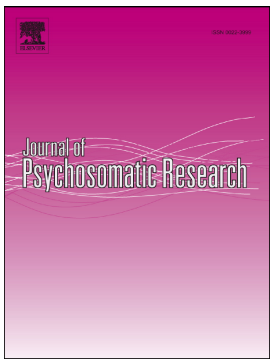

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Depression and anxiety symptom trajectories in coronary heart disease: Associations with measures of disability and impact on 3-year health care costs

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Keywords: coronary heart disease, depression, anxiety, symptom trajectories, latent class growth analysis, costs

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.

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 healthcare 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 15-50%[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] [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.

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 2008-2011.

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 no less than 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 carer) 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 carers 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.

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).

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 (.854), a significant BLRT score (<0.001), a low LMR-LRT score (0.36), and a low BIC (27654.9). The 4-class solution had a higher BIC and lower entropy, and the clinical interpretation was not as robust. The 6 and 7 class solution model fit indices had the lowest entropy scores, in addition to having a less clear clinical interpretation, therefore overall were deemed weaker than the 5-class solution (Table 1). Figure 1 provides a graphical representation of the five different classes, where the individual patient trajectories, as well as the mean trajectory for each class, are shown, alongside the intercept, slope, and quadratic values. The five classes were as follows: 'stable low' symptoms (n=558), 'chronic high' symptoms (n=55), high then 'improving' symptoms (n=15), low then 'worsening' symptoms' (n=64), and 'fluctuating' symptomatology (n=111).

Table 2 summarises the characteristics of each class. Class 1, 'Stable low', comprised 69.5% of the sample, and had a higher male, white, and older percentage of participants than the other classes. Patient in this class had consistently low scores of depression and anxiety (mean range of 4.4-5.4 HADS total score). Class 2, 'Chronic high' had consistently high symptoms of depression and anxiety, with a mean HADS score ranging from 24.0 at baseline to 22.3 at 36 months. This class had the highest percentage of current chest pain, low physical and mental quality of life, and proportion (89.1%) having a psychiatric disorder at baseline. Class 3, 'Improving' was a small group of 15 individuals with a marked decrease in their symptoms over the three-year follow-up. At baseline, the mean HADS score (24.3) was very similar to the 'chronic high' class, and yet the patients on this class had a marked decrease in their symptoms, reaching a mean of 8.2 at 36 months. This group had the highest percentage of recent life events and social problems at baseline. Members of this class were also relatively young, better educated, and appeared to have less severe disease (e.g. fewer comorbidities and cardiac interventions). Class 4, 'Worsening' showed deteriorating HADS scores over the follow up period. This class had the highest percentage of non-white ethnicity. Finally, Class 5, 'Fluctuating' consisted of individuals who hovered around the cut-off point through the follow-up period. This class had the lowest proportion of males, the highest percentage of participants who were divorced or widowed and was the least educated group.

Multinomial logistic regression analysis

In the logistic regression analysis, the comparison group was the 'stable low' class. Therefore, we measured the effect each variable had on the relative risk (RR) of belonging to a class as opposed to the 'stable low' class.

Demographics

Table 3a describes the (mutually adjusted) association between class membership and socio-demographic variables. Compared with the 'stable low' class, the symptomatic classes were younger (with the largest effect amongst the 'chronic high' class), and had higher proportions of women, (with the largest effect in the 'fluctuating' class). They were also associated with non-white ethnicity (particularly the 'worsening' class), and less years of education completed (significant among the 'fluctuating' and 'worsening' classes). Patients in the 'fluctuating' and 'chronic high' classes were more likely to be separated/widowed, an effect not seen in the other symptomatic classes.

