

Symptoms of depression and anxiety and 11-year all-cause mortality in men and women undergoing Coronary Artery Bypass Graft (CABG) surgery

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Short title: Distress and mortality after CABG surgery

ABSTRACT

Objectives: To investigate the overall and the sex-specific association of preoperative and one-year post coronary artery bypass (CABG) surgery symptoms of depression and anxiety with 11-year all-cause mortality.

Methods: A multicenter prospective study including 1,125 patients who completed the Hospital Anxiety and Depression Scale (HADS) before an elective CABG surgery, of whom 850 completed the HADS again at one-year follow-up. Information on all-cause mortality was obtained through the Israeli Ministry of Internal Affairs Register. Multivariable adjusted Cox regression models quantified the association of symptoms of depression and anxiety with all-cause mortality.

Results: Females comprised 22.7% of the cohort and were 5.5 years older than males (70.0 ± 9.3 and 64.4 ± 10.3 years, respectively). Controlling for sociodemographic and lifestyle factors, illness severity and post-surgery participation in cardiac rehabilitation, there was little evidence of an association between preoperative symptoms of depression and mortality in males [adjusted hazard ratio (aHR_{males})=1.03, 95% CI 0.99-1.07, $p=0.21$] or females (aHR_{females} =1.01, 95% CI 0.95-1.08, $p=0.7$). One-year postoperative symptoms of depression were associated with mortality in both males (aHR_{males} =1.05, 95% CI 1.01-1.10, $p=0.03$) and females (aHR_{females} =1.07, 95% CI 1.02-1.13, $p=0.013$). Preoperative symptoms of anxiety were unrelated to mortality overall, but among females postoperative symptoms of anxiety predicted 11-year mortality (aHR_{females} =1.07, 95% CI 1.00-1.14, $p=0.049$). There was no HADS by sex interaction (p for interaction=0.12-0.99).

Conclusions: Symptoms of depression one-year after surgery were positively related to mortality with little evidence for sex differences. These findings underscore the need for identification and treatment of psychiatric symptoms in patients undergoing CABG surgery.

Key words: Anxiety, Depression, Cardiovascular disease, Mortality, Multicenter study, Sex

Clinical Trial Registration: ClinicalTrials.gov: [NCT00356863](https://clinicaltrials.gov/ct2/show/study/NCT00356863)

Acronyms:

CABG: Coronary artery bypass grafting

CR: Cardiac rehabilitation

HADS: Hospital Depression and Anxiety Scale

HADS-D: Hospital Depression and Anxiety Scale - depression subscale

HADS-A: Hospital Depression and Anxiety Scale - anxiety subscale

aHR: Adjusted hazard ratio

CAD: Coronary artery disease

MDD: Major depressive disorder

CHF: Congestive heart failure

MI: Myocardial infarction

MCMC: Markov Chain Monte Carlo

INTRODUCTION

Coronary artery bypass grafting (CABG) surgery is a common treatment for coronary artery disease (CAD) and is usually associated with improved clinical outcomes. However, a significant proportion of patients experience depression and anxiety both pre- and postoperatively. Depression has been reported in 14%-47% [1] and anxiety in 15%-52% of patients [2].

Evidence suggests that depression and anxiety are associated with postsurgical outcomes such as cardiac events, level of function and quality of life [3]. Moreover, some have reported increased mortality in patients with elevated levels of depression and anxiety undergoing CABG surgery although not all studies have been consistent. Major Depressive Disorder (MDD) at discharge from hospital was associated with a twofold increased 12-month cardiac events in 309 patients but not with cardiac death. MDD and elevated symptoms of depression were associated with somewhat greater risk for cardiac-related but not with all-cause mortality at 10-year follow-up [4, 5]. Elevated symptoms of depression before and after surgery were associated with a twofold increase in all-cause mortality among 817 patients undergoing CABG surgery [1] while in another study there was little evidence for an association between preoperative depressive symptoms and all-cause 6-year mortality among 440 patients [6]. A recent systematic review demonstrated an increase in all-cause mortality in relation to preoperative depression in four of the seven studies reviewed [7].

Data on the impact of anxiety on morbidity and mortality following CABG surgery are scarce. Tully and co-investigators have shown that patients who had generalized anxiety disorder (GAD) prior to surgery were at a greater risk of major adverse cardiovascular and cerebrovascular events up to five years after CABG surgery but panic disorder was not associated with greater morbidity [8].

Heightened symptoms of anxiety before surgery were associated with increased postoperative mortality [6] and preoperative trait anxiety was positively related to 8-year mortality [9] but these studies were relatively small and based on samples recruited from single centres. Furthermore, the scale utilized by Tully and co-investigators [6] to assess symptoms of anxiety (the Depression

Anxiety Stress Scale (DASS)) included items describing physiological symptoms (e.g. breathing difficulties, feeling faintness) which are common to CAD and as such may reflect preoperative illness severity. Moreover, previous studies did not measure postoperative anxiety. Preoperative anxiety may have been influenced, at least in part, by the uncertainty associated with the invasive procedure, which may resolve after surgery. Anxiety measured after surgery may be a better reflection of a person's psychiatric symptomatology.

Studies have demonstrated differences between men and women undergoing CABG surgery including less favorable cardiac and psychiatric risk profiles, a delayed referral of women for surgery, gender disparities in functional gains following CABG surgery, with women showing worse outcomes, and lower referral and uptake of cardiac rehabilitation programmes (CRP) among women [10-15]. A small number of studies of patients after myocardial infarction (MI) showed gender disparities in the impact of depression on clinical outcomes with women showing more adverse effects [16-18]. However, none of the studies cited above have stratified their analysis by sex.

In this study, we investigate the associations between symptoms of depression and anxiety, using the Hospital Anxiety and Depression Scale (HADS), and all-cause mortality up to 11 years after CABG surgery in a large (N=1,125) and sociodemographically diverse sample of men and women undergoing CABG surgery from seven medical centers. In the present study, we used the HADS which focuses on cognitive and emotional components of depression and anxiety and is therefore well suited for patients after CABG surgery. Our analyses are stratified by sex to explore the sex-specific impact of poor mental health on mortality following CABG surgery.

