The Assessment and Treatment of Psychological Morbidity in Women with Cardiac Syndrome X

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Abstract

Background: Cardiac Syndrome X, the triad of angina pectoris, a positive exercise ECG for myocardial ischaemia and angiographically smooth coronary arteries, has an undetermined pathogenesis and ineffective treatment regimen. As such, this thesis was concerned with the identification and treatment of psychological morbidity in women with Cardiac Syndrome X. The thesis contains original work, entirely undertaken by the author unless otherwise stated. **Methods:** The thesis is split into three studies. Study One explored the psychosocial differences between women with Syndrome X, coronary heart disease (CHD) and an age-matched control. Study Two was a pilot study to explore the impact of a six-week moderate intensity exercise program on women of a similar age to patients diagnosed with Syndrome X. Study Three was an exploration of cardiac rehabilitation as a treatment for psychological morbidity in women with Cardiac Syndrome X. **Results:** Study One showed that women with Syndrome X had higher levels of psychological morbidity than women with CHD and the healthy control. Study Two demonstrated that a six-week moderate intensity exercise program improved psychological well-being and quality of life in healthy middle-aged women. Study Three showed that an eight-week exercised based cardiac rehabilitation program improved psychological and physiological morbidity and quality of life in women with Cardiac Syndrome X. **Conclusion:** Women with Cardiac Syndrome X have high levels of psychosocial morbidity. Moderate intensity exercise improves psychological well-being in healthy women of a similar age to patients diagnosed with Syndrome X. Cardiac rehabilitation was identified as a successful and accessible treatment for psychological and physiological morbidity in women with Cardiac Syndrome X.

Abbreviations

31P-NMR	Phosphorus-31 nuclear magnetic resonance spectroscopy
ACE	Angiotensin converting enzyme
ANOVA	Analysis of variance
AT	Autogenic training
BMI	Body mass index
CABG	Coronary artery bypass graft
CBT	Cognitive behavioural therapy
CHD	Coronary heart disease
CMR	Cardiac magnetic resonance imaging
CR	Cardiac rehabilitation
CRP	C-reactive protein
ECG	Electrocardiography / electrocardiogram
EEG	Electroencephalography
ERA	Estrogen Replacement and Atherosclerosis
ET-1	Endothelin-1
FMD	Flow mediated dilatation
GP	General practitioner
GTN	Glyceryl trinitrate
HADS	Hospital Anxiety and Depression scale
HAQ	Health Anxiety Questionnaire
HERS	Heart and Estrogen / Progestin Replacement Study
HHR	Heart rate reserve
HLOC	Health locus of control
HRM	Heart rate monitor
HRT	Hormone replacement therapy
Kcals	Kilocalorie
LBBB	Left bundle branch block
LMP	Last menstrual period
LV	Left ventricle
LVF	Left ventricular function

MI	Myocardial infarction
NCA	Normal coronary arteries
NCCP	Non-cardiac chest pain
PC	Dr. Pornpat Chandrruangphen
PET	Positron emission tomography
POMS	Profile of Mood States
PSW	Progressive shuttle-walk test
PWV	Pulse wave velocity
SGH	Support gap hypothesis
SPA	Social physique anxiety
TENS	Transcutaneous Electrical Nerve Stimulation
TM	Transcendental meditation
$VO_{2\,max}$	Maximum volume of oxygen uptake
WHI	Women's Health Initiative

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Table of Contents

Abstract 2

Abbreviations 3

Acknowledgements 5

Table of Contents 6

List of Figures 9

List of Tables 10

1: General Introduction 12

1.1 Preamble 12
1.1.1 Coronary Heart Disease 12
1.1.2 Cardiac Syndrome X 17
1.2 Aims and Objectives of the Thesis 22

2: Physiological Aspects of Cardiac Syndrome X 23

2.1 The Pathophysiology of Cardiac Syndrome X 23
2.1.1 Myocardial ischaemia 24
2.1.2 Pain Perception 32
2.1.3 Endothelial Dysfunction 35
2.1.4 Insulin Resistance 41
2.2 The menopause and hormonal influence 43
2.3 Treatment 46
2.4 Summary 50

3: Psychosocial Aspects of Cardiac Syndrome X 53

3.1 Psychosocial Aspects of Cardiac Syndrome X 53
3.2 Treatment 61
3.2.1 Meditation and relaxation 61
3.2.2 Cognitive Behavioural Therapy 62
3.2.3 Group treatment 67
3.2.4 Exercise Treatment and Cardiac Syndrome X 68
3.3 Social support 72
3.3.1 Social Support, Isolation and CHD 75
3.3.2 Social Support and Gender 79
3.4 Family History 82
3.5 Menopause 85
3.6 Summary 89

4: A Psychosocial Investigation of Cardiac Syndrome X 92

4.1 Aims and Objectives of Study Two 93
4.2 Methodology 94
4.2.1 Ethical Approval 94
4.2.2 Inclusion and Exclusion criteria 95
4.3 Participant identification and recruitment 96
4.3.1 Cardiac Syndrome X 96
4.3.2 Coronary Heart Disease 97
4.3.3 Healthy Controls 99
4.4 Study Visit 100
4.5 Questionnaires 102
4.6 Statistics 103
4.7 Results 105

4.7.1 Subjects ... 105
4.7.2 Medications, hospitalisations and illness ... 106
4.7.3 Hospital Anxiety and Depression Scale ... 107
4.7.4 Health Anxiety Questionnaire ... 107
4.7.5 Life events ... 108
4.7.6 Familial History of CHD ... 109
4.7.7 Social Contact ... 109
4.7.7.1 Friends ... 109
4.7.8 Relatives and Confidant ... 110
4.8 Gynecological factors ... 111
4.8.1 Oestrogen plasma levels ... 111
4.8.2 Multivariate analysis ... 112
4.9 Discussion ... 114
4.9.1 Study Limitations ... 120

5: Psychological Benefits of Exercise in the Older Woman ... 122

5.1 Exercise and the older woman ... 123
5.2 The Psychological impact of exercise ... 125
5.2.1 Exercise and psychological benefit among the older population ... 127
5.2.1.1 Physical fitness and exercise intensity ... 129
5.2.1.2 Self-efficacy ... 132
5.2.2 The psychological impact of exercise in older women ... 134
5.2.3 Cross sectional and Acute Studies of the Psychological Impact of Exercise in Women ... 135
5.2.4 Longitudinal Studies of the Psychological Impact of Exercise in Women ... 138
5.2.5 Choice of exercise intervention ... 144
5.2.6 Proposed Mechanisms for the Psychological Effect of Exercise ... 148
5.2.7 Summary ... 152
5.3 Aims and Objectives of Study Two ... 153
5.4 Methodology ... 154
5.4.1 Ethical Approval ... 154
5.4.2 Participants ... 155
5.4.2.1 Inclusion and Exclusion Criteria ... 155
5.4.3 Participant identification and recruitment ... 156
5.4.4 Randomisation and Baseline Study Visit ... 157
5.4.5 Post-exercise and six-week follow-up assessment ... 160
5.5 Questionnaires ... 161
5.6 Exercise Intervention ... 163
5.7 Statistics ... 165
5.8 Results ... 165
5.8.1 Subjects ... 165
5.8.2 Baseline data ... 167
5.8.2.1 Group Differences ... 167
5.8.2.2 Social Network, Friends, Relatives and Confidant ... 168
5.8.2.3 Gynaecological Factors ... 168
5.8.3 Post intervention ... 168
5.8.3.1 Compliance and Performance ... 168
5.8.3.2 Hospital Anxiety and Depression Scale ... 169
5.8.3.3 Health Anxiety Questionnaire ... 170
5.8.3.4 SF-36 Quality of Life ... 170
5.8.4 Six-week follow-up ... 171
5.9 Discussion ... 174
5.9.1 Study Limitations ... 177

6: Cardiac Rehabilitation and Cardiac Syndrome X ... 180

6.1 Cardiac Rehabilitation ... 180
6.1.1 Cardiac Rehabilitation and Psychological Health ... 185
6.1.2 Quality of Life and Cardiac Rehabilitation ... 188
6.1.3 Women and Cardiac Rehabilitation ... 191

6.1.4 Mechanistic Pathway 194
6.1.5 Summary 197
6.2 Aims and objectives of Study Three 199
6.3 Methodology 201
6.3.1 Ethical Approval 201
6.3.1.1 Active Syndrome X Patients 202
6.3.2 Cardiac Rehabilitation 202
6.3.3 Study Interventions: Cardiac Rehabilitation and Symptom Monitoring Control 204
6.3.3.1 Cardiac Rehabilitation 204
6.3.3.2 Symptom Monitoring Diary 207
6.3.4 Participant Recruitment 208
6.3.5 Inclusion and Exclusion Criteria 212
6.3.6 Visit One: Consent and Randomisation 212
6.3.7 Visit Two: Post-Rehabilitation and Symptom Monitoring 215
6.3.8 Eight-Week Follow-up 216
6.3.9 Active Syndrome X patients 219
6.3.10 Questionnaires 220
6.3.11 Statistics 223
6.3.12 Sample Size Calculation 223
6.4 Results 224
6.4.1 Subjects 224
6.4.2 Baseline analysis 226
6.4.2.1 Symptoms, medications and hospitalisations 226
6.4.2.2 Family history of CHD 226
6.4.2.3 Gynecological factors 226
6.4.2.4 Social network 228
6.4.2.5 Comparison of rehabilitation and control groups 228
6.4.3 Post-intervention 229
6.4.3.1 Adherence and attrition 229
6.4.3.2 Psychological measurements 229
6.4.3.3 Symptom severity and frequency 230
6.4.3.4 Physiological measurements 231
6.4.4 Follow-up: Eight-weeks post-intervention 231
6.4.4.1 Rehabilitation group: Continuation of exercise at follow-up 233
6.4.5 Active Syndrome X Patients 233
6.4.5.1 Psychological Comparison of Active and Baseline CR Study Data 233
6.5 Discussion 235
6.5.1 Study Limitations 240
6.6 Conclusion 241

7: General Conclusions 243

7.1 Study One: The Psychological Aspects of Cardiac Syndrome X 243
7.2 Study Two: The Psychological Effect of Exercise Training in Healthy Postmenopausal Women 245
7.3 Study Three: Angina Frequency, Psychological Morbidity and Quality of Life in Women with Syndrome X: The Impact of Cardiac Rehabilitation 247
7.4 Summary 248
7.5 Future Research 249
7.5.1 Cardiac Rehabilitation, Exercise Intervention and Physical Activity 249
7.5.2 Improved Social Support 250
7.5.3 Stress Reduction and Relaxation 250

8: References 252

9: Appendices 277

10: Publications 335

List of Figures

Figure 1.1.1: A normal ECG trace showing the five labelled phases.....13
Figure 1.1.2: As ECG showing ST-segment depression.....14
Figure 1.1.3: An angiographic image showing normal coronary arteries.....16
Figure 1.1.4: An angiographic image of diseased coronary arteries.....16
Figure 4.7.1: The effect of social network size on the HADS and HAQ scores of Syndrome X patients.....110
Figure 4.8.1: Plasma Oestrogen levels of the three groups on the basis of HRT use.112
Figure 5.4.1: The study design, questionnaires administered and information gained at each time point of the study.....159
Figure 5.8.1: The effect of exercise on the HADS scores of healthy postmenopausal women.....169
Figure 5.8.2: The effect of exercise on the HAQ scores of healthy postmenopausal women.....170
Figure 5.8.3: Changes in Total HADS score of the two groups over the duration of the study.....171
Figure 5.8.4: Changes in SF-36 Physical functioning score of the two groups over the duration of the study.....172
Figure 5.8.5: Changes in SF-36 energy score of the two groups over the duration of the study.....173
Figure 6.1.1: A suggested model for the non-participation of women in cardiac rehabilitation.....184
Figure 6.3.1: The design of Study Three.....218
Figure 6.4.1: The impact of CR on six subscales of the SF-36 in women with Cardiac Syndrome X.....230
Figure 6.4.2:The long-term impact of CR on the SF-36 sub-scales in women with Syndrome X.....232
Figure 6.4.3: The difference between HAQ scores of active and inactive Syndrome X patients.....234

List of Tables

Table 4.2.1: The inclusion criteria for the three groups of volunteers participating in Study One. 95
Table 4.2.2: The exclusion criteria for the three groups of volunteers participating in Study One. 96
Table 4.3.1: Age and number of patients approached to participate from the Royal Brompton & Harefield NHS Trust cardiac catheterisation lists. 98
Table 4.3.2: The response rate from the cohort of CHD patients approached to participate by mail. 99
Table 4.7.1: The demographic characteristics of the three study populations. 105
Table 4.7.2: Percentage of patients with concomitant medical conditions and cardiovascular risk factors. 106
Table 4.7.3: Mean scores of the Health Anxiety Questionnaire (HAQ) sub-scales for all three groups. 108
Table 4.8.1: Results of multiple regression analysis showing the variables most closely associated with total Health Anxiety Questionnaire (HAQ) score. 113
Table 5.4.1: The inclusion and exclusion criteria employed for participants in Study Two. 156
Table 5.8.1: The demographic characteristics of the three study populations. 166
Table 5.8.2: The gynaecological characteristics of the total cohort and two randomised groups 167
Table 6.1.1: The four phases of cardiac rehabilitation. 182
Table 6.3.1: Details of the cardiovascular and active rest station of the CR exercise program 205
Table 6.3.2: The three activity levels on the CR exercise program 206
Table 6.3.3: The pain scale used for diary completion in Study Three. 207
Table 6.3.4: Patient recruitment from the Women's Heart Clinic 209
Table 6.3.5: The response rate from the cohort of Syndrome X patients approached to participate by mail. 211
Table 6.3.6: The inclusion and exclusion criteria for participants in Study Three. 212
Table 6.4.1: The demographics of the Cardiac Syndrome X patient population participating in Study Three. 225

Table 6.4.2: The reason for hysterectomy among hysterectomised women with Cardiac Syndrome X. 227

1: General Introduction

1.1 Preamble

Chest pain is most commonly associated with Coronary Heart Disease (CHD), the leading cause of death in the Western World [1]. It is estimated that among the developed nations over two million people die annually as a result of CHD [1], and as a result over one million Europeans undergo coronary angiography every year [2].

1.1.1 Coronary Heart Disease

Coronary angiography is the most accurate diagnostic test for establishing the existence of diseased, narrowed or blocked coronary arteries, the hallmark of CHD. Coronary heart disease is normally identified when the arteries supplying blood to the heart become obstructed by atherosclerotic plaque, a fatty deposit that builds up within the arterial wall. Although the presence of atherosclerotic plaque defines the diagnosis of CHD, the vascular endothelium is recognised as a key factor in the development of the disease [3]. Major CHD risk factors including hyperlipidaemia, diabetes, hypertension and smoking are known to damage the endothelium or interfere with its ability to repair after injury [4]. Endothelial damage provokes an inflammatory response that attracts macrophages (key cells in the immune response) and lipids, setting the stage for the development of atherosclerotic plaque [3].

Atherosclerosis can limit the supply of oxygen rich blood to the heart muscle (myocardium) resulting in myocardial ischaemia: a reduction in blood flow to the

heart muscle, which is not sufficient to maintain myocardial oxygen demand. Ischaemia can result in the patient experiencing chest pain, also known as angina pectoris. In the most extreme cases, atherosclerosis can totally occlude an artery, starving the cardiac muscle of oxygen, resulting in Myocardial Infarction (MI), causing permanent damage or death of the heart muscle. The acute rupture of atherosclerotic plague is associated with a thrombotic occlusion of the coronary artery also resulting in an acute MI.

Chest pain is the most common symptom of CHD that will initially lead patients to seek medical advice. From a preliminary consultation with a family doctor, subsequent referral often includes an electrocardiography (ECG). An ECG shows the electrical activity that result in coordinated myocardial contractions. The ECG trace is defined at five points, each illustrating a different phase of the heartbeat. These points are labelled as PQRST (Figure 1.1.1).

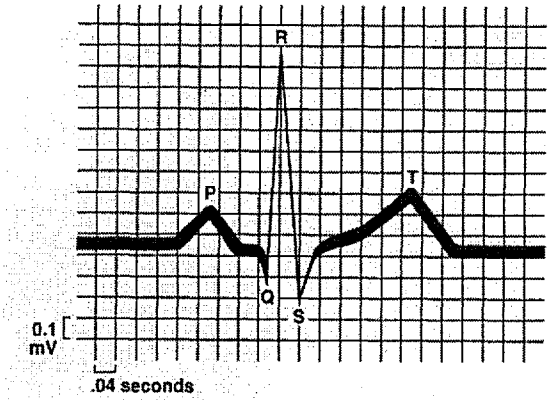


Figure 1.1.1: A normal ECG trace showing the five labelled phases.

A stress-test ECG requires a patient to exercise at an increasing intensity in order to uncover any evidence of myocardial ischaemia. The heart muscle requires more

oxygen and consumes more energy as it beats faster. If there is inadequate blood-flow in response to higher demand, patients can experience exercise-induced myocardial ischaemia and accompanying angina. This can be diagnostically indicated by the phenomenon known as ST-segment depression (Figure 1.1.2) on the patient's ECG. The characteristics are of down-sloping or planer ST-segment depression, as up-sloping ST-segment depression is rarely indicative of myocardial ischaemia and is often associated with a 'false positive' exercise test, an incorrect positive result, often caused by drug interaction, hyperventilation or cardiomyopathy [5]. A true positive stress-test for myocardial ischaemia in the presence of exertional angina is usually indicative of CHD.

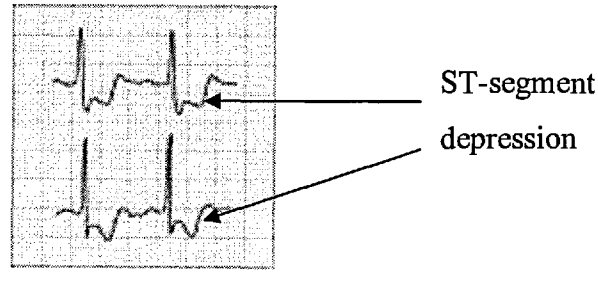


Figure 1.1.2: As ECG showing ST-segment depression.

Following a positive stress-test, patients are normally referred for coronary angiography, which accurately identifies the extent and severity of narrowed or occluded coronary arteries. During angiography, a small catheter is inserted into the femoral artery (although other large arteries can be used), which is then fed into the descending and ascending aorta into the orifices of the coronary arteries. Contrast dye is then injected into the coronary arteries, and the radiographic dye within the artery is imaged and recorded by X-ray (Figure 1.1.3), demonstrating any

malformations or narrowing. Angiography represents the final stage in the diagnosis of CHD, the procedure is invasive and carries with it an increased risk for further complication, including arterial damage (1%), myocardial infarction (often resulting in the need for immediate bypass)(0.5%), or death (0.1%) [6]. Nevertheless, angiography remains the best way to detect the location and extent of narrowing or stenosis within the coronary arteries (Figure 1.1.4). This enables physicians to determine the most suitable treatment for the patient, whether management through medication, angioplasty, stent or bypass surgery is the best option.

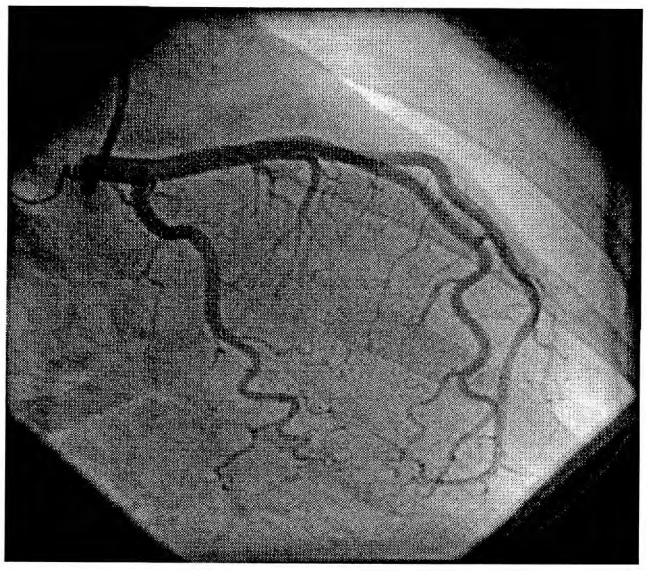


Figure 1.1.3: An angiographic image showing normal coronary arteries.

Figure 1.1.3 illustrates normal, smooth coronary arteries, whereas the irregular contours of figure 1.1.4 illustrate a diseased artery, almost totally occluded by atherosclerotic plaque.

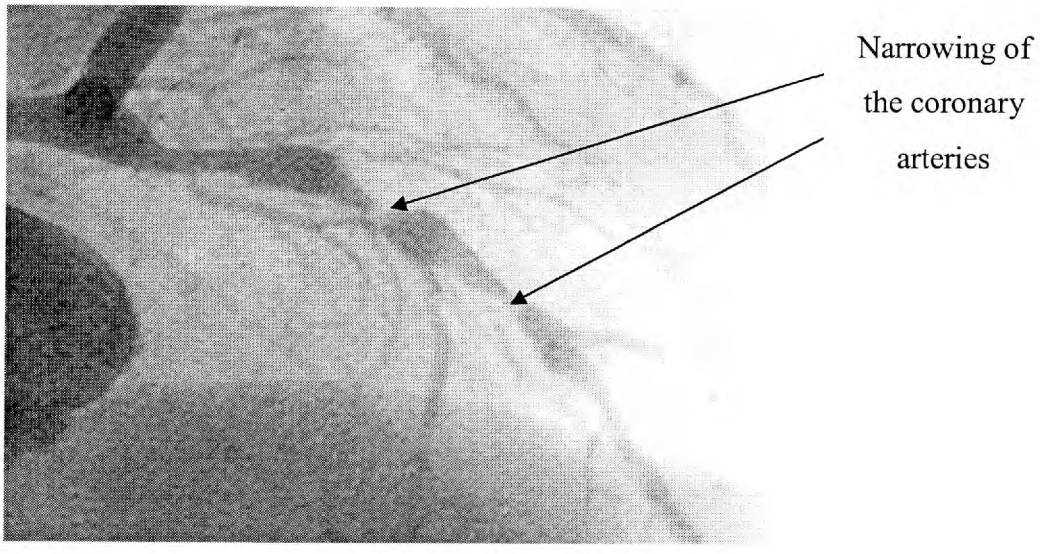


Figure 1.1.4: An angiographic image of diseased coronary arteries.

However, normal or nearly normal coronary arteries are found in approximately 20% of patients who undergo coronary angiography [7] (Figure 1.1.3). A distinct sub-population of patients continue to experience angina following of a positive stress-test for myocardial ischaemia, despite normal angiography, and the majority of these patients are women [7]. The triad of angina pectoris, transient ischaemic ST-segment depression and angiographically smooth coronary arteries is commonly referred to as Cardiac Syndrome X [8], and is named after 'group X', the patients in Kemp *et al*'s study with chest pain and normal coronary arteries [8]. The triad of symptoms was further illustrated later in the same year [9], accompanied by Kemp's editorial [10].

1.1.2 Cardiac Syndrome X

Cardiac Syndrome X (also simply known as Syndrome X) has an undetermined pathogenesis and unreliable treatment regime. The symptoms of Cardiac Syndrome X are not markedly different from those of angina pectoris with coronary artery disease confirmed by angiography. Syndrome X patients often report crushing central chest pain, heaviness, tightness or the feeling of a constricting band round their chest. Many patients experience a combination of these symptoms. Some patients report that pain radiates up in to the neck or down the left arm, while some experience shortness of breath. Many patients report extreme fatigue and tiredness. Most Syndrome X patients experience their pain on exertion, during periods of stress or arousal, or occasionally during periods of inactivity and rest. Patients may have been experiencing symptoms for many years before seeking medical help. Some

patients suffer an acute episode of chest pain, resulting in a relatively rapid clinical response in light of the accompanying ECG changes.

The presence of chest pain is the most common reason for a patient's referral from General Practitioner (GP) to a cardiologist [11]. It is generally assumed that the onset of CHD is later in women than men [12]. However, as some women eventually diagnosed with Syndrome X experience their symptoms at a relatively young age, there are often significant barriers to cardiological referral. Many patients report that they are often prescribed gastro-oesophageal medication, anti-depressants or painkillers, and only receive a cardiological referral after many return visits or emergency admission through Accident and Emergency. However, this may also be related to women's description of chest pain, which has been shown as more diffuse and less concrete than that of men [13]. As almost all patients have an entirely normal resting ECG, it is not until patients undergo a stress-test ECG that the ST-segment depression becomes apparent. At this point patients are referred on for further tests, which may culminate in angiography.

Following a normal coronary arteriogram, patients are often confused and frightened by their continuing and persistent chest pain. Before undergoing angiography, due to severity and frequency of their symptoms, patients are often 'prepared for the worst', while the possibility of gaining a normal outcome can be neglected [14]. Many patients are counselled regarding the chances of angioplasty and stent placement, and are often consented for such procedures prior to angiography. Following the diagnosis of Syndrome X, patients may find it difficult to reconcile the discrepancy between the initial prognosis and subsequent diagnosis [14]. Patients may also interpret any

information provided by the health professional in light of their own beliefs about their illness [15]. As a result, many patients feel confused and vulnerable as, in spite of angiographically normal coronary arteries, an excellent prognosis [16] and reduced risk of developing subsequent coronary stenosis [17], they continue to experience pain.

It should be noted that not all patients who continue to experience chest-pain following normal angiography should be labelled as suffering from Cardiac Syndrome X. Patients experiencing non-cardiac chest pain (NCCP) or minimal arterial stenosis are often categorised as patients with Syndrome X (see Chapter Two). However, only those patients with totally angiographically smooth coronary arteries who demonstrate ST-segment depression in the presence of continuing angina fulfil the full diagnostic criteria for Cardiac Syndrome X. Furthermore, Cardiac Syndrome X should not be confused with Metabolic Syndrome X [18], now most commonly referred to at the metabolic syndrome. The criteria for the clinical diagnosis of the metabolic syndrome includes: abdominal adiposity; abnormal lipid profile; insulin resistance and hypertension, and is a risk factor in the development of CHD [18]. Cardiac Syndrome X was later given the 'cardiac' prefix in order to avoid confusion with the metabolic syndrome [19].

Despite the reassurance of negative angiography, many Cardiac Syndrome X patients find their chest pain symptoms so excruciating that they often present themselves to Accident and Emergency. Here their symptoms are monitored until they are later discharged, having shown no clinical signs of either myocardial infarction or acute coronary syndrome. Frequently patients spend prolonged periods in Coronary Care undergoing additional tests, which shed no further light on a physiological or

pathological cause of their symptoms, but may add to patient's existing anxiety [20]. In an attempt to treat patient's chest pain, cardiologists often rely on conventional anti-anginal therapy such as nitrates, betablockers and calcium-channel blockers (see section 2.4). For immediate relief glyceryl trinitrate (GTN) is often prescribed. Such treatments are often only moderately successful, as although some patients report a marked reduction in their symptoms with therapy, others report little change in the frequency and severity of their chest pain.

Consequently, alternative explanations are being sought for the development and maintenance of symptoms associated with Syndrome X, including psychological well-being and issues relating to quality of life. The global disease burden of depression is greater than ischaemic heart disease, cerebrovascular disease and tuberculosis [21], and has been estimated to cost $43.7 billion per year in morbidity and mortality in the USA alone [22]. It has been suggested that patients affected by chronic disease have a higher risk of depression than the general population [22], and therefore the identification and treatment of psychological morbidity in patients with existing physical impairment is gaining credibility. However, as Syndrome X patients are normally treated in cardiology clinics or general practice, patient's access to psychological intervention is restricted, as is the psychological researchers' access to the patient group. Consequently, psychological and social (psychosocial) research into Syndrome X has been limited thus far.

Understanding the psychology of patients who suffer with Syndrome X may uncover new therapeutic options, and treatments that may address both the patients' psychological and physiological health. Previous psychological studies of

Syndrome X have often included a diverse patient population with NCCP [23;24], while studies of patients with the full diagnostic criteria have been hampered by their relatively small sample size [25;26].

As Syndrome X is found most commonly in women [7], it is important to determine the specific psychosocial factors apparent in this patient group. Comparing women with Syndrome X to female CHD patients and healthy women of similar age will enable the most representative psychosocial research to be undertaken. Similarly, menopause and the mid-life transition is an important psychosocial marker in a woman's life. Comparing the influence of gynaecological and menopause factors in relation to psychological morbidity may highlight the importance of menopause among the three patient groups. The identification of specific psychosocial factors linking women with Syndrome X may also prompt the use of previously unrecognised treatment regimes.

1.2 Aims and Objectives of the Thesis

The aims of this thesis are therefore to:

1. Undertake one of the largest psychological assessments of women with the full diagnostic criteria for Cardiac Syndrome X;
2. Identify any differences in psychological morbidity between women with Syndrome X, CHD and a healthy female control group;
3. Explore the suggested link between menopause, oestrogen depletion and Syndrome X;
4. Identify any external factors which may be associated with increased psychological morbidity in women with Syndrome X;
5. Identify and pilot a possible treatment that may counter the effects of any increased psychological morbidity; and
6. Perform a large randomised controlled-trial of that treatment in an attempt to reduce physiological and psychological morbidity in women with Cardiac Syndrome X.

2: Physiological Aspects of Cardiac Syndrome X

The aim of this chapter is to review the current literature regarding the pathophysiology of Cardiac Syndrome X. It seeks to identify current knowledge while highlighting the paucity of data concerning patients with the full diagnostic criteria for Cardiac Syndrome X. The various mechanistic pathways proposed as the physiological basis of the condition are discussed, along with the limitations of all previous research. Various treatment modalities also receive critical review. However, as the exact pathogenesis of Cardiac Syndrome X is unknown, a universally effective pharmacological treatment regime has yet to be established

2.1 The Pathophysiology of Cardiac Syndrome X

For nearly three decades researchers and clinicians alike have tried to identify the cause of cardiovascular symptoms experienced by patients with Cardiac Syndrome X. Studies in patients with the full diagnostic criteria of chest pain, ST-segment depression and angiographically smooth coronary arteries are relatively uncommon. Most of the previous work in this area has been performed with patients grouped on the basis of angiographically normal or *near* normal coronary arteries. Patients with up to 50% stenosis in a major coronary artery are often included in such studies, casting doubt on the applicability of findings in relation to Syndrome X, by definition requiring angiographically smooth coronary arteries. Similarly, many studies do not include patients with exercise induced ST-segment depression, illustrated by a review of Syndrome X which noted that of 12 papers purporting to explore Syndrome X, only 6 included patients presenting with ST-segment depression [27]. Nevertheless,

research into patients with normal or near normal coronary arteries, along with work into those labelled as suffering 'non-cardiac chest pain' (NCCP), continues to provide the basis for both the pharmacological and physiological treatment of Cardiac Syndrome X.

One of the more active areas of research in recent years has been focussing on the concept of underlying myocardial ischaemia as the physiological cause of Syndrome X. Studies have focused on the re-creation of symptoms in order to explore cardiac blood flow, ventricular function, endothelial function and more recently myocardial perfusion in an attempt to identify any abnormality which would be indicative of myocardial ischaemia during periods of stress.

2.1.1 Myocardial ischaemia

Myocardial ischaemia occurs when insufficient or inadequate blood flow results in the heart muscle failing to receive the required level of oxygen. As the heart rate increases, during activity or periods of stress, myocardial oxygen demand increases. Therefore, exercise induced ischaemia can be provoked by increasing the patients heart rate using techniques such as atrial pacing, which stimulate heart-rate through the use of a pacemaker-type device. In some of the earliest invasive studies investigating NCCP, Cannon *et al* explored the response of 33 patients with chest pain in the presence of angiographically smooth coronary arteries to the vasoconstrictor ergonovine during atrial pacing [28]. The protocol was designed to firstly limit blood flow by constricting the coronary arteries with ergonovine, while artificially increasing the patient's heart rate through the use of a pacemaker. Only

two of the 15 men and 18 women demonstrated ST-segment depression under stress, and as a result this was not a true study of Syndrome X. As a control group was not included, the authors were unable to accurately gauge the normalcy of any response. Nevertheless, they found that patients who experienced chest pain during pacing demonstrated significantly lower cardiac venous flow, a higher coronary resistance and a higher left ventricular end-diastolic pressure. Patients who had abnormal vasodilator reserve showed a reduced left ventricular ejection fraction during exercise compared with patients with appropriate vasodilator reserve. The authors therefore concluded that they had found evidence of myocardial ischaemia in patients with angiographically normal or near normal coronary arteries.

Unfortunately, the authors failed to state whether the noted abnormalities were related to age or gender, if the sub-population of patients who experienced an acute pain response to ergonovine included a higher proportion of women, or indicate the gender of the two patients who demonstrated ST-segment depression. As the majority of patients with Syndrome X are postmenopausal women [7], it would have been of interest to note whether the incidence of abnormal left ventricular (LV) function was more prevalent in this age and gender group.

In order to assess the development and frequency of LV function abnormalities in patients with chest pain in the presence of normal coronary arteries, Opherk and colleagues studied a group of patients with either Syndrome X, left bundle branch block (LBBB) with a negative stress-test ECG, or chest pain without ECG changes of any kind who were followed-up after four years [29]. While patients with LBBB showed a marked deterioration in LV function over the four year period of the study,

Syndrome X patients remained stable showing no reduction in LV performance. The authors present both groups of study patients under the banner of 'Syndrome X' and conclude that their work identifies two sub-groups with distinctly different prognosis, while maintaining that LV function deteriorates in their patient population as a whole. However, patients with LBBB are usually categorised by their condition *per se*, and as a result, this study represents a comparison of two entirely different patient populations. LV function did not deteriorate over time in their study patients with the full diagnostic criteria for Cardiac Syndrome X. Subsequent research in a patient population which fulfilled the stringent criteria for Syndrome X, with a follow-up of an average of seven years also failed to find any deterioration in LV function [30].

In order to further explore the suggested myocardial ischaemia and related LV function abnormalities in patients with chest pain and normal coronary arteries, Cannon *et al* built on their previous work using angiography and contrast venticulography before and after atrial pacing following the administration of ergonovine [31]. Twenty-four patients with typical chest pain during pacing demonstrated significantly lower increases in coronary blood flow and decreases in coronary resistance compared with 26 patients without pacing-induced chest pain. After administration of ergonovine, those who had typical pain either at rest or during pacing demonstrated a significantly lower increase in flow and decrease in coronary resistance than those without pain. As no additional narrowing of the coronary arteries was found during angiography following the administration of ergonovine, the authors interpreted their findings as evidence of myocardial ischaemia, which they argued was as a result of abnormalities of the small coronary arteries or coronary microcirculation.

As with previous work by Cannon and colleagues, a sizeable number of patients chosen to participate in the study did not have angiographically smooth coronary arteries, some presenting with up to 30% stenosis in a major coronary artery, and only two patients developed ST-segment depression during pacing, thus failing to fulfil the true diagnostic criteria for Syndrome X. Diverse coronary flow resistance has subsequently been found when comparing the major coronary arteries in women with <50% stenosis [32] without documented ST-segment depression.

Following on from these findings, Sax *et al* sought to ascertain whether the noted abnormalities in coronary vasodilator response in Syndrome X patients was an indication of a greater dysfunctional global vasodilator reserve [33]. Strain-gauge plethysmography was used to compare their hyperaemic responses to forearm ischaemia with those of an age-matched normal control group. The forearm flow response in patients with Syndrome X was significantly reduced after three and five minutes of ischaemia, peaking at a 21% reduction in vasodilatation in comparison with controls after 10 minutes of ischaemia. Correspondingly, the vascular resistance after ischaemia was also consistently higher in the patients with Syndrome X, which lead the authors to conclude that the abnormalities in coronary vasodilator response previously observed [31] were also apparent in the peripheral arterial bed.
Cannon *et al* conclude that the combined results from their previous work indicate that the pain and symptoms experienced in patients with normal or near normal coronary arteries is caused by myocardial ischaemia, resulting from coronary microvascular dysfunction, or microvascular angina [34]. Although the authors acknowledged that the developmental pathway responsible for the manifestation of

symptoms was still unknown, they argued that abnormal vasomotor response noted during vasodilator studies of patients with normal or near normal coronary arteries indicated that the symptoms were microvascular in origin.

In an attempt to demonstrate the existence of myocardial ischaemia through the use of imaging technology, Buchthal *et al* used phosphorus-31 nuclear magnetic resonance (31P-NMR) spectroscopy to identify metabolic and haemodynamic evidence of ischaemia in women with chest pain the presence of normal coronary arteries, following an isometric handgrip exercise [35]. Twenty percent of the woman with chest pain had myocardial metabolite decreases indicative of ischaemia, not shown in controls. However, there were no significant differences between the two groups regarding haemodynamic variables at rest and during exercise, magnetic resonance imaging and radionuclide perfusion studies of the heart, or changes in brachial flow during the infusion of acetylcholine. Nevertheless, the authors conclude that in spite of the overwhelming majority of women with chest pain demonstrating no myocardial metabolites abnormalities, the noted difference in the remaining 20% of patients was consistent with the existence of myocardial ischaemia caused by microvascular coronary artery disease.

The development of Cardiac Magnetic Resonance (CMR), with higher resolution and increased sensitivity, has enabled the proposed microvascular abnormalities to be more fully explored. Panting *et al* performed myocardial-perfusion CMR in 20 patients with the full diagnostic criteria for Syndrome X in comparison with 10 controls, both at rest and during an infusion of the vasodilator adenosine [36]. While the myocardial perfusion index increased in both the sub-endocardial and sub-

epicardial layers in controls following the administration of adenosine, increases in the myocardial perfusion index were only noted in the sub-epicardium in patients with Syndrome X. These demonstrated perfusion abnormalities, the reduction in sub-endocardial myocardial perfusion index along with a reduction in the ratio of sub-endocardial to sub-epicardial myocardial perfusion reserve index seemed to support the presence of myocardial ischaemia in patients with Syndrome X. However, the use of CMR as a tool for the detection of ischaemia through myocardial perfusion is still under development. The authors admit that as yet, CMR is unable to generate reliable absolute measures in humans, and that further research in needed. However, they argue that their findings are supported by previous work by Buchthal and colleagues [35].

The ischaemic nature of chest pain, experienced by patients with Syndrome X, has been called into question as not all studies have confirmed the presence of myocardial ischaemia [37]. Crake *et al* measured coronary sinus oxygen saturation during incremental atrial pacing [38] (refer section 2.1.1, paragraph one). As the coronary sinus is the main coronary vein, a larger decrease in oxygen saturation would be expected in proportion to increased cardiac activity in patients with myocardial ischaemia. While the majority of patients with confirmed coronary disease demonstrated abnormal decreases in oxygen saturation, the majority of patients with Syndrome X had coronary sinus oxygen saturation changes similar to that of normal controls. The authors concluded that abnormal myocardial perfusion (the passage of blood and therefore oxygen through the heart muscle) and resulting myocardial ischaemia was not the dominant mechanism associated with the symptoms observed in patients with Cardiac Syndrome X.

Rosano *at al* used markers of myocardial ischaemia, including an increase of coronary sinus blood pH and reduction in coronary sinus oxygen saturation, to assess the ischaemic response to pacing in a heterogeneous group of patients with NCCP [39]. The majority of patients had Syndrome X, compared with a matched group with confirmed CHD. Metabolic changes suggestive of myocardial ischaemia were found only in a small percentage of patients with Syndrome X, whereas metabolic indicators of ischaemia were found in all patients with CHD. A link between reduced coronary flow reserve and the presence of myocardial ischaemia was also unsubstantiated by their study.

Camici and colleagues also failed to identify any indicators of myocardial ischaemia in patients with the full diagnostic criteria for Syndrome X, in comparison with age (although not sex) matched controls [40]. Heart rate, great cardiac vein flow, left ventricular end diastolic pressure, coronary resistance, myocardial oxygen consumption and many other markers of potential myocardial abnormality were all essentially identical to those of controls. Normal LV function was identified, supporting the work of Opherk *et al*, who found no evidence of declining LV function after four year follow-up in patients with Syndrome X [29]. Metabolic markers taken following pacing at rest showed no changes associated with myocardial ischaemia, although differences in metabolites of myocardial energy expenditure were noted between Syndrome X patients and controls.