Cardiac risk factors and comorbidities

Controlling for all demographic variables, associations with cardiac risk factors and comorbidities are shown in Table 3b. Compared with the 'stable low' class, the symptomatic classes were associated with being a current smoker, and having chest pain (with particularly strong associations for the 'chronic high' class). However, other measures of disease severity, notably a history of myocardial infarction or heart failure, were not associated with class membership. The pattern for comorbidity was

inconclusive. Compared with the stable low group, there were no statistically significant associations with comorbid disease, although some of the results showed relatively large effect sizes, but with wide confidence intervals (e.g. the association between the 'improving' class and diabetes and cancer). However, there was no evidence that the symptomatic classes experienced more multi-morbidity than the 'stable low' class.

Disability and psychological factors

Table 3c describes the association of social problems, quality of life, and mental health variables. The multivariable model we ran for these variables also was controlled for demographics, and additionally controlled for smoking and chest pain, since these were significantly associated to our latent classes as described above. Social problems were associated with the 'chronic high' class and with the 'worsening' class, however there was no difference between classes in terms of recent adverse life events. The physical component of quality of life was lower in all classes except for the 'improving' class, with the strongest effect on the 'chronic high' class. Finally, there was no association between reported life-time history of depressive episodes and class membership, however, unsurprisingly; there were very strong associations between baseline psychiatric diagnosis and membership in any of the symptomatic classes. Similarly, there was a strong association with mental components of quality of life.

Examination of medical notes for depression and anxiety

After examination of GP medical notes for each patient, we identified the number of patients per class which had either a referral to a mental health specialist, or active

management of depression or anxiety by their GP. The results were as follows: 77/558 patients in the 'stable low' class were identified in this manner, amounting to 13.8% of the class total. The 'chronic high' class had 30/55 (54.5% of the total), the 'improving' class had 4/15 (26.7% of the total), the 'worsening class' had 31/64 (48.4% of the total), and the 'fluctuating' class had 40/111 (36.0% of the total).

Health-care costs

Table 4 describes the differences in mean costs across the three-year follow-up for each class. The highest costs across all domains were in the 'chronic high' class (mean of £9,613 total societal costs), and in the 'worsening' class (mean of £9,073 total societal costs). This contrasted sharply to the classes with the lowest total societal costs: the 'stable low' class had a mean of £4,640 and the 'improving' class had a mean of £3,791. Thus, the average cost of a patient on the 'chronic high' class was approximately double that of a patient on the 'stable low' class. A subgroup analysis of costs, using the data on mental health service use gathered from the GP notes, found that in the 'chronic high' class, the patients with referrals to psychiatry services or under management of depression by their GP had lower mean societal costs (£8,127) than those who did not (£11,396). The subgroups using mental health services in the other four classes had higher mean costs than those not using these services. Thus, patients with unidentified chronic depression/anxiety were the subgroup with highest health care costs overall.

We also calculated the median costs, to counter the skewed nature of cost data, and again the highest costs across all domains (primary, secondary, total healthcare and total societal costs) were in the 'chronic high' (median total societal cost £4,421) and

'worsening' (median total societal cost £4,148) classes. These costs are over 2 times higher than in the 'stable low' class (median total societal cost £2,097.6). Meanwhile, the costs for the 'fluctuating' (£2,411.1) and 'improving' (£2,200.6) classes were similar to the 'stable low' class.

The regression analysis (Table 4) showed significantly higher total societal costs across the three-year period for patients on the 'chronic high' class and 'worsening' class, as compared to the 'stable low' class. This held after adjusting for demographic, social, risk factor and disease severity variables. In the model, all variables aside from the latent classes mentioned above were non-significant predictors for costs.

Discussion

We described five trajectories of symptoms of depression and anxiety in CHD patients across a three-year period with 7 unique time points. These trajectories showed distinct patterns of psychiatric morbidity, and compared with the 'stable low' group had an association to specific demographic, lifestyle, disability, and chest pain risk factors. There were substantial differences in health-care costs between the trajectories across the follow-up period.