MATERIALS AND METHODS

Design

This study is part of a prospective controlled multicentre study described in detail elsewhere [19, 20]. In summary, it aimed to assess the effect of an educational intervention, designed to improve uptake

of cardiac rehabilitation (CR), on CR participation rate and the effect of CR participation on patients' outcomes after CABG surgery. We approached consecutive patients scheduled for CABG surgery (Jan/2004-Nov/2007) in seven cardiothoracic departments across Israel. Patients were interviewed 1-2 days before (baseline) and approximately one-year after surgery (follow-up) by trained research interviewers.

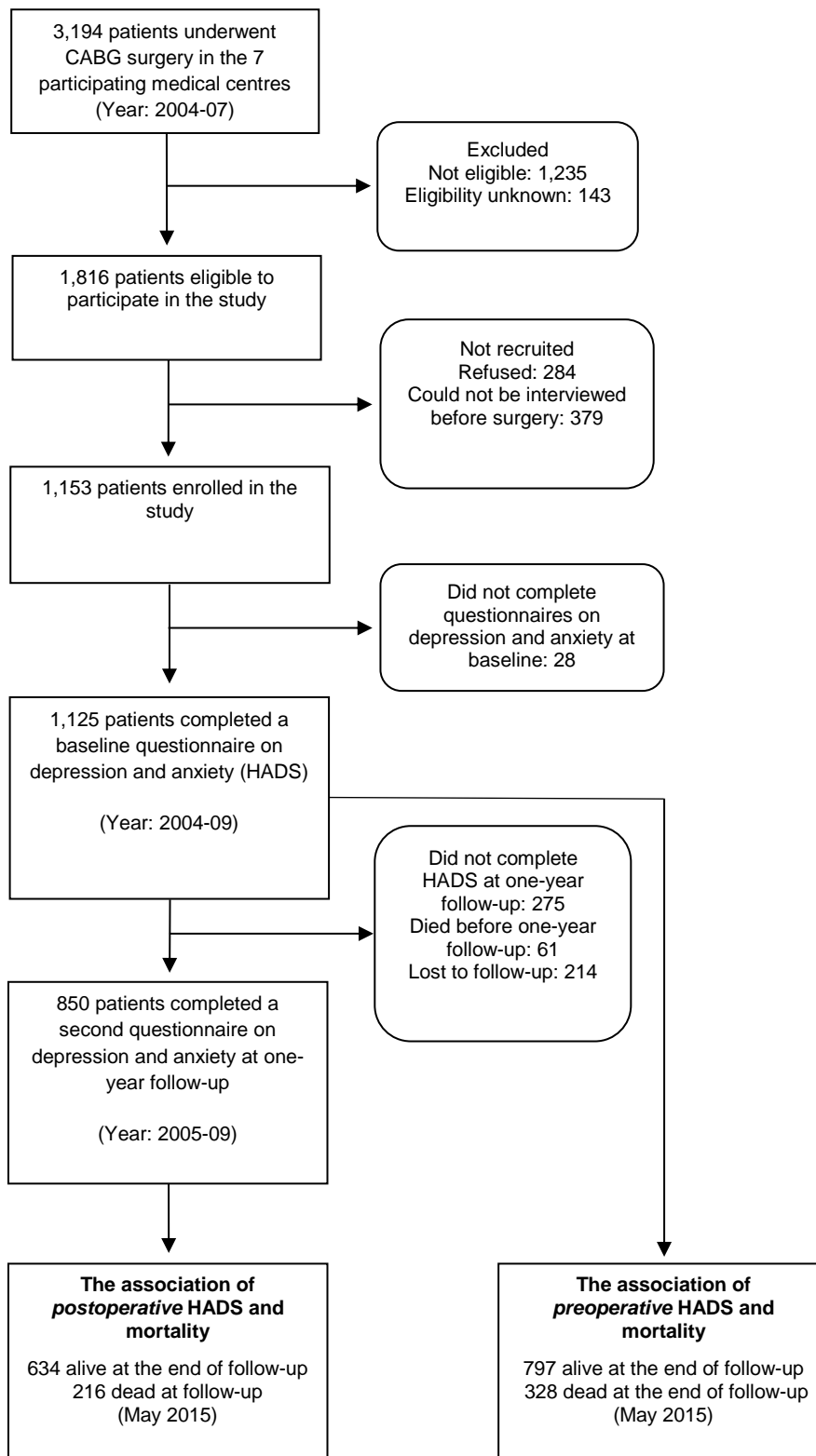
Patients were excluded from the primary study if they had severe co-morbidities for which CR was contra-indicated [e.g. congestive heart failure (CHF) stage IV]; were institutionalized; had severe cognitive impairment (e.g. general stroke with severe disability); could not understand the study languages: Hebrew, English, Russian, and Arabic; or resided farther than 30km from a CR facility. Patients were excluded if they could not be interviewed (baseline interview) prior to surgery (e.g. due to emergency operation) since their mental or cognitive state could have been affected by surgery. No exclusion occurred in relation to the type of CABG procedure.

Informed consent was obtained from all patients. The study received approval from the Sheba Medical Centre Ethics committee.

Participants

Overall, 1,816 out of 3,194 (57%) were eligible to participate, 1,153 (64%) of whom were enrolled in the primary study. HADS was completed by 1,125 patients (98%) at baseline and by 850 (76%) again at one-year (Figure 1). A hundred and seventy of the 1,125 patients who were included in this study had undergone valve replacement procedure together with the bypass procedure.

Figure 1: Study population and sample



Measures

Sociodemographic data [age, sex, marital status, ethnicity, level of education, employment status, income level (categorized according to the national average household income)], behavioural parameters (e.g. tobacco use and physical exercise), and co-morbidities were collected through a face-to-face interview. Results of blood markers (e.g. serum creatinine) were abstracted from medical records.