Evidence to support the presence of myocardial ischaemia in patients with Syndrome X is far from conclusive. Many studies using the full diagnostic criteria

for Syndrome X have failed to identify any physiologic or metabolic markers of ischaemia [37;40]. Those studies which have, have mainly focussed on a heterogeneous patient population including patients with such complications as hypertension and minor stenosis [29;31]. In fact, myocardial ischaemia may not be the cause of Syndrome X, as Kaski *et al* [41] succinctly state:

> "The association of effects on chest pain compared with exercise tolerance and ST-segment changes may indicate that Syndrome X is likely to be heterogeneous with multiple pathogenic mechanisms. It may therefore be speculated that the chest pain in such patients may not necessarily be due to myocardial ischaemia." (pp 623, Kaski 2002)

Nevertheless, as myocardial ischaemia has been identified among patients fulfilling the strict diagnostic criteria for Syndrome X [36], myocardial ischaemia may be a factor in certain patients with Cardiac Syndrome X. The heterogeneous nature of the patient population, even in studies employing the full diagnostic criteria, may limit any definitive conclusions regarding the ischaemic nature of Syndrome X [42].

Incidentally, during their study using CMR imaging, Panting *et al* found that 90% of Syndrome X patients reported severe or the worst ever pain experienced during the administration of adenosine, whereas 40% of control reported mild discomfort, the remaining 60% reporting no symptoms at all [36]. These discrepancies in pain perception in Syndrome X patients have been the focus of much recent research, as many feel it is an alternative explanation for the chest pain experienced by patients with Syndrome X.

2.1.2 Pain Perception

While many research groups were exploring the ischaemic nature of the chest pain experienced by patients with Syndrome X, others began to question the expression of angina in the presence angiographically normal coronary arteries. Were Syndrome X patients experiencing a magnification of what others would see as insignificant or inconsequential pain, and if so, why? Researchers therefore began to focus on exploring the pain itself: the sensation, sensitivity and perception of pain.

Patients' responses to various adverse stimuli were explored in order to ascertain whether patients with Syndrome X experienced an abnormal visceral pain perception. Turiel *et al* found that patients with Syndrome X had a significantly lower threshold and tolerance for forearm ischaemia and electrical skin stimulation than patients with confirmed coronary disease [43]. The authors suggest this may in part explain a higher incidence of painful ischaemic episodes reported by Syndrome X patients in comparison to those with CHD. However, without a normal control group, it is impossible to determine what is considered a normal or abnormal pain response. The only firm statements the authors are able to discern is what constitutes a different response from that of patients with coronary disease.

In order to ascertain the existence of any unusual pain response stemming from the coronary arteries, Cannon *et al* compared cardiac sensitivity to catheter manipulation, pacing at various stimulus intensities and intracoronary injection of contrast medium during angiography in a variety of patients; those with chest pain in the presence of

normal or near normal coronary arteries; a hypertrophic cardiomyopathic group; angiographically significant coronary disease patients and those with valvular heart disease [44]. Eighty one percent of patients with normal or near normal coronary arteries experienced chest pain during catheter manipulation, in comparison with 46% of patients with hypertrophic cardiomyopathy and six percent of patients with significant coronary disease. No patients with valve disease experienced pain through stimulation. The authors therefore concluded that abnormal cardiac sensitivity may contribute to the perception of the like-like pain reported by patients with normal or near normal coronary arteries. Conversely, patients with chest pain and normal coronary arteries were found to have a higher pain threshold to thermal stimulation from subsequent cutaneous pain threshold testing than patients with coronary artery disease or hypertrophic cardiomyopathy [44]. However, no relationship between cardiac sensitivity identified through catheter manipulation and cutaneous sensitivity testing was found.

The authors acknowledge the limitations of their study, including the omission of a normal control, which clouds any statement regarding the normalcy of patient's pain response. For example, patients with chest pain in the presence of normal or near normal coronary arteries may report heightened sensitivity in comparison to other pathological groups, but without a normal control it is impossible to accurately state whether that response is abnormal. As with previous research performed by Cannon and colleagues [28], only a small percentage of patients demonstrated ST-segment depression, thus failing to fulfil the diagnostic criteria for Syndrome X. Although differences in intra-coronary pain sensitivity were identified, the reason for the phenomena was not established.

In order to understand the neuronal activity in response to chest pain in Syndrome X, changes in regional cerebral blood flow were used as an index of neuronal activity using positron emission tomography (PET) activity during dobutamine stress echocardiography [45]. This technique should be able to discriminate the areas of the brain that are metabolically active during pain stimuli, while dobutamine artificially increases heart rate. Both patients and controls showed similar cerebral activity during the administration of dobutamine, associated with the sensation of a fast heart rate. However, Syndrome X patients demonstrated cerebral activity in the presence of intense chest pain and ischaemic-like ECG changes in a distinctly separate area of the brain, the insula/frontal operculum junction, not seen in controls or patients with known coronary disease. In spite of the presence of ST-segment depression in the Syndrome X patients, evidence of any LV function abnormalities were not found during the concurrent echocardiography [45]. The localised area of neural activation resulting from chest pain perception without any accompanying LV dysfunction has therefore cast doubt on the assumption that chest pain in Syndrome X is ischaemic in origin. The authors argue that altered central neural handling may result in an abnormal pain sensation, rather than an effect of any underlying myocardial ischaemia.

Gender differences in pain perception have also been explored in relation to the μ-opioid system [46]. The activation of the μ-opioid system suppresses sensory and affective qualities of pain in distinct brain structures [47]. As women express higher levels of perceived pain through noxious stimuli than men [48], it has been suggested that circulating sex hormone may regulate regional μ-opioid receptor

concentrations [49]. Research suggests that women in a low oestrogen and low progesterone state are less able than men to employ the μ-opioid system, thereby having a limited ability to suppress pain [46].

Finally, it has been suggested that any abnormal intracardiac pain sensitivity may be as a results of the normal bell-curve distribution of pain perception [50]. Cannon argues that patients with Syndrome X may simply represent the opposite end of the pain spectrum from a sub-group of CHD patients with 'silent ischaemia', myocardial ischaemia without the presence of accompanying chest pain. Cardiac vigilance, coupled with chest pain intensity has been shown to determine the perceived importance of cardiac pain in patients with suspected MI [51], highlighting the significance of pain perception. Although almost impossible to test empirically, Cannon's theory represents an interesting approach to the pain conundrum of patients with Cardiac Syndrome X.

2.1.3 Endothelial Dysfunction

Although much of the work regarding vascular impairment and functional abnormality of the coronary vasomotor response in patients with Syndrome X has proved inconclusive, some groups have continued to explore endothelial function and its affects on the smooth muscle of the vascular wall. The vascular endothelium, which lines the entire circulatory system, affects vascular constriction and dilatation through the expression of diverse vasoactive substances such as the vasodilator nitric oxide and the family of endothelin vasoconstrictors.

Quyyumi *et al* explored the endothelial function of patients with normal coronary arteries through monitoring the relationship between patients response to acetylcholine (an endothelium-dependant vasodilator, which can also act as a vasoconstrictor in the presence of endothelial dysfunction) and coronary flow response during atrial pacing [52]. Although patients participating in the study were grouped on the basis of having 'normal coronary arteries', the population was heterogeneous, comprising of both hypertensive and normotensive patients, those with minor stenosis, previous history of MI and impaired ventricular function at rest and during exercise, all of which have now been shown to independently affect endothelial function [53]. Nevertheless, the authors found that in a sub-population of patients with an impaired coronary flow response during atrial pacing, endothelium-dependant relaxation response to acetylcholine was also reduced. The authors recognise some of the limitations of their study, including a lack of a control group, but maintain to have found a link between endothelial function and reduced vasodilator reserve in patients with 'normal' coronary arteries.

In order to more accurately explore a suggested endothelial dysfunction, patients with the full diagnostic criteria for Cardiac Syndrome X were compared to patients with atypical chest pain and angiographically normal coronary arteries without ECG ST-segment depression on the basis of their response to intracoronary acetylcholine [54]. In this carefully controlled study, Egashira *et al* noted a marked reduction in response to acetylcholine in patients with Syndrome X, suggesting impaired endothelium-dependant vasodilatation. Interestingly, the authors found that the response was limited to the smaller coronary vessels and that no differences were found between groups when the larger coronary arteries were studied, in accordance with previous

research [55]. Microvascular endothelial dysfunction and coronary blood flow regulation abnormalities have also been shown among patients with minimally diseased coronary arteries [56]. This lead Egashira *et al* to conclude that endothelium-dependant dilatation in the coronary microcirculation may be the cause of suggested myocardial perfusion abnormalities, which in turn may be related to the presence of myocardial ischaemia in patients with Syndrome X.

Several studies have found impaired endothelium-dependant coronary vasodilatation in patients with chest pain in the presence of normal or near normal coronary arteries. Lekakis *et al* sought to ascertain whether peripheral vascular endothelial function was similarly impaired [57]. Flow mediated dilatation was measured following reactive hyperaemia and the subsequent administration of nitro-glycerine to compare the endothelium-dependent and independent response. Flow mediated dilatation was significantly lower in Syndrome X and CHD patients in comparison to controls, demonstrating impaired endothelium-dependant vasodilatation. However, no difference in nitro-glycerine induced response, a measure of endothelium-*independent* vasodilatation was found.

Other studies have shown that plasma levels of endothelin-1 (ET-1), an endothelium-derived vasoconstrictor, were significantly higher in patients with chest pain and normal coronary arteries than that of normal controls [58]. While Kaski and colleagues explored ET-1 levels in subgroup of patients with ST-segment depression, the majority of his patients showed no ECG changes indicative of myocardial ischaemia. The most significant differences were found in those patients with previous myocardial infarction or LBBB, while endothelin levels in Syndrome X patients were

only marginally raised. In light of these findings, coupled with their earlier research [59], the authors concluded that endothelial dysfunction resulting in an increase in vasoconstricting endothelins may be the cause of the suggested 'microvascular angina' in patients with chest pain in the presence of normal coronary arteries.

Newby *et al*, while failing to find an overall increase in ET-1, noted a reduced responsiveness to ET-1 consistent with increased ET-1 production [60]. Although Newby *et al* followed the strict diagnostic criteria for the inclusion of Syndrome X patients, neither the oestrogen level nor menstrual cycle were recorded or taken into account in the timing of the procedures. This was most likely as a result of including both males and females in the sample, which along with a failure to note patients lipid profiles, could have influenced the results. Nevertheless, elevated ET-1 levels have been found in a mixed group of men and pre-menopausal women with Syndrome X in comparison to a group of patients without evidence of ischaemia [61]. Although patient and control groups were closely matched, the control was made up of patients undergoing cardiac investigation for spurious symptomology and therefore could not be classified as a 'normal' control.

Cox *et al* noted that reduced coronary vasomotor responses (the usual action of constriction and dilatation of the coronary vessels) in patients with chest pain and normal coronary arteries were related to the presence of elevated endothelin levels [62]. Along with elevated endothelin levels, gender was also found to be related to reduced coronary vascular response. Although the average age of the female sub-population was 55 years, serum oestradiol concentrations were unrelated to either endothelin or vascular response. However, as a normal control was not included in the study, the

authors were unable to state whether this factor is unique to patients with Syndrome X or a more generalised effect of gender.

Changes in endothelial function have been shown to arise in patients with hypertension, hyperchoesterolaemia and smoking, along with other recognised cardiovascular risk factors, including oestrogen depletion and the onset of the menopause [28;53]. Due to the relationship noted between sex hormones and endothelial function, gender has become a significant predictor of vascular reactivity [63]. The vasoactive properties of oestrogen have been linked to endothelial impairment and myocardial ischaemia [63], while studies of healthy women have demonstrated a significant change in endothelial function at the time of menopause [64]. As a result, the vasodilator effects of oestrogen are now widely recognised and controlled for (for example, matching patients menstrual cycle) when performing studies of endothelial function. Although no concurrent change in vasomotor function was shown, a reduction in ET-1 levels in post-menopausal women with coronary artery disease was noted following the short-term administration of oestradiol [65]. The acute administration of 17ß oestradiol has been shown to improve endothelial function in women with Syndrome X [66]. However, the authors did not measure any change in symptomology related to increased plasma oestrogen concentration and failed to include a control group to provide a normal response.

The use of intravascular ultrasound has enabled the relationship between the presence of sub-clinical atherosclerotic plaque and endothelial function to be fully explored. Intracoronary endothelial function, as measured by the intracoronary infusion of acetylcholine, was compared to the proliferation of atherosclerotic plaque in patients

with chest pain in the presence of normal coronary arteries or minor stenosis [67]. Perhaps unsurprisingly, as the patient population was a heterogeneous group of smokers, hypercholesterolaemics, hypertensives and diabetics without a normal control, an inverse relationship between plaque burden and endothelial function was found.

Endothelial dysfunction has also been related to increased pulse wave velocity (PWV) [68]. A pulse wave from each heart beat travels from the heart down the arterial wall in advance of blood flow [69]. The more rigid the wall of the artery, the faster the wave moves, and thus increased pulse wave velocity is an early indicator of arterial stiffening [69]. Arterial stiffening is characteristic of the development of atherosclerosis, which is a leading determinant of future myocardial ischaemic events in patients with confirmed coronary artery disease [70]. Impaired endothelial function and PWV was observed in a group of predominantly pre-menopausal women with Syndrome X and not identified in a sex matched control group. The authors argue that this could be indicative of generalised arterial dysfunction in the Syndrome X patients. As intravascular ultrasound was not performed, the possibility that the observed increases in PWV in this particular patient population was atherosclerotic in origin and not generalised arterial dysfunction, could not be ruled out.

Atherosclerosis is associated with endothelial dysfunction [53], which in turn has been linked to increased levels of C-reactive protein (CRP), a marker of chronic inflammation related to the development of vascular disease [71]. Recently, CRP has been investigated in relation to Syndrome X. In a carefully controlled study, higher levels of CRP were related to more frequent and prolonged chest pain in patients with

Syndrome X, along with an increased number of ischaemic episodes as measured by 24 hour Holter monitor [72]. Therefore, patients with a lower ischaemic threshold had higher levels of CRP [72]. As CRP is a marker of inflammation that increases in response to injury, infection and pain [73], the authors acknowledge that increased CRP levels related to ischaemic events could be due to the mere presence of chest pain alone. However, as CRP was related to ischaemic episodes with or without the presence of chest pain, the authors argue that CRP is independently related to the pathogenesis of Syndrome X, and not simply a non-specific response to pain.

Little is known about the effect of CRP in relation to arterial stiffness and endothelial function in patients with Syndrome X. In a carefully controlled study, the relationship between CRP levels and carotid artery stiffness was compared between Syndrome X patients and a normal control group [74]. Results showed that Syndrome X patients had significantly higher CRP levels and carotid artery stiffness than controls. The authors suggest there maybe a causal link between inflammation and the development of endothelial dysfunction, which in turn may be related to the presence of sub-clinical atherosclerotic plaque. However, as endothelial dysfunction and atherosclerosis have not been universally identified in patients with Syndrome X, further research is needed to identify the incidence of elevated CRP and its pathogenic effect in patients with Syndrome X.

2.1.4 Insulin Resistance

Impaired endothelial function has been noted in diabetics [75] and hypertensives [76], and as hyperinsulinaemia, indicative of insulin resistance, is often common to both conditions [77], it has been suggested that insulin resistance may be the link between

endothelial dysfunction and Syndrome X [78]. Dean *et al* sought to determine the incidence of insulin resistance in patients with Cardiac Syndrome X, although the inclusion of patients with LBBB among the sample population reduced the impact of their results. A glucose tolerance test provoked hyperinsulinaemia in patents with Syndrome X, but not among the normal control group [78]. This lead the authors to conclude that peripheral insulin resistance may be related to the microvascular dysfunction often noted during studies exploring endothelial dysfunction in Syndrome X. These findings were supported by Bøtker *et al* who found a 40% reduction in glucose uptake by insulin in Syndrome X patients compared to controls [79], while a similar degree of insulin resistance was shown in patients with Syndrome X and variant angina [80]. Chauhan *et al* compared patients with the true diagnostic criteria for Syndrome X with CHD patients and normal controls, as patients with CHD may be expected to demonstrate some degree of insulin resistance [81]. Stimulated hyperinsulinaemia was found in patients with CHD, and although there was a significant difference between the markers of insulin resistance in CHD patients and controls, the results from Syndrome X and CHD patients were broadly similar.

However, not all studies have established insulin resistance in patients with Cardiac Syndrome X. Cavallo Perin and colleagues found no difference in glucose uptake by insulin or glucose effectiveness between patients and controls [82]. The study groups were strictly matched for risk factors associated with insulin resistance, including familial history of Type II diabetes, hypertension and body mass index. The findings were therefore consistent with normal glucose and insulin metabolism in patients with Syndrome X. However, the authors do not discount the presence of insulin

resistance altogether, suggesting instead that associated factors such as family history of Type II diabetes or the presence of lipid profile abnormalities, uncontrolled in other studies, may cause hyperinsulinaemia in a sub-population of patents with Syndrome X. Any relationship between insulin resistance and Syndrome X maybe incidental, as the actual association may lie between the patient and the independent risk factors themselves.

2.2 The menopause and hormonal influence

Cardiac Syndrome X is found most commonly, but not exclusively, in postmenopausal women [7]. The higher prevalence of postmenopausal women in Syndrome X study populations lead many to question the role of ovarian hormones and menopause in the pathogenesis of the condition [30]. Preliminary investigations identified a possible link between Syndrome X and oestrogen deficiency based on the incidence of Syndrome X in hysterectomised and postmenopausal women [83]. Of 107 women with Syndrome X, 61% developed anginal chest pain following the onset of either surgical or natural menopause. Only 11% of Syndrome X patients were experiencing normal menstrual cycle at the time of the study, with an incidence of hysterectomy four times greater than a similar aged population. Incidentally, patients experiencing menopausal symptoms reported that chest pain was often accompanied by hot flushes, while peri-menopausal women reported a greater frequency of symptoms during the luteal phase of the menstrual cycle, when oestrogen levels are naturally at their lowest.

In light of the possible link between Syndrome X and oestrogen deficiency, studies exploring the impact of hormone replacement found that 17β oestradiol reduced the

frequency of angina episodes in postmenopausal women with Syndrome X [84]. All patients had developed symptoms following the onset of menopause, 46% had undergone hysterectomy before they developed chest pain, while the majority of patients were still experiencing menopausal symptoms such as night sweats and hot flushing. Following treatment with 17β oestradiol, a significant fall in chest pain frequency was noted, however there were no concurrent changes in pre- and post-treatment measures, such as heart rate, exercise duration, time to pain or ST-segment depression. The dissociation between chest pain and physiological measures of ischaemia lead the investigators to question the role of myocardial ischaemia in the pathophysiology of Cardiac Syndrome X. Rosano *et al* suggest instead that the analgesic properties of oestrogen may explain the results, adding that oestrogen replacement therapy may successfully combat the chest pain associated with Syndrome X [84]. Gender differences in pain perception [48] and the impact of sex hormones on the μ-opioid system previous mentioned [46] (refer section 2.1.2) also provide further support for the analgesic properties of oestrogen.

Acutely administered conjugated equine oestrogens were also shown to have a positive effect on ventricular repolarisation in patients with Syndrome X measured by ECG [85]. The QT interval is a measurement that represents the total time from ventricular depolarization to complete repolarisation. This process begins at the start of the ECG Q wave and extends to the end of the T wave (see Figure 1.1.1). Long QT intervals are suggestive of myocardial distress. Following the administration of intravenous equine oestrogens, QT intervals were lengthened and QT dispersion reduced in Syndrome X patients in comparison with a control group. The authors argue this may be related to sensitivity to adenosine in patients with Syndrome X.

However, plasma oestrogen levels associated with these changes were far higher than the expected normal range for healthy pre-menopausal women, suggestive of an unrealistic clinical dose. Time-to-pain and ST-segment depression, working capacity and exercise time have also been shown to increase in a small group of postmenopausal women with Syndrome X following the acute administration of transdermal 17β oestradiol [86]. No changes in exercise capacity were observed in the control group. Although changes in exercise test parameters were noted, no mention was made of the severity and frequency of chest pain experienced by the Syndrome X patients for the duration of the study.

The acute and chronic effects of transdermal oestrogen therapy have also been explored in relation to Syndrome X [87]. Coronary and brachial artery endothelial function was measured in a group of postmenopausal women with Syndrome X following either an acute or six-week application of transdermal oestrogen. Endothelium dependant flow-mediated dilatation increased significantly following both the acute and long-term administration of oestrogen, although no concurrent reduction in chest pain was found. As the group sizes were small and unequal, symptomology and oestrogen plasma levels remained unchanged. As data from two different hormone preparations were pooled, the authors were unable to draw any conclusion regarding clinical benefit, in spite of the noted improvements in endothelial function. Further studies have also found that esterified oestrogen had little effect on chest pain frequency or exercise parameters in a group of women with Syndrome X, although an improvement in measurements of quality of life was found [88].

For many years, hormone replacement therapy (HRT) was seen as a safe preparation with a primary indication for the relief of menopausal symptoms and treatment of osteoporosis, while many advocated its use for the primary prevention of CHD [89]. However, in recent years a number of large scales studies including HERS (Heart and Estrogen / Progestin Replacement Study) [90], WHI (Women's Health Initiative) [91] and the population based Million Women Study [92] have cast serious doubt on these assumptions. Patients in the treatment arm of HERS showed an *increased* incidence in CHD related events in the first two years. These findings were subsequently confirmed by the Estrogen Replacement and Atherosclerosis (ERA) trial [93]. The Million Women Study found that an increased relative risk of breast cancer was associated with long-term HRT use, a finding also supported by WHI (which was halted early due to an increased prevalence of invasive breast cancer). As a result, clinicians have now begun to question the role of HRT in general clinical practice, while the discordant findings relating to HRT and Syndrome X have undermined the confidence in HRT as a treatment for this condition.

2.3 Treatment

As patients initially present with symptoms indicative of CHD, many begin their treatment with traditional cardiovascular medications such as nitrates, betablockers and calcium-channel blockers such as diltizem. For immediate relief glyceryl trinitrate (GTN) is often prescribed. However, research exploring various therapeutic interventions specifically targeting patients with Syndrome X has been far from conclusive [94].

As previously mentioned, due to the number of postmenopausal women identified in study populations of Syndrome X, various hormone replacement therapies including transdermal oestrogen, conjugated equine oestrogen's, along with combinations of oestrogen and progesterone have been trialled with varying degrees of success [84;85;87;88]. Some have demonstrated reduced angina frequency and severity, while others have shown little or no symptomatic affect. In light of the recent studies indicating early cardiovascular harm [90] and an increased relative risk of breast cancer [92], the use of HRT as a treatment for Syndrome X may now be on the decline.

Imipramine, an analgesic with independent anti-depressant effect, has been shown to reduce chest pain symptoms in patients with normal or near normal coronary arteries [95]. Others studies have found that imipramine reduced angina frequency without increasing quality of life [96]. The latter investigation explained this lack of improvement in terms of the side effects associated with imipramine, as although a reduction in pain is normally associated with an improvement in quality of life, this effect was lost in light of additional symptomatology. It should be noted that the patient groups in both studies failed to fulfil the exact diagnostic criteria of Cardiac Syndrome X.

The use of benzodiazepines such as diazepam have also been suggested as a treatment for chest pain symptoms due to their analgesic, neuralgic, anti-inflammatory and muscle relaxant effect [97]. However to date, no studies have examined the use of benzodiazepines in patients with Syndrome X.

Trials of electrical neuromodulation devices, such as the transcutaneous electrical nerve stimulation (TENS) machine have been moderately successful in the treatment of Syndrome X [98]. Such devices work on the principle of Melzack and Walls 'Gate Control' theory of pain [99], stimulating underlying nerve fibres to inhibit, or close the gate to the transmission of pain. TENS machines stimulate these nerve fibres through an electrical current applied to the skin. Although Jessurun and colleagues studied a small, heterogeneous group of patients with angiographically smooth coronary arteries and disparate concomitant aetiology, chest pain episodes were reduced in relation to an improvement in myocardial perfusion [98]. As such, more tightly controlled trials would be needed to assess the impact and benefit of TENS as a treatment for Syndrome X

The possible beneficial effect of statin therapies, traditionally used for their lipid-lowering properties, have also been explored in relation to exercise induced ischaemia and endothelium dependant flow mediated dilatation (FMD). Previous research had shown an improvement in exercise induced ischaemia and FMD in hypercholesterolaemic patients following a 12-week treatment of simvastatin [100]. This study was an un-blinded trial without a placebo, and as such was not especially conclusive. In a more tightly controlled study of patients with the full diagnostic criteria for Syndrome X, prevastatin or placebo was administered for three months [101]. Mixed changes in chest pain were reported, although improvements were found in exercise induced ischaemia, exercise time and FMD.

Sub-lingual nitrates, epidermally applied nitrate patches and oral nitrate preparation are often administered to patients with Syndrome X due to their effectiveness as a

treatment for CHD. Observational studies have suggested that nitrate use is effective in controlling symptoms in 40-50% of Syndrome X patients [30]. As yet, no randomised placebo-controlled trails have confirmed the efficacy of nitrates in this patient group. Exercise tolerance and its relationship with the administration of sub-lingual isosorbide dinitirate (ISDN) in patients with Syndrome X was compared to patients with CHD [102]. Although the patient populations were small and a normal control was omitted, the authors found that ISDN significantly worsened exercise tolerance in Syndrome X with the exact opposite true for the CHD group. A slight improvement in exercise duration and time to ST-segment depression had been previously noted in patients with Syndrome X following the administration of sub-lingual nitro-glycerine [103], although a much greater improvement was shown in the comparison group of patients with CHD. However, sub-lingual nitro-glycerine failed to produce any significant increase in exercise duration or time-to-ischaemia in a further group of patients with Syndrome X, while exercise time decreased in 25% of Syndrome X patients [104]. Due to the lack of properly controlled double-blind studies relating to the use of nitrates in Syndrome X, any quantitative conclusions drawn from the existing data should be treated with caution. Anecdotal evidence regarding the efficacy of nitrates seems unsupported by the existing research.

Calcium channel blockers such as diltizem, nisoldipine, amlodipine and nifedipine, along with adenosine triphosphate sensitive potassium channel openers, including nicorandil are also often used in the treatment of Syndrome X. The efficacy of these preparations has yet to be firmly established [94]. Increased exercise time and time to ST-segment depression were noted in a small group of Syndrome X patients in double-blind crossover trial of the angiotensin converting enzyme (ACE) inhibitor

cilazapril [105]. Nisoldipine was found to be as equally effective as ramipril (an ACE inhibitor) at increasing exercise duration and time-to-pain in a small patient group without placebo control [106]. Nifedipine evoked an impaired coronary vasodilator response in comparison with patients suffering coronary artery spasm, although no control was included in order to determine the normal response [107]. In contrast, attempts to correct impaired coronary flow reserve using diltizem in a group of patients with Syndrome X was unsuccessful [108]. In a comparison of three preparations, 10 patients with Syndrome X were administered a betablocker (atenolol), a calcium channel blocker (amlodipine), and a nitrate (isosorbide-5-mononitrate) as a double-blind crossover trial in order to assess any changes in chest pain [109]. Only atenolol was found to significantly improve chest pain episodes. While these studies provide an interesting base for further research, the small sample sizes and methodological inconsistencies limit the scope of any findings. Further large-scale placebo control trials are required to accurately assess the efficacy of such preparations in the treatment of Cardiac Syndrome X.

2.4 Summary

Since the initial description of the pattern of symptoms which have become known as Cardiac Syndrome X, clinicians and researchers have tried to identify the physiologic environment and possible causes which promote the symptomology associated with this debilitating condition. Various possible pathways have been suggested, including underlying myocardial ischaemia and insulin resistance, both of which may be related to endothelial dysfunction. Similarly, endothelial dysfunction may be related to the vasodilatory effects of oestrogen, which in turn may be related to the menopause, pain perception and unusual neuronal activity on the basis of the chest pain stimulus.

However, in spite of the development of techniques such as Cardiac Magnetic Resonance (CMR) and Positron Emission Tomography (PET), due to the pathological heterogeneity within the patient population, clinicians are still no closer to finding a physiological model or successful hypothesis for the development and maintenance of Cardiac Syndrome X.

Very few studies have been conducted with the strict diagnostic criteria of Syndrome X, with many focussing on patients with minor stenosis (<50%), without documented ECG changes or in the presence of LBBB. Although Syndrome X is found in a predominantly female menopausal or postmenopausal population, fewer still concentrate on women alone. While male Syndrome X patients may make up approximately 25% of the patient population, gender specific research may be more applicable in this condition, especially in light of the suggested association with the development of Syndrome X and the menopause in women.

Ideally, clinicians and health care professionals would be concerned only with diagnosis and treatment, however, in the current financial climate, the burden of cost has become all-consuming. In 1995 it was estimated that the cost of diagnosis for a patient with Syndrome X fell between £2,200 and £3,830 depending on the clinical presentation [30]. Each subsequent NHS outpatient appointment costs approximately £120 and every night spent under observation in coronary care another £521 [110]. Thus the cost of diagnosis and long-term treatment of patients with Syndrome X is substantial. Without an accurate pathogenic model or a reliable and cost-effective treatment, the financial burden of these patients will remain a drain on scant NHS resources.

Cardiac Syndrome X is an unusual condition. Patients experience debilitating pain and symptoms that currently have no known cause. They are treated in traditional cardiology clinics with cardiovascular medications that have not definitely been proven effective. They have a good long-term prognosis but this is combined with a very poor quality of life. Patients with Syndrome X have no definitive physiological cause for their symptoms and as such no effective treatment regime. As a result they continue to lead lives governed by their chest pain.

3: Psychosocial Aspects of Cardiac Syndrome X

The aim of Chapter Three is to review the current literature regarding psychological morbidity in patients with Cardiac Syndrome X. The relatively small number of studies performed in patients with the full diagnostic criteria for Syndrome X will be explored, and the existing literature put into context. Although much of the previous psychosocial research in patients with Syndrome X can be criticised for small sample size and methodological inconsistencies, the results remain useful to some degree. Furthermore, although the majority of studies involving unexplained chest pain sufferers have been performed in patients lacking the full diagnostic criteria for Syndrome X, these studies may act as a framework when attempting to understand the psychological puzzle of women with Cardiac Syndrome X. Data from studies involving breast cancer survivors and women from a number of patient populations will also be addressed in order to explore the impact of social support and the perception of risk due to family history of disease. Finally, the psychosocial impact of menopause will be explored, as Syndrome X occurs predominantly in postmenopausal women.

3.1 Psychosocial Aspects of Cardiac Syndrome X

Psychological studies of patients with the full diagnostic criteria for Cardiac Syndrome X are relatively uncommon and limited by small sample sizes. However, it has been suggested that patients with Syndrome X suffer greater levels of neuroticism and anxiety than patients with confirmed coronary disease.

Ruggeri *et al* assessed the relationship between psychosocial morbidity and physiological markers in a small mixed-sex group of Syndrome X and CHD patients with similar angina frequency [26]. All patients underwent a 24-hour ECG Holter monitor, exercise stress test and a battery of seven psychological measures including the Beck Depression Inventory [111] and Hamilton Anxiety Rating Scale [112]. Syndrome X patients suffered significantly higher scores on all measures of anxiety, depression and neuroticism. No differences were found between Syndrome X and CHD patients exercise capacity during stress testing or frequency of ischaemic episodes during Holter monitoring. Syndrome X patients were then split into two groups on the basis of their assessed anxiety level. Syndrome X patients with higher levels of anxiety did not differ significantly in terms of exercise capacity or angina frequency from patients with lower levels of anxiety, although highly anxious patients had a significantly higher number of ischaemic episodes of greater duration than their less anxious counterparts. The difference in age between the Syndrome X (45 years) and CHD (49 years) patient groups may support the previously noted disparity in age of onset. The authors conclude that as Syndrome X patients with high levels of neuroticism and anxiety experience a greater number of ischaemic episodes during daily life, neuroticism may be causally related to changes in microvascular function. They acknowledge that the presence of associated psychological morbidity may only moderate the threshold for ischaemia in the presence of some unknown underlying physiological dysfunction. Nevertheless, they argue that a new treatment regime for Syndrome X patients should be created that includes traditional cardiovascular medication along with anxiolytic and anti-depressant medication to moderate the impact of associated psychological morbidity.

In order to explore the social and psychological characteristics of women with Syndrome X, Corlando *et al* compared 30 women with Syndrome X with a similar number of CHD patients and healthy controls on the basis of sociodemographic, familial and psychological variables [113]. All patients completed five questionnaires including the Maudsley Personality Inventory [114], Illness Behaviour Questionnaire [115] and various symptom inventories, along with specially created demographic and familial information scales. The authors found comparable sociodemographic and familial environment within the Syndrome X group. The majority of Syndrome X patients came from a poorer socio-economic background with lower levels of academic achievement than CHD patients and the control group, and had suffered a greater incidence of traumatic bereavement or emotional trauma. It was also found that the onset of symptoms was related to such periods of extreme stress or traumatic life events in patients with Syndrome X. However, any evidence of increased psychological morbidity was not found. Scores on each measure were comparable with those of CHD patients and controls, despite increased levels of sociodemographic and familial stressors [113]. Hostility, neuroticism and irritability scores were also low, suggesting that 'Type A' behaviour, characterised by stressed, aggressive, hostile behaviour was not apparent in patients with Syndrome X. As a result, the authors argue that comparable psychological morbidity in the presence of higher levels of sociodemographic and familial trauma indicate that patients with Syndrome X are limited in their ability to express emotion in light of a disproportionate ability to cope. Further research is clearly required in order to fully explore the impact of sociodemographic factors on patients with Syndrome X.

Atienza *et al* approached the assessment of quality of life in 66 men and women with Syndrome X through the creation and validation of their own specific questionnaire [116]. They found that quality of life was significantly impaired in Syndrome X patients, which was in turn related to the severity and frequency of angina episodes. Quality of life worsened in patients whose symptoms deteriorated, and improved in patients whose symptoms abated. As this investigation represents a validation study, there are no standards of reference for the scale used, especially as a normal control population was not included. However, the authors argue that as patients with a reduced quality of life score also had the worst angina frequency and severity as noted in self-report angina diaries, the questionnaire is thought to accurately reflect quality of life in patients with Syndrome X.

The deleterious affect of angina on quality of life in patients with CHD, regardless of intervention, has been recognised for some time [117]. In an assessment of quality of life and health status in a group of patients with 11 chronic illnesses (asthma, diabetes, arthritis, back pain, sciatica, hypertension, angina, anxiety, depression, myocardial infarction and stroke), angina patients thought their general health to be worse than all others groups (apart from those with chronic anxiety), despite reporting pain score of less than half of those expressed by patients with sciatica, arthritis, back pain and chronic anxiety [118]. Chest pain with or without confirmed coronary artery disease increases heart-focussed attention [119]. Improvements in quality of life have been shown following both bypass surgery [120] and angioplasty [121], only as long as there is a concurrent reduction in the frequency, severity and duration of chest pain.

As previously mentioned, psychosocial investigations of Syndrome X are limited, with many studies primarily focussed on the general area of 'non-cardiac chest pain'. NCCP studies do not use patients with the full diagnostic criteria for Syndrome X. Patients are assessed on the basis of non-specific chest pain, while NCCP sample populations in psychosocial research include patients without angiography [23;122], without a positive exercise test for myocardial ischaemia [24;123-125] or with abnormal or partially obstructed coronary arteries [126-128]. Nevertheless, in spite of the lack of uniform inclusion criteria, studies of NCCP may act as a guide when exploring psychosocial morbidity in Syndrome X.

The prevalence of NCCP within the general population has been estimated at 35% [129], although chest pain symptoms noted in this population based study were stratified as either gastro-oesophageal or musculosckeletal in origin, without medical examination. Higher levels of anxiety and neuroticism were higher in participants reporting chest pain, while depression and healthcare seeking behaviour was unrelated to chest pain status. Quality of life was impaired only in those participants with the most severe symptoms.

In an investigation of the psychosocial state of patients with NCCP, Bass *et al* followed 46 patients with minimally diseased coronary arteries [130]. Patients underwent clinical interview 24 hours after angiography, but before the angiography results were made known, in order to assess the patients physical, psychological and social functioning. After a 12-month period the patients were re-examined. It was found that patients whose chest pain had failed to improve, or had increased in frequency, had significantly higher psychiatric morbidity at the baseline assessment

than patients whose chest pain frequency and severity had abated. Due to the presence of chronic chest pain, psychiatric morbidity and the increased use of psychotropic drugs a year after negative angiography, the authors conclude that patients with continuing non-cardiac chest pain were:

> '...a chronically neurotic and socially maladjusted group in whom psychiatric disorder presents with predominantly somatic symptoms.' [130]

They also argue that continuing to prescribe cardiac medications for such patients only served to reinforce the patients concerns about their heart and reflect the physicians' uncertainty regarding the nature of their pain. Others have suggested that physicians without psychiatric training may be unable to detect underlying psychiatric morbidity in patients presenting with diffuse symptomology [131], as both depression and anxiety related panic disorders are often masked by physical manifestation.

A number of studies have compared patients with NCCP to patients with other chronic pain syndromes. Patients with chronic rheumatoid knee pain and normal controls were found to have lower levels of anxiety and depression than a mixed group of NCCP patients with angiographically smooth coronary arteries without ECG changes indicative of ischaemia [125]. The authors suggest that the higher levels of anxiety and depression in NCCP patients could be related to a lack of emotional support, along with an increased tendency towards problem-focussed coping. Such factors were unrelated to physical limitation differences between the two patient groups. Although patients reported similar pain severity, the location, diagnosis and prognosis of the two groups were such that the use of patients with chronic

rheumatism as a comparison against those suffering acute chest pain could be called into question.

Ho *et al* compared similarly gender mixed patients with chest pain and angiographically smooth coronary arteries without a positive exercise test for myocardial ischaemia or oesophageal abnormalities, to patients with either endoscopic abnormalities or those waiting cholecystectomy for symptomatic gallstone disease [132]. Following psychological assessment, the group of patients with non-cardiac and non-oesophageal chest pain were found to have a higher prevalence of lifetime psychiatric diagnosis. This, the authors believed, was accounted for by the increased frequency of panic disorder, obsessive-compulsive disorder and major depressive episodes within the group. In a recent review of chest pain and panic disorder, the absence of CHD, being of young age, female and having high levels of self-reported anxiety were predictive of panic disorder in patients with chest pain [133]. Beitman *et al* found that 34% of NCCP suffered from comorbid panic disorder, which was related to higher anxiety, depression, hostility and paranoia [134]. Interestingly, Ho *et al* found no relation between duration of chest pain and psychiatric morbidity, despite the longer duration of suffering experienced by patients with non-cardiac and non-oesophageal chest pain [132].

Lantinga *et al* identified significantly higher levels of neuroticism in a predominantly male group of patients with normal or near normal coronary arteries and persistent chest pain in comparison to a group of patients with confirmed coronary disease [135]. No differences were found in self-reported anxiety and depression between men with minimally diseased coronary arteries and normal controls [136]. Spousal reporting of

patient's anxiety and depression levels differed between groups, although the benefit of such subjective reporting of the patient's psychological health has yet to be proven.

It has been suggested that certain psychosocial characteristics may cause the continuing behavioural limitations expressed by patients with NCCP [137], while Cannon *et al* have interpreted their findings in light of a behavioural response to pain [44]. They suggest that an increased pain sensitivity identified in patients with chest pain and NCA without documented ST-depression may provoke a behavioural response in the form of anxiety, depression or panic disorder, which could be a secondary consequence of patients heightened awareness of chest pain.

A study that examined the quality of life of women in the presence or absence of ischaemia and angiographically documented coronary stenosis or NCA, found that patients with chest pain, NCA and without ischaemia had the poorest quality of life [138]. Patients with Syndrome X and ischaemic CHD were found to have lower levels of depression than CHD and NCA patients without evidence of ischaemia. The authors explain their findings in terms of functional impairment, suggesting that patients who are able to exercise to the ischaemic threshold and beyond may have a better quality of life, as they are less functionally impaired. Women in this study without ischaemia, NCA and chest pain weighed more and suffered a greater number of physical symptoms, which may support the author's suggestions.