Thirty one percent of participants reported high depression and anxiety symptomatology either initially only (2%), increasingly (8%), continually (7%), or intermittently (14%). This highlights the prevalent, chronic, and unstable nature of affective symptoms in patients with CHD. Whilst many associations with being in the symptomatic classes were expected (smoking, poorer quality of life, greater social

problems), it is noteworthy that none of the more objective measures of disease severity, psychiatric history, cardiac risk factors other than smoking, or comorbidities played a significant role. However, reporting of chest pain was strongly associated with being in all the symptomatic groups, save the 'improving' class. This reflects a recent finding which identifies a strong association between depression and angina independent of cardiac severity [23]. Our data show that only a minority of individuals with symptoms of anxiety and depression received any specific interventions, which may be due to underreporting of symptoms by the patients themselves, and perhaps to subthreshold symptoms not meeting diagnostic criteria that encourages the GP to suggest treatment. At the same time, there were large differences in health-care costs between the symptomatic classes and the 'stable low' class, even after adjusting for chest pain and other variables, indicating that depression and anxiety symptoms are potentially modifiable determinants of costs. Our trajectories were indeed the only variable significantly associated with health-care costs across the three-year period.

Strengths and limitations

This is the first study to conduct longitudinal trajectory analysis of depression and anxiety symptoms in a representative primary care, CHD population. Previous studies that have done follow-ups of these symptoms in primary care have been limited to measuring two time points over a 3 month period [24, 25] . Similar growth models on CHD patients have been done posterior to a cardiac event, measuring symptoms up to 12 months after an MI or CABG [14] [26], and likely reflect more on the adjustment and reaction to the particular event. Growth models identifying trajectories of depression have also been used to find associations with future conditions such as dementia [27],

and a follow-up of the data used in our model could strengthen the association of late-life depression to vascular dementia [28], given the mean age of our study population. A limitation of our study is the lack of objective clinical measures of heart disease that could have been used to further strengthen the results and identify key associations and differences between the distinct trajectories. There were some missing data in measurements of HADS across time, however our model accounts for this. The small number of patients in the 'improving' class reduces the precision of results, reflected in the wide confidence intervals pertaining to that class. Finally, we have used the HADS as our primary measure given its use of both depression and anxiety symptoms, as we have made the case that they should both be considered in assessing mental distress amongst CHD patients. Our intention was not to determine the trajectory of standalone depression or anxiety as defined by the DSM or ICD, thus we did not use the PHQ-9 for this analysis, as it would have restricted the discussion on the long-term trajectory of symptoms of distress in CHD. In a previous study we found the HADS was a better predictor of costs and quality of life than the PHQ-9 in our study population [4], theorising this finding being due to the inclusion of anxiety symptoms which also play an important role in the chronicity of living with CHD.

Implications

Existing studies surrounding the long-term effect of depression and anxiety in CHD mostly use a cut-off score taken from a validated scale. This fails to take into account the dimensionality of these conditions and is assuming an increased risk of mortality just by scoring one or a few points more on a scale, in which some symptoms could well be overlapping with the very condition (CHD) they are being related to. Studies which do

include a 'subthreshold' trajectory, together with a 'persistent' trajectory [29], are limited by cut-off points also, and its unlikely patients never waver from these limits across each of the time points measured. The time periods used to define persistent depression/anxiety are often smaller to the ones largely understood to be necessary for clinical diagnosis (for example persistent anxiety across 3 months [30]), or have time periods too wide apart (e.g. 2 years) for accurate measurements of the effect mental disorders may have on a chronic condition or acute event as part of the condition [31]. Finally, as mentioned previously, most studies measure depression and anxiety in hospitalised patients, either after experiencing and acute cardiac event, or scheduled for an intervention. The consequent follow-up across studies is usually intended to obtain mortality outcome data. However, trends of long-term survival after MI and revascularisation are indeed improving [32], and since most of these patients do survive, there is comparatively little analysis into the consequences of chronic symptoms of depression and anxiety on CHD patients' everyday lives, or how much contribution these symptoms make on the costs which patients incur upon the health care system. Specifically, the question is what are these chronic symptoms actually telling us about patients' experiences of living with CHD, and how much do they really fluctuate over time?