Patients completed the HADS - a 14-item screening questionnaire measuring symptoms of anxiety (7 items) and depression (7 items) which enquires about the last week. The score of each sub-scale can range between 0 and 21 when a higher score indicates worse symptoms. A score of eight or above on either sub-scales is considered clinically significant [21]. The authors of a review of the psychometric properties of the HADS reported that the sensitivity and specificity for this cut-point were 0.70 and 0.90, respectively, when compared to depressive and anxiety disorders (including major depressive disorder and generalized anxiety disorder) as identified by a gold standard measure such as the Structured Clinical Interview for DSM (SCID) [21]. The Hebrew version of HADS was found to have good psychometric properties [22]. In the present study, the internal reliability of the total scale was 0.89. It was 0.81 for the depression (HADS-D) sub-scale and 0.82 for the anxiety (HADS-A) sub-scale.

Body mass index (kg/m^2) was calculated from height and weight measured during the interview.

We used Charlson's co-morbidity index [23, 24] as a proxy for disease severity. It includes diabetes, MI, peripheral vascular disease, gastrointestinal tract disease, liver and kidney disease, stroke, cancer and HIV. Patients were assigned a value based on their number of co-morbidities. Patients completed a detailed and validated physical activity questionnaire and their physical fitness in $\text{Vo}_2 \text{ ml/kg/min}$ was estimated [25].

Mortality data were obtained from the Israel National Population Register, using individuals' unique national identification number. Mortality data were updated until May 2015 i.e. 11 years 5 months from study onset.

Statistical Methods

We used Cronbach's alpha to assess the HADS's internal consistency and t-tests and Pearson chi-square tests to compare participants on continuous and categorical variables, respectively (Table 1).

The outcome variables are death and time-to-death after completing the HADS. We examined the association of pre- and postoperative HADS with all-cause mortality using multiple Cox proportional hazard regression. Initially, we controlled for age and sex (in the overall models) and then for sociodemographic factors (ethnic origin, marital status, levels of education and income, employment status). Finally, we also controlled for illness severity and comorbidity (valve replacement surgery, levels of haemoglobin and creatinine, and Charlson's index), BMI at study entry, smoking status, level of physical activity and primary study arm (intervention/control). In models of the association of one-year postoperative HADS with mortality we additionally controlled for CR status and for concordant baseline measure of HADS. To account for clustering by hospital, we stratified the analyses by hospital. Covariates were selected a priori and retained in the models irrespective of statistical significance.

We examined the association of HADS with mortality using the HADS sub-scales as continuous and then as binary measures, distinguishing between patients who scored <8 and ≥ 8 . Analyses were also carried out by sex and HADS by sex interaction terms were added.

Age-adjusted survival curves are presented in Figure 2 according to sex and level of depression/anxiety during baseline and one-year postoperative assessment.

All p-values are two-tailed.

Missing data

The analyses were conducted using imputed dataset of the covariates: marital status, levels of education, income, smoking status, BMI at study entry, haemoglobin and creatinine. There were 1,051 individuals with complete data at baseline while 831 had complete data at both assessments. We conducted multiple imputations using Markov Chain Monte Carlo (MCMC) [26] method which assumes that data are missing at random [27]. We generated 20 imputed datasets for each covariate including all variables used in the analysis.

Analysis was carried out using Stata 14.1.

RESULTS

Vital status was available for all the participants. Of the 1,125 (23% women), 328 (29.2%) died by the end of the follow-up (May 2015) and 850 (75.6%) completed the HADS again at one-year (216 of whom died by May 2015) (Figure 1). Median follow-up time 9 years, 4 months.

Sixty-one patients (22%) died before the second assessment while the remainder were lost to follow-up. Baseline HADS-D score differed between participants, those lost to follow-up, and the deceased ($p=0.002$) but not mean HADS-A score ($p=0.3$). These groups differed on age ($p<0.0001$), serum hemoglobin ($p=0.006$), and Charlson's score ($p=0.04$), the prevalence of valve replacement ($p<0.0001$) and CHF ($p=0.001$), but not on mean serum creatinine ($p=0.08$) or the prevalence of diabetes ($p=0.5$).

Sample characteristics

Table 1 summarizes baseline characteristics of patients overall and by sex. Women were older and more likely to have died by 2015. They were more likely to be recent immigrants, of the lowest level of educational attainment, not employed at the time of surgery, and of low income compared to men. Women were also less likely to be married at the time of surgery. Most indicators of co-morbidity and illness severity appeared similar between men and women before surgery but a greater proportion of women required valve replacement and their level of hemoglobin and creatinine were lower. Almost 70% of women never smoked, compared to 28% of men. Compared to men, a smaller proportion of women engaged in physical activity and a greater proportion had a $BMI \geq 30 \text{ kg/m}^2$.

Elevated scores (≥ 8) of HADS-D and HADS-A was reported by 19.1% and 25.2% of the sample prior to surgery, respectively. Elevated HADS-D/HADS-A were greater among women (25.1% vs. 17.4%, $p=0.006$; 31.8% vs. 23.2%, $p=0.006$, respectively). Of the 850 patients who completed the HADS again one-year after surgery, 22% had $HADS-D \geq 8$ and 25% $HADS-A \geq 8$, with women predominance (results not shown).