In order to explore the behavioural basis for elevated anxiety noted in patients with NCCP, Aikens *et al* sought to ascertain the number of co-existing health related fears apparent in a mixed group of NCCP patients presenting with chest pain at an

Accident and Emergency department [139]. None of the patients had a positive stress-test for myocardial ischaemia, while a number of patients had up to 50% stenosis in a major coronary artery. The authors found that cardiopulmonary fear was the best predictor of cardiac complaints, suggesting that the fear of cardiopulmonary sensations may increase levels of perceived pain, resulting in greater disability and cardioprotective behaviour. Therefore increased anxiety may be triggered by either real or perceived cardiac stimuli or the deviation from cardioprotective behaviour, which may in turn provoke an attack of NCCP. However, the origin of cardiopulmonary fear manifestation, the basis of NCCP behaviour in such patients was not explored within this study.

3.2 Treatment

A number of studies have tried to address the complex problem of treating of the psychosocial morbidity identified in some patients with persistent NCCP and Syndrome X. Various psychological techniques and therapies have been explored, with varying degrees of success.

3.2.1 Meditation and relaxation

In one of the few psychological intervention studies using the full diagnostic criteria for Syndrome X, Cunningham *et al* explored the affect of Transcendental Meditation (TM) on nine postmenopausal women with Syndrome X [25]. Changes in a number of physiological factors were measured pre- and post- intervention, including exercise duration, heart rate and blood pressure. Quality of life was also recorded. Time to ST-segment depression, frequency of chest pain and quality of life all improved following the course of meditation. Although the authors recognise the

methodological limitation of this small pilot study, they argue that their findings may best be explained in terms of an integrated, psychophysiologic adaptive response involving cortical, autonomic, neuroendocrine and cardiovascular systems.

Stress reduction and relaxation therapy is currently encouraged as a self-administered technique for the treatment for many conditions, including chronic diseases such has CHD [140], cancer [141] and those manifesting in chronic pain [142]. As yet, there is little data regarding the systematic pathway by which relaxation is effective. However, meditation is thought to reduce catecholamines, the collective term for the hormones adrenaline, noradrenaline and dopamine, which are involved in readying the body for the "fight-or-flight" response to stress. When these hormones are released, the heart beats stronger and faster, while blood pressure rises. Regular practitioners of TM have been shown to have lower levels of urinary catecholamines metabolites [143], while a reduction in catecholamine levels has been shown in non-meditators following an intervention program of TM [144]. However, studies have been far from conclusive, as increased levels of urinary catecholamines, along with other autonomic indices of arousal, have been shown in regular meditators in comparison with novices [145].

3.2.2 Cognitive Behavioural Therapy

Mayou *et al* explored the impact of Cognitive Behavioural Therapy (CBT) on 37 men and women with non-cardiac chest pain, randomising patients into 12 weeks of CBT or an assessment only control [23]. The majority of patients randomised into the study had not undergone angiography and were all relatively young (49 ± 9 years). The Cognitive Behavioural approach used in this study had been designed for use within a

non-cardiac chest pain population [146] and adhered to the main principals of CBT to address non-cardiac chest pain in three ways. Firstly, the treatment aimed to offer an alternative, non-cardiac explanation for the patients symptoms by addressing the problem as a combination of physical, cognitive and behavioural factors, while challenging any catastrophic (i.e. 'I have chest pain, therefore I must be having a heart attack') interpretations of their symptoms. Secondly, the technique aimed to teach patients how to cope with symptoms using behavioural interventions such as relaxation and controlled breathing. Finally, the authors hoped to address problems that may have maintained the patient's symptoms, including stress or anxiety caused by work, family or relationship difficulties. The majority of patients randomised into the CBT arm of the study showed clinically significant improvements in almost all the outcome measures, including symptom severity and frequency, while improving mental state, quality of life and increasing social activities. Patients in the assessment only control also showed an improvement, although less pronounced than with CBT. This may in part be due to the fact that the assessment involved reassuring the patients of the benign nature of their illness, along with suggesting relaxation techniques and particular coping styles.

Van Peski-Oosterbann *et al* have also explored a previously piloted method of CBT [147] in patients with non-cardiac chest pain, randomising 65 men and women into either four to twelve weeks of CBT (depending on the severity of their symptoms) or a 'usual care' control [24]. Patients were relatively young (51 ± 13 years) and excluded on the basis of a positive exercise test for myocardial ischaemia. A significant number of patients within the CBT group were pain free at the six-month follow-up, while a treatment effect was shown in reducing anxiety and improving quality of life.

The authors suggest that CBT should primarily be available for those patients with the greatest level of disability, in order to maximise the potential benefit, while patients with fewer episodes of chest pain should only be offered CBT if their symptoms persist.

While CBT has been shown to be a useful tool in the treatment of non-cardiac chest pain, the technique does have its limitations. Many clinicians are reluctant to refer patients for treatment outside their area of specialisation, due to time-consuming problems associated with availability and access, along with a lack of knowledge pertaining to such therapies. Patients may also be unhappy to be treated within an overtly psychological environment due to the generally held misconceptions and prejudices surrounding psychological treatment and advice. Mayou *et al* acknowledge that the relatively high dropout rate (41% of the assessment only group and 25% of CBT) and general recruitment problems in their study could have been improved with a greater integration with cardiac care and more obvious backing from cardiologists [23]. Patients may also become confused when one 'medical' treatment regime is abruptly halted in favour of a more psychological one.

Furthermore, not all studies of CBT have shown positive results. A mixed gender group of 57 patients with both positive and negative ECG exercise tests for myocardial ischaemia were randomised into an investigation of a brief (<two hour) post-angiography intervention based on the principals of CBT [148]. Before randomisation, patient's symptomology, psychological health, well-being and mood were assessed. Once the negative angiography results had been made known, patients randomised into the intervention arm of the study met with a cardiac nurse who

discussed the likely causes of their symptoms, coping strategies (including controlled breathing), relaxation advise and information regarding a graded increase in activities to encourage the patients to return to a normal life. Patients were also given a booklet, which reinforced the information they had been given, along with a tape of relaxation and breathing exercises. Control patients received no additional information and were routinely discharged.

Three months after angiography, patients were re-contacted and reassessed. Both groups had slightly improved chest pain, mood and limitation of activities, however there were no significant differences in the key outcome variables between the CBT and usual care group. A non-significant improvement was in fact identified following usual care [148]. The authors noted a difference in patients who were reassured by the negative outcome of angiography, and those who remained worried or were critical of treatment. Such a brief intervention may have been appropriate for patients who were happy with their prognosis but inappropriate and inadequate for patients who required extra support. The authors also acknowledge that their intervention may have been miss-timed. Patients are often informed of the chances of angioplasty and stent placement during their diagnostic angiography and are often consented for such procedures in advance. Patients may be better suited to participating in such brief, CBT based interventions following an appropriate period of adjustment, when they can come to terms with their new diagnosis and have a chance to discuss it with family members or their primary care physician. Similarly, an advice and relaxation tape provided 24 hours after hospital admission for acute MI may have been more effective in reducing anxiety and promoting life style change if the intervention had been more suitably timed [149].

The authors also found that a number of patients were unhappy with psychological assessment and treatment, as they felt such an intervention implied that their symptoms were 'all in the mind'. The difficulties Sanders *et al* experienced when attempting to deliver a psychological treatment within a cardiological environment mirror those of Mayou *et al* [23], with patients becoming suspicious of a sudden change in treatment from a cardiological approach to a psychological one. As a result, the authors argue for greater interaction between disciplines in the education and treatment of patients following negative angiography in order to ensure that patients who are vulnerable to prolonged NCCP are identified and offered appropriate psychological treatment.

In light of the attitude of patients offered psychological treatment following negative angiography, Peski-Oosterbaan *et al* explored patients' willingness to accept psychological treatment, and sought to determine the optimum time for offering such treatments to patients with continuing chest pain [123]. Over one thousand patients without specific symptoms of angina or a positive stress-test ECG who suffered from unexplained chest pain were questioned in relation to their interest in 'medical psychological treatment' as therapy for their symptoms. There was no relationship between frequency, severity and duration of chest pain and patients willingness to participate in psychological treatment. Nevertheless, patients whose activities were limited by chest pain were more likely to show an interest in psychological treatment than those whose activities were unaffected.

3.2.3 Group treatment

Potts *et al* explored the use of group psychological treatment to treat both psychological and physiological morbidity in patients with non-cardiac chest pain [128]. Fifty-six patients with <50% stenosis in one or more coronary artery and continuing chest pain were randomised into a crossover study of either treatment or a waiting list control. The treatment was delivered in six sessions over eight weeks to groups of up to six people, and adhered to a broadly behavioural approach. Patients were given the opportunity to discuss their experiences of pain, while also undergoing education and counselling on the nature of their chest pain, relaxation exercises and the use of biofeedback devices to pre-empt and control pain.

It was found that group psychological treatment was associated with a significant reduction in anxiety and depression, along with an improvement of sickness impact and perceived physical impairment. Patients also reported a significant improvement in chest pain frequency and exercise duration, although the length and severity of chest pain episodes were unaffected. Patients were also less likely to believe they had heart disease following treatment, which was significantly related to the frequency of chest pain episodes.

The author's rationale for exploring group psychological treatment was motivated by the desire to find a less labour-intensive and more cost-effective method of delivering psychological treatment to patients with non-cardiac chest pain. They conclude that group psychological treatment had a comparable effect on chest pain symptoms as individual therapy, therefore supporting their treatment regime. However, they failed to acknowledge the impact of the treatment group structure, the additional social

support that it may provide, and the unintentional transformation of the treatment program into a support group.

Support groups have become an integral tool in encouraging patients to cope and adapt to both acute and chronic disease, psychological trauma and psychiatric illness. Support groups were developed and became popular throughout the 1970s and early 1980s. Support and self-help groups initiated by healthcare professionals, doctors and social workers are becoming more common as more is known about the importance of education and post-diagnostic support. It is predicted that within 20 years, self-help groups will become the dominant form of treatment for a number of psychopathologies and non-psychiatric illnesses [150]. Support groups have proved beneficial for breast cancer sufferers, with improvements in quality of life, depression and anxiety found in patients who participated in either a standard cognitive-behavioural or a complementary and alternative medicine support group [151]. Support groups have also had a positive impact on HIV/AIDS patients' ability of cope with disease [152]. Patients with chronic non-malignant pain reported increased social support as one of the most beneficial aspects of the group [153], while support group attendance had a positive impact of the perceived support structure of patients with CHD [154].

3.2.4 Exercise Treatment and Cardiac Syndrome X

It has been suggested that patients with chest pain who suffer co-morbid anxiety or depression may be more likely to avoid those activities that may trigger chest pain symptoms, including physical activity [139]. Reduced levels of physical activity may result in a loss of fitness, which may limit physical ability. This may contribute to a

further loss of fitness, perpetuating a 'vicious cycle' of inactivity, incapacity and emotional distress [155]. Increasing levels of physical activity has been shown to improve both physiological and psychological morbidity among cardiac patients [156;157], while breaking the cycle of inactivity. Although patients with NCCP and Cardiac Syndrome X have been the subject of various pharmacological studies [30;88;95;96;109], very little research has explored the impact of exercise on either the psychosocial or physiological morbidity in patients with Syndrome X.

An early case study suggested that aerobic exercise may help alleviate dyspnoea and improve subjective symptomology through enhanced physical ability in patients with Syndrome X [158]. Eriksson *et al* addressed the physical deconditioning apparent in many Syndrome X patients through the use of an eight-week moderate intensity exercise program [159]. Twenty-six middle-aged women with the full diagnostic criteria for Syndrome X were randomly assigned to one of three conditions; eight weeks of exercise training; eight weeks of mind and body relaxation classes followed by eight weeks of exercise training, or a normal care control. The exercise training was performed on a cycle ergometer three times per week for 30 minutes at 50% HRR. Whether the exercise was performed individually or as part of a group was not mentioned. Time to pain improved following exercise training regardless of group assignment, although pain severity was unaffected, while peak heart rate and peak systolic blood pressure increased. Urinary catecolamines decreased following the mind and body relaxation classes, but were unaffected by the exercise participation. The authors conclude that an eight-week program of moderate intensity exercise improves exercise performance in women with Syndrome X, while advocating the

use of physical training as a tool to break the vicious cycle of chest pain and physical decondtioning [159].

It could be argued that the study design employed by Eriksson *et al* could have increased potential bias, as patients completed a different number of pre- and post-intervention assessments depending on their group assignment. As neither relaxation therapy nor exercise were recognised treatments, the combination of both in one treatment group could be called into question. A cross-over study design may have more accurately assessed the impact of both treatments while increasing the power of the study through the more effective use of he relatively small sample size. The authors also failed to include any follow-up period. Eriksson *et al* also omitted to note the impact of the exercise intervention on commonly used indices of cardiovascular risk factors, such as resting systolic and diastolic blood pressure, heart rate or BMI, while the effect of the various treatments on symptom severity and frequency in daily life also was not recorded. Nevertheless, Eriksson *et al*'s preliminary study demonstrates the potential benefit of low-to-moderate intensity exercise in women with Cardiac Syndrome X.

Building on the work of Eriksson *et al* [159], Tyni-Lenne explored the individual impact of exercise and relaxation therapies on exercise capacity, quality of life and coping in a small group of women with Syndrome X [160]. Twenty-one patients were randomly assigned to eight-weeks of thrice-weekly cycle ergometer group exercise at 50% HHR calculated from a baseline $V0_2$ treadmill test, eight-weeks of twice-weekly group relaxation classes or a usual care control. Health related quality of life improved in both intervention groups in comparison with the control group, while

general coping capacity was unaffected by the exercise or relaxation training. Distance walked in six minutes improved following the exercise intervention, while perceived exertion increased in both the exercise and relaxation groups. No change was shown among controls.

Tyni-Lenne *et al* demonstrated that exercise capacity could improve in women with Syndrome X. However, as baseline angina frequency was not mentioned, and concomitant changes in symptom frequency or severities were not recorded, the impact of exercise or relaxation therapy on the symptoms associated with Syndrome X is unknown. Interestingly, all patients received counselling regarding dietary advice and physical activity before starting the study, but were then instructed *not* to change their lifestyle for the duration of the project. While the authors recognise that the counselling may have affected the normalcy of the control group, it could be argued that the timing and inclusion of such a session may have compromised the entire study design, especially in light of the lack of follow-up. The authors also recognise that the small sample size (seven patients in each treatment arm) may have affected the power of the study, and recommend further research with a larger patient population.

An exercise component was also included in a trial of group psychological treatment for patients with non-cardiac chest pain [128]. Patients were included without ECG changes in the presence of up to 50% stenosis of one or more coronary artery, and therefore did not fulfil the full diagnostic criteria for Cardiac Syndrome X. 'Light physical exercise' was included as part of the treatment package, although the exact nature of the exercise intensity was not recorded. A significant improvement in

exercise capacity was found following the intervention in comparison with controls, suggesting that the exercise intervention was of a level to promote cardiovascular fitness. Patients showed significant improvements in various indices of psychological well-being and quality of life following the group treatment package, along with improvements in symptom frequency and severity. However, the impact of the exercise alone is impossible to ascertain, due to the number of individual therapies used in combination to create the treatment regime.

Therefore, an exercise intervention may be beneficial in the treatment of patients with Cardiac Syndrome X. While the current literature suggests that exercise may modify certain symptom parameters [128;159;160], methodological inconsistencies and confused outcomes measures cloud the value of such results. As a result, the impact of exercise on psychological morbidity in patients with Syndrome X has not been properly addressed.

3.3 Social support

Social support is often defined as the assistance and protection given to others, especially on an individual basis [161]. Support can be tangible or emotional, not always intentional but is often now viewed as reciprocal, an 'exchange of resources' [162]. Langford *et al* propose four categories of social support into which all acts of support can be assigned [161]. These include emotional support, which encompasses love, caring and nurturing behaviour; instrumental (tangible) support which involves the provision of goods, services or aid; informational support, as the title suggests, relates to information provided to a person at a time of stress; and finally appraisal support, which reaffirms and upholds the actions or decisions of

another. The adequacy of tangible support has been investigated in relation the prognosis of patients with CHD [163] when it was noted that inadequate tangible support was a significant predictor of both morbidity and mortality. While no mention of causality is made, it is clear that the impact of social support on long-term illness has a discernible effect.

A number of antecedent factors are suggested as essential in the formation and maintenance of effective social support; namely social network, embeddedness and climate. Social network is the base from which a person could draw their social support, the individual's friends, family and acquaintances [161]. Although a lack of social network can lead to social isolation, an issue in itself, a large social network does not necessarily lead to an increase in social support. Social embeddedness relates to the strength and depth of the bonds which exist between the person and the individuals within their social network [164], while social climate is the personality of the environment, the nature of the relationship between the person and their network, its compassion and understanding [165]. Without a social network, a sense of embeddedness and a compassionate climate, socially supportive behaviours cannot optimally occur.

Further definitions have been put forward to expand the concept of social support. In a review of recent literature, Hupcey [166] grouped various theoretical definitions into five distinct categories, including: the type of support; the recipients' perceptions; the intentions or behaviours of the provider; social network and the reciprocity of the support. Hupcey goes on to illustrate the factors that influence the provision and acceptance of social support. These included the potential disparity between what is

expected and what is received, along with further alluding to the motivation for providing support. Obligation or demand may force people to provide tangible support, but if forced, the emotional and social climate may actually diminish as a result. Heller *et al* have suggested that the perception and interpretation of the support provided is more important that the nature of the support itself [167]. Accurate and positive interpretation is essential in maintaining the reciprocity of the support relationship, as a poor perception or inaccurate interpretation may result in the withdrawal of support.

Expectation of social support, and satisfaction with it, may differ depending on the nature of the relationship between the person and their network of support [168]. Family members may often be expected to provide support, which leads to greater levels of dissatisfaction if support is neither forthcoming nor meets the persons expectations. It has been suggested that support from friends maybe viewed more positively, as it is given without obligation or duty, and that unsatisfactory support from friends maybe viewed less negatively than similar behaviour by family members [169]. The degree of satisfaction with social support may have a greater influence on physiological and psychological distress than the amount of support *per se* [170].

Other studies have suggested that the way support is viewed may be associated with certain personality traits and characteristics. This has been proposed as it has been noted that some recipients are never satisfied with the support they receive, despite the very best intentions of friends and family [166]. The psychoanalytic approach suggests that experience in early childhood may affect the way help and support is perceived in later life. However, studies have thus far failed to show any relationship

between a lack of supportive experiences in early life, the size of the social network and satisfaction with the social support provided [171]. Nevertheless, certain personality traits appear to be related to the size of social support network, suggesting that more extroverted, confident individuals have a larger support structure [171]. Others have suggested that neuroticism may affect the influence of social support on distress and health complaints [170]. The relationship between personality variables, social support and isolation has also been tentatively shown to be gender specific, as women's perceptions of social support may be more related to certain personalities such as extroversion, than those of men [172].

Although many studies have noted the beneficial effects of social support, a negative effect has also been found. A person may draw comfort and support from their social network, but relations within that network can themselves be a source of stress [173]. Negative relationships may have a greater affect on reducing well-being than positive relationships have on increasing it [174]. Again, how the support is perceived by the recipient may lead to a negative effect, as could miss-timed support [175].

3.3.1 Social Support, Isolation and CHD

It has been argued that the prognostic impact of depression in patients with CHD is as detrimental to the patient's health as ventricular dysfunction or atherosclerosis [176]. Epidemiological studies have consistently found a link between depression, social isolation and predicted morbidity and mortality in CHD patients [177]. The degree of health risk associated with social isolation has even been compared with that of cigarette smoking [178]. Social isolation has been shown to predict morbidity in both the general population and patients with chronic illness, including CHD [179] and has

been related to improvements in patients recovery from and adaptation to long-term ill health [180]. Evidence suggests that isolation can be used as an index of social support, as many studies have found that participants with little or no social network have limited access to any form of social support [179]. Nevertheless, when questioned, socially isolated participants in the study by Brummetts *et al* were not dissatisfied with the number of social contacts within their support network, rather the quality of the relationships within their network group.

Studies exploring the relationship between mortality and social isolation have suggested that there is a causal link between level of illness, isolation and delay in seeking medical care [179], and that individuals who are sicker become more isolated [179]. Others have suggested that the relationship between social support and the progression of CHD can be viewed in light of two major models: the stress-buffering model and the main effect [181]. The stress-buffering model implies that social support is only beneficial in the presence of 'high stress', whereas the main effect model holds that social support has an effect on disease regardless of other physical or psychological risk [182]. This may be as a result of a healthier lifestyle, observed in patients with a greater social network, or as a result of a depleted social network during periods of inactivity and fatigue, normally associated with ill health.

Neither view was supported by the research of Brummetts *et al*, which found no relationship between social isolation and the degree of functional state or health perception [179]. Others have suggested that socio-economic status could account for the link between social isolation and mortality [183]. While this view has been

supported by studies exploring social support, depression and mortality [184], there is as yet little evidence to link socio-economic status with social isolation alone.

The effects of social support on outcome following a diagnosis of CHD, myocardial infarction or subsequent cardiac intervention (i.e. CABG, angioplasty or stent) have been comprehensively explored. Population based studies have consistently identified a link between social support and CHD morbidity and mortality in men, while disease severity and proliferation have been shown to be related to a lack of support in women [185]. Having a close confidant has been shown to halve the risk of having further cardiac events in the 12 month post-MI period [186], while higher than expected levels of post-operative symptomology in CABG patients has also been linked to lower levels of pre-operative social support [187]. Women with CHD and greater social support reported higher mental and physical functioning, life satisfaction and fewer depressive symptoms than CHD women with less social support [188], although support was unrelated to severity and frequency of cardiovascular symptoms. However, patient's experience of NCCP seems unrelated to social support [189].

Knox *et al* explored social support and hostility in relation to increased risk of CHD in light of a family history of CHD [190]. A large social support network was linked to reduced likelihood of myocardial infarction in high risk women, whereas social support was unrelated to cardiovascular events in a high risk group of men [190]. A reduced risk of experiencing angina was linked to higher network adequacy in both high and low risk women, while the relative absence of social support in women with high levels of hostility was also associated with increased risk of myocardial

infarction [190]. Social support may therefore be more important in the development of CHD in women with a previous family history of CHD, although the authors acknowledge that missing data, more often from high risk older men, may have biased results.

While the relationship between social support and CHD is normally viewed in a positive light, a few mainly observational studies have explored the behavioural re-enforcement of incapacitating symptoms by patients immediate care givers or significant relations [191]. The only demographic characteristic related to increased symptom frequency in the ERA (Estrogen Replacement and Atherosclerosis) participants was marriage; married patients experienced more symptoms [188]. Ikowitz *et al* sought to examine the relationship between various dimensions of CHD (i.e., illness severity and degree of disability) and the patients' significant others response to the expression of these symptoms [192]. The patients were predominantly male, while all married participants identified their spouses as their significant other. A solicitous response to the patient's symptoms, such as expressions of sympathy and encouraging rest and withdrawal from responsibilities was associated with greater illness severity and disability. This was proposed to demonstrate that positive attention from significant others may inadvertently encourage the re-enforcement of illness behaviours. Depressive symptoms could also be exacerbated by the caregiver's positive attention, also shown in studies of spousal overprotectiveness [193]. The authors acknowledge that while their findings are consistent with the operant-conditioning model of symptom development and proliferation, which states that behaviour is linked to a specific stimulus through a process of reinforcement, further

research is needed in order to explore these preliminary findings in terms of gender and the role of marital satisfaction.

3.3.2 Social Support and Gender

Women are traditionally viewed as society's carers. Women are most likely to be the primary providers of childcare, and are often responsible for caring for older family members. Therefore, it is not surprising to find that women are more frequently cited as providers of social support both within the family and outside it [194]. Robinson and Steel found that women were more likely to turn to the support of another woman when needed, and in some cases were against seeking support from male friends and relatives feeling they didn't have the time to help. This may be more of a reflection of the woman's attitude, rather than the male family members willingness to provide support.

The husband's perceived support of their perimenopausal wives has been explored in a population based community sample [195]. In this fascinating study, the husband's beliefs and concerns relating to the menopause, their understanding of menopause and the source of that understanding were recorded, along with their perceived support of their wife through the menopausal transition. Thirty-two percent of husbands reported offering no support. However, most were able to provide emotional support, being sensitive to their wives' needs (57%) and trying to be active listeners (14.6%). Others reported providing additional instrumental support (6.5%) while some found that avoiding confrontation was the best support strategy (6.5%). Encouragingly, even those who believed they were unsupportive expressed a desire to help.

Twenty-seven percent of respondents reported that they knew nothing or nearly nothing about the menopause, while 57% of those husbands who had any knowledge regarding the menopause gained this information from their wives. Mansfield *et al* suggest that a lack of information pertaining to the menopause may be an important barrier to a husband's provision of support during menopausal transition [195]. They illustrate their views with a statement from one respondent:

> "I did very little since I was extremely ignorant. I was not supportive." [195]

While the wives' view of their husband's support was not addressed, the authors did expand the study to explore the additional mid-life burdens experienced by the husbands, including work pressures and ill health. They suggest that these additional burdens may also prohibit husbands from providing the optimum support to their wives, while the converse may be true. Women's menopausal transition may hamper a wife's ability to provide optimum support to her husband while he faces his mid-life challenges. However, others have suggested that nonspousal support may be more pertinent to women with CHD, as due to discrepancy in age of onset between men and women, women are less likely to be married at the time of their first ischaemic event [196].

Studies involving the physiological effects of social support using blood pressure measurements in laboratory conditions have found that women have greater success at reducing stress through support than men [197]. Support from a female partner was associated with reduced measures of stress in men, whereas a negligible reduction in

stress was noted in women supported by a male partner [198]. However, few studies have examined the gender composition of social support networks.

As a result, the majority of research regarding gender specific effects of social support comes from studies of marriage and bereavement. Epidemiological studies have shown time and again that marriage provides greater health benefits for men than for women [199], although for both sexes the benefits of marriage outweigh the elevated mortality rates associated with remaining single [199]. Relative risk is an expression of the number of times more likely something is to happen in one group compared with another, with a relative risk of one demonstrating equal risk. The relative risk of premature mortality for single men has been shown to range from 2.1 to 2.9 in comparison to married men [200]. For single women in comparison to their married counterparts, the relative risk of premature mortality was only 1.4 [200]. Studies of bereavement have shown similar findings, that widowhood has more negative effects on men than women [201;202]. Nevertheless, it is difficult to draw conclusions regarding the impact and effect of social support in such relationships without further gender specific research.

The Support Gap Hypothesis (SGH) maintains that, in light of research regarding the positive health benefits of marriage in men, men gain and women lose in respect to the exchange of social support within marriage [203]. Most research exploring the SGH has concentrated on the provision of emotional support, traditionally viewed as a feminine domain. It has been shown that men are less comfortable and less skilled in dealing with emotional issues and discussing other distressed states than women [204]. This may lead to women being 'sought out' to provide emotional support, as

previously mentioned. Research has found that even in times of stress, when the husbands support of an ill wife is more crucial than ever, both husband and wife perceive wives as being able to provide more support than husbands [205]. Husbands may be able to offer more tangible support than their wives [206], however few studies have found a discernible difference is the type of support provided by men and women [207;208].

Further studies have explored the supportive demands in the marital relationship, viewing the concept of the SGH as support satisfaction: the discrepancy between experienced and desired support. It has been suggested that women have greater demands and higher expectations of the support provided by their husbands, so feel dissatisfied [209]. Contrastingly, their husbands, who have lower expectation, have higher satisfaction with their perceived levels of support [209]. The view that women have higher desired levels of support has been maintained by Xu and Burleson who also found a discrepancy between desired and experienced emotional and esteem (appraisal) support in women, but not in men [210]. Therefore, it could be argued that when a woman becomes ill, her expectations of support from her husband increase, which may result in further dissatisfaction if the desired support is not fully provided.

3.4 Family History

A family history of disease may lead individuals to become fatalistic about the likelihood of developing similar symptoms [211], particularly in light of increased public awareness regarding the heritability of certain diseases or conditions. It has been suggested that direct exposure to heart disease and modelling of heart-focussed illness behaviour is more prevalent in patients with chest pain and angiographically

smooth coronary arteries than heart disease patients or normal controls [212]. Studies of Accident and Emergency department utilisation by NCCP pain patients found that exposure to cardiac symptoms of close friends or family was a predictor of patient's cardiac symptoms and medical help-seeking behaviour [213]. The authors were unable to fully explain their findings, suggesting a number of possible models in order to explain the relationship, including observational learning or rule governed behaviour, where patients are influenced by friends and family relating to perceived consistencies and correlations between themselves and the symptoms / behaviours of the family member. Both suggested pathways require further research.

Parental cardiac disease has also been shown to have an effect on cardiac anxiety [214] as patients with elevated cardiac anxiety score reported a higher prevalence of parental cardiac problems and disease. Eifert suggests that previous experience of cardiac disease may create a psychological vulnerability to cardiophobia in light of other psychosocial triggers [215]. This supports the view that exposure to parental illness has a direct effect on a persons level of health anxiety and concern [216] and that exposure to a particular disease may make individuals more vulnerable to developing anxieties relating to that disease. This may be particularly relevant in the formation of heart focussed health anxiety in women, as role modelling (a fearful model transmitting fear to an observer) has been shown to occur more frequently in women then men [217].

In a study investigating the perceptions of a family history of heart disease, Hunt *et al* found that women were significantly more likely than men to report a positive family history and ascribed a greater importance to 'family illness and weakness' in the

aetiology of CHD than individuals who reported no previous family history [218]. These findings have been supported by further research showing that women report a perceived family history of CHD with a lone parental mortality, whereas men required a greater number of affected relatives before judging themselves to have a family history of heart disease [219]. Furthermore, Richards *et al* found that participants from deprived areas were more fatalistic about their likelihood of developing CHD than their more affluent counterparts [220]. Participants from deprived areas were often able to report first hand experience of angina and death from CHD in young relatives, compared with the respondents from affluent areas who were more likely to deny familial history of heart disease. Greater perceived vulnerability to heart disease was linked with more frequent exposure to heart disease in family members, along with greater identification with cardiac stereotypes and high-risk groups. Perceived increase risk of heart disease as a result of a family history of heart disease was most apparent in the deprived population, and is neatly illustrated by the following extract from Richards *et al*'s work, taken from an interview with a 57-year old male:

> "Well, wi' this runnin' in the family, it's always on my mind, you know, that if I'm gonnae die – it's gonnae be a heart attack, know? I don't think of myself dyin' wi' anythin' else."

Moreover, it has also been suggested that there is a link between familial history of breast cancer, perception of risk and heightened anxiety leading to greater self-awareness and increased likelihood of breast examination [221]. In an investigation in to the perception of breast cancer risk in breast clinic and general practice attendees, both groups over-estimated the population risk by more than two-fold [222]. This was

accompanied by 69% of the combined group reporting the ten year risk estimates as five times higher than the actual figures [222]. Surprisingly, the perception of this risk of breast cancer was unaffected by a familial history of breast cancer. Healthy volunteers with a positive family history were more anxious than breast cancer clinic attendees with a similar history [223]. Nevertheless, other studies have found that women with a family history of breast cancer had higher levels of anxiety and viewed themselves at great risk of developing breast cancer than those without a family history [224].

3.5 Menopause

The menopause or climacteric transition appears to be a common thread in the development of Syndrome X in women, as oestrogen depletion has been linked to the onset of Syndrome X [83]. Menopause has both biological and social implications, changes related to oestrogen depletion and the cessation of fertility occur both socially and physically [225]. It has been argued that the menopause may have negative effects on women's mental health, such as increasing mood disorders and depressive illness [226], along with psychiatric disturbances [227]. Studies have also shown that women who have experienced stressful life events run an increased risk of developing mental illness around the time of the menopause [228].

However, recent research has failed to establish a link between menopausal endocrine changes and negative mood. In a community-based population of mid-life women, health status, psychosocial and lifestyle variables were shown to be related to mood and over-all well-being, whereas menopausal status was not [229]. Psychosocial and lifestyle factors, along with health experience may have a greater effect on mood

during the menopause than hormone levels [230], while a combination of psychosocial factors and experience of ill health have shown a greater affect on self rated measures of health status than the menopausal transition [231]. To date, studies have failed to identify a direct link between mood and hormone levels in any stage of the menopausal transition, as mood and hormonal levels were shown to fluctuate independently [232]. Well-being has been shown to improve and the incidence of depressive illness fall during the menopausal transition, irrespective of the decline in circulating hormones [233]. Nevertheless, menopause may act as a catalyst, making women more vulnerable to negative moods caused by previously unremarkable events, such as daily difficulties and poor health perception [230]. It has also been suggested that menopause may be seen as an opportunity to legitimise symptoms of anxiety and depression that a woman may have experienced for many years, using the 'excuse' of menopause, she can finally seek help [225].

Viewing the menopause only in terms of the cessation of ovarian function fails to address the significant social changes that many women experience during the climacteric. Evidence suggests that a number of psychosocial factors play an important role in determining a patient's quality of life during the menopause [234], and that the most accurate predictor of women's experience of the menopause was their pre-menopausal general health [235]. However, one of the most prominent models of menopause, the biomedical approach, fails to take into account the social and cultural aspects of the menopausal transition. In a recent review, only six percent of publications investigating menopause and depression or mood made mention of social or psychological factors [236], despite evidence which suggests that marital status, job

satisfaction and recent life events have a greater impact on well-being during middle-age than menopausal status [233].

In an attempt to challenge the view of menopause from that of 'deficiency, decline, decay, deterioration and disease', Vanwesenbeeck *et al* sought to determine whether menopausal symptoms were more associated with psychosocial factors than menopausal status [237]. From studying over four thousand women, the authors found that personality and psychosocial factors were more strongly related to menopausal symptomology than menopausal status itself. Women who had undergone surgical menopause suffered the most psychological and somatic symptoms. Increased vasomotor symptoms were more prominent in the postmenopausal group, confirming their menopausal status. Vanwesenbeeck and colleagues conclude that 'menopausal symptoms' should not be confused with indicators of underlying stressful conditions, associated with midlife rather than the menopause. These findings are in accordance with Becker *et al*, who found that higher rates of psychological distress in a similar population of women was unrelated to menopausal status [238].

Morse *et al* identified that demand for concomitant medication during the climacteric transition was determined not only by menopausal status, but also by a number of social and demographic variables, including social support [239]. Women with a social network had a more positive outlook regarding the menopause and were less likely to be depressed [240], while a lack of a suitable confidant has been shown to be related to psychological morbidity in the years following menopause [226]. Therefore, it has been argued that the menopause should be seen as the combination of biological, social and psychological factors – a biopsychosocial transition [241]. Oestrogen depletion may be

the biological trigger for the onset of clinically defined menopause, but the concurrent social and psychological environment in which the menopause is presented should also be considered.

For the majority of women, the primary purpose of hysterectomy is to improve quality of life [242]. Substantial decreases in depression and anxiety have been found following hysterectomy [243], with improvements in symptoms, quality of life and psychological function showing no regression over time [244]. However, this effect may be moderated by age, as women who undergo hysterectomy aged <30 years have been shown to suffer higher levels of psychological morbidity and disruption from pain than older hysterectomised women [245]. A history of psychiatric morbidity prior to hysterectomy may be an important predictor of physical and psychiatric well-being post-hysterectomy [246]. Increased physical and psychological symptomology following hysterectomy has also been identified in a non-psychiatric population [237]. Vanwesenbeeck *et al* found that women who had undergone surgical menopause suffered the most psychological and somatic symptoms than women who had experienced natural menopause [237]. This may be related to absent or inadequate HRT, as a greater improvement in physical and psychological symptoms has been found when hysterectomy was combined with the administration of hormone therapy [242].

The usefulness of HRT as a moderator of the suggested psychological morbidity associated with the menopausal transition has yielded both positive and negative results. While HRT has been shown to reduce anxiety disturbance and feelings of inadequacy, no concurrent reduction in depressive mood has been found [247]. Several

studies have shown that HRT only improves quality of life in patients with menopausal symptoms [248;249]. However, others have shown no improvement in anxiety, depression and associated psychological morbidity in symptomatic menopausal patients following the administration of HRT [250]. In a recent review, Freedman [251] advocates the use of HRT to improve quality of life through the reduction of menopausal symptoms, the cause of discomfort, embarrassment and the loss of self-esteem. However, recent studies such as WHI [91] and HERS [90] (see section 2.3), have raised concerns regarding the safety of HRT. Patients in the treatment arm of HERS showed an increased incidence in CHD, while WHI was halted due to an increased number of invasive breast cancers. The administration of HRT and its role for symptomatic relief during the menopause is therefore currently under review.

3.6 Summary

As there are so few psychosocial studies exploring patients with the full diagnostic criteria for Syndrome X, research examining the psychological aspects of NCCP and CHD has dominated this chapter. Although the common thread of chest pain links Syndrome X and NCCP patients, the association often ends there. The psychological morbidity often noted in patients with NCCP can act as a guide for future research into Syndrome X, but such results should not be extrapolated from one to the other. NCCP studies often include an extremely diverse patient population with broad defining criteria. Patients with motility, oesophageal and gastrointestinal irregularities, along with patients with angiographically proven minor (<50%) coronary disease are often grouped together as patients with NCCP. While psychological morbidity has been noted in patients with NCCP, these findings are

only suggestive of the degree and severity of psychological symptomology that may be apparent in patients with Syndrome X.

Social support, social isolation and the impact of close relationships have been linked to better health and psychological well-being in patients with CHD, but the effect of such psychosocial variables have yet to be explored in relation to Syndrome X. Social isolation appears to have a profound affect on recovery and adaptation to illness in patients with CHD, while marital support has been shown as both beneficial and detrimental to well-being. Social support may be similarly related to Syndrome X and requires further investigation. Known family history of coronary disease also appears to alter the perceived likelihood of developing CHD, while exposure to cardiovascular events in close family members may be related to psychological morbidity. Whether family history of CHD has any affect on the psychological health of patients with Syndrome X has yet to be determined.

Psychological treatments aimed at reducing anxiety, depression and associated psychological disorders have had mixed results. The only study of a psychological intervention in patients with the full diagnostic criteria for Syndrome X gained a positive result, although this small pilot study has yet to be expanded to treat a larger patient group [25]. Cognitive Behavioural Therapy (CBT) has proved useful for some NCCP patients [23;24], while for patients recruited from the cardiological environment, CBT has proved mostly ineffective [148]. Frequency and severity of symptoms should also be included in any psychological intervention aimed at patients with chest pain, as a reduction in symptoms may produce a concurrent improvement in quality of life.

Small sample size and the gender composition of study populations have hampered studies of Syndrome X. Only two psychosocial investigations of Syndrome X have focussed on women alone [25;113], although the concurrent menopausal transition, common to the majority of women with Syndrome X, has not been explored in a psychological setting. Natural or surgical menopause may be related to well-being, positive outlook and quality of life, which may in turn affect the psychological affect of women with Syndrome X, who often first develop symptoms during the menopausal transition. The 'medicalisation' of menopause is a contentious issue, and therefore the relationship between menopause, Syndrome X and psychological morbidity may add an interesting dimension to this ongoing debate.

In order to more fully understand the possible role of psychological morbidity in the development and maintenance of Syndrome X, it is essential that more refined, gender-controlled, large-scale studies are undertaken. Studies of NCCP can only contribute so much to the understanding of Syndrome X, as patients with Syndrome X are a distinctly defined patient group with specific symptoms and diagnosis, not merely a 'catch-all' condition for patients with similar non-specific pain. Not until an accurate assessment of psychosocial well-being is undertaken in this patient group will a suitable and effective psychological intervention become apparent. Previous psychological studies of Syndrome X and NCCP can act as a guide, but further research is needed in order to fully explore psychosocial morbidity in women with Syndrome X, and the contributory affect of menopause.

4: A Psychosocial Investigation of Cardiac Syndrome X

Chapter Four outlines the methodology and results of Study One, a comprehensive exploration of psychological morbidity in women with Cardiac Syndrome X. Women with Syndrome X were compared with a group of similar aged women with CHD, thus comparing patients experiencing similar symptoms in spite of differing aetiology and prognosis, along with a healthy control group. The impact of social support, menopausal, medical and family histories were explored in relation to psychosocial well-being in all three groups, while the relationship between oestrogen and psychological health was also explored. The results and implications of the study findings are discussed in detail.