This study sheds further light into the chronic and diverse nature of depression and anxiety symptomatology within a long-standing physical condition. It stresses the importance of long-term follow up of mood disorders in patients with CHD at the primary care level, and the limits in focusing on this comorbidity after an acute event in hospitalised patients. The findings underscore the fluctuation and ever-changing nature of these symptoms, and therefore studies which only report on a single measurement of

symptoms of depression and/or anxiety may be capturing transient states of mood instability, perhaps driven by a recent life event or sudden change in circumstances.

Furthermore, it is worth noting that these are patients belonging to a primary care register, with chronic health conditions that demand consistent visits to their GP to manage their CHD and relevant comorbidities. However, despite consistent reporting of high depression and anxiety symptomatology to our research team, only 55% of patients in the 'chronic high' class, and only 48% of patients in the 'worsening' class, had a mention of these symptoms in their medical notes. In addition, those patients in the 'chronic high' class not identified as having these symptoms by their GPs had the highest costs overall. This suggests the identification of patients with physical and mental comorbidity is still lacking, and failure to identify these patients signifies a burden on individual morbidity, and an added burden on health care systems by means of increased costs.

The optimal management of these patients remains unclear. A recent review on collaborative care for depression and CHD did not find a sustained treatment effect on adverse cardiac events and mortality [33], but did show benefit in addressing depression symptoms. Similar results have been found for diverse psychological treatments [34]. Our results suggest that the critical outcome for trials aimed at evaluating treatments for depression should be aimed at reducing healthcare costs associated with both depression and anxiety. These may arise from better disease management and improved symptom control, leading to reduced service utilisation. Our findings demonstrate the chronic and fluctuating course of symptoms of depression

and anxiety in CHD. Therefore, treatment and management of this comorbidity should be able to adapt in line with the chronic and fluctuating nature of symptoms, as well as allow for identification of subthreshold symptoms that merit closer follow-up even without meeting strictly defined criteria. This would in turn benefit the health care system as a whole, as we have shown depression and anxiety trajectories to be the biggest drivers of costs in long-term management of patients with this chronic physical condition.

Author's contributions

JP did the background literature, conducted the analysis, interpreted the findings, and wrote the first draft of the manuscript. MH supervised the study, assisted in the analysis and in the interpretation of the data, as well as revising the article. MK supervised the statistical models for the main analysis and assisted in the interpretation of the data. AT conceived and was the principal investigator for the original project. AM contributed to the interpretation of data and the discussion. All authors revised and approved the final manuscript.

