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Depression and anxiety symptom trajectories in coronary heart disease: Associations with measures of disability and impact on 3-year health care costs☆

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ABSTRACT

Background: As mortality from coronary heart disease (CHD) falls, years lived with disability increase. Depression and anxiety are known indicators of poor outcomes in CHD, but most research has measured distress symptoms at one time point, often following acute events. Here we consider the long-term trajectories of these symptoms in established CHD, and examine their association to distinct measures of disability and impact on costs.

Methods and results: 803 patients with diagnosis of CHD were recruited from primary care, and completed detailed assessments every 6 months for 3 years. Latent class growth analysis (LCGA) was used to identify 5 distinct symptom trajectories based on the Hospital Anxiety and Depression Questionnaire (HADS): 'stable low', 'chronic high', 'improving', 'worsening', and 'fluctuating'. The 'chronic high' group had highest association with reporting of chest pain (RRR 5.8, CI 2.9 to 11.7), smoking (2.9, 1.1 to 6.3), and poorer physical (0.88, 0.83–0.93) and mental (0.78, 0.73–0.84) quality of life. The 'chronic high' and 'worsening' trajectories had significantly higher health-care costs over the 'stable low' trajectory (107.2% and 95.5% increase, respectively). In addition, our trajectories were the only significant variable associated with increased health-care costs across the 3 years.

Conclusions: Symptoms of depression and anxiety are highly prevalent in stable CHD patients, and their long-term trajectories are the single biggest driver of health care costs. Managing morbidity in these patients, in which depression and anxiety play a key role in, should become the primary focus of policy makers and future clinical trials.

1. Introduction

Depression and anxiety are highly prevalent in Coronary Heart Disease (CHD) [1][2], and are associated with poorer quality of life [3,4], poorer disease outcome [5], and higher all-cause mortality [6,7]. Most studies linking depression and anxiety to poorer outcome in patients with CHD use a single, baseline measure taken usually following an acute event – either a myocardial infarction (MI) [8] or interventions such as bypass grafts [9]. Depression and anxiety are chronic, fluctuating conditions, and single measures do not provide sufficient information on the course or associated burden of these conditions over time [10]. Further, associations between depression, anxiety, and cardiovascular outcomes are likely to be reduced due to regression dilution bias [11]. Some studies have measured multiple time points of depression [12,13] or anxiety [14], finding persistent symptoms to be more predictive of adverse events and mortality, but these have also been done following an acute event, where the symptoms of depression and anxiety are likely to be exacerbated and directly related to the underlying event. This has failed to acknowledge the chronicity of these symptoms at the primary care level, where these patients mostly reside. The case for interventions in patients with this mental-physical comorbidity will largely be determined by their likely impact on health-care costs. There is limited information on the costs associated with depression or anxiety comorbid with CHD, with one study suggesting depression increases cardiovascular costs over five years from 15 to 50% [15]. In this study we use advanced longitudinal data analyses, which have previously been used to describe trajectories of depression and anxiety symptoms over time in general population samples [16]

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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[17] and primary care settings [18], to: (i) identify, measure, and group the trajectories of symptoms of depression and anxiety experienced by patients with CHD; (ii) measure which demographic, cardiac, social, and psychological risk factors are associated with these trajectories, in particular to test the extent to which more severe and prolonged symptoms of anxiety and depression are associated with underlying CHD disease severity, and (iii) measure the differences in health care costs between the trajectory groups.

2. Methods

We analysed a cohort of 803 patients with CHD recruited from 16 general practice (GP) surgeries in South East London, using data derived from the UPBEAT-UK project [19]. The aims of the original project were to understand further the relationship between depression and anxiety in a representative prevalent sample of people with CHD recruited from primary care. We were required to follow an opt-in procedure, and after initial contact by their GPs, 90% of those who responded agreed to participate in the study after meeting with our research team. These patients were followed-up for three years, undergoing assessments every six months. A baseline assessment which included measures of common mental disorders using the Clinical Interview Schedule - Revised (CIS-R), depression and anxiety using the Hospital Anxiety and Depression scale (HADS), as well as the Patient Health Questionnaire (PHQ-9), chest pain (Rose Angina Questionnaire), quality of life using the 12-item Short Form Survey (SF-12), social problems using the Social Problem Questionnaire (SPQ), and costs using the Client Service Receipt Inventory (CSRI), was applied during a face to face interview. Subsequently, bi-annual telephone interviews were conducted from six to 36 months after baseline assessment, which included all the above questionnaires with the exception of the CIS-R. At the end of the study, each patient had data from up to seven unique time points comprising a three-year follow-up period from 2008 to 2011.