Study One: The Psychological Aspects of Cardiac Syndrome X

4.1 Aims and Objectives of Study Two

In light of previous psychological research exploring patients with Cardiac Syndrome X, NCCP and normal or near normal coronary arteries, the following questions will be addressed:

- Do women with Syndrome X have higher levels of anxiety and depression than age-matched women with CHD and a normal control group?
- Have women with Syndrome X experienced a greater number of adverse life events than age-matched women with CHD and a normal control group?
- Do women with Syndrome X have a comparable social network to age-matched women with CHD and a normal control group?
- Do women with Syndrome X feel their life partner fulfils the role of confidant and primary support person? Is this comparable with age-matched women with CHD and a normal control group?
- Are life events, social network size, social situation and life-partner support related to psychological morbidity in patients with Syndrome X in comparison to age-matched women with CHD and a normal control group?

In light of research which links menopause and oestrogen depletion with the development of Syndrome X, the following research questions will also be explored:

- Do women with Syndrome X have lower oestrogen levels than age-matched patients with CHD and a normal control group?
- How prevalent are hysterectomy, oopherectomy and HRT use in women with Syndrome X, CHD and a normal control group?
- Is menopause or last menstrual period related to the onset of angina pectoris and associated symptoms in women with Syndrome X and CHD?
- Is psychological health related to oestrogen level, history of hysterectomy, oopherectomy, HRT use or age at last menstrual period in women with Syndrome X, CHD and a normal control group?

4.2 Methodology

4.2.1 Ethical Approval

In order to comply with guidelines regarding patient's participation in research, a submission was made to the Royal Brompton & Harefield NHS Trust Ethics Committee (London, United Kingdom) for permission to perform the study. Ethics approval was given on the proviso all participants gave written informed consent, and that copies of the consent form were given to the patient, kept locally and filed in the patient's medical records (Appendix A). It was also stated that prospective participants should not be approached if they were currently participating in another research study or had done so in the previous 60 days.

4.2.2 Inclusion and Exclusion criteria

The following criteria were employed to identify the eligibility of volunteers from all groups to participate in the study (Table 4.2.1).

Cardiac Syndrome X	Coronary Heart Disease	Healthy controls
Female		
Aged 35 to 85 years		
Willing to give written, informed consent		
Angiographically normal coronary arteries	Angiographically proven coronary artery disease (≥50% lesion in at least one major coronary artery, or major branch), including patients post-CABG, PTCA and MI	No previous history of any cardiovascular investigations such as an ECG stress-test or angiography
ST-segment depression, positive ECG stress-test for myocardial ischaemia	ST-segment depression, positive ECG tress-test for myocardial ischaemia	No known history of CHD, Syndrome X or angina pectoris
A minimum of two chest-pain episodes per week	A minimum of two chest-pain episodes per week	Do not suffer from chest-pain
Diagnosis > six months	Diagnosis > six months	

Table 4.2.1: The inclusion criteria for the three groups of volunteers participating in Study One.

Table 4.2.2 illustrates the exclusion criteria that were also employed when assessing the eligibility of volunteers as suitable for participating in the study.

Cardiac Syndrome X	Coronary Heart Disease	Healthy controls
History of, or currently under investigation for, any other serious or chronic illness		
Known history of psychiatric illness		
Participation in any other research study within the previous 60 days		
Inability or unwillingness to provide written informed consent		

Table 4.2.2: The exclusion criteria for the three groups of volunteers participating in Study One.

4.3 Participant identification and recruitment

4.3.1 Cardiac Syndrome X

Consecutive female Syndrome X patients aged < 85 years with chest pain, positive exercise ECG stress-test for myocardial ischaemia and angiographically smooth coronary arteries were recruited from the Women's Heart Clinic at the Royal Brompton & Harefield NHS Trust (London, United Kingdom). The Women's Heart Clinic is a specialised clinic for Syndrome X patients. A patient's eligibility was confirmed from an examination of their medical records before their clinic appointment and were subsequently approached to participate following their consultation. Each prospective participant was asked if they would be interested in taking part in a study which may help to improve the understanding of women with Syndrome X, how patients cope with their illness and how it affects their everyday lives. All patients were given a study information sheet to give further details concerning the study (Appendix B), a modified version of the informed consent

document, approved by the Royal Brompton & Harefield NHS Trust Ethics Committee for CHD or Syndrome X patients. If the patient expressed an interest in taking part, a study appointment was made, either later on the same day or on an alternative date convenient to them.

4.3.2 Coronary Heart Disease

Female CHD patients aged < 85 years with angiographically proven cardiovascular disease (>50% stenosis in one or more major coronary artery) including patients having undergone angioplasty, coronary artery bypass grafting and myocardial infarction were recruited from the Royal Brompton & Harefield NHS Trust. Eligible patients were identified from the diagnostic coding relating to patients on the cardiac catheterisation lists from 1st January 2000 to 1st February 2002 and approached to participate by mail. All patients received a personalised letter inviting them to participate in a study exploring women with Cardiac Syndrome X and how this condition affects their everyday lives. The letter outlined the rationale behind the study, the definition of Cardiac Syndrome X and why patients who suffered similar anginal pain were required as a comparison group. All patients received an information sheet containing a detailed description of the study (Appendix C), a modified version of the informed consent document, approved by the Royal Brompton & Harefield NHS Trust Ethics Committee for CHD or Syndrome X patients. Patients also received a brief questionnaire to enable them to express an interest and confirm eligibility (Appendix D), which they could complete and return in an enclosed 'freepost' envelope. Mail shots were performed on three occasions between 1st January 2001 and 1st February 2002. Table 4.3.1 illustrates the patient sample targeted on each occasion.

Patient population	Number
All women aged < 85yrs with a diagnostic coding for CHD who underwent cardiac catheterisation between 1.1.00 and 31.12.00	160
All women aged < 85yrs with a diagnostic coding for CHD who underwent cardiac catheterisation between 1.1.01 and 31.7.01	103
All women aged < 65yrs with a diagnostic coding for CHD who underwent cardiac catheterisation between 1.8.01 and 1.2.02	50

Table 4.3.1: Age and number of patients approached to participate from the Royal Brompton & Harefield NHS Trust cardiac catheterisation lists.

Table 4.3.2 illustrates the relative response rates from the total number of woman taken from the cardiac catheterisation lists coded as suffering from CHD, who were approached to participate in the study by mail.

Participation	Number of patients
Total number of patients contacted	**313**
Returned reply form but did not attend appointment	15
Transport problems (distance from hospital too great)	11
Concomitant medical problems (too ill)	5
Elevated risk of terror attack in London	1
Replied and declined to take part	10
Currently participating in other research	2
< 2 episodes of angina per week or <50% stenosis	6
Returned reply form without their name	3
Suffered Syndrome X	2
Total responders not participating	**55**
Total participants replied and participating	**100**
Response rate	**49%**

Table 4.3.2: The response rate from the cohort of CHD patients approached to participate by mail.

4.3.3 Healthy Controls

Female age-matched healthy volunteers with no previous history of chronic illness were recruited from the nursing and ancillary staff of the Royal Brompton & Harefield NHS Trust and from associated women's groups. Nursing and ancillary staff at the Royal Brompton and Harefield NHS Trust were first approached with a general email request for volunteers to participate in a research study exploring the psychological aspects of Cardiac Syndrome X. A modified version of the informed consent document, approved by the Royal Brompton & Harefield NHS Trust Ethics

Committee for healthy volunteers (Appendix E) was included in the email. If an interest was expressed, eligibility was checked by telephone or email and a study appointment made. Volunteers from the Imperial College Women's Club were approached in a similar way, while volunteers from the University of London Women's Club also came forward on a 'word of mouth' basis. Two groups of Women's Institute branch members also agreed to participate in the study following a short talk. All volunteers received an information sheet before agreeing to participate in the study.

4.4 Study Visit

Once a Syndrome X, CHD patient or healthy control had expressed an interest in participating in the study and a study appointment made, all participants were treated in exactly the same way. All study visits took place in a quiet, private room on a one-to-one basis, where the project was fully explained and any questions answered. Patients were advised that their GP would be informed of their participation in the trial if they requested, however no patient made that request. All participants gave written informed consent using the consent form approved by the Royal Brompton & Harefield NHS Trust Ethics Committee. No participants who attended a study meeting refused to participate or give written informed consent.

Once the participants had provided informed consent, they were then guided through and asked to complete a number of questionnaires (see section 4.5). The method of completion of each individual questionnaire was explained to the participant, while plenty of time was set aside to answer any questions. Written instructions were also given at the start of each new set of questions within the questionnaire. The

individual questionnaires were grouped together to create a battery of tests, with the initial questions tailored towards patients who suffered chest pain, and normal controls who did not (Appendix F). Patients who had been approached to participate during their routine clinic visit were often able to attend their study visit on the same day. These patients would then most likely complete the questionnaires in the clinic waiting area and return them the same day. The majority of participants took the questionnaire home following their study visit and then, after completion, returned it using a 'freepost' envelope. Participants were requested to complete the questionnaires alone answering all the questions as required, and were also encouraged to explain any answers more fully or give any additional information they thought might be appropriate. Patients also gave a non-fasting blood sample following their study visit, drawn using butterfly and vacutainer.

On receipt of the questionnaires, each participant was assigned a unique study number. Syndrome X patients were coded in series from 1001 – 1100, CHD patients from 2001 – 2100 and healthy controls from 3001 – 3100. A list of the participants' names and identification numbers were kept electronically, while the questionnaires were coded according to the methods stated by the authors [252-255] and entered on to an EXCEL (Microsoft, Redmond, Washington) spreadsheet. Data was then transferred to SPSS Version 10 (SPSS Inc, Chicago, Illinois) for statistical analysis (see section 4.6). The original questionnaires were then filed by study number. The original consent forms were kept locally, while copies were sent to the local ethics committee and filed in the patients' notes. Blood samples were analysed for 17β-oestradiol, measured by standard radioimmunoassay (Abbott IMX System, Abbott Diagnostics, Berkshire) by the Royal Brompton and Harefield NHS Trust biochemistry

department. Blood samples were kept at room temperature as advised by the local laboratory and were batch analysed in the same laboratory for standardisation.

4.5 Questionnaires

The Health Anxiety Questionnaire [252] (HAQ) (Appendix G) has been developed using the cognitive behavioural model of anxiety [256] which divides health anxiety into two parts: development and maintenance. The HAQ is split into four sub-scales that focus on: health worry preoccupation; fear of illness and death; reassurance seeking behaviour and interference with life. Developed and validated in medical, psychiatric and healthy volunteers [252], the 22 questions have a four-point Likert scale response format.

The Hospital Anxiety and Depression Scale [253] (HADS) (Appendix H) measures clinically significant anxiety and depression in general medical patients. The 14-item questionnaire is split into two sub-scales (anxiety and depression) using a four-point Likert scales response format. Anxiety and depression scales have also been combined to create a total score [189]. The scale has been validated with both outpatients and inpatients [257], along with NCCP patients [258] and has been used extensively in studies with non-psychiatric clinical populations.

The List of Threatening Experiences [254] (Appendix I) is a widely used list of 12 life events which have been shown to have a marked or moderated effect on psychological well-being. Each of the 12 experience questions has a yes/no response format, the total number of events were recorded and classified into three groups: no events; one or two events and three or more events.

A demographic information scale [255] (Appendix J) was used to assess social support and isolation by recording the patients living circumstances, frequency of contact with friends and relatives and size of social network. This measure investigates the frequency contact with adults, both outside and within the normal household, differentiating between friends and family along with identifying any specific confidant. The four reported levels represent the following frequencies of social contact: 1) every day; 2) three times per week; 3) once a week; 4) once a month.

Additionally, participants were asked to complete questions regarding their menopausal status, menstrual and gynaecological history, including details of hormone therapy, hysterectomy and last menstrual period. Questions were also asked relating to any known family history of CHD, their current medications and previous life-long hospitalisations pertaining to their heart or general admission (Appendix F). Hospital admissions for childbirth were disregarded.

4.6 Statistics

The data were analysed using Pearson's Correlation Coefficient, T-tests, ANOVA and Tukey post hoc tests; overall comparisons of categorical data were performed using Chi-square. Statistical significance level was set at $p<0.05$. The study was performed as an independent-subjects design, using two-tailed tests. Post-hoc tests were used only following a significant main effect, thus reducing the chance of Type I errors. Data are expressed as mean ± standard deviation. Graphical representation of the data includes standard error bars. The first set of analyses compared the three groups of subjects; Syndrome X, CHD and healthy controls. The second set of analyses included only the Syndrome X patients and sought to identify the social and medical

variables that were associated with anxiety, depression and health anxiety scores. The sample size is based on previous large-scale studies of patients with Syndrome X [30] and non-cardiac chest pain [122].

Multiple regression analysis with mean substitution for missing variables was used to identify the variables most closely associated with health anxiety in Syndrome X patients. The total HAQ score was the dependent variable; this was normally distributed as assessed by histogram. The following were entered as independent variables: age, marital status (as two dummy variables), the use of HRT, history of hysterectomy, oestrogen level, size of social network (large or small), family history of coronary heart disease under the age of 60 years and number of life events (as 0, 1-2, 3+), HADS anxiety score and HADS depression score. Constant variance of the residuals was assessed by inspecting the normal probability plots that fitted a straight line. The linearity assumption was assessed for anxiety and depression scores by examining the quadratic relationship; there was negligible difference in R^2 between linear and quadratic equations. The results for the final model are shown in Table 4.8.1.

4.7 Results

4.7.1 Subjects

One hundred female Syndrome X patients (60 ± 9yrs), 100 female CHD patients (65 ± 9yrs) and 100 healthy age-matched female volunteers (61 ± 10yrs) participated in the study. Age of onset for Syndrome X patients (54 ± 8yrs) was significantly younger than for CHD patients (60 ± 9yrs, $p<0.001$). However, there was no significant difference in duration of chest pain between the Syndrome X (6 ± 5yrs) and CHD (5 ± 5yrs) patients. Table 4.7.1 illustrates the demographics characteristics of the three patient groups.

	Syndrome X	**CHD**	**Controls**
Age range	39-80 yrs	45-80 yrs	45-83 yrs
Single	4%	8%	11%
Married	71%	59%	60%
Separated	3%	4%	2%
Divorced	16%	10%	11%
Widowed	5%	18%	16%
Patients living alone	17%	29%	31%

Table 4.7.1: The demographic characteristics of the three study populations.

4.7.2 Medications, hospitalisations and illness

Syndrome X patients underwent their first cardiac admission at a significantly younger age (51.8 ± 11.2yrs) than CHD patients (59.9 ± 10.1yrs, $p<0.001$), whereas CHD patients had a greater number of cardiac admissions (1.6 ± 1.28) than patients with Syndrome X (0.85 ± 1.28, $p<0.001$). There were no differences between the three groups concerning number of non-cardiac admissions.

Patient's pre-existing medical conditions were categorised into six broad groups. Table 4.7.2 illustrates the number of patients from each group with cardiovascular risk factors or pre-existing medical conditions. Patients could suffer more than one illness or risk factor.

	Syndrome X	CHD	Controls	Significance
Current smokers	11%	11%	15%	0.630
Hypertension	33%	58%	25%	0.001
Hypercholesterolemia	26%	68%	9%	0.001
Respiratory	17%	14%	11%	0.474
Gastric / abdominal	20%	16%	14%	0.511
Neurological	15%	7%	7%	0.087
Endocrinological	16%	32%	4%	0.001
Musculoskeletal	33%	29%	23%	0.287
Other	17%	16%	13%	0.716

Table 4.7.2: Percentage of patients with concomitant medical conditions and cardiovascular risk factors.

Syndrome X patients took fewer cardiovascular medications (2.1 ± 1.7) than CHD patients (4.21 ± 4.9, $p<0.001$). Syndrome X and CHD patients suffered an equivalent number of other concurrent medical conditions, which were significantly greater than controls ($p<0.01$). Nevertheless, CHD patients took more non-cardiovascular medications than Syndrome X patients ($p<0.05$) and healthy controls ($p<0.001$).

4.7.3 Hospital Anxiety and Depression Scale

Syndrome X and CHD patients both had higher total HADS scores (12.2 ± 6.3 and 10.4 ± 6.5 respectively) than the healthy controls (7.7 ± 4.7, $p<0.001$). Syndrome X patients recorded significantly higher anxiety scores (7.17 ± 3.9) than both CHD patients (5.9 ± 3.7, $p<0.05$) and healthy controls (4.9 ± 3.1, $p<0.01$). Syndrome X and CHD patients both had significantly higher depression scores (5.0 ± 3.2 and 4.9 ± 3.5 respectively) than the healthy controls (2.8 ± 2.2, $p<0.01$). Clinical levels of anxiety (>11) were found in 16% of Syndrome X patients compared with 10% of CHD patients and 5% of healthy controls ($p<0.05$). Similar number of Syndrome X and CHD patients had clinical levels of depression (9% and 7% respectively) while no patient in the control group was clinically depressed.

4.7.4 Health Anxiety Questionnaire

Both Syndrome X and CHD patients had higher total Health Anxiety Questionnaire scores than controls ($p<0.01$) (Table 4.7.3). Syndrome X and CHD patients had significantly higher scores than healthy controls on the scales measuring health worry and preoccupation ($p<0.001$), fear of illness ($p<0.01$) and life interference ($p<0.001$).

Syndrome X patients had significantly higher scores than the CHD patients on the interference with life scale ($p<0.05$).

	Health Worry	Fear of Illness	Reassurance Seeking	Interference with Life	Total HAQ Score
Syndrome X	4.81 ± 3.50	4.21 ± 3.26	1.31 ± 1.23	3.54 ± 2.45	14.26 ± 8.68
CHD	4.79 ± 3.29	4.76 ± 3.26	1.18 ± 1.04	2.83 ± 2.42*	13.92 ± 7.87
Control	3.04 ± 2.33#†	2.87 ± 2.44†#	1.26 ± 1.14	0.85 ± 1.08#†	8.28 ± 5.92#†

* p =<0.05 compared with Syndrome X, # p = <0.01 compared with Syndrome X,

† p =<0.01 compared with CHD

Table 4.7.3: Mean scores of the Health Anxiety Questionnaire (HAQ) sub-scales for all three groups.

4.7.5 Life events

There was no significant difference between the number of life events (expressed as none, one or two, and three or more) experienced by Syndrome X, CHD patients and controls. Syndrome X patients who reported three or more stressful life events had higher general anxiety (8.8 ± 4.6 v 5.7 ± 2.9 and 6.6 ± 3.2, $p<0.01$), reassurance seeking (1.72 ± 1.4 v 0.8 ± 0.8 and 1.25 ± 0.9, $p<0.01$) and total HAQ score (17.1 ± 10.7 v 11.7 ± 5.6 and 12.7 ± 7.3, $p<0.05$), while CHD patients who reported three or more life events had higher general anxiety (6.9 ± 3.8 v 5.7 ± 3.7 and 3.2 ± 2.1, $p<0.01$), depression (5.5 ± 3.6 v 4.4 ± 3.3 and 2.8 ± 3.3, $p<0.05$) and total HAQ score (15.9 ± 8.1 v 13.3 ± 7.5 and 10.1 ± 6.7, $p<0.05$). No differences were found among the controls.

4.7.6 Familial History of CHD

Sixty-six percent of Syndrome X patients reported some family history of CHD, compared to 65% of CHD patients and 48% of controls ($p<0.05$). Thirty-four percent of both the CHD and Syndrome X patient groups reported a sibling or parent with CHD before the age of 60 compared to 9% of controls ($p<0.001$). No measure of family history of CHD was significantly associated with HADS anxiety or depression or HAQ health anxiety scores for any group.

4.7.7 Social Contact

4.7.7.1 Friends

Data regarding patient's social network were split into two categories: patients who reported having no friends or a small social network (six or fewer friends) and patients with a large social network (seven or more friends). The two categories were created by grouping responses either side of the median. There were no differences between Syndrome X, CHD patients and healthy controls in the size of social network (56%, 55% & 47% respectively with a small social network, $p=0.42$). No differences were found between the three groups in the frequency of contact with friends, either by phone or in person.

Syndrome X patients who reported a small social network (six or fewer friends) had significantly higher levels of HADS depression ($p<0.05$), HAQ health worry ($p<0.01$), interference with life ($p<0.01$) and total HAQ score ($p<0.01$) than those who reported a large social network (Figure 4.7.1). CHD patients with a small social

network also had higher levels of HADS depression (5.2 ± 3.4 v 3.8 ± 3.5, $p<0.05$) and interference with life (3.5 ± 2.5 v 2.1 ± 2.1, $p<0.01$) than those with a large social network. There were no differences in the HADS or HAQ scores of the control groups on the basis of their social network.

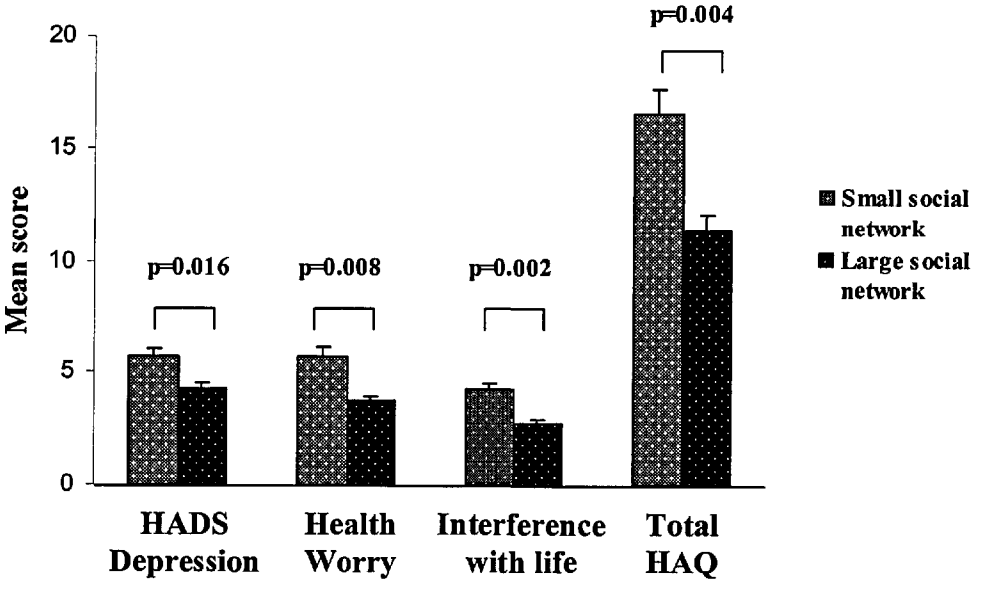


Figure 4.7.1: The association between social network size and the HADS and HAQ scores of Syndrome X patients.

4.7.8 Relatives and Confidant

The number of relatives or frequency of contact with those relatives, either by telephone or visiting was unrelated to sub-scales of the HADS and HAQ for any group. There were no differences in the number of participants from each group who named their spouse as confidant. Choice of confidant was unrelated to psychological morbidity in any group, as was the frequency of contact with that person.

4.8 Gynecological factors

Forty-five percent of Syndrome X patients had undergone hysterectomy in comparison with 39% of CHD patients and 24% of controls ($p<0.01$). Sixty-seven percent of Syndrome X patients were prescribed hormone replacement therapy compared to 29% of CHD patients and controls ($p<0.001$). No difference in the number of patients having undergone oopherectomy was found. Syndrome X and CHD patients experienced their last menstrual period (LMP) at a significantly younger age than controls (43.9 ± 8.1 yrs vs. 45.7 ± 6.2 yrs and 49.0 ± 7.2 yrs, $p<0.001$). The onset of chest pain in Syndrome X patients occurred within fewer years of the LMP in comparison with CHD patients (9.5 ± 9.8 yrs verses 14.9 ± 9.1 yrs, $p<0.001$). There were no differences in the age at hysterectomy between the three groups. A history of hysterectomy or current HRT use had no effect on the various scales of the HADS or HAQ for any group.

4.8.1 Oestrogen plasma levels

The independent laboratory range for oestrogen was lowered from a minimum detectable level of < 37 pmol/L to < 18 pmol/L during the study. Therefore, patients whose level was found to be less than < 37 pmol/L were re-coded as 36 pmol/L for the purpose of standardising the analysis. 17β oestradiol samples were not recorded for 2% of Syndrome X patients, 12% of CHD patients and 6% of controls due to laboratory or phlebotomy difficulties.

Syndrome X patients had higher 17β oestradiol levels (199.9 ± 218.3 pmol/L) than CHD patients (112.2 ± 168.2 pmol/L) and controls (137 ± 190.3 pmol/L, $p<0.01$). However, there were no differences in the levels of plasma oestrogen of the Syndrome X, CHD patients or healthy controls when the three groups were compared on the basis of HRT use (Figure 4.8.1). Oestrogen level was unrelated to any measure of the HADS or HAQ for any of the three groups. The number of years elapsed since the last menstrual period was also unrelated to either measure within the HADS or HAQ for any group.

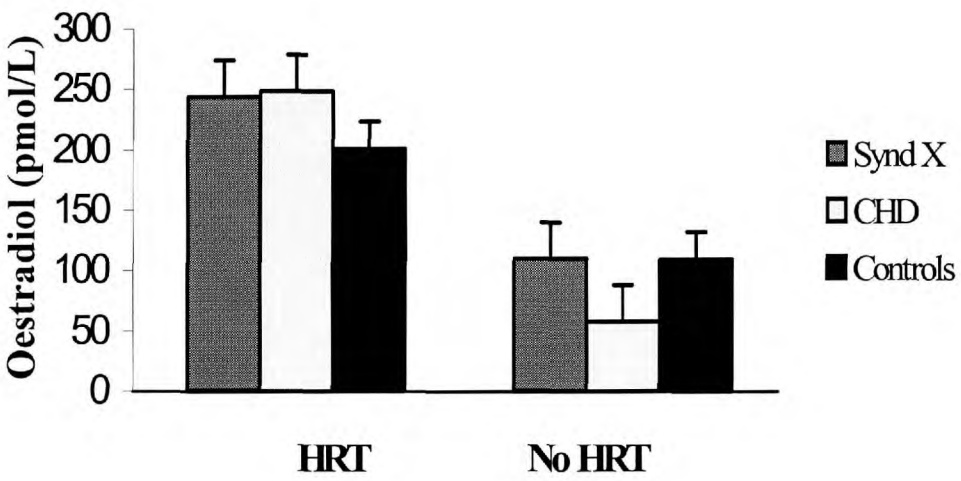


Figure 4.8.1: Plasma Oestrogen levels of the three groups on the basis of HRT use.

4.8.2 Multivariate analysis

The second part of the hypothesis concerned the possible reasons for high levels of health anxiety in Syndrome X patients. In the multiple regression analysis, a small social network ($p=0.003$), divorced/separated or widowed status ($p=0.005$), not taking HRT ($p=0.008$) and a high HADS anxiety score ($p<0.001$) emerged as the variables

independently associated with health anxiety score. They accounted for 41.9% of the variance (Table 4.8.1).

	Unstandardised B-coefficient	Standard error	Standardised coefficient	Significance
Constant	2.193	3.266		0.50
Age	-0.022	0.035	0.058	0.52
Single	2.010	1.492	0.115	0.18
Divorced, widowed, separated	-1.980	0.694	-0.246	0.005
HRT	1.654	0.694	0.224	0.019
Oestrogen level	-0.001	0.001	-0.036	0.69
Hysterectomy	-0.238	0.638	-0.034	0.71
Social network size	-0.956	0.308	-0.276	0.003
Stressful life events	0.599	0.397	0.131	0.13
Family history of CHD in person < 60 years	-0.165	0.621	-0.023	0.79
Anxiety score	0.349	0.086	0.396	<0.001
Depression score	0.104	0.106	0.097	0.33

Table 4.8.1: Results of multiple regression analysis showing the variables most closely associated with total Health Anxiety Questionnaire (HAQ) score.

4.9 Discussion

In order to accurately quantify the psychological morbidity in women with Cardiac Syndrome X, one of the original study aims was to enrol a large population of women with the full diagnostic criteria of Syndrome X. In this rigorous, closely matched cross sectional study, 100 women with the full diagnostic criteria for Syndrome X were compared with 100 age and gender matched CHD patients and 100 similarly matched controls.

Syndrome X patients had significantly higher levels of anxiety and felt their health interfered more with their everyday lives than CHD patients and controls. Both Syndrome X and CHD patients had much higher levels of health anxiety and were significantly more depressed than controls, suggesting a greater concern about their respective illnesses. However, the higher level of general anxiety found in Syndrome X patients (as measured by the HADS) cannot be accounted for by the presence of chest pain. Patients with CHD were chosen as a suitable control group for Syndrome X patients as a result of their similar symptomology yet widely differing prognosis. This is an important new finding, as previous studies have attributed higher levels of anxiety in patients with NCCP to the anxiety and depression associated with all chronic medical conditions [259].

Ruggeri *et al* found higher levels of anxiety and depression in a mixed sex group of patients with Syndrome X compared with a similar group of CHD patients [26]. However, the present study only explored anxiety and depression levels in women with Syndrome X, CHD and a similar sex- and age-matched control. It may be that men with Cardiac Syndrome X are as affected by psychological morbidity as the

Syndrome X women who participated in the present study. This would require further investigation.

Syndrome X and CHD patients showed increased health anxiety when exposed to three or more threatening life events. Previous studies have suggested that threatening life events may be a more important factor in the development of psychological morbidity in women during middle-age than menopausal status [233]. Studies have also shown that women who have experienced stressful life events run an increased risk of developing mental illness around the time of the menopause [228]. A number of questions in The List of Threatening Experiences consider the patients' recent experience of serious illness [254]. It may be that patients with CHD and Syndrome X had elevated scores as a result of their diagnosis. However, studies of life events in relation to psychiatric symptoms suggest that a higher frequency of adverse life events is secondary to previous psychological morbidity [260].

Syndrome X patients had a similar sized social network with a similar frequency of contact with friends and relatives as CHD patients and healthy controls. However, Syndrome X patients who reported having a large social network of friends were significantly less anxious and depressed and had lower levels of health related anxiety than those Syndrome X patients who reported having a small social network. The number of friends within the social network had less impact on measures of health related anxiety in CHD patients, and no affect of the psychological health of controls. Interestingly, the number of relatives within the social network had little or no affect on psychological morbidity in any of the study groups. The choice of confidant, husband, family member or friend and the frequency of contact with that person also

appeared to have little impact on anxiety or depression in patients with Syndrome X, CHD or the normal control group. Itkowitz *et al* have suggested a link between an overprotective significant other and a decline in productive and independent behaviour [192]. The authors argue that this may result in increased 'illness behaviours' which may in turn impair quality of life. These findings were not supported by the present study, as frequency of contact with a significant other was unrelated to psychological morbidity in any group. A small network of friends appears to have the largest impact on the psychological morbidity of patients with Cardiac Syndrome X.

The relationship between depression, social isolation and predicted morbidity and mortality in CHD patients has been previously documented [177]. Social isolation has been shown to predict morbidity in both the general population and patients with chronic illness, including CHD [179]. Having a close confidant has been shown to halve the risk of having further cardiac events in the 12 month post-MI period [186], while social support has also been related to patients recovery from and adaptation to long-term ill health [180]. However, the results from the current study fail to support those of Biggs *et al*, who found that the experience of NCCP was unrelated to social support [189]. Studies of NCCP may not accurately reflect the experience of patients with Syndrome X. Extrapolation from one chest pain syndrome to another may be unproductive due to the specific nature of the factors associated with Cardiac Syndrome X - including the impact of an inadequate social network identified during the course of the current study.

Syndrome X patients reported a previous family history of CHD comparable with CHD patients, both of which were far higher than controls. Previous studies exploring family history of CHD in patients with NCCP have found conflicting results. While Mayou *et al* showed that NCCP patients had less family history of heart disease than patients with CHD [11], Aikens *et al* found that 58% of NCCP patients reported cardiac symptoms in at least one parent, and 21% in at least one sibling [213]. Sixty-six percent of Syndrome X patients in the current study report familial history of CHD. Aikens *et al* found that an exposure to cardiac symptoms in others was associated with the patients own cardiac symptoms and help-seeking behaviour [213]. Nevertheless, results from the current study found that a positive familial history of CHD was unrelated to psychological morbidity in any group. Eifert *et al* suggested that direct exposure to heart disease is more likely in patients with chest pain and angiographically smooth coronary arteries than heart disease patients or normal controls [214]. The present study identified an almost identical pattern of family history of CHD in the Syndrome X and CHD patient groups. A strong positive family history of CHD maybe relevant in the physiological development of Syndrome X, but appears to have little affect on the psychological health of the three groups under investigation in this study.

Study One confirms the finding that postmenopausal women with Syndrome X have a higher incidence of hysterectomy [83]. Previous studies have reported an average hysterectomy prevalence of 17.4% in British women aged 40-80yrs [261] and of 13.6% in a British urban community sample [262]. The higher frequency of hysterectomy found in healthy volunteers in this study (24%) may reflect regional variation, as previous large-scale studies have noted countrywide differences in HRT use and

hysterectomy [263]. However, hysterectomy was unrelated to psychological health in any group participating in the current study. Previous studies have suggested that hysterectomy may be related to reduced anxiety and depression [243], although these findings were not supported by the present study. A longitudinal study design, as employed by Kjerulff *et al* may be a more sensitive method for assessing well-being and psychological health pre- and post-hysterectomy.

The greater number of Syndrome X patients prescribed HRT may reflect the impact of previous studies advocating the use of HRT as a treatment regime in Syndrome X [84]. The frequency of HRT use in the CHD and control group (29%) reflects the previously documented national average (33%) [263]. In the multivariate analysis, HRT was associated with increased health anxiety: it may be that women who are anxious about their health are more likely to be prescribed HRT. Køster *et al* found that women prescribed HRT and those who had undergone a surgical menopause suffered a significantly higher number of concomitant health conditions than a matched control group [235]. However, evidence to support the suggested oestrogen depletion in Syndrome X patients was not found. Oestrogen depletion may be a factor in the development of Syndrome X, and therefore a sample taken at the time of diagnosis may be a more accurate marker of possible cause. As the study population only included patients who had been diagnosed with Syndrome X for more than one year, this was outside the remit of the current study. An exploration of menopausal symptomology and reason for hysterectomy in women with Syndrome X merits further research.

Syndrome X patients were on average eight years younger than CHD patients at the time of diagnosis, a finding that is reflected in the general age disparity between the Syndrome X and CHD patient groups. While every care was taken to age match the groups as closely as possible, due to the differences in aetiology and age of onset in the two conditions, exact age matching was not possible. Age was unrelated to levels of anxiety or depression measured by either questionnaire in any group, so any slight age discrepancy is not responsible for the study findings.

This study has drawn attention to a number of psychosocial factors that should be addressed in order to more effectively manage and treat patients with Cardiac Syndrome X. It may be beneficial to target any therapeutic intervention to reduce the noted anxiety and depression that this study has identified in women with Syndrome X. As Syndrome X patients with small social networks suffer higher levels of psychological morbidity, future research should target treatments involving social interaction, where an emphasis is placed on group participation and relationship. Many patients report increased pain frequency and severity during periods of stress, including the cumulative affect of a number of adverse life events. An intervention that is also concerned with stress reduction and prevention may play an important role in the treatment of Syndrome X.

The results from the present study may also impact upon research into the modification of illness behaviour through the adjustment of health beliefs, a strategy which has had little success in patients with Syndrome X [148]. Leventhal *et al* [264] described a number of factors they believed predicted illness behaviour, and while health beliefs were noted, social factors such as social support, modelling behaviour

and heritability were all implicated in the formation of health behaviours. It could be argued therefore, that the social environment identified in the current study should be incorporated into any future studies relating to the modification illness behaviours in Syndrome X, including the adjustment of health beliefs.

4.9.1 Study Limitations

The cross-sectional design and sample selection methods used during this study may be identified as limiting factors. Cross-sectional studies cannot identify the direction of causality, whereas a longitudinal study design may more accurately assess the cause-effect relationship. However, cross-sectional studies may provide a more accurate representation of the study population. The commitment required by patients who participate in studies lasting many years may promote self-selection bias [231]. Nevertheless, the control group and a number of the CHD patients were recruited into the study on the basis of their response to a request for volunteers, which may have resulted in selection bias on the basis of previous psychological morbidity or increased health awareness. In an attempt to reduce bias, patients and volunteers were recruited from similar clinics, the same hospital referral area and physical location. The floor and ceiling effect of the questionnaires employed in this study should also be taken into account. No control group member had ever suffered chest pain, however the possibility that some controls may have suffered from sub-clinical CHD should be noted.

Recent discussions in the medical press [265] have shown that cardiologists and internists continue to dismiss women with Syndrome X. The psychosocial and gynaecological components associated with Syndrome X will therefore continue to be

misunderstood. Treatment modalities that address the psychosocial elements of the condition may result in clinical improvement of some patients with this syndrome. Until such psychosocial factors as those identified in this study are recognised within the dichotomous pathology of this debilitating condition, we will be no closer to finding a useful and effective treatment armamentarium for patients with Cardiac Syndrome X.

5: Psychological Benefits of Exercise in the Older Woman

Chapter Five will explore the use of exercise and physical activity as a method for improving psychological morbidity in women of a similar age to those diagnosed with Cardiac Syndrome X. Middle-aged and postmenopausal women are currently under-represented in the literature. Although there are conflicting outcomes and methodological limitations associated with much of the existing research, exercise may be an important tool for improving psychological health among older women. Building on previous research, Study Two seeks to determine the impact of a brief moderate-intensity exercise program on the psychological health and well-being of healthy postmenopausal women. However, the mechanistic pathways by which exercise improves mood, well-being and psychological morbidity are yet to be determined. Several suggested psychological mechanisms have been put forward to explain the benefits of exercise and include distraction [266], social reinforcement [267] and mastery [268]. Suggested physiological mechanisms include the widely reported 'runners' high' and the impact of beta-endorphins [269], improved regulation of catecholamines and serotonin (known collectively as monoamines) [270] and the thermogenic model of temperature and mood [271]. However, despite many years of research, there is still no definitive explanation for the association between physical activity and mental health.

5.1 Exercise and the older woman

The roots of health promotion, increasing physical activity and fitness in order to ameliorate health and longevity can be traced back as far as ancient China [272]. It is widely acknowledged that the accumulative, detrimental effect of everyday stress on cardiovascular morbidity and mortality can be tempered by exercise [273], while exercise and physical fitness are associated with a wide range of health benefits for postmenopausal women, including maintaining bone density, muscle tone and cardiovascular health [274], reducing the risk of osteoporosis, CHD and physical morbidity related to obesity.

However, physical activity and aerobic fitness in women has not always been encouraged. Historically, women have been discouraged from sporting activities, and not until western cultural beliefs were radically transformed by the feminist movement of the late 19th and early 20th century were women encouraged to be active [275]. Women were forbidden from competing in any official marathon until 1972, while the maximum women's Olympic running distance was limited to 1500 meters until the 1984 Olympics [276]. It has been argued that the influence of previous traditions, where men are perceived as more closely associated with exercise programs than women, may still endure among the older generation today [275]. This may inhibit older women from exercising, or alternatively, instil a greater sense of achievement and empowerment in older women who do. However, recent research has suggested that less than 50% of women aged 50 – 64 years report participating in any form of regular physical activity [277]. Middle-aged women do not seem to make physical activity a priority [278]. In a study exploring the patterns of vigorous physical activity in the WHI observational cohort, it was found that only between 13% and

16% of women aged 55 – 79 years, grouped on the basis of ethnic origin, participated in regular vigorous exercise [279]. Patients were asked to reflect on their physical activity at four ages (aged 18, 35, 50 years and current age), and of all patterns and combinations of physical activity, no vigorous activity over all time periods was by far the most common (26% to 41% depending on ethnicity). The largest decline in activity occurred between 50 years and the current age, with the prevalence of vigorous activity of most racial groups dropping by two thirds. These results are supported by previous research, which found that only 18% of women aged 45-64 years participated in regular vigorous activity, falling to 16% of women aged 65-74 years [280].

It has been suggested that in order to successfully encourage women to participate in physical activity, any exercise program should be as accessible as possible [278]. Dearden and Sheahan argued that exercise should be convenient, enjoyable, include external rewards and incentives while providing behavioural success, behavioural shaping and self-management [278]. They also acknowledge the role of social support, encouragement from family and friends and community support. A women's emotional commitment to exercise, her enthusiasm, motivation and past physical activity can also contribute to the success or failure of long-term life style modification [274].