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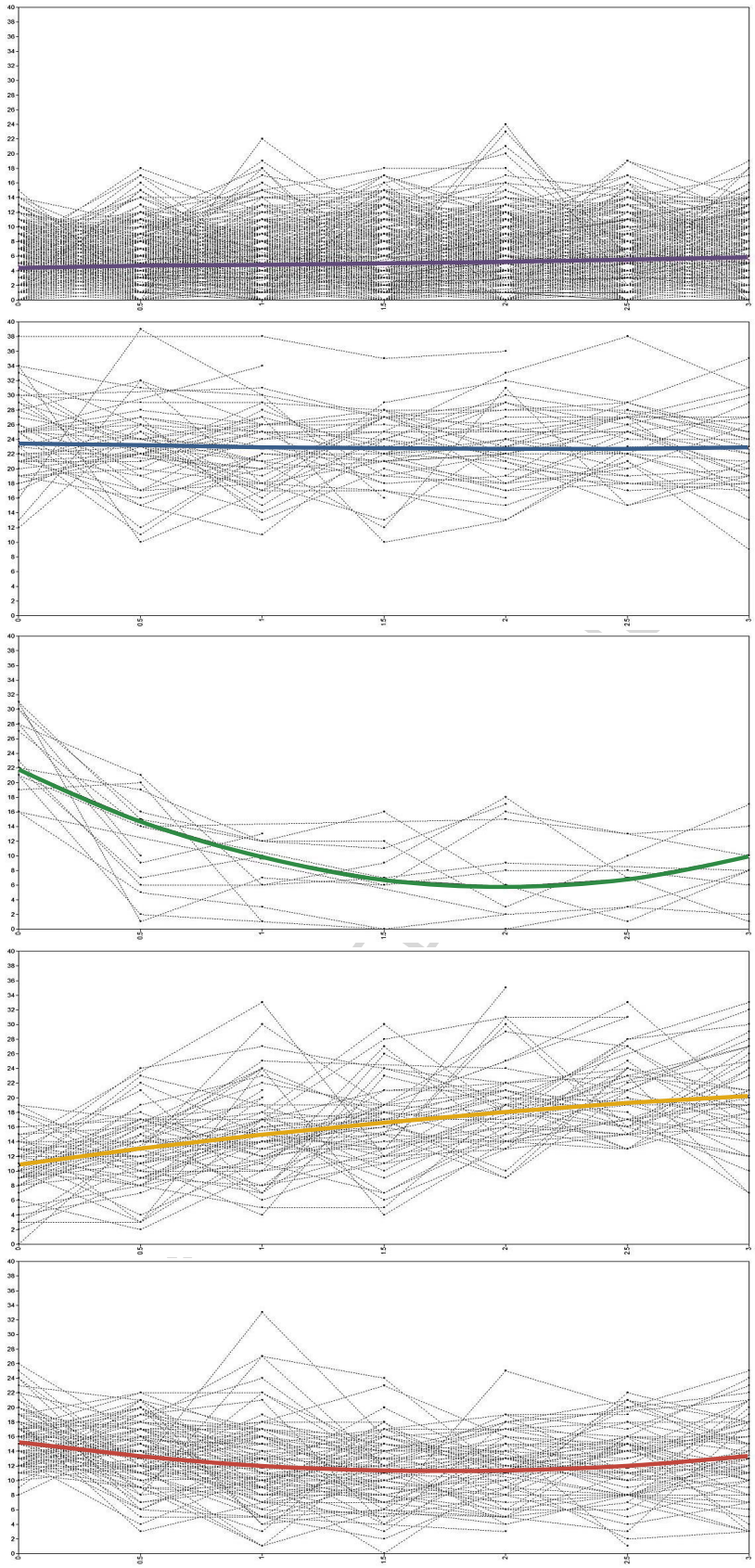
Figures and tables



Class 1: Stable low

N: 558
Intercept: 4.45
Slope: 0.28
Quadratic value: 0.04

Class 2: Chronic high

N: 55
Intercept: 23.52
Slope: -0.80
Quadratic value: 0.19

Class 3: Improving

N: 15
Intercept: 21.77
Slope: -16.05
Quadratic value: 4.03

Class 4: Worsening

N: 64
Intercept: 10.79
Slope: 4.63
Quadratic value: -0.51

Class 5: Fluctuating

N: 111
Intercept: 15.14
Slope: -4.55
Quadratic value: 1.29

Figure 1: Individual patient trajectories of depression and anxiety symptoms across time, grouped according to latent classes

No. of classes	BIC	LMR-LRT	BLRT	Entropy
3	27693.5	0.0537	<0.0001	0.842
4	27667.9	0.0609	<0.0001	0.848
5	27654.9	0.3674	<0.0001	0.854
6	27650.2	0.4949	<0.0001	0.84
7	27649.8	0.4262	<0.0001	0.84

Table 1: Latent Class Growth Analysis model fit statistics for different number of classes. BIC: Bayesian Information Criteria; LMR-LRT: Lo-Mendell-Rubin test; BLRT: Bootstrap likelihood ratio test.