Characteristics at baseline	Total	Males n=870	Females n=255	p-value
Age in years, mean (SD)	65.7 (10.4)	64.4 (10.3)	70.0 (9.3)	<.0001
Deceased by end of follow-up, n (%)	328 (29.2)	219 (25.2)	109 (42.8)	<.0001
<i>Ethnicity* n (%)</i>				
Jewish-Israeli	829 (73.7)	653 (75.1)	176 (69.0)	0.009
Russian-Israeli	241 (21.4)	170 (19.5)	71 (27.8)	
Arab-Israeli	55 (4.9)	47 (5.4)	8 (3.2)	
<i>Marital status, n (%)</i>				
Single	26 (2.3)	19 (2.1)	7 (2.8)	<.0001
Married	846 (75.2)	717 (82.4)	129 (50.6)	
Divorced/separated	95 (8.4)	72 (8.3)	23 (9.0)	
Widowed	158 (14.0)	62 (7.1)	96 (37.6)	
<i>Education, n (%)</i>				
0-10 years	356 (31.9)	249 (28.9)	107 (42.1)	<.0001
11-12 years	280 (25.1)	225 (26.1)	55 (21.7)	
13+ years	480 (43.0)	388 (45.0)	92 (36.2)	
<i>Employment status, n (%)</i>				
Not working	707 (62.8)	489 (56.2)	218 (85.5)	<.0001
Partly-time employment	130 (11.6)	112 (12.9)	18 (7.1)	
Full-time employment	288 (25.6)	269 (30.9)	19 (7.4)	
<i>Income, n (%)</i>				
Below average	660 (60.7)	456 (54.3)	204 (82.6)	<.0001
Average	252 (23.2)	221 (26.3)	31 (12.6)	
Above average	175 (16.1)	163 (19.4)	12 (4.9)	
<i>Co-morbidity and illness severity</i>				
n (%) with diabetes	474 (42.1)	355 (40.8)	119 (46.7)	0.095
n (%) with valve replacement	170 (15.1)	108 (12.4)	62 (24.3)	<.0001
n (%) with congestive heart failure (CHF)	135 (12.0)	96 (11.0)	39 (15.3)	0.066
Serum creatinine $\mu\text{mol/L}$, mean (SD)	1.12 (0.5)	1.2 (0.5)	1.0 (0.5)	0.0002
Haemoglobin g/L, mean (SD)	13.3 (1.7)	13.7 (1.7)	12.3 (1.3)	<.0001

Characteristics at baseline	Total	Males n=870	Females n=255	p-value
Charlson Co-Morbidity Index				
<i>No co-morbidities</i>	186 (16.5)	145 (16.7)	41 (16.1)	.49
<i>1 co-morbidity</i>	368 (32.7)	291 (33.5)	77 (30.2)	
<i>2 co-morbidities</i>	258 (22.9)	198 (22.8)	60 (23.5)	
<i>3+ co-morbidities</i>	313 (27.8)	236 (27.0)	77 (30.2)	
Smoking, n (%)				
Never smoked	418 (37.2)	244 (28.1)	174 (68.5)	<.0001
Past smoker [†]	458 (40.8)	402 (46.3)	56 (22.1)	
Current smoker	247 (22.0)	223 (25.7)	24 (9.4)	
Body Mass Index kg/m², n (%)				
<25	294 (26.6)	231 (27.0)	63 (24.9)	<.0001
≥25<30	497 (44.9)	409 (47.9)	88 (34.8)	
≥30	316 (28.6)	214 (25.1)	102 (40.3)	
Reporting any physical activity, n (%)	380 (33.8)	316 (36.3)	64 (25.1)	0.001
VO₂max, mean (SD)	35.3 (6.7)	37.8 (5.1)	27.0 (4.7)	<.0001
Mental health				
Symptoms of depression, mean (SD)	4.4 (3.8)	4.1 (3.8)	5.5 (3.9)	<.0001
n (%) with HADS-D≥8	215 (19.1)	151 (17.4)	64 (25.1)	0.006
Symptoms of anxiety, mean (SD)	5.2 (4.0)	5.1 (4.0)	5.9 (4.0)	0.004
n (%) with HADS-A≥8	283 (25.2)	202 (23.2)	81 (31.8)	0.006

*Ethnicity – Jewish-Israeli: born or emigrated to Israel earlier than 1989; Russian-Israeli: immigrated to Israel from the former Soviet Union in or after 1989; Arab-Israeli: Israeli citizens defining themselves as Arab-Israeli.

[†]Past smokers: patients who stopped smoking for at least 6 months before assessment

[‡]P value for comparing male and females

Table 1: Sociodemographic, behavioural and clinical characteristics of the study sample at baseline overall and by sex (N=1,125)

Preoperative HADS and all-cause mortality

HADS-D was associated with increased all-cause mortality [hazard ratio (HR)=1.05, 95% confidence interval (CI) 1.02-1.09, $p<.0001$] which diminished slightly after adjustment for sociodemographic factors (Table 2). Additional adjustment for BMI, smoking status, indicators of illness severity, comorbidity and level of physical activity attenuated this association further [adjusted HR (aHR)=1.01, 95% CI 0.98-1.05, $p=0.41$]. Further analysis by sex showed no evidence of an association between depression score and all-cause mortality in both men (aHR=1.03, 95% CI 0.99-1.07, $p=0.21$) and women (aHR=1.01, 95% CI 0.95-1.08, $p=0.7$) and no evidence of an association between HADS-A and mortality in either men (aHR=0.98, 95% CI 0.94-1.02, $p=0.23$) or women (aHR=1.01, 95% CI 0.95-1.06, $p=0.83$) (Table 2).

Hazard ratio (95% CI)													
P value													
Total						Men				Women			
Predictors	N	Unadjusted	Adjusted*	Adjusted†	Adjusted§	N	Unadjusted	Adjusted†	Adjusted§	N	Unadjusted	Adjusted†	Adjusted§
		Model					Model				Model		
<i>Symptoms of depression</i>													
HADS-D continuous	1125	1.05 (1.02-1.09)	1.04 (1.01-1.08)	1.04 (1.01-1.08)	1.01 (0.98-1.05)	870	1.05 (1.02-1.09)	1.07 (1.02-1.11)	1.03 (0.99-1.07)	255	1.03 (0.98-1.09)	1.03 (0.97-1.09)	1.01 (0.95-1.08)
		<.0001 [‡]	0.007 [‡]	0.012 [‡]	0.41		0.06	0.002 [‡]	0.21		0.24	0.39	0.7
HADS-D binary													
HADS-D<8	910	1.00	1.00	1.00	1.00	719	1.00	1.00	1.00	191	1.00	1.00	1.00
HADS-D≥8	215	1.61(1.23-2.12)	1.60 (1.21-2.12)	1.56 (1.17-2.07)	1.28 (0.95-1.71)	151	1.67 (1.20-2.33)	1.86 (1.31-2.64)	1.52 (1.06-2.20)	64	1.58 (0.97-2.59)	1.40 (0.84-2.32)	1.22 (0.72-2.08)
		0.001 [‡]	0.001 [‡]	0.002 [‡]	0.1		0.002 [‡]	0.001 [‡]	0.025 [‡]		0.068	0.2	0.46
<i>Symptoms of anxiety</i>													
HADS-A continuous	1125	0.99 (0.96-1.02)	1.00 (0.97-1.03)	1.00 (0.97-1.03)	0.98 (0.95-1.01)	870	0.99 (0.95-1.02)	1.00 (0.97-1.04)	0.98 (0.94-1.02)	255	1.00 (0.95-1.05)	1.02 (0.97-1.07)	1.01 (0.95-1.06)
		0.5	0.86	1.0	0.15		0.39	0.89	0.23		0.94	0.48	0.83
HADS-A binary													
HADS-A<8	842	1.00	1.00	1.00	1.00	668	1.00	1.00	1.00	174	1.00	1.00	1.00
HADS-A≥8	283	0.86 (0.65-1.13)	0.98 (0.75-1.30)	0.96 (0.73-1.27)	0.86 (0.65-1.14)	202	0.82 (0.58-1.15)	0.98 (0.69-1.38)	0.86 (0.60-1.2)	81	0.89 (0.56-1.43)	1.17 (0.69-1.80)	0.97 (0.59-1.59)
		0.27	0.9	0.8	0.29		0.24	0.9	0.38		0.63	0.65	0.9