In order to gain a better understanding of the variability in the frequency and intensity of physical activity undertaken by women of varying age groups, De Bourdeaudhuij and Sallis explored a number psychosocial determinants that may influence exercise participation [281]. The most notable barrier to exercise participation in older (50 – 65

years) women was the presence of perceived psychological or health related problems, while social support and self-efficacy also influenced physical activity in this age group. Interestingly, perceived health benefits did not significantly contribute to exercise participation in the older age group. The authors argue that in order to overcome the barriers to exercise in an older population, information should be available that promotes low-risk physical activity, thus challenging maladaptive and irrational preconceptions that may prohibit the older generations from participating in exercise [281].

It has been suggested that women who suffer from Social Physique Anxiety (SPA) may be less likely to participate in physical activity, resulting in poor cardiovascular fitness and increased associated risk factors [282]. SPA is defined as the degree to which a person becomes anxious when others observe or evaluate their physique [283]. In a study exploring the relationship between SPA and physical activity in postmenopausal women, high SPA was associated with lower levels of physical activity [284]. SPA was unrelated to age or the use of HRT. The authors conclude that Social Physique Anxiety may be a barrier to exercise participation in postmenopausal women, and that this may be related to the increased body fat in the women with high levels of SPA noted in this study.

5.2 The Psychological impact of exercise

Maintaining a physically active lifestyle has been shown to be positively related to psychological health, well-being, anxiety and depression [285]. Improving physical fitness has a concurrent positive affect on many psychological outcomes, such as depression, anxiety and mood among sedentary participants, from the very young to

the very old [286]. It has been argued that state anxiety is reduced almost immediately following acute exercise of any intensity [287], with the most marked reductions found in those who were initially un-fit or highly anxious. Exercise has been associated with the prevention and treatment of depressive illness in the clinical population [288], along with reducing the stress and anxiety of daily life [289]. Patients suffering clinical levels of anxiety and depression have shown a reduction in the severity of their symptoms following exercise [290], while moderate intensity exercise in combination with group psychotherapy was found to be more affective in improving well-being and quality of life in cancer survivors than group psychotherapy alone [291]. Research into the dose-response effect of exercise in major depressive disorder is currently in progress [292].

Despite many positive indices for exercise as a treatment for various psychological disorders, exercise has also been shown to have a deleterious effect on mood and performance, measured most commonly by the Profile of Mood States (POMS) [293]. Exercising a group of sedentary volunteers has produced negative mood effects [294], with mood improvements only shown in the participants who were initially unhappy [295]. Increasing the frequency of exercise in those who are already active has been shown to worsen mood [296], while mood disorders have developed following exercise deprivation among habitual exercisers [297]. Athletes and the very active have also been shown to become depressed when they were prevented from exercising [298].

It has been suggested that mood improvements in response to exercise will only be shown following increased or additional activity in fitter or more active participants [299]. Aerobics class participants gained greater improvements in mood

and anxiety following high- rather than low-intensity exercise class [300]. However, no improvements in mood or psychological well-being were found in young female aerobics class participants following an additional 15-week exercise program [301]. Similarly, the reduction in state anxiety observed in active young men and women following the first session of an eight-week exercise intervention was unchanged on completion of the entire program [302].

In an attempt to conduct a suitably thorough case-control study of the effect of exercise of psychological well-being in a non-clinical population, DiLorenzo *et al* enrolled healthy young men and women in a 12-week exercise programme [303]. Due to the intensive nature of the exercise program, gains in physical fitness were substantial, while depression and anxiety were significantly reduced following the exercise intervention and after a one-year follow-up. These findings support those of Blumenthal *et al* who found that 10-weeks of thrice-weekly moderate intensity exercise was associated with improvements in mood, depression and anxiety in a group of healthy men and women of diverse age [304]. DiLorenzo *et al* suggest several possible explanations for their findings, including the psychosocial benefits of the concurrent weight loss, enhanced body image, along with the impact of social support. Participants performed their exercises in the same groups on each occasion and friendships developed, often agreeing to continue exercising together following the conclusion of the study.

5.2.1 Exercise and psychological benefit among the older population

Methodologically rigorous studies of exercise, anxiety and well-being in the older population are limited, due in part to the problems involved in exercising a group of

patients who maybe physically impaired. However, subjective health and psychological well-being have been shown to be higher among older people who partake in regular exercise [275]. The relationship between exercise and positive health measures were stronger for older participants, while women who walked regularly were more likely to report better subjective health than men. The authors illustrate their findings as an exchange in that the social and physical investment that an individual makes in exercise participation affects their subjective health and well-being [275]. Home exercise training has also been shown to reduce stress and anxiety in a group of older adults, regardless of exercise intensity [305], while anxiety reduction and increased well-being have also been shown in elderly men following an eight-week once-weekly exercise programme [306].

Exercise has been shown to be as effective at reducing levels of depression in a mixed gender group of older adults suffering clinical depression as medication alone or medication and exercise combined [307]. Participants were followed-up after six months, when it was noted that continued exercise participation rates in both active groups were relatively high (66% and 64%) [308]. Participants in the exercise only group were more likely to be partially or fully recovered at follow-up than those who took medication alone, while those who reported regular aerobic activity at follow-up were less likely to be clinically depressed. The authors suggest that the unexpected finding that a combination of medication and exercise was less beneficial that exercise alone could be as a result of 'anti-medication sentiment'. Participants in the exercise only group may also have developed a heightened sense of personal mastery and positive self-regard, having treated their depression without pharmacological

intervention. As a result, the authors suggest that future research might focus on attitudinal and attributional factors associated with exercise participation.

Adverse life events, such as bereavement, trauma or tragedy, have also been shown to modify exercise participation among a mixed-sex group of older adults [309]. Although exposure to adverse life events did not significantly impact upon the behaviour of the group during the first few months of the exercise intervention (month one to six), the experience of life events had a significant negative effect on adherence to the exercise program during subsequent months (months seven to 24). Life stress can therefore have a negative impact on exercise behaviour. High state anxiety and low life satisfaction were also found to increase the likelihood of dropout from an exercise intervention in an older group of participants with major depressive disorder [310]. Participants with low self-esteem, lower life satisfaction and lower social support were less likely to gain positive benefits from the exercise intervention. Although the participants in Herman *et al*'s study were taken from a clinical, psychiatric population, similar psychosocial factors may be relevant to unsuccessful exercise outcomes in a non-clinical population.

5.2.1.1 Physical fitness and exercise intensity

The general consensus suggests that changes in psychological health and subjective well-being, as a result of cardiovascular exercise, may be attributable to changes in physical fitness [311]. However, the elderly or physically impaired may be unable to participate in a level of cardiovascular activity that would promote physical fitness, thus excluding an entire section of the community from potentially advantageous health interventions. McAuley *et al* sought to determine whether a program of

stretching and toning was as beneficial to the psychological well-being of a group of older adults (60 – 75 years) as aerobic activity resulting in increased cardiovascular fitness [311]. The additional benefit of participating in a group based exercise program in terms of increased social support was also explored. Both aerobic and non-aerobic programs had a positive impact on subjective well-being, although the improvements were not maintained in either group at a six-month follow up. The authors concluded that aerobic activity might not be necessary for psychological health gains. These results support those of an earlier literature review [312], which found that physical fitness *per se* was not implicated in the physical activity effects on well-being in older adults. Those participants who were more active and developed the greatest improvements in social support suffered the largest decline in well-being following the termination of the exercise program, irrespective of continued home based exercise participation. The authors therefore argue that an exercise environment that encourages frequent participation and promotes social interaction may be intrinsic in improving well-being through exercise in an older population [311].

In order to gauge the benefit of aerobic verses non-aerobic exercise on psychological well-being and mood, Lennox *et al* randomly assigned a mix-sex group of older adults to a 15-week aerobic (walk/jog) or non-aerobic (volleyball/weightlifting) exercise intervention or a waiting-list control [313]. Although the two exercise conditions were designed to differentiate between specific types of physical activity, both groups recorded similar increases in functional capacity and physical fitness following the exercise program. Interestingly, although substantial improvements in functional capacity were recorded in both groups, neither exercise intervention provoked any change in psychological well-being, depression or mood. The authors

suggest these findings may be related to the study design, which was scheduled to ensure that the post-intervention assessment did not simply measure the acute effect of the most recent exercise class. Other longitudinal studies may have unintentionally recorded the acute effect of any exercise intervention and ascribed those results to the long-term impact of the exercise program (refer section 5.2.3). The authors therefore conclude that they found little evidence to link exercise with improvements in psychological well-being in older adults of normal mood [313]. Their argument would have been strengthened by a follow-up assessment, which unfortunately was not included in the study.

In order to determine whether increases in aerobic fitness were necessary to promote improved psychological well-being following physical activity, Norris *et al* compared the impact of aerobic and non-aerobic physical activity on measures of job- and life-stress in a group of young male police officers [314]. Positive changes in perceived job stress were evident only following the 10-weeks aerobic training program, while improvements in psychological health and well-being were found in both groups. The authors admit that their attempts at creating an anaerobic fitness regime were relatively unsuccessful, as improvements in physical fitness were noted in both groups. However, Norris *et al* also suggest that the positive benefits of the anaerobic program may be related to improved muscle tone and body image, feelings of mastery and the impact of the exercise group dynamic.

In a carefully controlled study by Moses *et al,* the relationship between exercise intensity, aerobic fitness and psychological well-being were explored in a group of sedentary healthy middle-aged men and women [315]. Participants were randomised

into ten weeks of moderate- or high-intensity exercise, an attention placebo or a waiting list control group. The attention placebo group was designed to mimic the group dynamic of the exercise participants, receiving the same interaction, information and advice without the exercise intervention. Participants were also followed-up three months after the completion of the program. Tension, anxiety and confusion were substantially reduced after the ten-week programme in the participants undertaking moderate intensity exercise. However, a significant *increase* was shown in the three scales among the high intensity exercise, attention-placebo and control groups. Equal modest improvements in physical well-being were found in the moderate and high intensity exercise groups, while reductions in perceived coping deficits and depression were shown only in the moderate intensity groups, with further improvement evident at the three-month follow-up. The authors conclude that while changes in physical fitness and improvements in well-being are not linearly related, an aerobic component is essential for promoting improvements in well-being following physical activity. The authors also suggest that moderate intensity exercise may have been more enjoyable and less demanding, thus creating goal attainment, positive feelings of self-control while limiting distress through physical injury.

5.2.1.2 Self-efficacy

In order to explore the link between anxiety and exercise, Katula *et al* studied the effect of low, moderate and high intensity exercise on a mixed-gender, sedentary elderly population, in light of the participants self-efficacy [316]. Self-efficacy is defined as 'beliefs in one's capabilities to organise and execute the courses of action required to produce a given attainment' [317]. In terms of exercise participation, self-

efficacy is often reflected in the question: Do I believe that I can do this? Katula *et al* found a significant reduction in anxiety following light intensity exercise, no significant change in anxiety following moderate intensity exercise, and an increase in anxiety following high intensity exercise. The authors explain their results in terms of the challenge set by the intervention: the moderate intensity exercise provided participants with an optimally challenging task. However, the authors also indicate that the exercise environment may have influenced overall changes in anxiety. The light intensity exercise, which promoted the greatest reduction in anxiety, was performed in familiar surrounding in a socially stimulating environment, while the moderate and high intensity exercise were performed in a socially isolated, unfamiliar environment. The authors therefore conclude that the exercise environment and intensity, along with the participants self-efficacy should be taken into account when promoting exercise as a method for improving psychological well-being [316].

While self-efficacy has been identified as an important predictor of exercise and other health related outcomes [318], it has also been identified as an outcome of exercise. Both short- and long-term exercise interventions have been shown to improve self-efficacy in middle-aged adults [319]. In a study examining the relationship between exercise, self-efficacy, anxiety and cortisol (a hormone involved in the 'fight-or-flight' adaptive reaction to stress) in physically active men, a single episode of high intensity exercise was related to improved self-efficacy and anxiety [320]. Cortisol levels were inversely related to self-efficacy immediately after exercise and positively correlated with anxiety following a 20-minute rest period. However, as similar reductions in anxiety were found in the control group, the authors suggest that the

effective benefits associated with acute exercise may in fact be as a result of psychological distraction; taking a break from everyday life.

5.2.2 The psychological impact of exercise in older women

Studies of the long-term impact of exercise on women's psychological health are limited. Those studies that are performed concentrate on a clinical population, either from menopause clinics or psychiatric outpatients and therefore fail to address the non-clinical, normal population [234]. In a review of the literature regarding the effect of exercise on mood adjustment from 1975 to 1993, middle-aged women were under-represented in studies of non-clinical populations [286]. Of the 29 studies which fulfilled the methodological criteria for inclusion in Byrne and Byrne's review, only two clinical studies focussed on women alone [321;322], although both studies showed improvements in clinical depression following an exercise intervention. Byrne and Byrne noted a number of methodological inconsistencies that were rife throughout the literature, including bias in the study populations, a paucity of follow-up data and a lack of standardisation in the exercise intervention. Nevertheless, the authors maintain a 'cautious optimism' when promoting the use of exercise for the alleviation of psychological symptoms and the prevention of distress.

Bhui and Fletcher suggest that the higher prevalence of anxiety and depression in women may be related to exercise participation [323]. They found that women had higher levels of psychological morbidity then aged matched men from a similar population. However, although the women were less physically active, and any activity undertaken was of a lower intensity than men, the intensity of activity was unrelated to anxiety and depression in either sex. The women also experienced lower

incomes and were less available to work, which they argued supported the 'healthy worker effect'; that those who work are invariably healthier [323].

Williams and Lord [324] found that a program of exercise improved cognitive function, psychological distress and mood in a sample of community-dwelling older woman. Exercise history has also been shown to moderate mood in a group of middle-aged women regardless of menopausal status [325]. Women who undertake regular exercise or who are active in their everyday lives have been shown to have a lower prevalence of HRT use [326] and report less menopausal symptomology [230], an outcome which is unaffected by either social or endocrinological change [327]. The acute affects of exercise on the production of cortisol have been explored in a small group of healthy postmenopausal women [328]. With an intervention aimed at bicycling to exhaustion, the authors failed to find the hypothesised relationship between depression and cortisol response, but acknowledge that the small sample size and stable psychological profile of the participants may have confounded the results. However, little is know of the long-term psychological effect of exercise on a woman's quality of life, well-being, psychological health and mood.

5.2.3 Cross sectional and Acute Studies of the Psychological Impact of Exercise in Women

In order to explore the interaction between menopausal status and exercise participation on mood, pre- and postmenopausal women who participated in regular exercise were compared against women of similar menopausal status who did not [327]. Their results showed that women who exercised scored significantly lower on negative mood dimension and higher on positive mood dimensions than non-

exercisers, regardless of menopausal status. However, participants were questioned directly following an exercise class, which could have artificially inflated mood scores. In fact, subsequent analysis confirmed a significant difference between mood state in both the pre- and postmenopausal exercise group immediately before and after the exercise intervention. Nevertheless, the authors argue that the results demonstrate the positive effect of exercise on mood, and that menopausal status does not modify the beneficial psychological response to exercise in women.

Slaven and Lee built on these findings by comparing the psychological well-being in four groups of middle-aged women (pre-menopausal, peri-menopausal, postmenopausal with HRT, postmenopausal without HRT) on the basis of exercise participation [325]. Exercisers in all groups reported higher psychological well-being scores and fewer menopausal symptoms than non-exercisers, with or without the use of HRT. The authors concluded that middle-aged women who choose to exercise are less likely to experience menopause-related distress, regardless of HRT use or menopausal status. Slaven and Lee were able to expand these findings by examining mood and symptom reporting of pre-menopausal exercisers compared to postmenopausal exercisers with or without HRT, before and after their regular exercise session. The authors showed an acute effect of exercise on mood and symptom reporting, regardless of menopausal status or HRT use. This may have been as a result of post-exercise endorphin changes or bias built into the study as a result of expectation and motivation on behalf of the exercise group. However, these findings are consistent with previous research, which found increased positive mood in a young group of women who exercise regularly following an aerobic exercise class, regardless of the time of day [329].

Blanchard *et al* explored the acute effect of a single bout of high intensity exercise on anxiety levels in a group of middle-aged breast cancer survivors [330]. Patients were split into two groups on the basis of pre-test anxiety scores. It was found that women with high baseline levels of anxiety had significantly lower anxiety levels post exercise, whereas patients with a low baseline level of anxiety had higher anxiety levels following the acute exercise intervention. The authors dismiss the slight increase in anxiety among the low-anxiety group, stating that; '...the increase is not something that should concern clinicians or nurses' (pp1619). It is interesting to note that while the authors maintain that further research is required on the basis of their findings, no further mention is made of the negative impact the intervention had on 47% of their study population.

Furthermore, not all studies have found a link between positive mood, symptom reporting and exercise participation among postmenopausal women. Guthrie *et al* found no significant relationship between the level of physical activity, psychological well-being and menopausal symptoms experiences during the midlife transition [331]. Indeed, the authors found that increased hours of leisure time activity were related to higher levels of interpersonal stress. The level of physical activity also had no affect on the women's experience of troubling heath-related symptoms, menopausal or otherwise. This cross-sectional study was unable to explore the direction of the various associations, although the authors propose that these anomalous findings might reflect that women under stress may exercise more. Alternatively, they suggest that women who exercise frequently may be unable to fulfil the demands placed on

them in other areas of their lives as a result of time pressures and other commitments [331].

Resistance training was shown to have little effect on anxiety in a group of college age women [332]. Anxiety levels did not change following a single session of either low, moderate or high intensity exercise. Low intensity exercise was found to reduce anxiety, whereas higher intensity exercise actually increased anxiety in a similar group of age-matched men. The authors, using a more precise manipulation of exercise intensity, replicated these results, although both sexes suffered increased anxiety following the high intensity exercise intervention [332].

5.2.4 Longitudinal Studies of the Psychological Impact of Exercise in Women

Few longitudinal studies have explored the effect of exercise on the psychological health and well-being of healthy postmenopausal women, while a lack of methodological rigor has been identified in the majority of studies exploring the effect of exercise on normal mood [313]. Most longitudinal research into exercise in women is undertaken in a clinical population [333], with the majority of studies involving cancer survivors [334;335]. Few studies employ any form of follow-up [333;334;336], while fewer still have gained positive results.

In one of the few case-control studies of the impact of exercise on psychological well-being in normal, inactive postmenopausal women, Norvell *et al* randomly assigned patients to either a 12-week aerobic or passive exercise program, or a sedentary control [337]. Aerobic exercise did not produce any significant improvements in psychological well-being, while the passive exercise group gained greatest

improvements in psychological health. However, improvements in physical fitness were related to changes in psychological distress, depression and perceived stress. The impact of a 12-week exercise program on the psychological health, functional status and CHD risk factors of a group of obese middle-aged (55–70 years) women has also been explored [333]. All women were previously inactive and of low socio-economic status. Although the exercise group showed an improvement in all the physiological and functional measures, significance was not achieved due in part to high dropout rates (43% of the exercise group). However, women in the exercise group showed significant increases in life satisfaction following the 12-week exercise program. Unfortunately, the long-term effects of the exercise program on the physical and psychological health of participants in either study were not recorded.

In light of the relatively high dropout rate common to both physiological and psychological studies of exercise, Labbé *et al* assigned a group of healthy young women into either an exercise intervention alone or combination with a motivational program [338]. As the motivational program had no additional benefit on either dropout rates of psychological morbidity, the two groups were combined, and as a result the study was analysed without a suitable control. Following six-weeks of twice weekly exercise classes comprised of talks and track-running, both trait anxiety and depression scores were reduced. However, exercise capacity was not accurately measured either at baseline or post-intervention, with no definite workload parameters for the participants to follow. State anxiety was correlated with exercise participation at six-week follow-up, but the authors fail to state the direction of the association. Without the use of a suitable control, prescribed exercise workload or suitable assessment at follow-up, the results should be treated with caution. In fact,

the authors intimate that the exercise program may have inadvertently become a support group, as the participants expressed anxiety at the culmination of the project and the cessation of the motivational support of the group.

In order to determine the impact of exercise on psychological well-being, mood and body esteem in a group of breast cancer survivors, women of an unspecified age were randomised into three session of cardiovascular exercise per week for 12 weeks, or a usual care control [335]. Exercise provided no additional improvements in psychological health and mood in comparison to the usual care control, although the data suggest a trend towards additional psychological benefit in the women who were randomised to the exercise arm of the study. The authors acknowledge that their study was initially statistically under powered due to time and financial limitations, which were further compounded by the expected drop-out rate. Although there was no significant difference between the groups, the authors still argue that exercise could improve psychological well-being in breast cancer survivors. Unfortunately, the long-term impact of the intervention was not recorded, as a follow-up assessment was omitted from the study design.

Breast cancer survivors were once again the focus of research in a study exploring the effects of cardiovascular exercise on cardiopulmonary outcomes and quality of life [334]. Postmenopausal women were randomly assigned to 15 weeks of thrice-weekly cardiovascular activity to a moderate intensity prescribed workload, or a usual care control. Women who underwent the exercise intervention showed significant improvements in quality of life, happiness, self-esteem, physical well-being and fatigue in comparison to the control group. Cardiopulmonary function and peak

power output both showed significant improvements. Fatigue and anxiety were also significantly reduced while quality of life and perceived energy increased following 10 weeks of thrice weekly exercise in a mixed gender group of breast, colon and lung cancer survivors [339]. Unfortunately, neither study included any form of follow-up, and as a result the long-term impact of exercise on the positive outcomes identified during both studies was not explored.

In a study exploring the effect of an exercise intervention on a group of sedentary postmenopausal caregivers, participants were randomised into a 12-month program of dietary advice and health promotion, or 12 months of moderate intensity exercise (30 – 40 minutes exercise, four times a week) [336]. Both groups received frequent contact throughout the course of the study. Exercise was found to be no more effective in reducing psychological morbidity than the health education control. Both groups showed significant improvements in depression, stress and subjective burden, while anxiety was unaffected. The authors explain their findings in light of the social support provided by the research team to both groups. However, statistical analysis reveals that self-reported social support was unaffected following the intervention in both groups, while the health education control received less actual contact than the exercise group. In spite of the author's conclusions, social support does not appear to be a factor in reducing psychological morbidity in this study. Depression was identified as a barrier to participation and subsequent psychological and physical improvement in this group of sedentary postmenopausal women.

In order to explore the high rates of attrition from almost all studies exploring both the psychological and physiological impact of exercise in women, Annesi [340]

compared the attrition rates and emotional change in a pilot study of 12 weeks of high versus low intensity exercise in sedentary, clinically obese middle-age women. Both groups also received cognitive behaviour modification training in an attempt to encourage exercise compliance. Attrition from the twice-weekly high intensity program was significantly higher than for the thrice-weekly low intensity group (66% verses 23%), while any changes in well-being and mood among the remaining high intensity group members were not assessed. Positive changes in mood and anxiety were found in the low-intensity group following the 12-week exercise intervention. While some physiological changes were noted, changes in $VO_{2\ max}$ were unrelated to anxiety or mood, while there was no relationship between actual and perceived weight change. Furthermore, there was no relationship between actual change in waist/hip circumference and change in body area satisfaction. The authors acknowledged the methodological flaws in this pilot study, such as the under utilisation of the control group and lack of follow-up. It could also be argued that comparing attrition from high and low intensity exercise participation on the basis of cognitive behavioural intervention may not be the most appropriate study design. Nevertheless, the authors argue that this study highlights the lack of relationship between psychological and physiological changes as a result of low intensity exercise, and that physiological improvements may be unrelated to improvements in depression, anxiety and body image [340].

The relationship between physiological and psychological changes following exercise has also been called into question by Cramer *et al* [268]. Fifty middle-aged mildly obese, yet otherwise healthy women were randomised into either 15-weeks of moderate intensity group-based brisk walking or an assessment only control. While

general well-being improved following the exercise intervention, no changes were found in anxiety, 'daily hassles' or mood. Although improved well-being was significantly correlated with changes in pre-and post-intervention resting heart rate, all other measures of sub-maximal cardiopulmonary fitness were unrelated to changes in psychological health. The authors explain the lack of psychological improvement in terms of the demographics of the study sample and the extra demands created by the daily exercise regime. Many of the women also experienced little or no weight-loss, despite prior expectation, which the authors argue could have promoted feelings of disappointment and negativity. While improvements in sub-maximal cardiopulmonary fitness were noted, significant changes in $VO_{2\ max}$ were not. This lead the authors to conclude that despite the lack of psychological improvement following the exercise intervention, substantial improvements in physical fitness were not required to incite positive changes in psychological health [268].

In summary, previous research suggests that exercise participation among middle-aged women may promote psychological well-being and improvements in positive mood, although the necessity for such improvements to be accompanied by concurrent improvements in physical fitness has yet to be determined. However, healthy, normal postmenopausal women remain under-represented in the literature, while many existing studies are incomplete or compromised by inconsistency. Such failings can be illustrated by a final study exploring the under-representation of ethnic minority women in studies of the impact of exercise on psychological well-being [341]. Participants were encouraged to walk more often in their daily lives through telephone motivation or behavioural counselling. However, no specific exercise plan was provided, and no instruction was given on the frequency and intensity of any

exercise participation. As both motivational and behaviour counselling provoked no differences in exercise participation, results from both groups were combined, resulting in a lack of suitable control. Although the study did include a three-month post-intervention follow-up, the ethnic minority women did not undergo any assessment of physical fitness or functional ability at any stage of the study. The authors identified a relationship between increased walking and vigour, however there was a lack of association between walking and improvements in negative mood. It is therefore clear that further methodologically rigorous studies are required to thoroughly explore the impact of exercise participation on the psychological well-being of middle-aged women from all walks of life

5.2.5 Choice of exercise intervention

Current guidelines from the Centres for Disease Control and Prevention and the American College of Sports Medicine advocate that all members of society, aged two years or older should engage in moderate intensity exercise for 30 minutes a day on most days of the week [342]. Moderate intensity exercise, working to 60 – 65% of the heart rate reserve (see section 5.6) appears to create the optimal environment to promote exercise adherence [343]. Walking has been shown to have a higher compliance rate than other low to moderate intensity physical activity as it requires no special skills, equipment or facilities, and with the right motivation it can be easily incorporated into daily life [268]. Therefore, it is unsurprising to discover that brisk walking has been identified as the fastest growing physical activity in the United States [344]. Brisk walking has also been identified as particularly efficacious for post-menopausal women [345]. Asikainen *et al* found that 45 minutes of moderate intensity brisk walking performed daily in one long or two short bursts produced similar

improvements in $VO_{2\,max}$, weight, percentage body fat and BMI. Equal increases in estimated aerobic fitness were also found in obese sedentary women who participated in either four 10 minute bouts of brisk walking or one 40 minute brisk walk, five days a week [346]. Interestingly, those women who participated in the multiple-bout brisk walking group consistently exercised more frequently than the prescribed 40 minutes throughout the exercise program. As participant attrition from exercised-based intervention can be as high as 66% [340], using short frequent bouts of exercise as a method for maintaining exercise participation could therefore provide a realistic program for much of the adult population.

Coleman *et al* sought to evaluate the optimal method of prescribing 30 minutes of brisk walking six days a week [347]. Participants were assigned to one of three conditions: either one 30-minute bout of brisk walking; three 10-minute bouts; or any combination of bouts longer than five minutes to total 30 minutes of exercise. Participants completed the prescribed exercise for 16 weeks and were followed-up after a further 16 weeks, in order to gauge the long-term impact of the exercise program on lifestyle changes and cardiovascular risk. Participants in all conditions reduced their cardiovascular risk, with no one condition being more effective than any other. Life style changes and health related outcomes were maintained at 32 weeks, irrespective of the initial exercise intervention. The authors conclude that a flexible approach to exercise prescription, more akin to lifestyle change and health promotion, may be more effective than a rigorous, structured program in maintaining the recommended frequency and intensity of exercise in sedentary adults.

Similarly, Murphy *et al* sought to determine whether short intermittent bouts of brisk walking would elicit similar improvements in physiological and psychological health indices as one long continuous bout [348]. Middle aged men and women were randomly assigned to either three bouts of 10-minutes brisk walking or one bout of 30-minutes brisk walking, five days a week for six weeks. On completion of the intervention there was a brief washout period before participants crossed over to the alternative walking program. Physiological measures improved equally irrespective of the style of intervention, while feelings of tension and anxiety decreased significantly following both the short-bout and long-bout program. Perceived barriers to exercise were significantly decreased following the short-bout exercise program only, which the authors suggest may reflect the effort involved in setting aside a continuous period of 30 minutes for exercise in a busy day. Based on the studies compliance and attrition rates, the authors suggest that sedentary individuals may find it easier to maintain a brisk walking program if first accustomed to several short bouts spread throughout the day.

In order to assess the optimal exercise environment for healthy older adults, King *et al* compared the adherence and physiological impact of three exercise conditions [349]. Participants were randomly assigned to a high- or low-intensity home-based or high-intensity group-based 12-month exercise program. Participants in both home-based exercise programs reported significantly greater adherence than the group-based exercisers. High-intensity home-exercisers showed the greatest improvement in physical fitness. Lower-intensity exercise was associated with fewer exercise-related injuries while maintaining a high level of adherence and comparable gains in physical fitness. As the participants were more likely to adhere to a home-based exercise

program, regardless of the prescribed intensity, the authors concluded that healthy older adults might view a home-based exercise program more favourably. While other studies have failed to find any difference in adherence rates to home- or group-based exercise intervention [343], King *et al* argue that a home-based exercise regime may be more effective at creating the behavioural lifestyle changes recommended for maintaining functional capacity and quality of life.

Brown *et al* explored the impact of multi-modal intervention on a group of mild to moderately depressed women by comparing the impact of moderate intensity exercise, high dose vitamins and light exposure to a placebo vitamin control [350]. The study lacked a pre- and post-intervention assessment of physical fitness or functional ability and failed to include a follow-up. However, the authors found that the eight-week multi-modal intervention significantly improved the women's overall mood, self-esteem and well-being while reducing symptoms of depression. The multi-modal intervention was found to be equally useful for all women, regardless of their baseline levels of psychological morbidity. The authors argue in favour of the ease and simplicity of the intervention, while the program could be easily re-initiated by the individual should depressive symptoms re-occur. Changes in self-belief were also noted, as comments from one participant neatly illustrate:

> "I found there was something I could do within my own control. I didn't have to go to the doctor to get a prescription. It is such a helpless feeling to not know how to change your moods." [350]

Interestingly, similar improvements in mood, well-being and depression were found in the control group, although the relationships were not as strong. Brown *et al* describe these findings as the unintentionally supportive nature of study protocol, and regression towards the mean.

5.2.6 Proposed Mechanisms for the Psychological Effect of Exercise

One of the most prominent psychological theories for the impact of exercise of psychological well-being is the distraction hypothesis [266]. The distraction hypothesis postulates that exercise provides a diversion from unpleasant stimuli or painful somatic complaints, leading to improved positive affect [351]. Exercise may offer a time away from the daily routine, and thus a distraction from the demands of daily life [271]. While distraction may offer short-term improvements in well-being and mood, it has been suggested that in light of the long-term anxiolytic effects of exercise, other mechanisms may also be involved [352].

The effect of social interaction has also been suggested as a factor in mood improvements following exercise [267]. However, home-based lone exercise programs have been shown to be more effective at improving psychological health and well-being as group-based exercise [349]. As an independent hypothesis, the social interaction theory has little credibility [271], although the social interaction offered by a group exercise program may be of value to isolated individuals with limited social support. As a result, the social interaction model should not be dismissed outright.

A further proposed psychological mechanism to explain the effect of exercise on well-being is the mastery hypothesis. The mastery hypothesis proposes that

command of a challenging pursuit creates a feeling of independence and success, improving mood and self-esteem [271]. It could be argued that the mastery hypothesis is a component of Bandura's theory of self-efficacy [317], which is concerned with a person's belief in their ability to perform a certain task or behaviour (see section 5.2.1.2). Improvements in self-efficacy have been found following a moderate intensity exercise program, which may be related to the challenge of the task; the moderate intensity exercise provided participants with an optimally challenging task [316]. However, the link between achieving self-efficacy and psychological well-being remains unclear [271].

One of the most popular physiological explanations for the link between physical activity and improvements in mood in recent years has been the proposed increase in production of beta-endorphins and the resulting 'runners' high' [269]. Beta-endorphins are endogenous opioids, which are thought to stimulate a change in mood and modify pain perception. Short bursts of very high intensity exercise have been shown to stimulate the release of beta-endorphins, with peak beta-endorphin levels noted as two to four times greater than baseline values [353]. However, increased beta-endorphin levels were only provoked following continuous endurance exercise only if the workload exceeded 70% $V0_{2max}$, or if the exercise duration exceeded 60 minutes [269]. Schwartz and Kindermann conclude that while endurance exercise of 60-minute duration or longer may lead to an increase in beta-endorphins, no increases in endogenous endorphins can be expected following leisure-time sports or healthy sporting activities [269]. Therefore, this type of effect would not be expected in the brisk walk scenarios.

Another physiological explanation for the link between exercise and mood is related to the regulation of catecholamines and serotonin, known collectively as monoamines. Serotonin is a neurotransmitter, as are many of the catecholamines, which also circulate throughout the body in response to certain conditions, such as stress (refer section 3.2.1). As neurotransmitters, monoamines can affect arousal and attention. Monoamine production, transmission, re-uptake or metabolism is generally believed to be impaired among the clinically depressed. This has led to the pharmacological development of selective serotonin reuptake inhibitors, including fluoxetine (Prozac) [271]. Although the relationship between clinical depression and the monoaminic system is far from conclusive [354], it has been suggested that exercise may normalise monoaminic function in clinically depressed patients [270]. Although much of the work in this area has been undertaken in animal models biased by concurrent environmental stressors [355], Chaouloff concludes that acute and chronic exercise *probably* affects the monoaminic systems [270], although the exact mechanistic pathway has yet to be determined [354]. As no clear conclusions can be drawn for existing human studies of exercise and monoaminic brain activity [354], further research is required explore the impact of exercise on the various neurotransmitters thought responsible for the development of clinical depression.

A further physiological hypothesis, the thermogenic model, suggests that increased body temperature following exercise is responsible for noted mood improvements [271]. The link between physical activity, core temperature and mood has not been supported by detailed meta-analysis [352], although Petruzello *et al* suggest further research is required due to the paucity of data available relating to the thermogenic model.

The assessment of cortical activation following exercise using electroencephalography (EEG) has identified increased EEG alpha wave activity following exercise [356]. An EEG records the variation in electrical potential between electrodes placed on the scalp and is employed as an index of brain activity within the cerebral cortex. The general consensus maintains that increased EEG alpha wave activity reflects decreased cortical activation and is interpreted as indicative of a relaxation response or anxiety reduction [352]. However, the presence of spontaneous EEG changes following exercise is far from conclusive [357]. Further research is required to explore the link between cortical activity, anxiety and exercise, as studies of EEG alpha activity and exercise are limited by various methodological irregularities, including incomplete statistical analysis and a failure to assess concurrent changes in self-reported anxiety [352].

It has been suggested that those factors associated with the process of exercise may be more closely related to improvements in psychological morbidity than the physiological impact of the exercise itself [289]. In a recent review of depression and physical activity, Dunn *et al* questioned whether physical inactivity lead to depressive symptoms or if conversely, depressive symptoms lead to inactivity. Alternatively, the authors question whether a third factor, such as social support mediates this relationship [288]. Similarly, when discussing the aetiology of depression in relation to the dose-response effects of physical activity, Dunn *et al* [288] state that:

"Its is highly likely that depression, like high blood pressure, has multiple aetiologies, and that exercise, acting on multiple biological and psychological systems, could lead to synergistic adaptations that effectively reduce symptoms of these disorders." [288]

5.2.7 Summary

Previous studies have demonstrated the positive impact of exercise on the psychological health and well-being of the older population [305-308], although methodological irregularities cloud the value of much of the research. The relationship between improvements in psychological health and physical fitness also remain unclear [266-268], while the exact mechanistic pathway that links exercise and psychological functioning is also unknown [269-271]. Although many studies have explored the impact of physical activity on the psychological health of older women among the clinical population [333-335], healthy postmenopausal women continue to be under-represented in research. Further, methodological rigorous studies are required to determine whether physical activity promotes improvements in psychological well-being in relation to physical fitness among healthy, postmenopausal women.

Therefore, Study Two sought to determine whether a brief, controlled exercise intervention improved psychological morbidity and quality of life among healthy, postmenopausal women, irrespective of any accompanying changes in physical fitness. By establishing the impact of exercise on psychosocial functioning in healthy women of a similar age and background to those suffering from Cardiac Syndrome X, Study Two acts as a pilot for subsequent studies exploring the psychological and physiological impact of exercise in women with Syndrome X.

Study Two: The Psychological impact of Exercise in Healthy Postmenopausal Women

5.3 Aims and Objectives of Study Two

In order to assess the impact of moderate intensity exercise on the psychological well-being of healthy postmenopausal women, the following questions are addressed:

- Does six-weeks of moderate intensity exercise have any impact on anxiety and depression in a group of healthy postmenopausal women?
- Does six-weeks of moderate intensity exercise provoke any change in quality of life in a group of healthy postmenopausal women?
- Do healthy postmenopausal women need to continue exercising in order to maintain any psychological benefit gained from six-weeks of moderate intensity exercise?
- Will the cessation of exercise have an impact on levels of anxiety, depression and quality of life six-weeks after a program of moderate intensity exercise?

In light of the findings from Study One (refer section 4.7), the following research questions will also be explored:

- Is menopausal symptomology related to anxiety, depression and quality of life in healthy postmenopausal women?
- Is psychological health related to history of hysterectomy, oopherectomy, HRT use or age at last menstrual period in healthy postmenopausal women?
- Is social network size, social situation and life-partner support related to psychological morbidity healthy postmenopausal women?

5.4 Methodology

Study Two was performed as a sub-study of a project entitled; 'The Effect of Exercise Training on Cardiovascular Risk Factors and Endothelium-Dependent Vasomotion in Postmenopausal Women' in collaboration with Dr. Pornpat Chandrruangphen (PC).

5.4.1 Ethical Approval

In order to comply with guidelines regarding volunteer's participation in research, a submission was made to the Royal Brompton & Harefield NHS Trust Ethics Committee for permission to perform the study. As Study Two was performed as a sub-study of 'The Effect of Exercise Training on Cardiovascular Risk Factors and Endothelium-Dependent Vasomotion in Postmenopausal Women', the projects were split and defined by two separate ethics applications. Ethics approval was given on the proviso that all volunteers who had primarily agreed to participate in 'The Effect of Exercise Training on Cardiovascular Risk Factors and Endothelium-Dependent Vasomotion in Postmenopausal Women' were given the opportunity to decline to participate in Study Two. However, all volunteers who gave their consent to participate in 'The Effect of Exercise Training on Cardiovascular Risk Factors and Endothelium-Dependent Vasomotion in Postmenopausal Women' also gave their consent to participate in Study Two.

In the time that elapsed between gaining ethics approval for Study One and the subsequent submission for Study Two, ethical guidelines relating to the collection of certain sensitive, personal information were revised. As a result, the Royal Brompton & Harefield NHS Trust Ethics Committee refused to allow The List of Threatening

Experiences [254] or any similar scale to be used in Study Two, or any future studies undertaken within the Trust.

5.4.2 Participants

All participants who gave consent to take part in the study entitled: The Effect of Exercise Training on Cardiovascular Risk Factors and Endothelium-Dependent Vasomotion in Postmenopausal Women were approached to participate in Study Two. Participants were recruited into 'The Effect of Exercise Training on Cardiovascular Risk Factors and Endothelium-Dependent Vasomotion in Postmenopausal Women' only if they also fulfilled the inclusion criteria for Study Two. Therefore the inclusion and exclusion criteria for both studies were combined.

5.4.2.1 Inclusion and Exclusion Criteria

Table 5.4.1 illustrates the inclusion and exclusion criteria employed when recruiting volunteers to participate in Study Two.

Inclusion Criteria	Exclusion Criteria
Healthy postmenopausal (absence of menstruation for at least one year) women	Participate in >2 episodes of planned exercise per week
On no medication known to affect the cardiovascular system or lipid/carbohydrate metabolism	History suggestive of cardiovascular disease or abnormal cardiovascular examination
Aged 50 to 65	Extremes of BMI: < 18 or > 34 kg/m^2
Willing to give written informed consent	Extreme dietary practices (where nutritional deficiencies are suspected)
	Contraindications to treadmill exercise test or exercise training
	Current cigarette smoking
	Resting systolic BP > 160 mm Hg, diastolic BP > 100 mm Hg or on anti-hypertensive treatment
	Abnormal 12-lead ECG
	Diabetes mellitus
	History of psychiatric illness

Table 5.4.1: The inclusion and exclusion criteria employed for participants in Study Two.