	Stable low (n = 558)	Chronic high (n = 55)	Improving (n = 15)	Worsening (n = 64)	Fluctuating (n = 111)
Demographics	%	%	%	%	**%**
Age (mean)	72.3 years	64.0 years	59.5 years	68.0 years	71.6 years
Male sex	74.7	67.3	60.0	64.1	51.3
White ethnicity	90.5	81.8	80.0	71.9	83.8
Divorced/widowed/separated	26.8	32.7	13.3	21.9	37.8
12+ years education	55.4	50.0	60.0	45.2	41.7
Cardiac risk factors					
Current smoker	9.0	29.1	33.3	20.3	17.1
Overweight	47.6	19.6	33.3	36.5	42.6
Obese	27.8	52.9	53.3	39.7	37.0
Cardiac history					
History of MI	57.5	60.0	53.3	56.2	59.5
Cardiac intervention	52.7	50.9	33.3	46.9	54.9

Heart failure	9.3	10.9	6.7	7.8	9.9
Current chest pain	34.8	78.2	53.3	54.7	68.5
Comorbidities					
Hypertension	54.8	56.4	46.7	56.2	58.6
Diabetes	23.1	40.0	40.0	26.6	23.4
COPD	9.7	14.5	13.3	12.5	17.1
Cancer	12.0	7.35	13.3	9.4	15.3
Multiple comorbidities	45.3	52.7	40.0	53.1	53.1
Social Problems and life events					
No social problems	55.9	7.3	6.7	34.4	28.8
One social problems	33.5	27.3	26.7	31.2	36.0
2+ social problems	10.6	65.4	66.7	34.4	35.1
Life event in past 6 months	55.0	67.3	80.0	60.9	63.1
Quality of life					

Mental Qol (mean score)	51.1	29.2	33.7	44.0	39.8
Physical Qol (mean score)	40.0	30.4	37.2	33.8	33.8
Psychiatric history					
One depressive episode	10.0	23.6	20.0	15.6	18.0
Two or more dep. episodes	6.4	32.7	20.0	17.2	17.1
Any CIS-R diagnosis	3.2	89.1	66.7	31.3	47.9

Table 2: Comparison of descriptive baseline characteristics according to all five latent classes. Values are percentages unless otherwise stated.

	Chronic high (n=55)	Improving (n=15)	Worsening (n=64)	Fluctuating (n=111)
a)Demographics	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Age group+	0.4 (0.3 – 0.5)**	0.3 (0.1 – 0.5)**	0.6 (0.5 – 0.9)**	0.8 (0.6 – 1.0)
Female sex	1.6 (0.9 – 3.1)	2.6 (0.9 – 7.9)	2.1 (1.2 – 3.8)*	2.6 (1.7 – 4.2)**
Non-white ethnicity	1.8 (0.8 – 4.1)	1.7 (0.4 – 6.9)	4.5 (2.2 – 9.1)**	2.3 (1.2 – 4.4)**
Widowed/divorced	1.7 (0.9 – 3.3)	0.5 (0.1 – 2.5)	0.9 (0.5 – 1.8)	1.4 (0.9 – 2.3)
12 or more years education	0.6 (0.3 – 1.0)	0.7 (0.2 – 2.1)	0.4 (0.2 – 0.7)**	0.5 (0.3 – 0.8)**
b) Cardiac risk/clinical				
Current smoker	2.9 (1.3 – 6.3)**	2.8 (0.7 – 10.7)	2.4 (1.1 – 5.2)*	2.0 (1.0 – 3.9)*
Overweight / Obese	0.6 (0.3 – 1.4)	1.4 (0.3 – 6.8)	1.0 (0.5 – 2.0)	1.3 (0.8 – 2.3)
History of MI	1.0 (0.6 – 1.5)	0.8 (0.3 – 1.8)	1.1 (0.7 – 1.5)	1.0 (0.7 – 1.3)
Previous cardiac intervention	0.9 (0.5 – 1.7)	0.4 (0.1 – 1.3)	1.0 (0.6 – 1.7)	1.5 (1.0 – 2.4)
Heart failure	1.9 (0.7 – 5.2)	1.4 (0.1 – 14.3)	1.1 (0.4 – 3.2)	1.0 (0.5 – 2.2)
Current chest pain	5.8 (2.9 – 11.7)**	1.6 (0.5 – 4.9)	1..7 (1.0 – 3.0)*	3.5 (2.2 – 5.6)**