*Adjusted for age, sex

†Adjusted for age, sex (the overall model only), marital status, origin/ethnicity, level of education, employment status, income level

[§]Adjusted for sociodemographics as above and for smoking status, BMI, physical activity, illness severity and co-morbidity: valve replacement surgery (yes/no), haemoglobin level, creatinine level, Charlson's index, study arm (intervention/control)

[‡]Indicates that the association is significant at the 0.05 significance level

Abbreviations: HADS-D= symptoms of depression component of the Hospital Depression and Anxiety Scale; HADS-A= symptoms of anxiety component of the Hospital Depression and Anxiety Scale

Table 2: Pre surgery symptoms of depression and anxiety and all-cause mortality by sex: hazard ratio and 95% CI

One-year postoperative HADS and all-cause mortality

Controlling for confounders as above, HADS-D score was associated with all-cause mortality (aHR=1.06, 95% CI 1.03-1.10, p=0.001) (Table 3). A HADS-D score ≥ 8 was associated with 1.8-fold increased 11-year mortality compared to HADS-D<8, (aHR=1.78, 95% CI 1.29-2.45, p<.0001).

Analysis by sex showed evidence of an association between HADS-D score and mortality among men (aHR=1.05, 95% CI 1.01-1.10, p=0.03) and among women (aHR=1.07, 95% CI 1.02-1.13, p=0.013).

A HADS-D score ≥ 8 was associated with 1.6-fold increased mortality in males (aHR=1.56, 95% CI 1.02-2.37, p=0.039) and a twofold increased mortality in females (aHR=2.12, 95% CI 1.23-3.65, p=0.007). There was no evidence for depression*sex interaction (p for interaction= 0.99).

Overall, HADS-A score was unrelated to mortality (aHR=1.03, 95% CI 1.00-1.07, p=0.097). Analysis by sex showed that postoperative anxiety was unrelated to mortality in men (aHR=1.01, 95% CI 0.97-1.06, p=0.65) but in women HADS-A score was associated with mortality (aHR=1.07, 95% CI 1.00-1.14, p=0.049). There was no anxiety*sex interaction (p for interaction=0.17).

The results from a complete case analysis were consistent with those from the imputation-based analysis.

Hazard ratio (95% CI)													
P value													
Total						Men				Women			
Predictors	N	Unadjusted	Adjusted*	Adjusted†	Adjusted§	N	Unadjusted	Adjusted†	Adjusted§	N	Unadjusted	Adjusted†	Adjusted§
		Model					Model				Model		
<i>Symptoms of depression</i>													
HADS-D continuous	850	1.07 (1.04-1.10)	1.06 (1.03-1.09)	1.06 (1.03-1.09)	1.06 (1.03-1.10)	665	1.06 (1.02-1.10)	1.07 (1.03-1.11)	1.05 (1.01-1.10)	187	1.07 (1.02-1.12)	1.05 (1.00-1.10)	1.07 (1.02-1.13)
		<.0001 [‡]	<.0001 [‡]	<.0001 [‡]	0.001 [‡]		0.002 [‡]	0.001 [‡]	0.03 [‡]		0.006 [‡]	0.071	0.013 [‡]
HADS-D binary													
HADS-D<8	698	1.00	1.00	1.00	1.00	548	1.00	1.00	1.00	120	1.00	1.00	1.00
HADS-D≥8	152	1.85 (1.38-2.47)	1.71 (1.27-2.31)	1.65 (1.22-2.24)	1.78 (1.29-2.45)	117	1.59 (1.09-2.35)	1.68 (1.14-2.49)	1.56 (1.02-2.37)	67	2.09 (1.28-3.40)	1.77 (1.07-2.91)	2.12 (1.23-3.65)
		<.0001 [‡]	<.0001 [‡]	0.001 [‡]	<.0001 [‡]		0.017 [‡]	0.009 [‡]	0.039 [‡]		0.003 [‡]	0.025 [‡]	0.007 [‡]
<i>Symptoms of anxiety</i>													
HADS-A continuous	850	1.02 (0.99-1.06)	1.04 (1.01-1.07)	1.03 (1.00-1.07)	1.03 (1.00-1.07)	665	1.00 (0.96-1.04)	1.03 (0.99-1.07)	1.01 (0.97-1.06)	192	1.06 (1.01-1.12)	1.06 (1.00-1.12)	1.07 (1.00-1.14)
		0.15	0.026 [‡]	0.058	0.097		0.87	0.21	0.65		0.032 [‡]	0.059	0.049 [‡]
HADS-A binary													
HADS-A<8	641	1.00	1.00	1.00	1.00	518	1.00	1.00	1.00	123	1.00	1.00	1.00
HADS-A≥8	209	1.16 (0.86-1.57)	1.25 (0.92-1.70)	1.19 (0.87-1.62)	1.20 (0.87-1.66)	147	0.96 (0.65-1.42)	1.20 (0.80-1.80)	1.11 (0.73-1.70)	64	1.57 (0.96-2.58)	1.22 (0.73-2.03)	1.28 (0.74-2.19)
		0.32	0.16	0.28	0.26		0.83	0.38	0.63		0.074	0.46	0.38