5.4.3 Participant identification and recruitment

Female postmenopausal healthy volunteers were recruited from the nursing and ancillary staff of the Royal Brompton & Harefield NHS Trust. Healthy volunteers who participated in Study One who also fulfilled the inclusion criteria were approached to participate by mail. At least 12 months had elapsed between the volunteer's participation in Study One and receiving an invitation to participate in

Study Two. Nursing and ancillary staff at the Royal Brompton and Harefield NHS Trust were first approached with a general email request for volunteers to participate in 'The Effect Of Exercise Training On Cardiovascular Risk Factors And Endothelium-Dependent Vasomotion In Postmenopausal Women', a research study exploring physiological effect of exercise on postmenopausal women. If an interest was expressed, eligibility was checked by telephone or email and a study appointment made.

5.4.4 Randomisation and Baseline Study Visit

Following consent by PC into 'The Effect of Exercise Training on Cardiovascular Risk Factors and Endothelium-Dependent Vasomotion in Postmenopausal Women', participants were randomly assigned into one of two groups. Participants randomised into Group One were able to continue exercising following the six-week exercise program, while participants randomised into Group Two were asked to refrain from exercising and instructed to return to their pre-study habits following the exercise regime.

Following randomisation, volunteers were introduced to Study Two. All study visits took place in a quiet, private room on a one-to-one basis (PC was not present), where Study Two was fully explained and any questions answered. It was made quite clear that the volunteers were under no obligation to participate in Study Two, and that their participation in 'The Effect Of Exercise Training On Cardiovascular Risk Factors And Endothelium-Dependent Vasomotion In Postmenopausal Women' would be unaffected if they declined to take part. Participants were advised that their GP would be informed of their participation in the study if requested, however no one

made that request. All participants gave written informed consent using the consent form approved by the Royal Brompton & Harefield NHS Trust Ethics Committee (Appendix K). No participant consented into 'The Effect of Exercise Training on Cardiovascular Risk Factors and Endothelium-Dependent Vasomotion in Postmenopausal Women' refused to take part in Study Two or give written informed consent.

Once the participants had provided informed consent, they were guided through and asked to complete a number of questionnaires (see section 5.5). The method of completion of each individual questionnaire was explained to the participant, while plenty of time was set aside to answer any questions. Written instructions were also given at the start of each new set of questions within the questionnaire. The individual questionnaires were grouped together to create a battery of tests, which participants were given at three time points throughout the study. Figure 5.4.1 illustrates the study design and questionnaires administered at each time point.

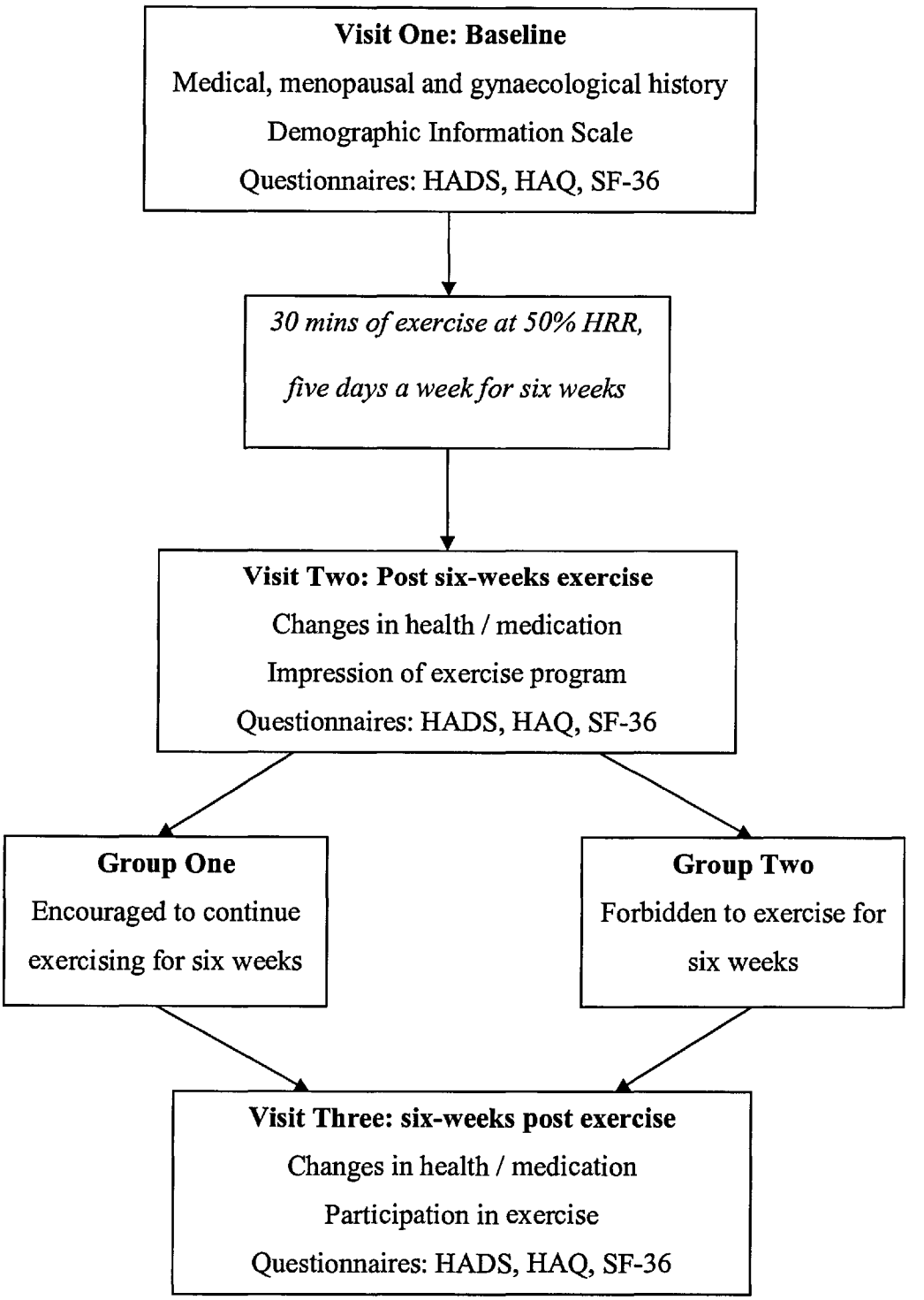


Figure 5.4.1: The study design, questionnaires administered and information gained at each time point of the study.

The participants were requested to complete the questionnaire at home and returned it using a 'freepost' envelope provided during their study visit. Participants were

requested to complete the questionnaires alone, answering all the questions as required, and were also encouraged to explain any answers more fully or give any additional information they thought appropriate

On receipt of the baseline questionnaires, each participant was assigned a unique study number from 1211 to 1290. A list of the participants' names and identification numbers were kept electronically. The questionnaires were coded according to the methods stated by the authors [252;253;255;358] and entered on to an EXCEL (Microsoft, Redmond, Washington) spreadsheet. Data was then transferred to SPSS Version 10 (SPSS Inc, Chicago, Illinois) for statistical analysis. The original questionnaires were then filed by study number. The original consent forms were kept locally, while copies were sent to the local ethics committee and given to the participant.

5.4.5 Post-exercise and six-week follow-up assessment

Participants returned for their second study visit shortly after completing the exercise program. The women discussed their experiences while undertaking the exercise program and were given the second collection of questionnaires. The participants were requested to complete the questionnaire at home and return it within five days using a 'freepost' envelope provided during their study visit. The method of completion of each individual questionnaire was explained, while plenty of time was set aside to answer any questions. Participants were requested to complete the questionnaires alone, answering all the questions as required, and were also encouraged to explain any answers more fully or give any additional information they thought appropriate. Participants were also instructed *not* to recall their previous responses. In order to reduce familiarity bias, the individual questionnaires within

the battery of tests were re-ordered for each visit (e.g., Baseline: HAD, HAQ, SF-36, visit two: HAQ, SF-36, HAD etc).

Women randomised into Group One then were encouraged to continue exercising following the six-week exercise intervention. Any suggestion of further exercise, such as gym membership, joining an exercise class or continuing the brisk walking program were encouraged and praised. Members of Group Two were told to stop exercising, to return to their pre-study habits and desist from any extra-ordinary physical activity until the completion of the study.

Six weeks after completing the exercise program, continued exercise participation or non-participation was checked through clinical interview. Participants in both groups also completed a third and final collection of questionnaires, including details of any exercise participation. Participants were again requested to complete the questionnaires alone, answering all the questions as required, and were also encouraged to explain any answers more fully or give any additional information they thought appropriate. Participants were also instructed *not* to recall their previous responses, and to return the questionnaire in the 'freepost' envelope provided within five days. Participants were thanked for their participation in the study and were advised that as the study had now ended, they were free to exercise as they wished.

5.5 Questionnaires

The Health Anxiety Questionnaire [252](HAQ)(Appendix G) has been developed using the cognitive behavioural model of anxiety [256] which divides health anxiety into two parts: development and maintenance. The HAQ is split into 4 sub-scales, which focus

on health worry preoccupation, fear of illness and death, reassurance seeking behaviour and interference with life, and has been developed and validated among medical, psychiatric and healthy populations [252].

The Hospital Anxiety and Depression Scale [253](HADS) (Appendix H) measures clinically significant anxiety and depression in general medical patients. The 14-item questionnaire is split into 2 sub-scales (anxiety and depression) using a four-point response format. Anxiety and depression scales have also been combined to create a total score [189]. The scale has been validated with both outpatients and inpatients [257], and has been used extensively in studies with non-psychiatric clinical populations.

The SF-36 [358](Appendix L) is a general health questionnaire divided into different aspects of quality of life: physical role limitation, emotional role limitation, physical functioning, pain, general health and energy. The SF-36 has been validated and used extensively in both clinical [359] and non-clinical adult populations [360].

A demographic information scale [255] (Appendix J) was used to assess social support and isolation by recording the patients living circumstances, frequency of contact with friends and relatives and size of social network. This measure investigates the frequency of contact with adults both outside and within the normal household, differentiating between friends and family, along with identifying a specific confidant. The four reported levels represent the following frequencies of social contact: 1) every day, 2) three times per week, 3) once a week, 4) once a month.

Additionally, participants were asked to complete questions regarding their menstrual and gynaecological history, including details (where applicable) of hormone therapy, hysterectomy, menopausal symptomology and last menstrual period (Appendix M). The degree of menopausal symptomology encountered by each participant was assessed through their experience of the following symptoms: hot flushes, night sweats, heat intolerance, sleep disturbance, vaginal dryness, periods of low mood, mood swings and loss of concentration. Participants were asked to indicate if they had experienced any of the named symptoms during the menopause, choosing one of the four following responses for each symptom: none, mild, moderate, severe. The four responses were coded from zero (none) to three (severe), and a total score created from the combined responses from each item, giving a maximum score of 24. Participants were also asked about any known family history of CHD, their current medications, previous life-long hospitalisations and level of physical activity. Hospital admissions for childbirth were disregarded.

5.6 Exercise Intervention

All participants taking part in Study Two underwent $V0_2$ treadmill testing (performed by PC) in order to identify their maximal heart rate. This was used to calculate 50% of their heart rate reserve (HRR), a level of moderate intensity exercise deemed as appropriate for the study population [361]. HRR is the difference between resting and maximal heart rate, while the heart rate at a given percentage of HRR is calculated using the formula below (Equation 5.6.1):

$$Exercise\ HR = \%\ of\ target\ intensity\ (HR_{max} - HR_{rest}) + HR_{rest}$$

Equation 5.6.1: The formula for calculating exercise heart rate at a certain training intensity.

Each participant was issued with a heart rate monitor (HRM) (Polar M21, Leisure Systems International, UK) for use during the training period. Participants received thorough training in the use of the heart-rate monitors (PC), while each participant also had an instruction booklet for reference during the study.

The Polar HRM consists of a wrist receiver (which looks like and doubles as a watch) and an electrode and transmitter unit that is strapped around the chest while exercising. The target heart rate during exercise was set at 50% of HRR calculated from the subject's resting heart rate and maximum heart rate obtained from the treadmill test. The target heart rate was programmed into the HRM to ensure that the subject exercised within her individual moderate-intensity zone for 30 minutes, five days a week. If the participant's heart rate rose above or fell below the target heart-rate window, an alarm sounded, drawing the participant's attention to their heart rate, enabling them to increase or decrease their pace accordingly. For most participants, this equated to either a brisk walk or slow jog. At the end of each exercise session, the participant entered the training data generated by the HRM into a log (date/time, exercise duration, time within zone, average heart rate, and energy expended (Kcals)). The accumulated data from all sessions was also stored on the HRM. At the end of the six-week training period, the HRM was returned and the accumulated exercise time kept by the monitor was recorded to evaluate overall compliance with the training programme (PC).

5.7 Statistics

The data were analysed using Paired and Independent Student's t-tests and Pearson's Correlation. Statistical significance level was set at $p<0.05$. The study was a randomised within-subjects design, using two-tailed tests. Data are expressed as mean ± standard deviation. Graphical representation of the data includes standard error bars. The first set of analyses combined the baseline data of whole group in order to identify any social and gynaecological variables that were associated with anxiety, depression and quality of life. The second set of analyses addressed the impact of six-weeks moderate intensity exercise on the psychological well-being of the whole group. The final set of analyses compared the data from the two randomised groups to explore the impact of the cessation or continuation of exercise on psychological well-being. The sample size calculation was performed on the basis of the physiological parameters under investigation by PC in the study entitled: 'The Effect of Exercise Training on Cardiovascular Risk Factors and Endothelium-Dependent Vasomotion in Postmenopausal Women'. As previously mentioned (see section 5.4), Study Two was performed as a sub-study of this protocol.

5.8 Results

5.8.1 Subjects

Twenty-three healthy postmenopausal women (56 ± 4 yrs) were enrolled in the study. Seventeen women successfully completed the six-week exercise intervention and all three study questionnaires. Baseline data from one participant who successfully completed the study was lost in a local postal dispute. Five women withdrew or were

withdrawn from the study for the following reasons: subsequent diagnosis of breast cancer (one), diagnosis of the metabolic syndrome (one), personal reasons (one), ankle injury (one) and time commitments (one). Data from the five women who failed to complete the study were included in the baseline analyses on an 'intention to treat' basis. Table 5.8.1 illustrates the baseline demographic characteristics of the participants consented into the study, along with those of the two randomised groups.

	Total Baseline (N = 22)	**Group One (N = 9)**	**Group Two (N = 8)**
Age range	51-66 yrs	51-65 yrs	51-66yrs
Single	4.5%	11.1%	-
Married	54.5%	77.8%	62.5%
Divorced	27.2%	-	12.5%
Widowed	13.6%	11.1%	25%
Participants living alone	22.7%	-	25%

Table 5.8.1: The demographic characteristics of the three study populations.

The gynaecological characteristics of the group were determined. Due to the lack of relationship between oestrogen level and psychological morbidity in the healthy control group noted in Study One, an oestrogen sample was not taken. Therefore, the participant's postmenopausal status was confirmed by an absence of menses for at least one year. The gynaecological characteristics of the group are shown in Table 5.8.2

	Total Baseline (N = 22)	Group One (N = 9)	Group Two (N = 8)
Age at last menstruation	47.7 ± 4.8 yrs	48.5 ± 4.1 yrs	46.8 ± 6.3 yrs
Years since last menstruation	8.5 ± 6.4 yrs	7.2 ± 5.2 yrs	10.0 ± 9.3 yrs
Hysterectomy (% of group)	45%	33%	37.5%
Age at hysterectomy	47.0 ± 7.6 yrs	46.0 ± 6.2 yrs	45.3 ± 9.1 yrs
Oopherectomy (% of group)	23%	22%	25%
Age at oopherectomy	50.2 ± 4.3 yrs	49.5 ± 2.1 yrs	50.0 ± 5.6 yrs
HRT use (% of group)	45%	33%	62%
HRT years	6.5 ± 4.1 yrs	8.0 ± 6.1 yrs	6.8 ± 3.4 yrs
Menopausal symptom score	9.9 ± 6.9	6.5 ± 5.7	10.3 ± 6.9

Table 5.8.2: The gynaecological characteristics of the total cohort and two randomised groups.

5.8.2 Baseline data

5.8.2.1 Group Differences

There were no differences in HADS or HAQ scores between the two groups at baseline. Participants in Group One had a higher SF-36 role limitation due to physical health score than Group Two (100 ± 0.0 vs. 65.6 ± 32.5, p=0.006). There were no other differences between the two groups on any other scale of the SF-36 at baseline.

5.8.2.2 Social Network, Friends, Relatives and Confidant

In line with Study One, data regarding social network were split into two categories: participants who reported having no friends or a small social network (six or fewer friends) and participants with a large social network (seven or more friends). The two categories were created by grouping responses either side of the median. There were no differences in the participant's HADS, HAQ or SF-36 total scores or sub-scales on the basis of their social network. The number of relatives or frequency of contact with those relatives, either by telephone or visiting was also unrelated to any scale of the HADS, HAQ or SF-36. Choice of confidant was unrelated to psychological morbidity, as was the frequency of contact with that person.

5.8.2.3 Gynaecological Factors

There were no differences in the participant's HADS, HAQ or SF-36 total scores or sub-scales on the basis of HRT use, hysterectomy or oopherectomy. Menopausal symptom score or years since the last menstrual period were also unrelated to any scale of the HADS, HAQ or SF-36.

5.8.3 Post intervention

5.8.3.1 Compliance and Performance

Participants performed 97% of the prescribed 15-hour (900 minute) exercise program (875.1 ± 177.4 minutes) in an average of 26 ± 5 sessions over a six-week period at the required workload calculated from their HRR (115.7 ± 4.4 BPM). All participants exercised at their calculated heart rate for the duration of the program as measured by the Polar HRM. However, participants failed to improve their $V0_2$ treadmill

performance following the six-week exercise program. In spite of the participants' excellent compliance and adherence to the prescribed workload, no change in physical ability or fitness as measured by $V0_2$ was shown. Therefore, in order to ascertain whether actual exercise participation in any way influenced psychological well-being, number of minutes spent exercising was used as an index of increased physical activity.

5.8.3.2 Hospital Anxiety and Depression Scale

A significant decrease in total HADS score (p=0.019) and HADS depression (p=0.015) was found following six-weeks of moderate intensity exercise (see Figure 5.8.1). Changes in the HADS depression and total HADS scales were unrelated to minutes spent exercising.

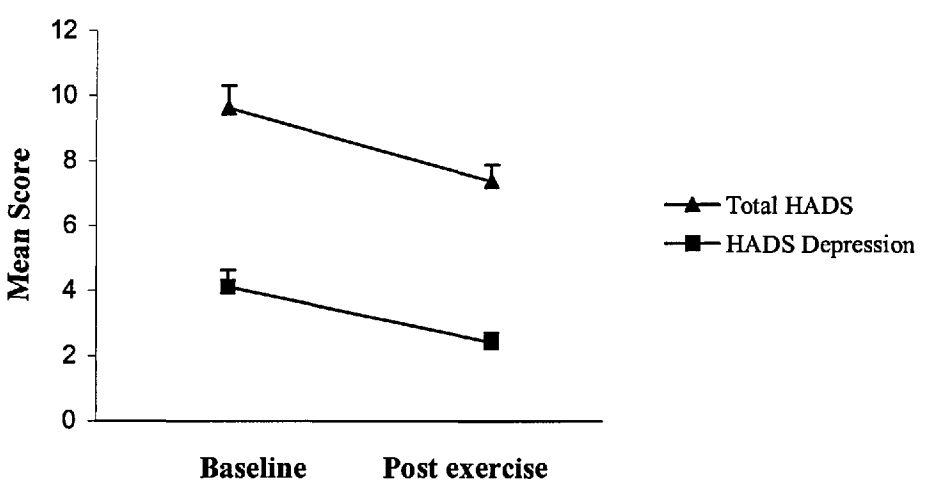


Figure 5.8.1: The effect of exercise on the HADS scores of healthy postmenopausal women.

5.8.3.3 Health Anxiety Questionnaire

A significant decrease in total HAQ score (p=0.001), health worry (p=0.001), fear of illness (p=0.037) and reassurance seeking behaviour (p=0.037) was found following six-weeks of moderate intensity exercise (see Figure 5.4.1). Decreased fear of illness and total HAQ scores were correlated with minutes spent exercising (R^2 = -0.55, p=0.027 and R^2 = -0.50, p=0.049 respectively). No significant change was found in interference with life following the exercise intervention.

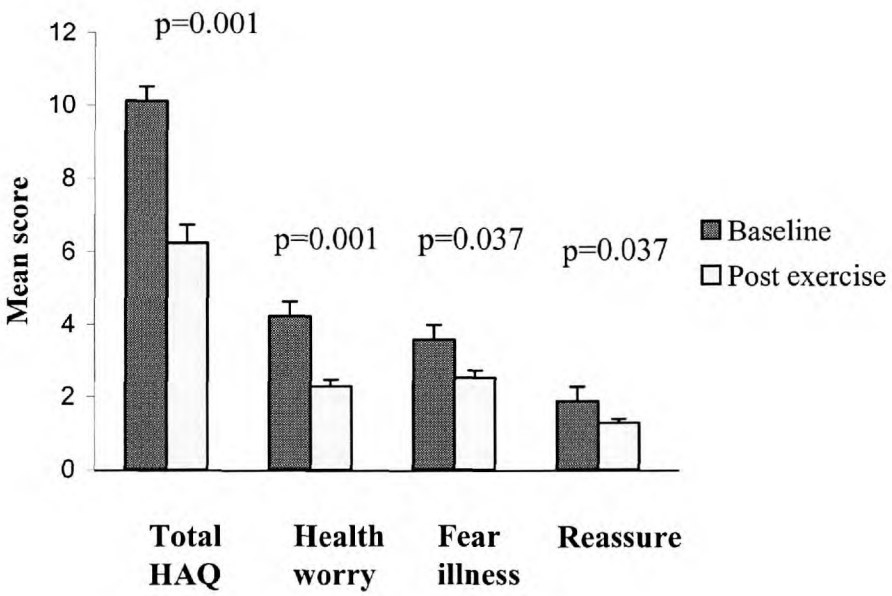


Figure 5.8.2: The effect of exercise on the HAQ scores of healthy postmenopausal women.

5.8.3.4 SF-36 Quality of Life

A significant increase in SF-36 well-being was noted following six-weeks of moderate intensity exercise (75.3 ± 16.7 vs. 81.6 ± 13.6, p=0.037), which was unrelated to minutes spent exercising. No significant changes were found in any other scales of the SF-36 following the exercise intervention.

5.8.4 Six-week follow-up

Following six-weeks of prescribed moderate intensity exercise, Group One were encouraged to continue exercising, while Group Two were forbidden from exercising and instructed to desist from any extra-ordinary physical activity. All participants in Group Two successfully 'failed' to exercise, while two members of Group One also failed to maintain any form of exercise regime.

Although there were no significant differences in the baseline HADS score between groups, Group One had lower Total HADS (5.5 ± 3.8 vs. 10.33 ± 5.5, p=0.05) and HADS anxiety score (3.7 ±2.6 vs. 7.1 ± 3.3, p=0.027) than group two following the exercise intervention. These differences increased at follow-up, with both HADS anxiety (3.3 ± 2.33 vs. 7.4 ± 3.5, p=0.013) and Total HADS (p=0.02) scores of Group One continuing to fall in comparison to Group Two (Figure 5.8.3).

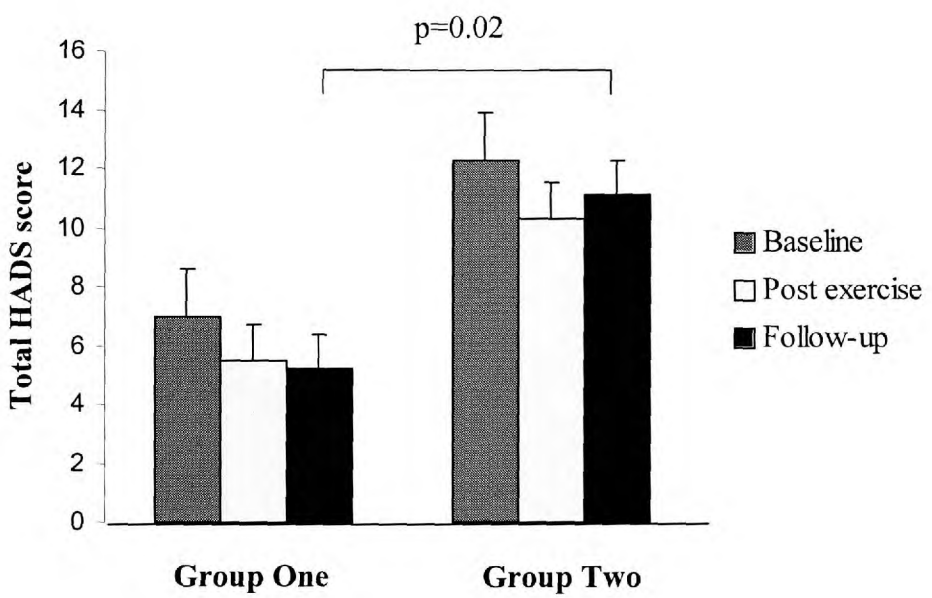


Figure 5.8.3: Changes in Total HADS score of the two groups over the duration of the study

Group One had higher SF-36 physical functioning score at follow-up than directly following the exercise program (p=0.013) not seen in Group Two (Figure 5.8.4).

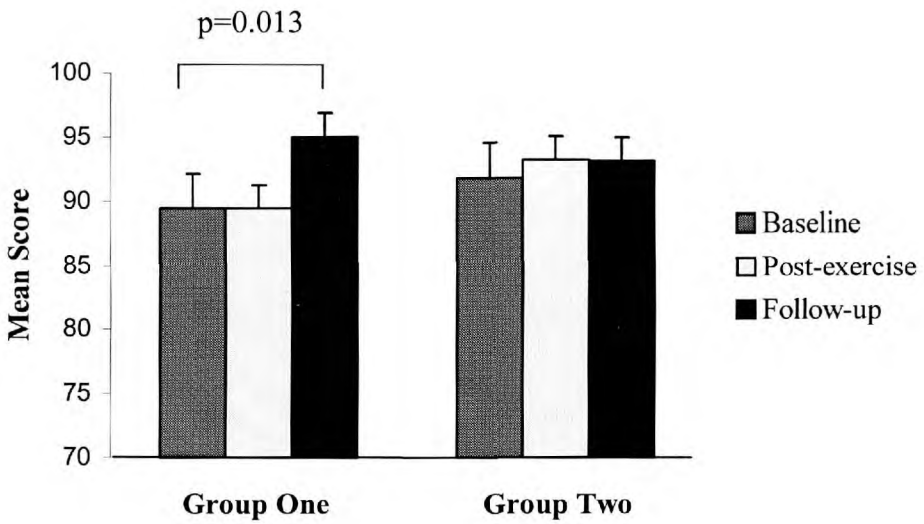


Figure 5.8.4: Changes in SF-36 Physical functioning score of the two groups over the duration of the study.

Group One also had significantly higher SF-36 energy levels than Group Two at follow-up (p=0.03), not found at baseline or directly following the exercise program (Figure 5.8.5).

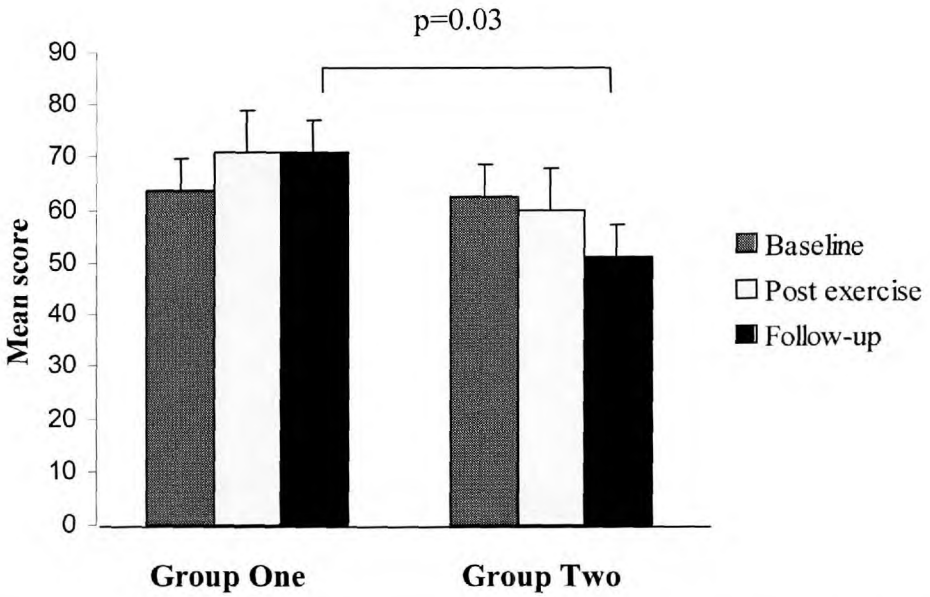


Figure 5.8.5: Changes in SF-36 energy score of the two groups over the duration of the study.

There were no differences in the HAQ scores between the groups post-exercise or at follow-up, while HAQ scores did not change in either group over the course of the six-week follow-up.

5.9 Discussion

Study Two was designed to assess the impact of a brief period of moderate intensity exercise on the psychological health and quality of life of healthy postmenopausal women of similar age and background to the majority of patients with Cardiac Syndrome X. Total HADS score and HADS depression were significantly reduced following six-week brisk walking programme. Total HAQ score and three of the four HAQ sub-scales also significantly improved following the exercise intervention, along with well-being, as measured by the SF-36. Many improvements were maintained after a six-week follow-up. Further declines in anxiety and total HADS were also shown in participants who continued to exercise, while Group One had significantly higher physical functioning at follow-up than directly following the exercise program. Such results confirm the continued self-reported exercise participation encouraged in Group One. The findings from Study Two support those of Courneya *at al,* who found that 12 weeks of moderate intensity exercise improved the quality of life, happiness, self-esteem, physical well-being and fatigue in a group of middle-aged breast cancer survivors [334]. Positive changes in mood and anxiety were found in sedentary, clinically obese middle-age women following a similar 12-week of low-intensity exercise program [340]. However, other studies of obese [268] and healthy [336] middle-aged women have failed to demonstrate any relationship between increased physical activity and improvements in psychological well-being.

Interestingly, despite an excellent adherence to the brisk walking protocol, there were no significant changes in the participants $V0_2$ following the exercise program. Improvements in psychological morbidity and well-being were therefore unrelated to

changes in physical fitness, as the exercise program failed to promote any changes in the participant's physical ability. Byrne and Byrne challenge the assumed causality between mood and physical fitness, arguing against the supposition that mood improvements following exercise are as consequence of measurable changes in aerobic fitness [286]. The current study supports this, illustrating that improvements in psychological morbidity can occur following physical activity, independent of any changes in physical fitness. Studies in an older population have consistently demonstrated that aerobic activity is not essential for promoting psychological health gains following exercise [311], while physical fitness *per se* was not implicated in the impact of exercise on well-being in older adults [312]. Others have argued that an exercise environment that encourages frequent participation and promotes social interaction may be intrinsic in improving well-being through exercise in an older population [311]. Anecdotally, those participants who exercised in the company of others, either with friends or family reported gaining a high level of enjoyment from the exercise program. However, the small sample size restricted any meaningful analysis of the impact of social interaction on improvements in psychological well-being following the six-week exercise intervention. Courneya *et al* also note the impact of uncontrolled social interaction when assessing the impact of a home-based exercise program [291]. Future studies should therefore explore the impact of social support and interaction on the successful participation in a home-based program of moderate intensity exercise. The social interaction hypothesis [267] (see section 5.2.6) may therefore be pertinent to the findings of the current study.

No significant changes in the majority of SF-36 scales were found following six-weeks of moderate intensity exercise or at the six-week follow-up, whether or not the participants remained physically active. A number of items in the SF-36 are

concerned with physical ability and the perception of pain. Many of the women participating in the study reported various very minor injuries associated with the exercise program, including blisters and muscle pain. The participants were warned of the possibility of such side effects at the beginning of the study, due in part to the sedentary state of the volunteers. However, these minor injuries may have contributed to the lack of improvements in quality of life as measured by the SF-36 in the women participating in this study. It has also been suggested that for a reduction in anxiety to occur, exercise participation should be maintained for a minimum of ten weeks [352]. As participants in Study Two exercised for a six-week period, the exercise program duration may not have been sufficient to promote a significant anxiolytic affect.

Lennox *et al* have described the problems associated with assessing changes in psychological health in a normal, non-psychiatric population [313]. They discuss the issues associated with monitoring changes in psychological health in groups of participants with essentially normal psychological well-being, including the 'ceiling effect' noted when measures leave the non-clinical population little room for improvement. The authors also question the long-term effect of exercise on mood and well-being, and ascribe many positive findings to the misinterpretation of the acute effect of exercise. Indeed, Lennox *et al* found that neither a 15-week aerobic or anaerobic exercise intervention provoked any change in psychological well-being, depression or mood in a group of older adults [313]. Incidentally, although Lennox *et al* scheduled the post-intervention assessments to ensure that the results did not simply reflect the acute effect exercise, a recent meta-analysis noted that there were no differences in the anxiolytic effects if measured immediately or 30 minutes after the

exercise class [352]. However, the fact that many of the improvements in psychological health of the participants in Study Two were maintained at follow-up, regardless of continued exercise participation, illustrates that the findings presented above (section 5.8) are not simply a reflection of the acute effect of exercise.

The data from Study One suggested that social network, familial contact and gynaecological factors had little impact on the psychological morbidity of healthy middle-aged women. These findings were supported by the baseline analysis of Study Two. Social network, familial contact, choice of confidant and frequency of contact with that person were unrelated to the psychological health of the postmenopausal women participating in this study. Gynaecological variables associated with the menopause, including the use of HRT, hysterectomy and menopausal symptomology were also unrelated to psychological morbidity. Previous research has suggested that hysterectomy may be related to reduced anxiety and depression [243], although these findings were not supported by either Study One or Study Two.

5.9.1 Study Limitations

The study population of healthy postmenopausal women free from cardiovascular risk factors could be identified as a possible bias. Participants may have already been contemplating exercise participation, and therefore more likely to come forward to take part in the study, reflecting the excellent program adherence rates. Baseline questionnaire measurements may have also been artificially raised in light of pre-intervention apprehension [352]. Participants were mainly recruited from a hospital environment and were all in full-time employment, which may not accurately reflect

the general population of similar-aged women. Given the nature of the study population, the floor and ceiling effect of the questionnaires employed in this study should also be taken into account. A six-week exercise intervention may not have been sufficient to change behaviour, and therefore not sufficient to provoke a psychological response when participation in that behaviour was denied. A six-week follow-up may have also been too brief to detect any long-term change, while a further measure physical ability may have confirmed continued exercise participation. The study may have been under powered due to the dropout rate and final sample size. A larger study population would have enabled the impact of social support on exercise participation and adherence to be more comprehensibly explored.

In their recent review, Bryne and Byrne describe a number of methodological limitations that impedes the impact of much of the previous research into exercise, depression, anxiety and mood [286]. These include a lack of suitable control, the omission of any period of follow-up and the lack of rigorous selection criteria when selecting participants from the 'normal population'. In an attempt to address these limitations, the current study employed a thorough participant selection process while employing a randomised active verses control study design.

While athletes and the very active have been shown to become depressed when prevented from exercising [298], participants in Study Two maintained many improvements in psychological health and well-being, regardless of their continued participation in exercise. This may be as a result of the carry-over effect of the exercise program, or an indication that the follow-up period was too brief to detect any meaningful change. As improvements in physical function were noted in the

group who continued to exercise independently during the six-week follow-up, the data would suggest that while a brief exercise intervention was shown to improve psychological health and well-being in a group of healthy postmenopausal women, continued exercised participation should be encouraged in order to maintain and improve psychological well-being and quality of life.

6: Cardiac Rehabilitation and Cardiac Syndrome X

The aim of Chapter Six is to explore cardiac rehabilitation as a treatment for the psychological morbidity identified during Study One in women with Cardiac Syndrome X. As Study Two demonstrated that exercise is a useful treatment for improving anxiety, depression and quality of life in normal postmenopausal women, this study (Study Three) seeks to determine whether a more supervised, controlled exercise program could be as effective for similar aged women with Cardiac Syndrome X. The concept and application of cardiac rehabilitation is explained in detail, while the existing literature regarding the usefulness of cardiac rehabilitation for the treatment of psychological morbidity is reviewed. Although much of the existing research contains methodological flaws and inconsistencies, the literature generally supports the use of cardiac rehabilitation to improve well-being and quality of life in many patient populations. However, women continue to be under-represented, both as rehabilitation participants and as subjects of cardiac rehabilitation research. Therefore, Study Three not only explores the impact of cardiac rehabilitation on a previously unexplored patient group, but also on an under-represented gender population.

6.1 Cardiac Rehabilitation

Eriksson *et al* and Tyne-Lenne *et al* suggest that exercise may improve quality of life and exercise capacity in patients with Cardiac Syndrome X [159;160]. However, the exercise intervention applied in both studies may not be accessible to the majority of patients with Syndrome X. Very few cardiology centres would have the time,

personnel or resources to provide monitored exercise classes specifically for patients with Syndrome X, such as those employed in this particular patient population. While it is recognised that all previous studies of Syndrome X and exercise are preliminary studies undertaken in atypical conditions, it could be argued that in order to promote a change in clinical practice, future research should look towards existing, proven exercise interventions. Cardiac rehabilitation may fulfil this role. The British Cardiac Society guidelines recommend that every major district hospital that treats patients with heart disease should provide a cardiac rehabilitation service [362].

Cardiac rehabilitation (CR) is a group- or home-based cardiovascular exercise program designed to restore physiological status, psychological well-being and vocational capability while reducing the risk of cardiac morbidity and mortality in patients with CHD [363]. Cardiac rehabilitation is defined by The World Health Organisation [364] as:

> "...the sum of activity required to ensure cardiac patients the possible physical, mental and social conditions so that they may, by their own effort, regain as normal a place in the community, and lead an active life."

The implementation of cardiac rehabilitation is grouped into four specific phases [365] (Table 6.1.1), reflecting the patient's ongoing recovery from cardiac events or surgical intervention. Unless otherwise stated, much of the CR research explored in this chapter is based on Phase II or III cardiac rehabilitation. Such programs have a standard duration of between six and twelve weeks, although it has been suggested that a four-week multidisciplinary CR course is as effective in improving

physiological and psychological function as a standard 10-week program [366]. As Phase I CR is performed as an inpatient service, the intervention is brief and concerned with mobilisation, while Phase IV is a long-term program, encouraging regular and continuous participation

Phase	Time course	Goals
I	Before discharge from hospital	Prevent deconditioning, prepare patients for daily living activities on discharge
II	The early post discharge period	Improve aerobic conditioning, functional capacity, muscular strength, endurance and flexibility
III	Four – six weeks after an acute event	Continue to improve aerobic conditioning, functional capacity, muscular strength, endurance and flexibility
IV	Long-term maintenance of changed behaviour	Maintain CR outcomes, continue to improve risk factor management in a non-clinical environment

Table 6.1.1: The four phases of cardiac rehabilitation.

In the United Kingdom a group-based rehabilitation is usually employed, but many centres also provide a concurrent home-based exercise program to compliment the exercise classes and provide patients with a long-term exercise plan [366]. Some centres with limited resources or a geographically disparate patient population provide entirely home-based rehabilitation programs [367]. There are currently studies being undertaken to compare the effectiveness of home versus hospital-based rehabilitation programs [368]. Early research suggests that a combined hospital-supervised and home-based CR is as effective as an entirely hospital-based program, while an entirely

home-based CR is less beneficial than an intervention with any hospital-based component [369]. Although the pivotal aspect of the CR program is exercise, some centres are able to offer a comprehensive rehabilitation program, including dietary advice, life-style modification, medication, pain management, relaxation classes and psychological assessment. However, it has been suggested that exercise-only rehabilitation classes promote similar improvements in cardiovascular risk reduction and all-cause mortality as the comprehensive rehabilitation programs [370]. The value of additional non-exercised based components of CR in women and the elderly has also been called into question, although the paucity of data relating to the impact of a concurrent psychosocial intervention among these patient groups may limit the value of such findings [371] .