Hypertension	1.1 (0.5 – 2.3)	1.0 (0.3 – 3.8)	0.9 (0.5 – 1.7)	1.1 (0.6 – 1.8)
Diabetes	2.1 (1.0 – 4.4)	4.1 (1.0 – 17.6)	0.9 (0.4 – 1.8)	1.0 (0.6 – 1.8)
COPD	0.9 (0.3 – 2.7)	1.3 (0.2 – 9.5)	0.9 (0.3 – 2.4)	1.8 (0.9 – 3.7)
Cancer	0.8 (0.2 – 2.4)	2.6 (0.4 – 14.4)	0.6 (0.2 – 1.6)	1.4 (0.7 – 2.7)
2 or more comorbidities	1.4 (0.6 – 3.4)	0.5 (0.1 – 2.7)	1.4 (0.6 – 2.9)	0.9 (0.5 – 1.6)
c) Social/psychological				
Social problems	1.7 (1.2 – 2.6)**	1.4 (0.9 – 2.4)	1.4 (1.0 – 1.9)*	1.2 (0.9 – 1.6)
Recent adverse life event	1.1 (0.4 – 3.4)	1.4 (0.2 – 8.8)	0.8 (0.4 – 1.6)	1.1 (0.4 – 3.4)
Quality of life – physical	0.88 (0.83 – 0.93)**	0.98 (0.90 – 1.06)	0.95 (0.92 – 0.98)**	0.95 (0.93 – 0.98)**
History of depressive episodes	1.5 (0.5 – 4.0)	1.5 (0.4 – 6.3)	1.3 (0.6 – 2.8)	1.3 (0.7 – 2.5)
Any CIS-R diagnosis	10.3 (2.9 – 37.0)**	9.6 (1.7 – 55.3)**	2.5 (1.0 – 6.1)*	5.9 (2.7 – 13.1)**
Quality of life – mental	0.78 (0.73 – 0.84)**	0.82 (0.74 – 0.90)**	0.92 (0.88 – 0.96)**	0.89 (0.86 – 0.92)**

Table 3: Multinomial logistic regression analysis of a) demographic, b) cardiac and clinical (adjusted for demographic), and c) social and psychological (adjusted for smoking and chest pain) variables as risk factors for class membership. Reference class is 'stable low' * significant at .05 level, ** significant at .01 level

	Stable low	Chronic high	Improving	Worsening	Fluctuating
Primary care (SE)	512.2 (27.3)	750.5 (99.5)	486.4 (81.1)	873.3 (434.3)	592.8 (61.1)
Secondary care (SE)	3,599.9 (281.2)	7,719.0 (2,295.7)	2,599.7 (738.3)	7,085.6 (1,728.4)	4,234.4 (767.8)
Total healthcare (SE)	4,549.6 (315.9)	9,311.9 (2,415.6)	3,654.6 (852.1)	8,880 (1,936.3)	6,187.5 (959.2)
Total societal (SE)	4,640.4 (318.6)	9,613,3 (2,431.3)	3,791.1 (903.4)	9,073.8 (5,187.5)	6,442.2 (973.3)
Adjusted* mean difference in total societal costs (95% CI)	Ref	5,136.8 (2,224.1 to 8,049.5)**	-369.3 (-5,536.9 to 4,798.3)	4,746.7 (2,073.3 to 7,420.1)**	1,790.3 (-344.2 to 3,924.9)

Table 4: Mean costs (GBP) (SE) across time for each latent class, and difference in total societal mean costs across 3-year follow-up for each latent class group as compared to the 'stable low' group.

*Adjusted for demographics (sex, age, ethnicity), social variables (relationship, education status), risk factors (smoking, BMI, documented MI), multiple comorbidities, and experience of chest pain. **significant at .01 level

Highlights

- 803 primary care patients with CHD were followed-up every 6 months for 3 years
- Latent class growth analysis determined depression and anxiety symptom trajectories
- Stable low, chronic high, worsening, improving, and fluctuating groups were found
- Chronic high group associated with poorer quality of life, increased costs
- Trajectories only variable significantly associated to higher health-care costs