* Adjusted for age, sex

†Adjusted for age, sex (the overall model only), marital status, origin/ethnicity, level of education, employment status, income level

[§]Adjusted for sociodemographics as above and for smoking status, BMI, physical activity, illness severity and co-morbidity: valve replacement surgery (yes/no), haemoglobin level, creatinine level,

Charlson's index, cardiac rehabilitation participation, study arm (intervention/control) and HADS-D or HADS-A score at baseline depending on outcome

[‡]Indicates that the association is significant at the 0.05 significance level

Abbreviations: HADS-D= symptoms of depression component of the Hospital Depression and Anxiety Scale; HADS-A= symptoms of anxiety component of the Hospital Depression and Anxiety Scale

Table 3: One-year post-surgery symptoms of depression and anxiety and all-cause mortality by sex: hazard ratio and 95% CI

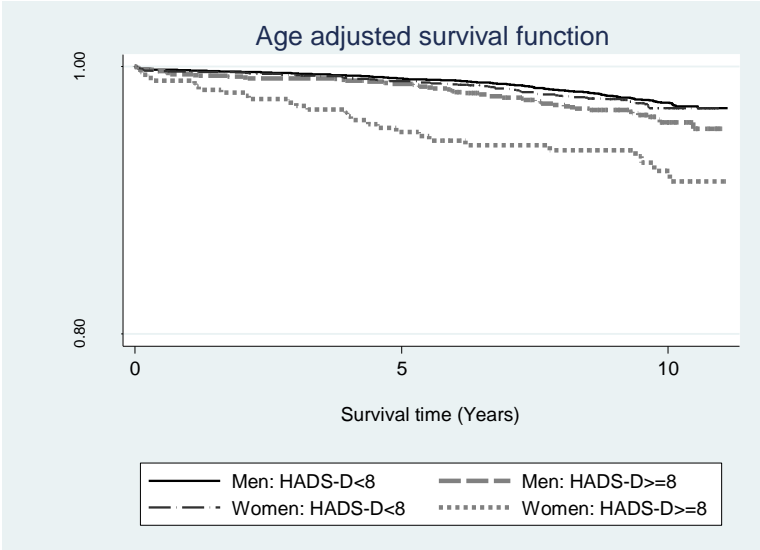
Table 4 shows the co-variates which remained significant predictors of all-cause mortality in at least one of the fully adjusted models. The covariates age, valve replacement procedure, level of creatinine, and Charlson co-morbidity index were associated with all-cause mortality in the fully adjusted models of the association of both pre- and postoperative depression or anxiety with all-cause mortality while the covariates sex, and level of education were associated with mortality in the fully adjusted models of the association of pre-operative depression or anxiety with all-cause mortality only (Table 4). Level of pre-operative haemoglobin was associated with all-cause mortality in all but one model – preoperative symptoms of depression and all-cause mortality.

	Pre-operative HADS scores		Post-operative HADS scores	
	N=1,125		N=850	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Co-variates	Symptoms of depression - HADS-D continuous			
Age (continuous)	1.07 (1.05-1.08)	<.0001 [‡]	1.06 (1.04-1.08)	<.0001 [‡]
Sex (female)	1.43 (1.06-1.92)	0.016 [‡]	1.29 (0.89-1.87)	0.18
Level of education (above average, average, below average)	0.87 (0.76-0.99)	0.038 [‡]	0.91 (0.76-1.08)	0.27
Valve replacement procedure (yes)	1.60 (1.23-2.07)	<.0001 [‡]	1.59 (1.13-2.26)	0.007 [‡]
Level of haemoglobin (continuous)	0.93 (0.87-1.00)	0.05	0.91 (0.84-1.00)	0.047 [‡]
Level of creatinine (continuous)	1.53 (1.31-1.78)	<.0001 [‡]	1.43 (1.14-1.79)	0.002 [‡]
Charlson co-morbidity index (0-9 morbidities)	1.17 (1.08-1.26)	<.0001 [‡]	1.22 (1.11-1.34)	<.0001 [‡]
	Symptoms of anxiety - HADS-A continuous			
Age (continuous)	1.07 (1.05-1.08)	<.0001 [‡]	1.06 (1.04-1.08)	<.0001 [‡]
Sex (female)	1.49 (1.11-1.99)	0.008 [‡]	1.38 (0.96-1.98)	0.087
Level of education (above average, average, below average)	0.87 (0.76-0.99)	0.035 [‡]	0.87 (0.73-1.04)	0.12
Valve replacement procedure (yes)	1.58 (1.22-2.06)	0.001 [‡]	1.50 (1.07-2.09)	0.018 [‡]
Level of haemoglobin (continuous)	0.93 (0.86-1.00)	0.039 [‡]	0.91 (0.84-1.00)	0.046 [‡]
Level of creatinine (continuous)	1.52 (1.31-1.77)	<.0001 [‡]	1.42 (1.15-1.76)	0.001 [‡]
Charlson co-morbidity index (0-9 co-morbidities)	1.19 (1.10-1.28)	<.0001 [‡]	1.23 (1.12-1.35)	<.0001 [‡]

