuals.

Another limitation of this study is the short duration of follow-up and the small sample size. On the other hand, LCA and LTA have several strengths. They combine the cross-sectional measurement and the longitudinal description of change in categories of the latent variable over time, and have considerable flexibility in describing progression and stability, providing a detailed examination of change over time that is difficult to obtain in continuous data analyses [13].

Conclusions

The results of the current study stress the importance of the assessment of depression and anxiety and follow-up of patients after an ACS. Identifying symptom profiles of depression and anxiety is an important step towards developing more tailored interventions to improve patient's prognosis and quality of life.

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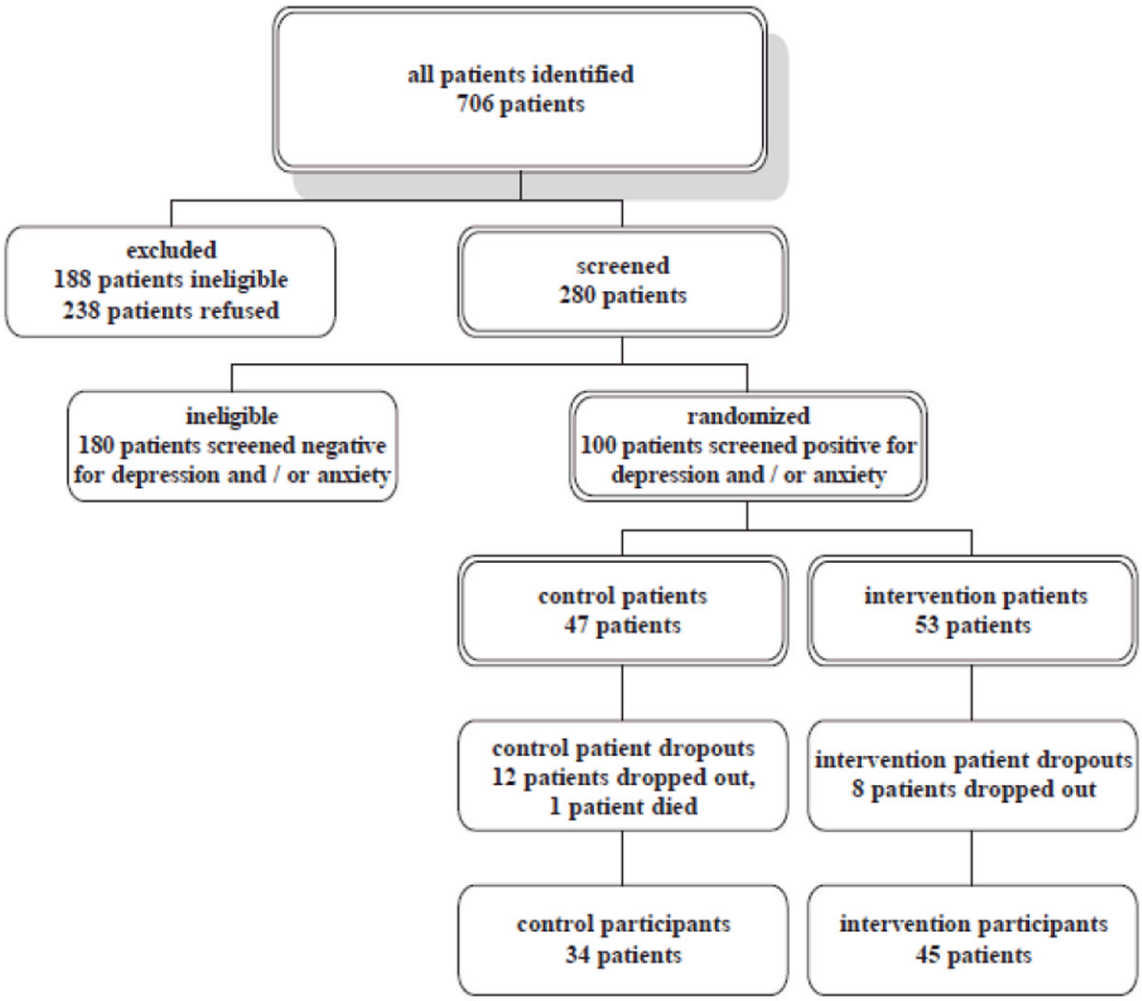

Figure 1.
Study Source Population: Screening Process

Table 1

Characteristics of study participants by treatment group assignment

VARIABLE	TREATMENT (N=45)	CONTROL (N=34)
Age (mean years)	59.9	60.7
Female (%)	31.1	35.3
White (%)	88.9	88.1
Major Depression History (%)	37.8	29.4
HADS Depression Scores (mean)	8.5	6.5
HADS Anxiety Scores (mean)	8.1	7.1

Table 2

Goodness-of-fit indices for the 2- and 3-class models

	G^2	AIC	BIC	Frequency*
2-class model	480.11	538.11	607.19	100
3-class model	435.57	523.57	628.38	32

*Frequency is the percentage of times the solution was selected out of 100 random sets of stating values.

Table 3

Item-response probabilities for the HADS

Anxiety	**Class I**	**Class II**
I feel restless as I have to be on the move	0.27	0.55
I feel tense or ‘wound up’	0.09	0.44
I get a sort of frightened feeling as if something awful is about to happen	0.76	0.38
Worrying thoughts go through my mind	0.21	0.67
I can sit at ease and feel relaxed	0.15	0.77
I get sudden feelings of panic	0.97	0.67
I get a sort of frightened feeling like “butterflies” in the stomach	0.95	0.69
Depression		
I look forward with enjoyment to things	0.14	0.76
I have lost interest in my appearance	0.96	0.85
I enjoy the things I used to enjoy	0.06	0.51
I can laugh and see the funny side of things	0.03	0.3
I feel cheerful	0.09	0.53
I can enjoy a good book or radio or TV program	0.02	0.3
I feel as if I am slowed down	0.45	0.75

Table 4

Membership probabilities by sex at baseline and 2-month follow-up

	Latent Class I		Latent Class II	
	Male	**Female**	**Male**	**Female**
Baseline	0.578	0.528	0.422	0.471
Follow-up	0.643	0.649	0.356	0.350

Table 5

Membership probabilities by age at baseline and 2-month follow-up

	Latent Class I		Latent Class II	
	Younger	**Older**	**Younger**	**Older**
Baseline	0.404	0.742	0.596	0.278
Follow-up	0.588	0.700	0.412	0.299