Many patients are referred for CR following MI, post-operative recovery from cardiac surgery including CABG and angioplasty, and for patients undergoing treatment for inoperable or medication-controlled CHD [363]. Heart transplant patients are also encouraged to undergo CR as part of their post-operative recovery program [363]. Although all cardiac patients should be routinely referred for CR, it has been estimated that only 30% of patients deemed eligible for rehabilitation had received a referral [196] and those who have the most to gain for CR are the least likely to receive it [372].

Women are less likely to be referred for CR than men [196]. A recent meta-analysis identified only one methodologically rigorous study of exercised-based rehabilitation in women alone, and found that while 54% of studies included women, on average women accounted for only 20% of the study population [370]. Although studies have

shown equal or greater improvements in functional capacity, coronary risk and psychosocial well-being in women than men following rehabilitation [373], women account for less than 3% of the patients participating in some CR studies [363]. It has been suggested that the gender bias in CR participation is maintained by a lack of gender specific research, resulting in a lack of empirical support for women's participation in CR [196]. Without gender specific research, clinicians may be unwilling to refer female cardiac patients for CR (see Figure 6.1.1).

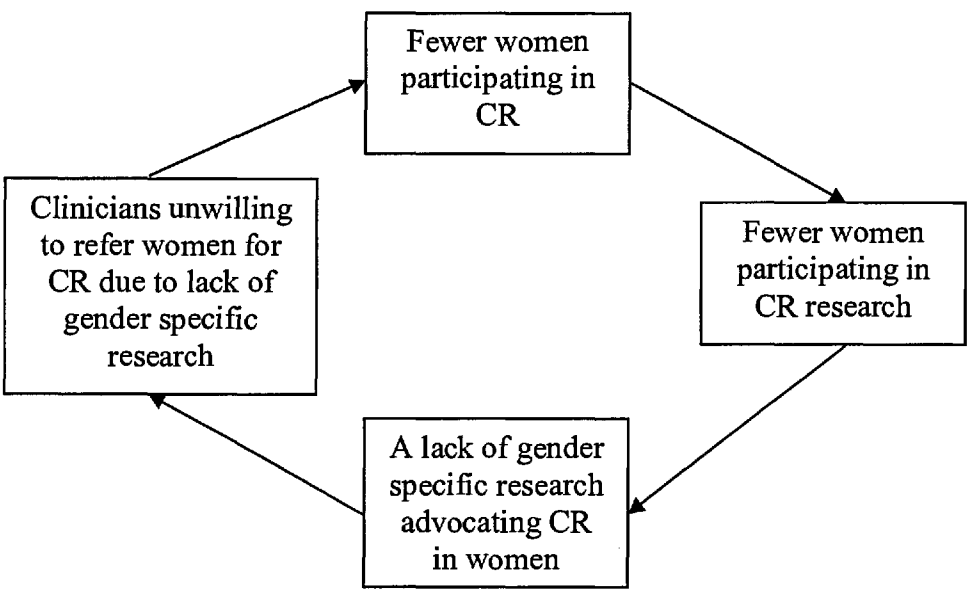


Figure 6.1.1: A suggested model for the non-participation of women in cardiac rehabilitation.

Several studies have attempted to ascertain whether CR is a cost-effective treatment for patients with cardiovascular disease. Marchionni *et al* calculated the cost of an eight-week group-based CR program in comparison with a home-based program and a usual care control [374]. Patients who took part in the home-based CR program amassed fewer additional healthcare costs than their group-based CR counterparts or usual care controls as a result of fewer medical visits and hospitalisations. Although

the cost of an eight-week group- or home-based exercise rehabilitation program is substantial (US$8841 and US$1650 respectively as of 2002) [374], the cost could be offset against the participants reduced burden on healthcare resources. These findings are supported by Dugmore *et al* who identified a trend for CR participants to take fewer drugs and report fewer hospital readmissions than a usual-care control five years following a 12-month CR program [375].

6.1.1 Cardiac Rehabilitation and Psychological Health

It has been argued that patients suffering from angina pectoris experience a number of distinct clinical manifestations which results in a number of specific psychosocial morbidities [376]. Decreased functional capacity relating to cold exposure, exertion, heavy meals and emotional triggers, coupled with the uncertainty surrounding possible treatment, may result in increased depression, emotional stress, anxiety, sexual dysfunction and job strain [376]. It has been suggested that as many as 50% of patients undergoing cardiac rehabilitation following myocardial infarction suffer from clinically high levels of psychological distress [377] and that interventions to reduce psychological distress have the potential to improve long-term cardiac prognosis [378]. Cardiac rehabilitation has been shown to improve depression [379], anxiety [156], symptoms of stress [157] and quality of life [374] in patients with CHD.

In a study exploring the impact of a Phase I hospital based rehabilitation program on patients anxiety, Thomas sought to determine whether a collaborative, patient-lead program would be more effective at reducing anxiety than the traditional, expert driven approach [20]. A collaborative program involving patients in every aspect of the learning process produced a far greater reduction in anxiety upon discharge in

comparison to the traditional, passive learning approach. By offering opportunities for active participation and partnership in the educational process, Thomas argued that patients would be instilled with a greater sense of power, choice and control, which resulted in reduced anxiety. Vicarious experience (learning through observing those similar to ourselves perform a behaviour) through peer support as part of Phase I CR among CABG patients also reduced anxiety, improved self-efficacy and accelerated recovery [380]. It would have been interesting to discover whether completing either program was associated with increased rates of Phase II CR participation, although such information was not included in either study.

Lavie *et al* sought to determine the impact of a 12-week exercise rehabilitation program on a group of consecutive CHD patients grouped by baseline levels of anxiety [381]. The study was performed without random assignment, normal control or any period of follow-up. Following rehabilitation, the number of patients categorised as highly anxious dropped significantly, while general levels of anxiety also fell. Patients described as highly anxious at baseline achieved the greatest improvements in anxiety, depression, quality of life and physiological indices of fitness in comparison with their less anxious counterparts. Comparable results were found among a group of elderly patients with high hostility scores [382]. Hostility scores fell significantly among the highly hostile elderly patients, while on completion of the 12-week CR program 64% of the high hostility group no longer met the criteria for their initial highly hostile classification. Anxiety, depression, quality of life scores and CHD risk factors improved significantly among all participants, irrespective of hostility scores. However, others have failed to demonstrate the positive impact of CR on hostility in patients having recently undergone a major cardiac event [383].

Similar results have been shown in both middle-aged [384] and elderly CHD patients [385] grouped on the basis of depression. Both groups of depressed and non-depressed patients gained equal benefit from CR participation, showing reduction in depression, anxiety and hostility scores, along with improvements in all measures of quality of life. Sixty-three percent of the elderly patients and 67% of middle-aged patients classified as moderately or severely depressed at baseline no longer fulfilled the criteria for severe or moderate depression following CR. All patients also improved in various physiological cardiovascular risk factor parameters. Unfortunately, neither study was designed to include any period of follow-up, so the lasting impact of such an intervention could not be determined. In a separate study improvements in psychological functioning were noted three months following a 12-week rehabilitation program in non-randomised group of CHD patients with minimal cardiac symptoms [386]. However, as patients were not assessed directly following the intervention period, any changes between post intervention and follow-up measures were not recorded.

In order to identify the patient's psychological and physiological characteristics most associated with failing to complete a CR program, Turner *et al* performed one of the largest prospective studies of CR participation and non-compliance undertaken thus far [372]. By monitoring the progress of 1902 (20% female) consecutive CR attendees, Turner *et al* were able to identify that a high baseline depression score was the single highest predictor of non-compliance among the sample population. Patients who experienced angina or had undergone angioplasty also were more likely to default than patients who had experienced MI or CABG. Age, gender or anxiety of initial

physical fitness had little impact on CR compliance. Although those patients who completed the CR program showed significant improvements in psychological morbidity and physical fitness, there was no relationship between baseline depression and changes in fitness, or between improvements in psychological morbidity and changes in physical fitness following CR [372].

6.1.2 Quality of Life and Cardiac Rehabilitation

It has been suggested that on any given day, an individual's quality of life lies as some point on a continuum that extends from an optimal quality of life, to the request for euthanasia and the refusal of resuscitation [376]. Generally, studies exploring the impact of CR participation on quality of life have positive outcomes. Health related quality of life has been shown to improve irrespective of age following home- or group-based exercise rehabilitation, with the very old gaining the most substantial improvements [374]. Obese CHD patients have shown similar significant improvements in cardiovascular risk factors and quality of life as non-obese CHD patients following CR [387]. Seki *et al* showed significant improvements in the quality of life of elderly CHD males following a six-month Phase III comprehensive rehabilitation program in comparison with controls [388]. Izawa *et al* also found that the quality of life of a self-selected group of acute MI patients improved following an eight-week group based rehabilitation program, although the lack of randomisation or appropriate control reduces the impact of their findings [389]. Dugmore *et al* found greater improvements in the quality of life of MI patients following a 12-month thrice-weekly exercise rehabilitation program than normal care control, although significant improvements were also found among the control group [375].

In order to ascertain which socio-economic and behavioural characteristics predict improvement in patients health related quality of life following CR, Oldridge *et al* explored the impact of a number of factors on changes in quality of life in acute MI patients directly following, and 12-months after, an eight-week CR program [390]. The only factors found to be predictive of change in quality of life at both time points were baseline quality of life and baseline cardiovascular risk. Poor quality of life at baseline was predictive of poor quality of life at both time points, whereas low cardiovascular risk (e.g. less smoking, higher exercise tolerance, previous cardiac surgery) at baseline predicted greater improvements in quality of life directly following and 12-month after CR. Marital status, occupation and education were only marginally predictive when combined with baseline quality of life and cardiovascular risk, while the authors conclude that the predictive value of male gender was compromised by the lack of female participants in the study (see Figure 6.1.1).

However, not all studies exploring change in quality of life following CR have gained positive results. In a recent meta-analysis, Taylor *et al* were unable to draw any definitive conclusions regarding the impact of CR on quality of life, as only two of the twelve suitably rigorous studies had showed greater improvement in quality of life following CR than among the control [370]. In a study of congestive heart failure patients exploring the impact of a 12-week twice-weekly exercise program, with a nine-month home exercise follow-up or usual care control [391], no differences in quality of life were found either following the 12-week group program or following the additional nine-month self-motivated home exercise program. Participants showed similar increases in exercise capacity and peak oxygen uptake irrespective of

their group assignment. Similarly, although initial improvements were seen in quality of life among patients randomly assigned to CR rather than usual care control following acute MI, these differences were lost at 12-month follow-up [390].

Hawkes *et al* compared changes in quality of life in patients who had undergone CABG in relation to their choice of participation or non-participation in a CR program [392]. The study lacked randomisation, a normal control or any measure of adherence rates among the CR group. The study failed to demonstrate any additional benefit in relation to quality of life in the patients who had participated in a CR program, either six- or 12-months post-operatively. The authors suggest this lack of additional benefit in quality of life following CR may be in relation to the sensitivity of the questionnaires employed or the overall positive impact of the CABG procedure in all study participants. However, in an accompanying editorial, Oldridge questioned effectiveness of the CR program employed in Hawkes *et al*'s study, and argues that the six once-weekly sessions may not have been sufficient to provoke any significant changes in quality of life [393]. O'Rourke *et al* found that anxiety and depression improved following a CR program in post-CABG patients, but in accordance with Hawkes *et al,* the effect was lost at the 12-month follow-up [394]. However, in reviewing the follow-up data in relation continued exercise participation, the authors conclude that:

> "...exercise...can hardly be expected to reduce psychological distress if it is not being carried out." [394]

6.1.3 Women and Cardiac Rehabilitation

While the majority of studies exploring the impact of CR are performed in a mixed-sex population [374;375;389;391], there are few methodologically rigorous studies of exercised-based CR on psychological morbidity and quality of life in women with CHD. Nevertheless, women have been shown to gain as much physiological and psychological benefit from participating in rehabilitation as men [395].

Lavie *et al* compared the impact of a 12-week exercise-based CR program on the depression scores of depressed and non-depressed women with CHD [396]. The study was performed without random assignment or any period of follow-up. Both depressed and non-depressed women showed significant improvements in depression, hostility, quality of life and various physiological parameters, while depressed women showed greater improvements in the majority of both psychological and physiological measures than their non-depressed counterparts. Kennedy *et al* showed an increase in quality of life in women with CHD following a 14-week CR program comprised of seven weeks of group-based and seven weeks of home-based exercises irrespective of age [397]. Participants were found to worry less about, and improve adaptation to, their diagnosis. However, as the study was performed without a suitable control group or any period of follow-up, the impact of the study findings is limited.

Lavie and Milani sought to determine the physical and psychological impact of CR on a group of elderly women with CHD, recognising that such a population has been rarely studied in the literature, despite the growing number of older women with CHD [398]. A convenience sample of elderly women referred to participate in Phase II cardiac rehabilitation were compared to all other patients referred for CR during the

same timeframe, resulting in very unequal group sizes (n=70 vs. n=574). At baseline, the elderly women had lower exercise capacity with higher percentage body fat and higher lipid profile than the comparison group of CHD patients. Following CR, all patients showed significant improvements in almost all physiological measures, although the elderly women had significantly greater improvements in body fat and BMI. Similar significant improvements were seen in the behavioural characteristics and quality of life of both groups. The authors argue that CR is as beneficial for the treatment of physiological and psychosocial morbidity in elderly women as in any other population of CHD patients. The authors maintain that as similar improvements in exercise capacity were seen in the elderly women, despite significantly lower exercise capacity at baseline, their relative clinical benefit following CR may be even greater. Interestingly, these results mirror those of an earlier study performed by Lavie and Milani, exploring the physical and psychological impact of CR on a mixed-gender group of elderly CHD patients [399]. Unfortunately, as with many other studies undertaken by Lavie and Milani [381;396], neither study included any period of follow-up, so the long-term impact of CR on the elderly CHD patient population remains unrecorded. These studies however do provide research evidence to promote elderly women's involvement in CR, attempting to break the cycle of poor CR referral and participation in this population group (see Figure 6.1.1).

Although many studies of cardiac rehabilitation fail to include any period of follow-up, it has been recognised that exercise participation drops significantly following the cessation of any formal CR program [400], especially among women [401]. In a study exploring predictors of women's continued participation in exercise following cardiac rehabilitation, the exercise behaviours of a convenience sample of female CR

participants were recorded for 12-weeks following the culmination of a CR program [402]. In spite of the non-naturalist environment (participation were requested to record any physical activity using a Polar heart rate monitor (refer section 5.6 and section 6.5.1), 48% of participants had ceased to undertake any recorded physical activity by week 12 of the study. Physiological and psychosocial variables were included in a further analysis in order to ascertain any significant predictors of continued exercise participation. Of the 13 variables included in the analysis, co-morbidity was a predictor of both exercise frequency and intensity, while instrumental support was also a predictor of exercise frequency and exercise persistence. The authors suggest therefore that the management of co-morbid conditions in women may be useful in addressing the frequency and intensity of exercise, whereas increasing instrumental support may be more effective in addressing persistence in exercise over time [402]. Other barriers to CR participation have been identified, including fear of further cardiac incident and too much work and too little time [403]. As the greatest percentage of variance in exercise accounted for by the variables included in the predictive model of Moore *et al* was only 18%, the authors rightly acknowledge that further research and more complete models are required in order to better understand women's exercise maintenance following CR [402].

In a study exploring both CR attendees and non-attendees from a consecutive group of CHD inpatients, higher post-discharge role-related behaviours (i.e. behaviour normally undertaken by the patient within the home or work environment) were associated with non-participation in a CR program [404]. However, the authors argue that by returning to previous role-related behaviours, far from demonstrating their

lack of need for any form of rehabilitation program, such patients were denying themselves the opportunity to modify the very behaviour that may have contributed to the onset of their CHD onset in the first place. King *et al* argue that such patients may loose the opportunity to acquire knowledge and develop new behaviours aimed at improving their long-term health [404]. Patient non-participation may also impact upon the value of existing CR research, due to the likelihood of self-selection bias [355]. It has been argued that existing results may not be applicable to all cardiac patients but only those referred, and willing to, undertake a CR program [355]. This underlines the need for further research into those patients' populations, such as women and the older generation, who are currently under-represented in the CR literature.

6.1.4 Mechanistic Pathway

Several suggestions have been put forward in an attempt to explain the psychological changes brought about by exercise-based rehabilitation programs. These include engendering feelings of empowerment in the participants through taking control of their own recovery [396], reducing uncertainty by providing patients with an optimistic yet realistic outlook of recovery [157], and the effect of socialisation and bonding with other similarly-affected patients [396], resulting in increased social support. The adequacy of social support has been investigated in relation to the prognosis of patients with CHD [163] when it was noted that inadequate tangible support was a significant predictor of both morbidity and mortality (refer section 3.3). Population based studies have consistently identified a link between social support and CHD morbidity and mortality in men, while disease severity and proliferation have been shown to be related to a lack of support in women [185]. Epidemiological studies have

also identified a link between depression, social isolation and predicted morbidity and mortality in CAD patients [177].

It has been argued that CR provides the social context through which coronary prevention interventions are delivered [187]. CR may promote coping through augmented psychological support [157] and this extra social support may have an important part to play in the patients recovery from, and adaptation to, chronic illness [180]. However, not all studies of CR have found a link between social support, physical or psychological benefit and CR participation [404]. In a study exploring both CR attendees and non-attendees from a consecutive group of CHD inpatients, social support was found not to be a factor that predisposed patients to participate in CR, or one that changed as a result of attendance [404].

In order to explain the positive impact of exercise on psychological well-being, it has been suggested that changes in psychological morbidity following exercise may be related to improved physical fitness (refer sections 5.2.1.1 and 5.2.6). In a study exploring the most appropriate tool for assessing psychological outcomes following a CR program, changes in measured physical fitness were unrelated to any improvements in psychological well-being or quality of life [405]. Although the authors found a strong correlation between depression, well-being and initial fitness, the post-intervention measures were unrelated to changes in physical ability. Similarly, in a study exploring changes in quality of life among elderly men with CHD, improvements in psychological morbidity and quality of life were found without concurrent increases in VO_2, in spite of excellent adherence to a six-month Phase III CR program [388]. No relationship between aerobic fitness, anxiety and depression was

identified among middle-aged male CHD patients following a combination of various home- and hospital-based CR programs [369]. Such findings mirror those of studies relating to many forms of exercise intervention in a wide variety of patient populations [268;312;313;340], not just among CHD patients undergoing CR.

Other suggested mechanisms for the psychological improvements noted following CR include changes in self-efficacy (refer section 5.2.1.2) [193]. It has been suggested that changes in self-efficacy may stimulate changes in the desired recovery behaviours and therefore should be viewed as an important outcome of CR [193]. It has also been suggested that women gain more from CR in terms of improvements in self-efficacy than men, and that these changes persist once they leave the program [403]. The authors argue that women's ability to overcome task and barrier efficacy (confidence to perform a certain task and perceived barriers preventing participation) should be built on in order to promote continued exercise participation, a primary goal of all CR programs.

A number of factors may inhibit self-efficacy change, including spousal over-protectiveness. Although research has failed to find a link between spousal overprotectiveness and self efficacy in the early state of recovery following MI [406], Berkhuysen *et al* sought to ascertain whether overprotectiveness inhibited changes in self-efficacy following either a low- or high-frequency CR program [193]. Improvements in self-efficacy were only realised following the low-frequency program, which the authors explain in terms of the negative impact of overprotectiveness on the more demanding high-intensity CR program. However, others have suggested that spousal support may have a positive impact on CR

participation [386]. While the research from Berkhuysen *et al* is an interesting preliminary exploration of self-efficacy, CR frequency and overprotectiveness, further research is required to fully explore the impact of CR outcomes as influenced by spousal behaviour.

Similarly, it has been suggested that there may be a relationship between locus of control and CR attendance among patients with CHD [407]. Health locus of control (HLOC) is normally split into two distinct constructs that reflect individuals' beliefs regarding the impact of their behaviour on their own health. Patients with higher *internal* HLOC believe they influence their own health outcomes, whereas patients with a high *external* HLOC believe external factors, chance, fate or powerful influence of others have a greater impact upon their health [407]. However, in a recent study exploring the influence of internal HLOC on CHD patients CR participation, there were no differences between attendees and non-attendees in relation to HLOC [407]. Further research is required to further explore the personality or behavioural characteristics that may influence a patient's participation in cardiac rehabilitation.

6.1.5 Summary

Cardiac rehabilitation is a widely available, established exercise intervention offered in the majority of UK hospitals with a cardiological service [362]. CR has been shown to improve depression [379], anxiety [156], symptoms of stress [157] and quality of life [374] in patients with CHD, although methodological inconsistencies, such as a lack of randomisation, control or period of follow-up [381;396;398;399] cloud the impact of much of the existing research. Although women are less likely to participate in CR [370],

studies have demonstrated the equal benefit gained by men and women participating in CR [373;395]. Preliminary research suggests that exercise may be a suitable treatment for improving exercise capacity and time-to-pain in patients with Cardiac Syndrome X [159;160]. However, studies exploring the impact of cardiac rehabilitation on psychological and physiological morbidity in women with Cardiac Syndrome X have not previously been undertaken.

Study Three: Angina Frequency, Psychological Morbidity and Quality of Life in Women with Syndrome X: The Impact of Cardiac Rehabilitation

6.2 Aims and objectives of Study Three

In order to assess the impact of an eight-week cardiac rehabilitation exercise program on the psychological well-being, symptom severity and frequency, physical fitness and cardiovascular health of women with Cardiac Syndrome X, the following questions will be addressed:

- Does an eight-week cardiac rehabilitation exercise program have any impact on anxiety, depression, cardiac anxiety and quality of life in a group of women with Cardiac Syndrome X?
- Does an eight-week cardiac rehabilitation exercise program improve the physical functioning and cardiovascular health of women with Syndrome X?
- Is symptom severity and frequency reduced following an eight-week cardiac rehabilitation exercise program in women with Syndrome X?
- Are any psychological effects acquired by women with Syndrome X participating in a cardiac rehabilitation exercise program maintained at an eight-week follow-up?
- Are women with Syndrome X required to continuing exercising in order to maintain any psychological benefits gain from an eight-week cardiac rehabilitation exercise program?

In light of the findings from Study One, the following research questions will also be explored:

- Are the principal findings from Study One, including the impact of social network on the psychological health of women with Syndrome X supported by Study Three?
- Following the elevated incidence of hysterectomy among Syndrome X patients in Study One, are there any patterns or trends in the reason for hysterectomy amongst women with Syndrome X participating in Study Three?
- Is menopausal symptomology, not previously recorded in Study One, related to anxiety, depression and quality of life in women with Cardiac Syndrome X?

6.3 Methodology

6.3.1 Ethical Approval

In order to comply with guidelines regarding patient participation in research, a submission was made to the Royal Brompton & Harefield NHS Trust Ethics Committee (London, United Kingdom) for permission to perform the study. Ethics approval was given on the proviso that all participants gave written informed consent (Appendix N), and that participants randomised into the symptom monitoring group were given the opportunity to participate in a cardiac rehabilitation program at the end of the study. Copies of the consent form were given to the patient, kept locally and filed in the patient's medical records. It was also stated that prospective participants should not be approached if they were currently participating in another research study or had done so in the previous 60 days.

In order to gain ethical approval, it was necessary to change the study design of Study Three. Study Three was originally conceived as a single-blind randomised control-trial. It was originally intended that patients randomly assigned into the control group would be blinded to the existence of the active group, with control participants recruited into a project assessing the impact of symptom severity and frequency on well-being and quality of life. However, the Royal Brompton & Harefield NHS Trust Ethics Committee refused to give permission to perform the study unless all participants were fully informed of the exact nature of the study, the randomisation process and treatment options. Also, in accordance with the new ethical guidelines regarding the collection of sensitive personal information (refer section 4.2.1), it was forbidden to ask participants about recent stressful life events.

6.3.1.1 Active Syndrome X Patients

Once ethical approval had been granted and recruitment for Study Three began, it became clear that there were a small number of Syndrome X patients who continued to take regular planned exercise in spite of their continuing symptoms. Although such patients were excluded from Study Three on the basis of their level of physical activity (refer section 6.3.5), it became clear that it would be interesting to explore the psychological health and well-being of a group of active Syndrome X patients. Therefore a further application was made to the Royal Brompton & Harefield NHS Trust Ethics Committee to assess the anxiety, depression and quality of life of active patients with Syndrome X in comparison to their inactive counterparts. Approval was granted on the proviso that all participants gave written informed consent (Appendix O), and that copies of the consent form were given to the patient, kept locally and filed in the patient's medical records. It was also stated that prospective participants should not be approached if they were currently participating in another research study or had done so in the previous 60 days

6.3.2 Cardiac Rehabilitation

Cardiovascular exercise is the core component of all universally available cardiac rehabilitation programs. Therefore, in order explore the impact of a non-specialised, routinely administered Phase III cardiac rehabilitation program, available in the majority of UK CR centres, it was decided that study participants would undertake the exercise component only. Some established CR centres also provide counselling, health promotion and dietary advice. However, as many centres are only able to offer the exercise element of rehabilitation, it was decided to investigate the impact of the exercise program only. This was to ensure findings of this study would be relevant to

the greatest number of CR centres, and could help provide a basis for the referral of Syndrome X patients as a part of a possible future treatment regime.

Although patients undergoing CR normally participate in twice-weekly classes, a large number of patients with Syndrome X have work or childcare commitments that prohibit them from being able to set-aside two afternoons a week to participate in the exercise classes. Therefore it was decided that Syndrome X patients would participate in a weekly CR exercise class, while taking part in a home exercise program specifically designed to the patient's individual needs and ability. A combination of home- and hospital-based CR have been shown to be as effective as hospital-base CR only programs in reducing psychological morbidity and improving quality of life in patients with CHD [369]. It was also hoped that patients would become familiar with the home exercise program, enabling them to continue with the program once the hospital-based rehabilitation classes had ended.

6.3.3 Study Interventions: Cardiac Rehabilitation and Symptom Monitoring Control

6.3.3.1 Cardiac Rehabilitation

Before starting a rehabilitation program, all patients had a thorough physical assessment in order to identify their suitability for the study, level of ability and physical impairment. The one-to-one appointment includes risk assessment, blood pressure monitoring, measurement of waist-hip ratio, BMI and a Progressive Shuttle Walk (PSW) test [408] which tests the patient's level of physical impairment using a non-invasive, non-threatening technique. The PSW is scored on the patient's ability to keep up with a taped beeping pace-monitor that controls the speed a patient walks between two cones spaced 10 meters apart. The lowest level (one) is a walking speed of 1.12 miles per hour, while the highest (fifteen) is a walking speed of 6.38 miles per hour. The measurement finishes or is halted when the patient become short of breath, feels unwell, is unable to keep up with the pace, or reaches 60-75% of their age-predicted heart rate. ECG, heart rate and blood pressure measurements are taken during the PSW test, which are used as a measure of suitability to participate in CR. Patients who develop any previously undiagnosed ECG abnormalities, hyper or hypotension during the PSW test are referred back to their clinician for further assessment and treatment.

Once the patient has been judged as suitable to participate in the cardiac rehabilitation exercise program, they are assigned to one of three levels depending on their risk of cardiac events, symptoms, diagnosis and performance on the PSW test. All CR classes are of mixed ability, so patients with all levels of fitness and the full range of

diagnosis exercise together under the supervision of a physiotherapist and two nurses. The Syndrome X study patients were amalgamated into the existing classes (routine procedure due to the constant patient turnover in CR groups), as this provides a normalising environment for all participants and a reflection of the normal population of CR participants. Nevertheless, all patients wear colour-coded badges so the patients exercise level, risk and diagnosis is immediately obvious to the CR staff in case of emergency.

Classes last approximately 80 minutes in total, and are set out as a circuit alternating between cardiovascular and active rest stations (Table 6.3.1), beginning with a 15-20 minute warm up with stretches.

Cardiovascular Station	**Active rest**
Step-ups on a medium step	Biceps-curls with weights
Treadmill	Lateral raises with weights
Stepper	Upright row with weights
Exercise bike	Theraband
Trampet	Sit-stands

Table 6.3.1: Details of the cardiovascular and active rest station of the CR exercise program.

Each patient has his or her own tailor-made exercise program, depending on his or her assessed level of ability. All patients start on level one and can progress through the levels during their course of rehabilitation. The aim however, is not to get the patients through all three levels, but for patients to work at an optimal level appropriate to their ability (Table 6.3.2).

Level One	Level Two	Level Three
One minute on cardiovascular station One minute of active rest	One minute on cardiovascular station Thirty seconds of active rest Thirty seconds of walking round the room	One minute on cardiovascular station One minute jogging or walking round the room

Table 6.3.2: The three activity levels on the CR exercise program.

Following the 45-minute circuit program, all patients perform 10-15 minutes of cool-down exercises.

The home exercise program was comprised of activities such as brisk walking, along with movement and strength exercises designed to provoke 60-75% of the patient's age-predicted heart rate in accordance with their individual needs. Patients were requested to perform at least one home-based CR session per week, while being actively encouraged to think of ways of improving their daily activity levels (for example, getting off the bus one stop early and walking the extra distance). Patients recorded their weekly home-based exercise participation, which was reviewed during each hospital-based CR session.

On completion of the eight-week course of the CR program, patients perform a second PSW test to ascertain any improvement of cardiovascular fitness and recovery. Waist-hip ratio, BMI and blood pressure measurements were also re-assessed. Percentage improvements were calculated and fed back to the patient, often giving the patient a sense of achievement and an incentive for further supervised exercise intervention.

6.3.3.2 Symptom Monitoring Diary

Both the CR and control groups were required to complete a symptom monitoring diary for the duration of the eight-week intervention period (Appendix P). All participants were asked to complete the diary each day, noting any symptoms they associate with their diagnosis of Syndrome X, their activity at the time, and what time of day they experienced their symptoms. Patients were also asked to grade their symptoms on a standard five-point pain scale, ranging for very mild to excruciating (see Table 6.3.3).

1 = Mild symptoms
2 = Discomforting symptoms
3 = Distressing symptoms
4 = Horrible symptoms
5 = Excruciating symptoms

Table 6.3.3: The pain scale used for diary completion in Study Three.

A copy of the pain scale was printed on the cover of the diary, along with a number of example entries, in order to make completion of the diary as clear and straightforward as possible. Participants were also asked to complete an entry each day, even if they experienced no symptoms. Patients were advised to write 'none', 'good day' or 'felt

fine' in order to ensure that all symptoms were recorded and potential missing symptom data was kept to a minimum.

6.3.4 Participant Recruitment

Female Syndrome X patients aged < 85 years with chest pain, a positive exercise ECG stress-test for myocardial ischaemia and angiographically smooth coronary arteries were recruited from the Women's Heart Clinic at the Royal Brompton & Harefield NHS Trust (London, United Kingdom). The Women's Heart Clinic is a specialised clinic for Syndrome X patients. A patient's eligibility (refer section 6.3.5) was confirmed from an examination of their medical records before their clinic appointment and were subsequently approached to participate following their cardiological consultation. Each prospective participant was asked if they would be interested in taking part in a study to explore the impact of cardiac rehabilitation on well-being, quality of life and symptoms associated with Syndrome X. All patients were given a study information sheet to give further details concerning the study (Appendix Q), a modified version of the informed consent document, approved by the Royal Brompton & Harefield NHS Trust Ethics Committee. If the patient expressed an interest in taking part, a study appointment was made on a date convenient to them. Table 6.3.4 illustrates the number of patients approached to participate through the Women's Heart Clinic.

	Number of patients
Patients contacted in clinic	**30**
Did not attend appointment	4
Called to withdraw	2
Agreed to participate	**22**
Agreed to participate - active	**2**
Percentage of patients contacted in clinic who agreed to participate Study Three	**80%**

Table 6.3.4: Patient recruitment from the Women's Heart Clinic.

Eligible Syndrome X patients who participated in Study One were approached to participate by mail. At least 18 months had elapsed between the patient's participation in Study One and receiving an invitation to participate in Study Three. All patients received a letter briefly outlining the study, an information sheet containing a detailed description of the study (Appendix Q), a brief questionnaire confirming eligibility (Appendix R) and a 'freepost' envelope. Participants were requested to complete the questionnaire and return it in the enclosed 'freepost' envelope if they were interested in taking part.

In order to recruit patients local to the rehabilitation centre at Harefield Hospital, eligible patients from The Harefield Hospital angiography list between 1st April 2001 and 31st March 2003 were identified from their diagnostic coding and approached to

participate by mail. All patients received a letter briefly outlining the study along with how and why they had been contacted to participate. All patients were also sent an information sheet containing a detailed description of the study (Appendix Q), a brief questionnaire confirming eligibility (Appendix R) and a 'freepost' envelope. Participants were requested to complete the questionnaire and return it in the enclosed 'freepost' envelope if they were interested in taking part. Mail shots were performed on two occasions between February and June 2003. Table 6.3.5 illustrates the response rate of patients contacted by post through participation in Study One or having undergone recent angiography at Harefield Hospital.

	Number of patients
Study One participants	99
Recent angiography at Harefield Hospital	292
Total number of patients contacted	**391**
Replied and declined to take part	10
Returned reply form but did not attend appointment	5
No Symptoms	10
CHD / AF	3
Work commitments	4
Transport / distance from hospital	19
Concurrent illness	16
Attended appointment but were unsuitable	3
Replied after recruitment was complete	1
Men contacted in error	2
Total responders not participating	**73**
Agreed to participate	42
Agreed to participate - active	12
Total participants replied and participating	**54**
Total number of patients contacted	**391**
Total number of patients responded	**127**
Response rate	**32%**

Table 6.3.5: The response rate from the cohort of Syndrome X patients approached to participate by mail.

6.3.5 Inclusion and Exclusion Criteria

Table 6.3.6 illustrates the criteria employed to identify the eligibility of volunteers approached to participate in Study Three:

Inclusion Criteria	Exclusion criteria
Female	History of psychiatric illness
Aged 30 to 80 years	History of any other chronic illness
Angiographically normal coronary arteries	Suffer any physical condition for which exercise is a contra-indication.
ST-segment depression, positive ECG stress-test for myocardial ischaemia	Participation in two or more periods of planned moderate intensity exercise per week during the past 6 months
A minimum of two episodes of chest pain symptoms per week	Participation in another research study within the previous 60 days
Willing to give written informed consent	Unwilling to give written informed consent
Diagnosis > six months	

Table 6.3.6: The inclusion and exclusion criteria for participants in Study Three.

6.3.6 Visit One: Consent and Randomisation

Once a potential participant had expressed an interest in taking part in the study and their eligibility was confirmed, patients attended their first study visit. All study visits took place in a quiet, private room on a one-to-one basis, where the project was fully explained and any questions answered. All aspects of the cardiac rehabilitation

program were described in detail, including the considerable commitment required to participate in such a program, the composition of the classes and the home-exercise component, along with the location of the rehabilitation program. Harefield Hospital is in a rural location, so all prospective participants were made fully aware of their need to travel to participate in the rehabilitation program, and that transport would be provided and travel expenses reimbursed if required. The symptom monitoring arm of the study was also fully explained, including the necessity for participants not to commence any self-motivated, independent exercise program while participating in the study, should they be randomised into the control group. Patients were advised that their GP would be informed of their participation in the trial. All participants gave written informed consent using the consent form approved by the Royal Brompton & Harefield NHS Trust Ethics Committee. Three potential participants who attended a study meeting were ineligible (either too active (two) or unable to provide informed consent due to a poor English comprehension (one)). No eligible Syndrome X patient who attended a study meeting refused to participate or give written informed consent.

Following consent, patients were randomly assigned to either eight-weeks of symptom monitoring or eight-weeks of cardiac rehabilitation based at the Harefield Hospital. Randomisation was performed using 64 identical opaque brown sealed envelopes containing an equal number of paper strips marked 'Rehabilitation' or 'Monitoring'. The envelopes were shuffled in front of the patient, who was then asked to pick one from the pile. The patient then opened the envelope themselves to discover their group assignment.

Following randomisation, patients assigned to the cardiac rehabilitation were given further information regarding their participation in the program, including arrangements for the pre-rehabilitation assessment appointment. Patients were also informed that due to the general waiting list for CR classes, they would have to wait between three and eight weeks to begin the rehabilitation program at Harefield Hospital. Patients randomised into the symptom monitoring arm of the study were asked to refrain from participating in any extra-ordinary physical activity or planned exercise until the completion of the entire 16-week study. Control participants were reassured that they would be offered cardiac rehabilitation following the conclusion of the study.

Both groups were then guided through the symptom monitoring diary (Appendix P). Participants in the rehabilitation arm were requested to start the diary on the Monday before starting their exercise program, while the symptom monitoring participants were instructed to begin the first Monday after the study visit (or right away if the study visit fell on a Monday).

Finally, all participants were guided through and asked to complete a number of questionnaires (refer section 6.3.10). The method of completion of each individual questionnaire was explained to the participant, while plenty of time was set aside to answer any questions. Written instructions were also given at the start of each new set of questions within the questionnaire. The individual questionnaires were grouped together to create a battery of tests. Participants took the questionnaire home following their study visit and returned it after completion using a supplied 'freepost' envelope. Participants were requested to complete the questionnaires alone answering

all the questions as required, and were also encouraged to explain any answers more fully or give any additional information they thought might be appropriate.

Following randomisation each participant was assigned a unique study number from 1001 to 1064. A list of the participants' names and identification numbers were kept electronically, while the questionnaires were coded according to the methods stated by the authors [252;253;255;358;409] and entered on to an EXCEL (Microsoft, Redmond, Washington) spreadsheet. Data was then transferred to SPSS Version 10 (SPSS Inc, Chicago, Illinois) for statistical analysis. The original questionnaires were then filed by study number. The original consent forms were kept locally, while copies were sent to the local ethics committee and given to the participant.

6.3.7 Visit Two: Post-Rehabilitation and Symptom Monitoring

Participants returned for their second study visit within ten days of completing the cardiac rehabilitation program or eight-week symptom monitoring control. All participants returned their symptom diaries, which were used as the focus of conversation during the second study visit. Syndrome X patients who had completed the exercise program also discussed their experiences.

All participants were then given the second collection of questionnaires (section 6.3.10), which they were requested to complete at home and return within five days of their study visit using a 'freepost' envelope provided. The method of completing each individual questionnaire was explained, while plenty of time was set aside to answer any questions. Participants were requested to complete the questionnaires alone, answering all the questions as required, and were also encouraged to explain

any answers more fully or give any additional information they thought appropriate. Participants were also instructed *not* to recall their previous responses. In order to reduce familiarity bias, the individual questionnaires within the battery of tests were re-ordered for each visit (e.g., Baseline: HAD, HAQ, SF-36, visit two: HAQ, SF-36, HAD etc).

In light of the findings from Study Two, all patients in the rehabilitation arm of the study were encouraged to continue exercising, either through joining a similar cardiovascular exercise class, Phase IV CR or by continuing the home-based rehabilitation program. Participants in the symptom monitoring arm of the study were requested to continue to refrain from participating in extra-ordinary physical activity. However, the control group were reassured that they would be offered cardiac rehabilitation at the end of the study.

6.3.8 Eight-Week Follow-up

Eight-weeks after completing the cardiac rehabilitation exercise program or symptom monitoring control, both groups completed a third and final collection of questionnaires (section 6.3.10). Patients randomised into the rehabilitation arm of the study were additionally asked about their current exercise habits. Participants were requested to complete the questionnaires alone, answering all the questions as required, and were also encouraged to explain any answers more fully or give any additional information they thought appropriate. Participants were also instructed *not* to recall their previous responses, and to return the questionnaire in the 'freepost' envelope provided within five days. Participants were thanked for their participation in the study and were advised that as the study had now ended, they were free to

exercise as they wished. At this point symptom monitoring patients were given the opportunity to participate in a CR program if they wished. Figure 6.3.1 illustrates the design of the study.