Using these data, we ran a latent class growth analysis (LCGA) [20] using longitudinal HADS scores as the main outcome variable across time. We have previously found the HADS to have a good sensitivity and specificity to detect anxiety and depression in CHD compared with the criterion of the CIS-R (using a cut-off of 12) [4]. Furthermore, the HADS has been shown to be a marker of general distress combining depression and anxiety [21]. Thus, we modelled the trajectories of the symptoms of depression and anxiety according to the total HADS score, from baseline to 36 months.

LCGA is a particular type of latent class analysis which uses growth mixture modelling techniques to identify individual growth trajectories in a sample across unobserved subpopulations (the categorical latent variables). These growth trajectories have different growth parameters (i.e. intercept and slope), and LCGA identifies those which have more in common with each other and classifies them into groups. Each group, or latent class, has a particular growth trajectory, and thus all individual growth trajectories within a particular class are homogeneous [20]. The LCGA model deals with missing data by using the maximum likelihood algorithm, which uses known data to estimate unknown parameters, by finding the values that maximize the probability of obtaining the observed data parameters.

Deciding the optimal number of latent classes for the LCGA model is informed by established fit indices. As there is not an established guideline for determining which fit indices are optimal, it is best to use several, in addition to taking into account one's own theoretical framework, interpretability, clinical translation, and other factors such as having $<$ 1% of the total sample in a single class [20]. We first ran a single-class growth model with random intercept and random slope for the subjects, to test whether a linear, quadratic, or cubic model would be more appropriate to capture the overall observed pattern of the trajectory. The coefficient of the cubic term was not significant, and the quadratic curve gave a better fit than the linear curve, therefore we fitted a quadratic LCGA model. We then constructed latent class models with increasing number of classes (from three up to seven), and assessed goodness-of-fit using Bayesian information criteria (BIC), the Lo-Mendell-Rubin test (LMR-LRT), and the Bootstrap likelihood ratio test (BLRT) on each model to determine the optimal number of classes, maintaining the requirement that they translate to trajectory classes with clear clinical interpretations.

Once the optimal number of classes was determined, the probabilities of each individual to belong to each of the latent classes were calculated using maximum posterior probabilities, and in this way each individual was assigned to one of the identified groups. We then used the latent classes as a categorical outcome variable to test for association with a variety of risk factors, using multinomial logistic regression analysis. First, we ran the model with our demographic variables, and then we controlled for these to test for the association with measures of cardiac risk factors, comorbidities, social problems, quality of life, and psychological factors.

We also compiled the GP medical notes for each individual patient, comprising the entire 3-year follow-up period. For this study, we identified any mention of active management of depression and/or anxiety, either through primary care services, or by referral to a specialist mental health service. This was done with the aim of identifying how many patients in each class were recognised as having symptoms of depression and/or anxiety throughout our study period.

Finally, we used the cost analysis gathered throughout the cohort study by the CSRI to identify which class had the lowest and highest costs across different service domains, which include primary, secondary, and informal (day-to-day career) costs. The primary care costs (comprising GP, practice nurse, and community nurse contacts) are added to the secondary care costs (comprising inpatient and outpatient visits) to make up the total healthcare costs. When adding the informal costs (consisting in assistance of daily activities by careers specifically because of their health problems), the result is the total societal cost. We then ran a regression analysis to determine the difference in mean costs between the classes, and whether these differences were significant after controlling for demographic, risk factor, and disease severity variables. These numbers are reported in Pounds Sterling (£), and taken from the Unit Cost of Health and Social Care 2012 and NHS Reference Costs 2011–12.

The LCGA models were estimated using Mplus 8, whilst the regression analyses were performed in Stata 14.

3. Results

The characteristics of the overall sample have been described elsewhere [22]. In summary, the population was mostly male (69.9%), white (87.3%), and retired (77.7%), with a mean age of 70.6 years. At baseline interview, 149 of 803 (18.6%) met criteria for a depressive or anxiety disorder according to the CIS-R. These were divided as follows: 54 had a mild, moderate or severe depressive episode, 29 had anxiety or panic disorder, and 66 had mixed anxiety and depression [19] %. Retention during 3-year follow-up was high: the average follow-up time was 2.64 years and the median was 2.94 years. 141 (17.9%) had missing data on one or more time points due to a decline to be interviewed or loss to follow-up. 44 died from cardiovascular causes during follow-up and 28 from other causes. Similar to previous work in this cohort which looked at variables related to missingness at each follow-up point [4], the only significant variables related to missing data were increasing age (after 2 years) and non-white ethnicity (after one year).

3.1. Latent class growth analysis

The five-class model yielded the optimal combination of statistical goodness-of-fit and clinical interpretation, as it had the highest entropy score (0.854), a significant BLRT score ($<$ 0.001), a low LMR-LRT score (0.36), and a low BIC (27,654.9). The 4-class solution had a higher BIC