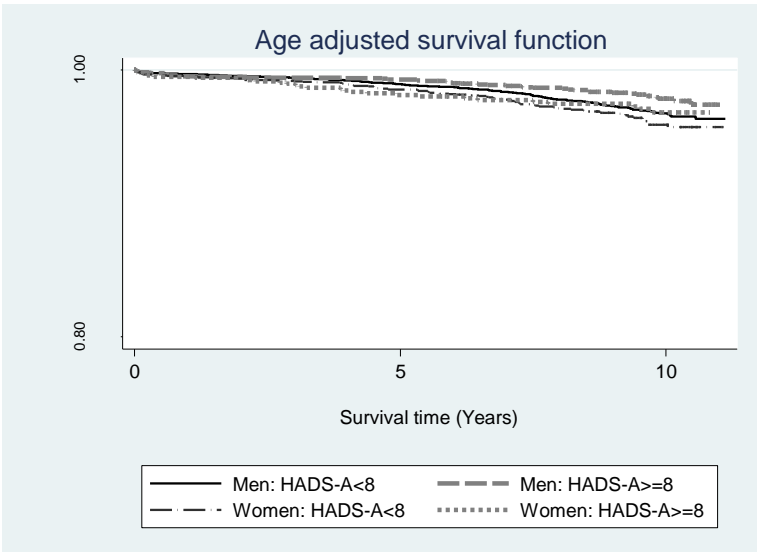
[‡]Indicates that the association is significant at the 0.05 significance level

Table 4: The association between the study co-variates and all-cause mortality in the fully adjusted models: hazard ratio and 95% CI

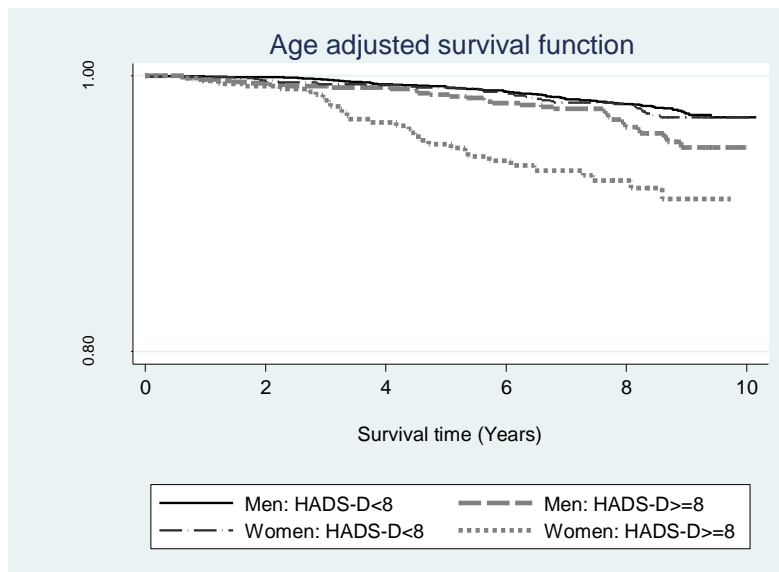
Age-adjusted survival curves by sex and depression/anxiety status at baseline and one-year after surgery are presented in Figure 2.



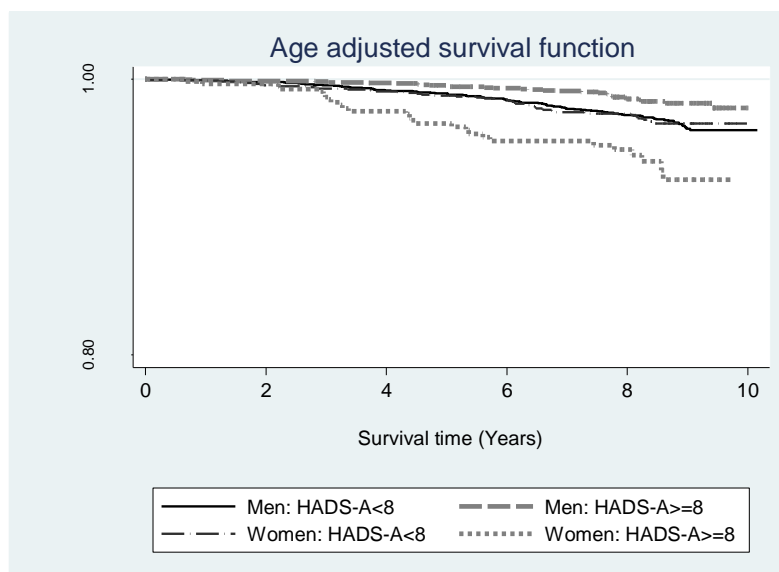
2a: HADS-D before surgery



2b: HADS-A before surgery



2c: HADS-D at one-year follow-up



2d: HADS-A at one-year follow-up

Figure 2a-2d: Age adjusted survival curves for men and women according to level of symptoms of depression (HADS-D) and anxiety (HADS-A) prior to and at one-year after surgery

DISCUSSION

A fifth of patients had elevated depression scores and a quarter had elevated anxiety scores before and one-year after surgery. The proportion of patients with elevated depression and anxiety scores was greater among women. These findings are consistent with previous research [2, 3, 28-30].

Overall, elevated HADS-D score before surgery was associated with increased 11-year all-cause mortality, although this association was consistent with chance after adjustment for illness severity, comorbidity, and lifestyle factors including level of physical exercise. Elevated depression score one-year after surgery was associated increased mortality. Analysis by sex showed that for both males and females increased symptoms of depression was associated with increased mortality. A score of eight or above on the depression scale was associated with 1.6-fold and a twofold increase in mortality in males and females, respectively. These findings are in keeping with previous research showing increased all-cause [1, 31, 32] and cardiac-related [5, 33] mortality in individuals with pre- and/or postoperative depression and with studies showing elevated mortality in patients with depression and CAD in general [34].

Preoperative symptoms of anxiety were unrelated to mortality. Our findings contrast with two studies, [6, 9] showing a positive association between preoperative anxiety and mortality, although these studies were markedly smaller, included shorter follow-up period, and were based on samples recruited from single centres. Furthermore, the instrument used to assess symptoms of anxiety in one study [6] included items describing physiological symptoms so that a higher score may have reflected more severe CAD. The use of a tool that focuses on the cognitive and emotional components of depression and anxiety, like HADS, has been proposed more suitable for this patients group [21]. Our results further showed no evidence of an association between postoperative anxiety and mortality although in women HADS-A score one-year after surgery predicted mortality. Studies on the associations between anxiety and mortality in other CAD patient groups have produced mixed results [35].

Results from the sex-specific analyses in the present study showed no evidence of sex-disparities. A very limited number of studies examined the sex-specific impact of depression and anxiety on clinical outcomes

in patients with CAD. Two studies of patients after MI showed that elevated symptoms of depression after MI were associated with increased cardiac mortality in both sexes [28, 30] while in another study symptoms of depression were more strongly associated with lack of improvement after CABG among women [16]. Two reports from the New Haven population-based cohort study of older adults have shown that depressive symptoms at recruitment were associated with CHD outcomes in women but not in men [17, 18]. In contrast, another population-based study of older adults [36] demonstrated elevated all-cause mortality in relation to depression only in men.

It has been argued that since depression and anxiety are more common in women this can explain some of the excess adverse outcomes in women but research evidence offers very little support for this [30, 37]. It has been further suggested that depression may be more persistent in women than in men and that it is this chronicity that places women at greater risk of poor physical health relative to men. Indeed, in this study 12.9% of women had persistent depression (i.e. scored above the conventional threshold at both time points) relative to 5% of men. Evidence also suggests that there may be sex differences in the response to and coping with poor mental health such that women tend to use more emotionally focused strategies (e.g. crying, ruminating) while men are more likely to adopt distraction strategies (e.g. engaging in hobbies, physical activities) [38]. Engaging in physical activities can be beneficial during recovery from CABG surgery. Furthermore, differences in participation in cardiac rehabilitation (CR) may affect disease progression. Men in this study were overall more likely to attend CR programmes (30% of men versus 15% of women attended CR after CABG surgery). However, in patients with elevated symptoms of depression ($\text{HADS-D} \geq 8$), 23% of men attended CR after surgery while only 7% of women did so, suggesting that women with depression are less likely than men with depression to benefit from CR treatment. There is evidence that CR treatment is also beneficial in terms of improving psychiatric symptoms [39-41]. Other concurrent psychosocial risk factors may also differ between men and women. Women, for instance, report lower levels of social support after MI relative to men [14] which may exacerbate the impact of depression and hinder recovery after CABG. Nevertheless, in our study, there was no statistical evidence for an excess mortality in women relative to men in relation to poor mental health.

This large prospective study was carried out in four languages in seven medical centres across Israel including hospitals from the public and the private sector, which strengthens generalizability. Women comprised 23% of the sample, similar to their proportion in the population undergoing CABG surgery in Israel and in other countries e.g. approximately 28% in the US [10]. Furthermore, the sample in this study was ethnically diverse including 21% immigrants from the former USSR (referred to Russian-Israelis) and Arab population residing in Israel (5%), similar to the proportion of these groups in the general population in Israel. Ninety-eight percent of patients who had enrolled in the primary study completed the HADS at baseline.

One limitation of this study relates to the primary study, which included patients who met the criteria of mobility and geographical proximity to a CR facility i.e. 57% of patients undergoing CABG surgery during the study period, criteria which most likely excluded patients with more severe medical conditions and the more disadvantaged patients. Thus, the risk for mortality reported here most probably reflects a conservative estimate of the true association between mental state and mortality. Furthermore, attrition between baseline and follow-up assessments may have introduced a selection bias. Relative to individuals who completed both assessments of HADS-D, patients who only completed the preoperative HADS had higher mean HADS-D score at baseline although their HADS-A score and some other indicators of illness severity and comorbidity were similar in both groups. Nevertheless, the exclusion of these individuals did most probably attenuate the associations. Despite the inclusion of an ethnically diverse population, this study was conducted in Israel and its generalizability to other populations should be treated with caution. Furthermore, it has been shown that heightened depression was associated with excess cardiovascular-related but not all-cause mortality in patients undergoing CABG surgery [5]. However, in this study we were unable to address causes of death separately. We were also unable to account for the type of procedure patients had undergone (on-pump versus off-pump) as we did not have this information. This factor may have influenced survival although we have no reason to assume that the type of procedure had been associated with the exposure (symptoms of anxiety and depression) and therefore is not clearly a confounder. The use of HADS as an instrument for measuring symptoms of depression and anxiety has

been criticized [42] as its factor structure was shown to be inconsistent across studies. In addition, one may argue the HADS uses British colloquial phrases and therefore may not be suitable for translation. However, we have assessed the psychometric properties of the HADS in cardiac patients' population in Israel prior to the present study. The results from this study showed that the HADS had good psychometric properties and a two-factor structure, which would be consistent with the depression and anxiety [22]. Lastly, the study design entails potential change over time. To account for this, we adjusted the analysis for the primary study's arm control/intervention.

There is accumulating evidence that depressive disorders as well as symptoms are associated with elevated mortality following CABG surgery. This highlights the need to address depression as part of these patients' long-term treatment plan. Our study emphasizes the importance of psychiatric symptoms occurring one-year after surgery and the heightened risk in women. Addressing depression at pre- and postsurgical stage is challenging and ought to involve the surgical team and secondary prevention facilities including CR programmes. Data are also needed on the effect of psychological and pharmacotherapy interventions for depression in patients undergoing CABG surgery. The role of anxiety in survival is unclear and further methodologically robust studies are required.

Conclusion

One in five patients had elevated symptoms of depression while one in four patients had elevated symptoms of anxiety before and one-year after surgery. Elevated symptoms of depression, especially symptoms present one-year after surgery were associated with increased mortality. Symptoms of anxiety were unrelated to mortality, although among women anxiety occurring one-year after surgery was associated with elevated mortality. The strong association between elevated psychiatric symptoms and mortality reinforces findings of previous studies. Interventions to improve psychiatric morbidity in this patient group may include psychological treatments such as

Cognitive Behavioural Therapy, and/or psychopharmacological agents. Current evidence from trials designed to treat depression in patients with coronary artery disease suggest that these treatments are moderately effective in relieving depression although their effect on clinical outcomes and survival is less evident [43]. Nevertheless, the high prevalence of psychiatric morbidity in this sizable patient group, a finding which is in keeping with findings from previous research, highlight the importance of addressing psychiatric morbidity in patients undergoing CABG surgery, which can contribute their better quality of life. The results from this and other studies also highlight the need for further large-scale studies exploring sex differences in the impact of poor mental health on recovery from CABG surgery.

Competing interest statement and source of funding

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The authors have no conflict of interest to report.

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