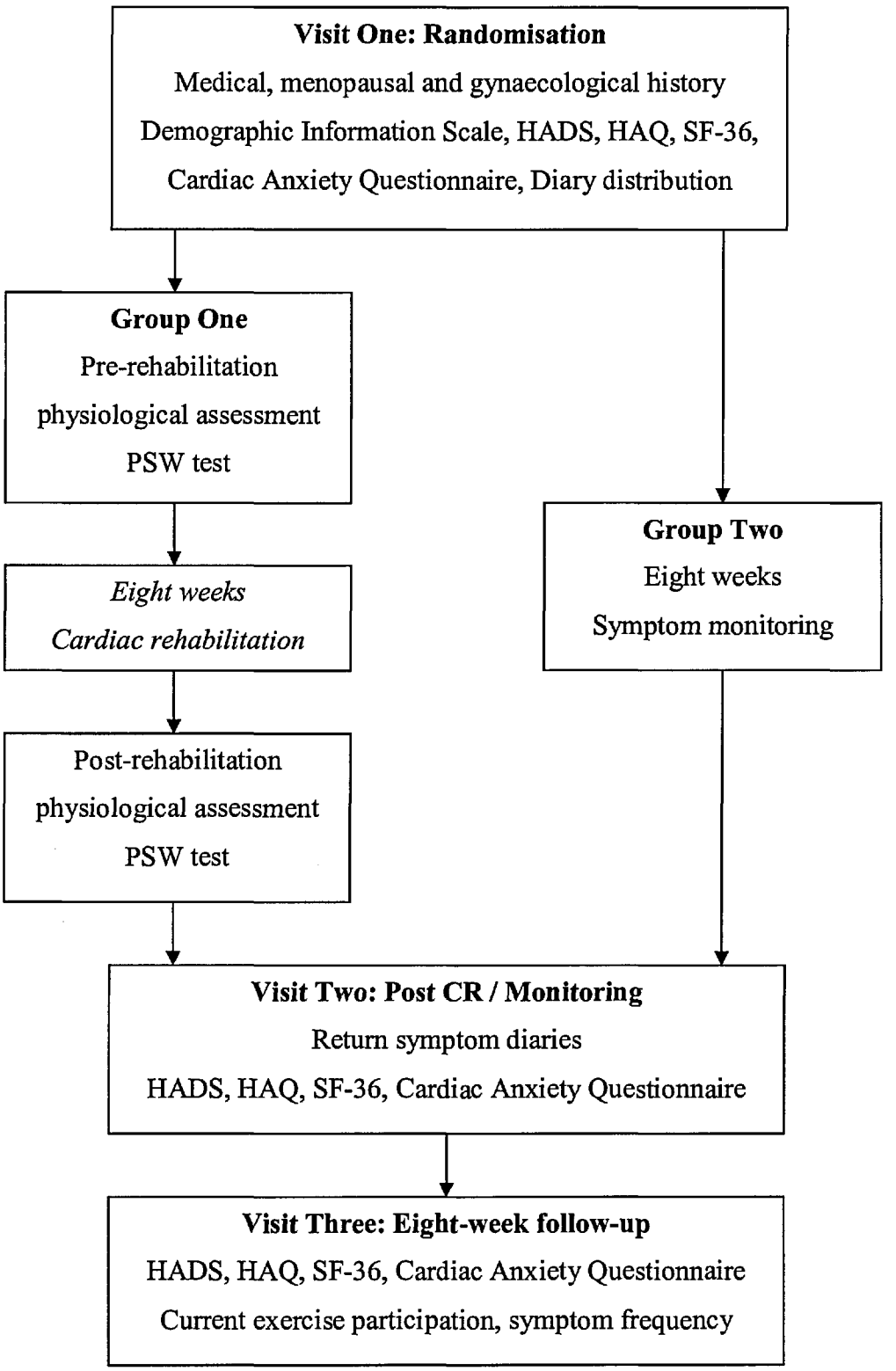


Figure 6.3.1: The design of Study Three.

6.3.9 Active Syndrome X patients

During the course of recruitment, it came to light that a small number of Syndrome X patients continued to participate in two or more episodes of planned moderate intensity exercise per week, in spite of their continuing chest pain symptoms. Patients who expressed an interest in participating in Study Three but were too active to fulfil the inclusion criteria were re-contacted regarding their participation in a sub-study of the rehabilitation project. Patients were advised that while they were ineligible to participate in the main rehabilitation study, they could still take part as a comparison group to the majority of Syndrome X patients who were inactive. Patients were informed that their participation would involve a single study visit to complete the exact same baseline questionnaires as the inactive patients with Syndrome X participating in the main study. The inclusion and exclusion criteria for the active participants matched those listed in section 6.3.5, although participating in two or more periods of planned exercise per week (an exclusion criterion became the main *inclusion* criteria for active patients with Syndrome X). If the patient was interested in taking part, a study appointment was made at a time convenient to them.

All study visits took place in a quiet, private room on a one-to-one basis, where the project was fully explained and any questions answered. Patients were advised that their GP would be informed of their participation in the trial. All participants gave written informed consent using the consent form approved by the Royal Brompton & Harefield NHS Trust Ethics Committee. No active Syndrome X patient refused to participate or to provide written informed consent. Participants were guided through and asked to complete a number of questionnaires (see section 6.3.10). The method of completion of each individual questionnaire was explained to the participant, while

plenty of time was set aside to answer any questions. Written instructions were also given at the start of each new set of questions within the questionnaire. The individual questionnaires were grouped together to create a battery of tests. Participants took the questionnaire home following their study visit and returned it after completion within five days of their study appointment using the 'freepost' envelope provided. Participants were requested to complete the questionnaires alone answering all the questions as required, and were also encouraged to explain any answers more fully or give any additional information they thought might be appropriate.

Participants were assigned a unique study number from 2001 to 2020 on receipt of their completed questionnaires. A list of the participants' names and identification numbers were kept electronically, while the questionnaires were coded according to the methods stated by the authors[252;253;255;358;409] and entered on to an EXCEL (Microsoft, Redmond, Washington) spreadsheet. Data was then transferred to SPSS Version 10 (SPSS Inc, Chicago, Illinois) for statistical analysis. The original questionnaires were then filed by study number. The original consent forms were kept locally, while copies were sent to the local ethics committee and given to the participant.

6.3.10 Questionnaires

The Health Anxiety Questionnaire [252] (HAQ) (Appendix G) has been developed using the cognitive behavioural model of anxiety [256], which divides health anxiety into two parts: development and maintenance. The HAQ is split into four sub-scales that focus on: health worry preoccupation; fear of illness and death; reassurance seeking

behaviour and interference with life. Developed and validated in medical, psychiatric and healthy volunteers [252], the 22 questions have a four-point Likert scale response format.

The Hospital Anxiety and Depression Scale [253] (HADS) (Appendix H) measures clinically significant anxiety and depression in general medical patients. The 14-item questionnaire is split in to two sub-scales (anxiety and depression) using a four-point Likert scales response format. Anxiety and depression scales have also been combined to create a total score [189]. The scale has been validated with both outpatients and inpatients [257], along with NCCP patients [258].

The SF-36 [358] (Appendix L) is a general health questionnaire divided into different aspects of quality of life: physical role limitation, emotional role limitation, physical functioning, pain, general health and energy. The SF-36 has been used repeatedly in CR research and was recently identified as an acceptable, sensitive and valid measure of health related quality of life in CR patients [410]. The SF-36 has also been previously used in patients with Cardiac Syndrome X [88].

The Cardiac Anxiety Questionnaire (CAQ) [409] (Appendix T) seeks to quantify heart-focussed anxiety, the fear of cardiac-related stimuli and sensations based upon their perceived negative consequences. This has been shown to increase the probability that individuals will become distressed and anxious about chest pain and/or other heart-related conditions [215]. The 18-item questionnaire is split into three subscales (fear, avoidance and heart focussed attention) and uses a five-point Likert scale

response format. It has been validated in cardiac outpatients, inpatients, psychiatric patients and normal volunteers [409].

A demographic information scale [255](Appendix J) was used to assess social support and isolation by recording the patients living circumstances, frequency of contact with friends and relatives and size of social network. This measure investigates the frequency contact with adults, both outside and within the normal household, differentiating between friends and family along with identifying any specific confidant. The four reported levels represent the following frequencies of social contact: 1) every day; 2) three times per week; 3) once a week; or 4) once a month.

Additionally, participants were asked to complete questions regarding their menstrual and gynaecological history, including details of hormone therapy, hysterectomy and last menstrual period (Appendix U). The degree of menopausal symptomology encountered by each participant was assessed through their experience of the following symptoms: hot flushes; night sweats; heat intolerance; sleep disturbance; vaginal dryness; periods of low mood; mood swings and loss of concentration. Participants were asked to indicate if they had experienced any of the given symptoms when they went through the menopause, choosing one of the four following responses for each symptom: none, mild, moderate or severe. The four responses were coded from zero (none) to three (severe), and a total score created from the combined responses from each item, giving a maximum score of 24. Participants were also asked about any known family history of CHD, their current medications, previous life-long hospitalisations and level of physical activity. Hospital admissions for childbirth were disregarded. As oestrogen level was found to

be unrelated to psychological morbidity in patients with Syndrome X in Study One, blood oestrogen levels were not measured in Study Three.

6.3.11 Statistics

The data were analysed using one-way ANOVA, paired and independent Students' t-tests and Pearson's Correlation; overall comparisons of categorical data were performed using Chi-square test. Statistical significance level was set at $p<0.05$. The study was a randomised within-subjects design, using two-tailed tests. Data are expressed as mean ± standard deviation. Graphical representation of the data includes standard error bars. In light of Study One, the first set of analyses combined the baseline data of the whole group in order to identify any social and gynaecological variables associated with anxiety, depression and quality of life in women with Syndrome X. The second set of analyses addressed the impact of an eight-week CR exercise program on the psychological well-being in comparison with a symptom monitoring control group. In light of Study Two, the impact of the cessation or continuation of exercise on psychological well-being was explored in the group of patients who participated in the CR exercise program. Additionally, a cross-sectional analysis was also performed to compare the baseline data of the whole group with that of the active Syndrome X patients.

6.3.12 Sample Size Calculation

In order to ensure a minimum 80% power of Study Three, data from Study One was used to establish the necessary sample size. The standard sample size calculation and normogram [411] were used to establish the sample size required to reduce the recorded levels of HADS and HAQ scores in Syndrome X patients to those of healthy age

matched women. The following assumptions were made for all the power calculations: 5% significance level, 80% power to detect a difference between groups, randomisation to the two groups in equal proportions. Power calculations for individual investigation were based on the following:

HADS Depression - a mean difference in HADS depression score between groups of 1.27 with a standard deviation of 3.9 required 65 patients

HAQ Health Worry – a mean difference in health worry between groups of 1.76 with a standard deviation of 3.5 required 100 patients.

HAQ Interference with life - a mean difference in life interference between the groups of 2.6 with a standard deviation of 2.45 required 28 patients.

Total HAQ score - a mean difference in total HAQ score between the groups of 5.98 with a standard deviation of 8.68 required 60 patients.

Therefore, a sample size of 64 participants was deemed sufficient to explore the impact of cardiac rehabilitation on psychological morbidity in women with Cardiac Syndrome X.

6.4 Results

6.4.1 Subjects

Sixty-four women with Cardiac Syndrome X were randomly assigned to either eight-weeks of cardiac rehabilitation (58.1 ± 9.4 yrs) or a symptom monitoring control group (56.4 ± 7.8 yrs, p=0.44). Each group contained 32 participants. One patient in each group failed to return baseline questionnaires and withdrew consent. Two

patients from the control group failed to attend the second and third study visit despite multiple appointments. Two patients withdrew from the rehabilitation arm of the study (broken leg (one), bereavement (one)) without completing post-rehabilitation or follow-up visits. One patient randomised to rehabilitation was hospitalised for unrelated gynaecological problems shortly after consent and was followed up on an intention-to-treat basis. Baseline data from one control participant who successfully completed the study was lost in a local postal dispute. Therefore, 28 patients randomised to receive CR and 29 monitoring control patients successfully completed Study Three. Baseline data from the 61 patients (57.3 ± 8.6 yrs) who returned the initial questionnaire, regardless of subsequent participation were included in baseline analysis. Table 6.4.1 illustrates the demographic characteristics of the 61 patients whose data was included in the baseline analysis, along with those of the two randomised groups.

	Total Group (n = 61)	**Cardiac Rehabilitation (n = 31)**	**Symptom monitoring (n = 30)**
Age range	38-73 yrs	38-73 yrs	42-71yrs
Single	6.6%	6.9%	6.7%
Married	72.1%	72.4%	73.3%
Divorced	13.1%	13.8%	10%
Widowed	8.2%	6.9%	10%
Participants living alone	6.5%	6.9%	6.7%

Table 6.4.1: The demographics of the Cardiac Syndrome X patient population participating in Study Three.

6.4.2 Baseline analysis

6.4.2.1 Symptoms, medications and hospitalisations

The age of onset (50.9 ± 8.8 yrs) and number of symptom years (6.8 ± 5.5 yrs) of the participants in Study Three reflect those of Study One (53.9 ± 8.1 yrs and 6.3 ± 5.2 yrs respectively). Eighty-seven percent of patients were taking at least one cardiovascular or respiratory medication (range 1 - 7, mean 3.0 ± 1.7), with 50% of participants having reported themselves as hypertensive or taking anti-hypertensive medication and 36% of patients reported themselves as hyperlimidaemic or taking lipid-lowering medication. Forty-eight percent of patients had undergone at least one hospital admission relating to symptoms associated with Syndrome X (range 1 – 9, mean 1.9 ± 1.6), while 95% of patients had undergone at least one other hospital admission (range 1 – 17, mean 4.4 ± 3.1).

6.4.2.2 Family history of CHD

Seventy-four percent of Syndrome X patients participating in Study Three reported some family history of CHD, while 49% reported at least one close relative with CHD onset before the age of 60. No measure of family history of CHD was related to any scale of the HADS, HAQ, CAQ or SF-36.

6.4.2.3 Gynaecological factors

Fifty-two percent of patients had undergone hysterectomy, while 34% had also undergone oopherectomy. The reasons reported by patients for hysterectomy are given in Table 6.4.2. Forty-two percent of patients were currently taking HRT, while

65% of patients had taken HRT at some point. However, only 14% of patients reported having undergone a gynaecological consultation. Mean menopausal symptom score was 10.2 ± 6.7 (range 0 – 23). Hysterectomy, oopherectomy, or current or pervious HRT use were unrelated to any scale of the HADS, HAQ, CAQ or SF-36.

Reason for Hysterectomy	Percentage of Hysterectomised Patients
Heavy / irregular menstrual bleeding	25.8%
Fibroids	22.6%
Doctor advice / unknown	12.9%
Endometriosis	12.9%
Ovarian cysts	9.7%
Prolapse	9.7%
Pre-menstrual syndrome	3.2%
Pre-cancerous cells	3.2%

Table 6.4.2: The reason for hysterectomy among hysterectomised women with Cardiac Syndrome X.

Menopausal symptom score was significantly correlated with CAQ avoidance (R^2 =0.315, p=0.014), total CAQ (R^2 =0.258, p=0.044), HADS depression (R^2 =0.309, p=0.016) total HADS (R^2 =0.326, p=0.010), HAQ health worry (R^2 =0.305, p=0.017), total HAQ (R^2 =0.323, p=0.011) and SF-36 emotional well-being (R^2 = -0.413, p=0.001). Age at last menstrual period was correlated with the following SF-36 measures: health related role limitation (R^2 = 0.359, p=0.011); energy (R^2 = 0.395,

p=0.005); social functioning (R^2 = 0.353, p=0.013) and pain (R^2 = 0.366, p=0.01). Age at hysterectomy was also correlated with HAQ interference with life (R^2 = -0.380, p=0.032), SF-36 energy (R^2 =0.436, p=0.013) and social functioning (R^2 =0.375, p=0.035).

6.4.2.4 Social network

In accordance with the methods employed in Study One, data regarding patients' social network were split into two categories: patients who reported having no friends or a small social network (six or fewer friends) and patients with a large social network (seven or more friends). The two categories were created by grouping responses either side of the median. Sixty percent of patients reported a small social network. Patients with a small social network had significantly higher levels of HADS depression (5.5 ± 3.7 vs. 3.5 ± 2.0, p=0.018), and total HADS (13.5 ± 6.2 vs. 10.6 ± 4.5, p=0.05), with greater impairment in SF-36 emotional role limitation (55.8 ± 45.1 vs. 80.5 ± 35.3, p=0.027) and emotional well-being (66.5 ± 18.2 vs. 77.3 ± 13.5, p=0.017) scores.

6.4.2.5 Comparison of rehabilitation and control groups

While there were no significant differences between the two randomised groups on any measure of psychological health, there was a definite trend for higher scores on all psychological measures among the patients randomised to receive CR. This initial non-significant discrepancy between groups squewed the subsequent analysis of any between-groups effect at all time points across the study. Therefore, the within-subjects effect of each group is presented below.

6.4.3 Post-intervention

6.4.3.1 Adherence and attrition

Twenty-eight patients completed the eight-week cardiac rehabilitation program with a 90% adherence rate. As mentioned above (see section 6.4.1), two patients withdrew while undergoing rehabilitation due to an unrelated leg fracture and a family bereavement. One patient failed to attend the post-rehabilitation physical assessment, while one patient failed to complete the study diary. Twenty-nine patients randomised to the control group successfully completed the eight-week symptom monitoring diary. As previously mentioned (see section 6.4.1), two patients failed to attend the second study visit and were treated as lost to follow-up.

6.4.3.2 Psychological measurements

Patients randomised into the CR arm of the study showed significant reductions in all three scales of the HADS: anxiety (8.1 ± 3.4 vs. 6.4 ± 3.1, p=0.001); depression (5.4 ± 3.6 vs. 4.4 ± 3.4, p=0.04) and total HADS (13.5 ± 5.9 vs. 10.8 ± 5.7, p=0.002). Patients randomised to CR also had significant lower levels of HAQ health worry (4.5 ± 3.0 vs. 3.4 ± 2.3, p=0.02), interference with life (2.4 ± 1.7 vs. 1.7 ± 1.8, p=0.004), total HAQ (11.8 ± 5.4 vs. 9.4 ± 5.9, p=0.007), and CAQ avoidance (1.5 ± 0.6 vs. 1.2 ± 0.5, p=0.022), while improvements were also shown in six of the eight scales of the SF-36 (see Figure 6.4.1).

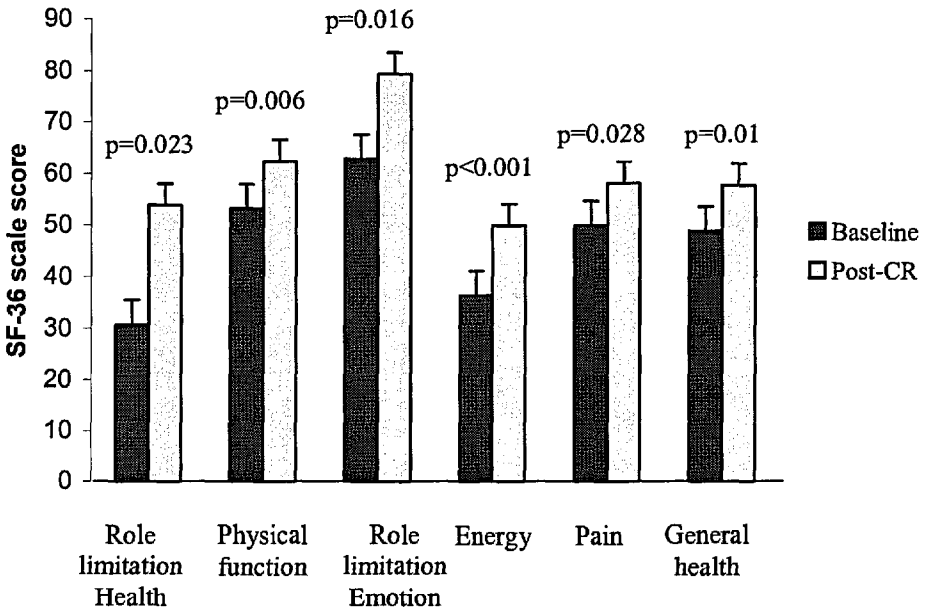


Figure 6.4.1: The impact of CR on six subscales of the SF-36 in women with Cardiac Syndrome X.

Reductions in HADS anxiety (7.0 ± 3.5 vs. 5.8 ± 3.2, p=0.02), total HADS (11.1 ± 4.9 vs. 9.7 ± 4.4, p=0.02) and SF-36 health related role limitation (25.8 ± 36.2 vs. 44.8 39.1, p<0.01), were also found among the control group. Additionally, reductions in CAQ fear (1.5 ± 0.7 vs. 1.3 ± 0.6, p=0.03) and total CAQ (1.5 ± 0.6 vs. 1.3 ± 0.6, p=0.016) were found only among the control.

6.4.3.3 Symptom severity and frequency

Total weekly symptom episodes were calculated from the symptom diaries of both groups, along with the weekly symptom pain-scale average. Symptom severity was significantly reduced following the eight-week rehabilitation program (2.0 ± 0.8 vs. 1.2 ± 1.1, p=0.009). However, both the rehabilitation (3.8 ± 2.3 vs. 2.0 ± 2.1, p=0.001) and control (8.0 ± 6.8 vs. 4.6 ± 3.8, p<0.001) group had a lower symptom frequency following the eight-week intervention than at baseline.

6.4.3.4 Physiological measurements

Following the eight-week intervention, patients randomised to receive CR had significantly lower resting diastolic blood pressure (84.7 ± 9.4 mmHg vs. 79.7 ± 7.3 mmHg, p=0.007), weight (79.4 ± 14.2 kg vs. 77.0 ± 14.8 kg, p=0.015) and BMI (29.1 ± 6.0 kg/m^2 vs. 28.4 ± 6.1 kg/m^2, p=0.003). Following CR, patients made highly significant improvements in distance walked (326.8 ± 111.0 m vs. 423.6 ± 133.0 m, p<0.001) and level attained (5.3 ± 1.6 vs. 6.7 ± 1.5, p<0.001) during the PSW test.

Interestingly, although PSW distance and level were found to be significantly correlated with HAQ interference with life (R^2 =-0.36, p=0.048 and R^2 =-0.39, p=0.032 respectively) and SF-36 physical functioning (R^2 =0.54, p=0.002 and R^2 =0.53, p=0.002 respectively) at baseline, these correlations were lost following CR. There were no other significant relationships between any measure of psychological well-being and physical ability either at baseline or following rehabilitation.

6.4.4 Follow-up: Eight-weeks post-intervention

Eighty-six percent of patients who had participated in the cardiac rehabilitation program were taking part in two or more planned session of physical activity (i.e., cycling, swimming, brisk walking etc) at the time of follow-up. Of these, 34% were participating in a Phase IV CR program or similar exercise class. Among the patients assigned to receive CR, reductions in HADS anxiety (8.1 ± 3.5 vs. 6.7 ± 3.3, p=0.01), total HADS (13.5 ± 6.3 vs. 11.5 ± 5.7, p=0.04), HAQ health worry (4.5 ± 3.0 vs3.5 ± 2.2, p=0.017), interference with life (2.4 ± 1.8 vs. 1.8 ± 1.6, p=0.026), total HAQ

(11.8 ± 5.4 vs. 9.9 ± 5.2, p=0.028), CAQ avoidance (1.5 ± 0.6 vs. 1.2 ± 0.6, p=0.024) and SF-36 energy (36.3 ± 20.7 vs. 45.7± 22.0, p<0.001) were maintained at follow-up in comparison with baseline levels. Significant positive improvements in SF-36 physical functioning (p<0.001), pain (p=0.006) and general health (p=0.01) scales at follow-up are illustrated in Figure 6.4.2. Total CAQ score was also lower at follow-up than post-intervention in comparison to baseline among the CR participants (1.45 ± 0.5 vs. 1.3 ± 0.4, p=0.038).

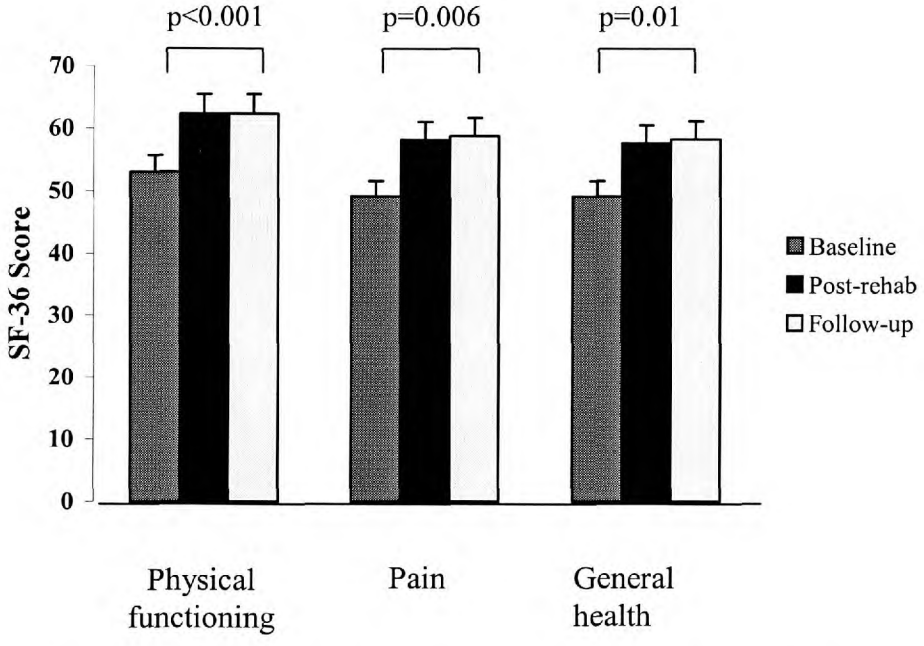


Figure 6.4.2:The long-term impact of CR on the SF-36 sub-scales in women with Syndrome X.

Among the control group, SF-36 health related role limitation (25.8 ± 36.2 vs. 43.9 ± 38.2, p=0.02), CAQ fear (1.4 ± 0.6 vs. 1.1 ± 0.6, p=0.02) and total CAQ (1.5 ± 0.5 vs. 1.3 ± 0.6, p=0.03) were the only measurements to maintain a significant difference from baseline at follow-up.

6.4.4.1 Rehabilitation group: Continuation of exercise at follow-up

While there was a noticeable trend for CR patients exercising at follow-up to make additional improvements in almost all measures of psychological morbidity in comparison with non-exercising CR patients, significant improvements within subjects or changes between groups of exercising and non-exercising CR patients were not found.

6.4.5 Active Syndrome X Patients

Twelve women with Syndrome X fulfilled the criteria of participating in two or more planned episodes of physical activity per week. As such these women were categorised into an Active Syndrome X patient group. There were no significant differences between the active and inactive Syndrome X patients on the basis of age (55.8 ± 10.5 yrs vs. 57.3 ± 8.6 yrs), age of onset (50.7 ± 9.4 yrs vs. 50.9 ± 8.8 yrs) and number of symptom years (5.1 ± 5.0 yrs vs. 6.8 ± 5.5 yrs). The active participant's gynaecological history and social network size were also not significantly different from the patients taking part in the main study.

6.4.5.1 Psychological Comparison of Active and Baseline CR Study Data

Compared with the inactive Syndrome X patients participating in the CR study, Active Syndrome X patients had significantly higher SF-36 health related role limitation (62.5 ± 44.5 vs. 29.0 ± 38.2, p=0.009), physical functioning (74.5 ± 21.6 vs. 55.5 ± 20.1, p=0.004), energy (56.2 ± 20.4 vs. 40.0 ± 23.0, p=0.027), pain (72.5 ± 21.3 vs. 51.8 ± 20.1, p=0.002) and general health (71.2 ± 21.7 vs. 48.7 ± 21.1, p=0.001) scores. Active Syndrome X patients also had lower CAQ fear (1.2 ± 0.3 vs.

1.5 ± 0.7, p=0.05), avoidance (0.7 ± 0.6 vs. 1.6 ± 0.7, p<0.001) and total CAQ (1.0 ± 0.3 vs. 1.5 ± 0.5, p=0.009) score than their inactive counterparts. Active patients also had lower HAQ health worry (p=0.003), interference with life (p=0.046) and total HAQ (p=0.024) scores (see Figure 6.4.3). However, there were no differences between active and inactive Syndrome X patients on the basis of HADS anxiety or depression.

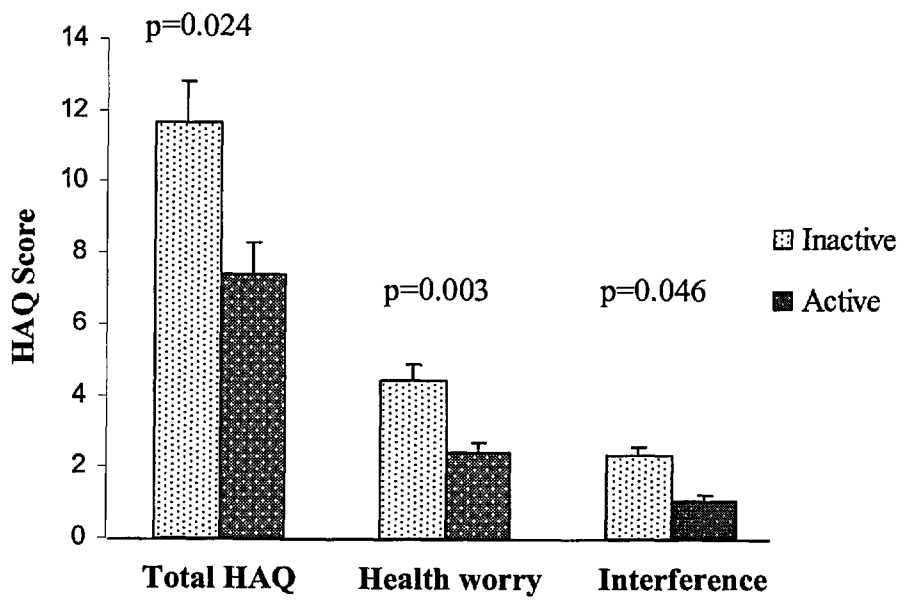


Figure 6.4.3: The difference between HAQ scores of active and inactive Syndrome X patients.

6.5 Discussion

Patients with Cardiac Syndrome X are currently not a target population for cardiac rehabilitation [363]. As such, Study Three represents the first known study of CR as a potential treatment for reducing psychological and physiological morbidity in women with Cardiac Syndrome X. Anxiety, depression and cardiac anxiety decreased while quality of life increased following eight-weeks of routinely administered cardiac rehabilitation in women with Cardiac Syndrome X. Not only did participating in CR have positive psychological benefits for this patient population, but reductions in physiological indices of cardiovascular risk were also noted, including significant reductions in diastolic blood pressure, weight and BMI. CR patients also significantly improved their PSW performance following rehabilitation, indicative of improvements in physical fitness, ability and time to pain. While symptom frequency fell in both groups, reductions in symptom severity were only noted among those participants who underwent rehabilitation. Many of the improvements in psychological morbidity were maintained at follow-up among the CR participants, while some measures of quality of life continued to improve.

Improvements in psychological morbidity were also noted among the control group following the eight-week symptom monitoring exercise. Similar results were found among patients assigned to the usual-care control arm of a study exploring Cognitive Behavioural Therapy (refer section 3.2.2) in patients with non-cardiac chest pain [146]. The authors explained their findings in relation to the initial study assessment and follow-up visit, which involved reassuring the patients of the benign nature of their illness, along with suggesting relaxation techniques and particular coping styles. All

patients in Study Three were given every opportunity to ask questions during all study visits, and accordingly many patients sought reassurance about their symptoms and the risk associated with their pain. The additional support provided by these study visits, along with further reassurance regarding their health status, may have inadvertently improved anxiety and well-being among all study participants, as noted among the control group.

The data from Study Three also indicates that Syndrome X patients who already engage in planned physical activity have a better quality of life and lower cardiac anxiety than their inactive counterparts. These findings support those of other cross-sectional studies comparing active and inactive participants from a number of populations. Slaven and Lee found that women who exercised scored significantly lower on negative mood dimension and higher on positive mood dimensions than non-exercisers, regardless of menopausal status [327]. In a similar study they concluded that middle-aged women who choose to exercise were less likely to experience menopause-related distress, regardless of HRT use or menopausal status [325]. However, it would be interesting to explore the optimal level of exercise whereby the additional impact of CR becomes redundant. Although active patients were excluded from the case-control study of CR, further studies could focus on the impact of additional exercise within an active Syndrome X patient population. The differences in psychological morbidity and quality of life noted between active and inactive Syndrome X patients lend weight to the findings of Study Three: Physical activity is psychologically beneficial for women with Cardiac Syndrome X.

Although patients randomly assigned to CR showed significant improvements in psychological well-being, quality of life and physical ability, the initial relationship between quality of life and physical ability found at baseline was absent following the completion of CR. There was no relationship between physical ability and any psychological measure at baseline, or with quality of life following CR. The relationship between physical ability and psychological well-being following CR participation remains unclear, as similar findings to those identified in Study Three have been shown among other patient populations. Turner *et al* found a strong correlation between depression, well-being and initial fitness, while post-intervention measures were unrelated to changes in physical ability [405]. Similarly, in a study exploring changes in quality of life among elderly men with CHD, improvements in psychological morbidity and quality of life were found without concurrent increases in physical fitness [388]. Further research is required to fully explore the relationship between improvements psychological morbidity, quality of life and physical ability following cardiac rehabilitation.

Many findings from the baseline analysis of Study Three support the results of Study One. Age of onset and symptom years were comparable, while the incidence of family history of CHD, either any history or that of a first degree relative aged less than 60, were actually higher among the Syndrome X patients in Study Three. Similarly, there was a slightly higher incidence of hysterectomy among Syndrome X participants of Study Three, although HRT use had fallen compared with the Syndrome X patients participating in Study One. This may be due to adverse publicity relating to HRT following the publication of a number of recent large-scale studies questioning increased relative risk of breast cancer and cardiac events

associated with HRT [90-92]. The impact of a small social network on the psychological morbidity of women with Syndrome X was also identified among the participants of Study Three. Syndrome X patients with a large social network have lower psychological morbidity than their more social isolated counterparts.

Interestingly, menopause symptom severity was highly correlated with many indices of psychological morbidity and quality of life. Healthy women participating in Study Two completed the same brief measure of menopausal symptom severity scale, but no relationship was found between any measure of psychosocial morbidity and menopausal symptomology. Further research should therefore be undertaken to explore the impact of menopausal symptomology on the psychological morbidity in women with Syndrome X, particularly in light of the high incidence hysterectomy and falling HRT use among this patient population. Although HRT may have little proven benefit in women with Syndrome X [88], it has been suggested that a physical and psychological symptoms may improve if hysterectomy is combined with the administration of hormone therapy among the normal population [242], while pain perception may also be influenced by HRT among postmenopausal women [412].

Many studies exploring the impact of cardiac rehabilitation on psychological morbidity, mood and quality of life failed to include any period of follow-up [381;396;398;399]. Others have failed to include post-intervention assessments, relying on follow-up data alone [386], while studies designed to include a follow-up assessment have failed to establish any long-term benefit of rehabilitation on psychosocial morbidity [390-392]. Oldridge *et al* suggest that CR only provides initial benefit, with little long-term impact on patient's mood and quality of life [413]. The authors failed to

identify any additional long-term psychological benefit from an eight-week comprehensive rehabilitation program in acute MI survivors at 12-month follow-up, despite initial differences between participants and controls. In light of these findings, the authors argue that a sufficient follow-up assessment period and a suitable control are essential components of CR research, especially in acute MI patients, in order to control for the natural history of recovery [413]. Without a suitable control or reasonable follow-up, as employed in Study Three, the true impact of CR on mood, psychological morbidity and quality of life will remain undetermined.

While CR has been shown as physically and psychologically beneficial to a diverse patient population, the barriers to non-participation remain the largest obstacle to overcome. It has been suggested that irrespective of referral failure, barriers to CR participation may be psychosocial in nature, as anxious participants with high self-efficacy and higher family income were found to be more likely to participate in CR [196]. However, the upheaval surrounding a cardiac event and the patient's own motivation to recover may be an equally important factor in CR participation [196]. In light of women's under-representation in rehabilitation classes and research [363], the specific psychosocial barriers to women's CR participation should also be identified and addressed. This is particularly important as women have been shown to gain both physical and psychological benefit from cardiac rehabilitation [157]. As women can overcome task and barrier efficacy more so than men following CR [403], this illustrates that women are able to conquer psychosocial obstacles to continued exercise participation. Therefore, it has been argued that in order to maximise positive outcomes and CR adherence in women, psychosocial barriers such as a dependant spouse, lack of social support or transport issues must be addressed within

the CR environment [414]. If women are enrolled in programs designed primarily for men, it is unlikely that their emotional and medical needs will be met [414].

It has been argued that therapeutic interventions must focus not only on living longer, but also living better [376], and focus on adding 'life to years' not simply 'years to life' [371]. In a recent review exploring the use of the SF-36 scale as a useful screening tool to assess quality life changes following cardiac rehabilitation, Brown addressed the question of the usefulness of implementing quality of life as an outcome measure [410]. It was suggested that implementing psychosocial measures would accomplish very little, as such information did not influence clinician's behaviour [415]. Sadly, although various health service frameworks highlight improvements in quality of life and psychological well-being as an integral to the success CR [410], it appears that the importance of quality of life in the many patient populations who may benefit from CR is being overlooked.

6.5.1 Study Limitations

As Study Three was primarily concerned with the treatment of psychological morbidity through cardiac rehabilitation, only those patients that participated in the CR arm of the study underwent any pre- and post-intervention physical assessment. All study participants should have undergone physical assessment at all three study time points, in order to comprehensively assess the impact of CR on cardiovascular risk factors and physical ability among women with Cardiac Syndrome X. It could also be argued that relying on a patient's self-reported physical activity over the eight-week follow-up raises the possibility of inaccuracies in these data. However, in line with previous research exploring the long-term behavioural change of

participants following an exercise intervention [308], it was decided that additional monitoring could compromise the naturalistic conditions of the follow-up period. The inclusion of a follow-up period was designed to explore the impact of CR participation on every-day normal life and asking patients to continuing to record their daily activity could have prolonged the 'research study' environment and biased behaviour. The study population may have been biased by the location of the CR program and the commitment required to participate, along with the sampled population itself. While every effort was made to include as many patients as possible through the organisation and payment of transport, our sample population may not reflect the entire cross-section of women with Cardiac Syndrome X. It should also be noted that a small number of Syndrome X patients participated in both Studies One and Three, which may reflect some of the similarities in the baseline comparison data. As only a small number of active Syndrome X patients were identified, the analysis should be interpreted in light of the large discrepancy in numbers between the active and inactive groups. Finally, the menopausal symptom score was taken from an un-validated schedule specifically designed for the purposes of this study. Further research is required to validate the scale, and once this has been undertaken, to explore the impact of high menopausal symptom score on psychological morbidity on this and other patient groups.

6.6 Conclusion

Study Three has demonstrated that a universally available Phase III cardiac rehabilitation program is an effective treatment for improving psychological morbidity, symptom severity, cardiovascular risk factors and quality of life in women with Cardiac Syndrome X. Cardiac rehabilitation is an established, available

treatment that is under the referral remit of almost all clinicians who may come into contact with patients with Syndrome X. Therefore, Study Three has demonstrated that an existing treatment framework can provide potentially huge long-term benefits to a patient population that currently has so few successful treatment options.

7: General Conclusions

This thesis explored the suggested psychological morbidity in women with the full diagnostic criteria for Cardiac Syndrome X. Further study was aimed at identifying and testing a treatment for any identified psychosocial distress apparent among this patient population. The thesis was composed of three main studies, which together sought to identify psychological morbidity, pilot a proposed treatment modality, and finally trial the suggested therapeutic regime in women with Cardiac Syndrome X.

7.1 Study One: The Psychological Aspects of Cardiac Syndrome X

The aim of Study One was to determine levels of psychological morbidity in women with Cardiac Syndrome X in comparison to that of an age-matched group of women with angina resulting from CHD, and an age-matched healthy control. One of the largest cross-sectional studies of Syndrome X was undertaken in order to identify any differences in psychological health and well-being. The impact of social and menopausal factors in relation to increased psychological morbidity in any of the three study groups was also explored.

Women with Cardiac Syndrome X were found to have significantly higher levels of psychological morbidity than age-matched women with angina resulting from CHD. Women with Syndrome X and CHD also had far higher levels of psychological distress than the healthy age-matched control group. Social support and size of social network seemed to have the greatest impact on psychological morbidity in women with Syndrome X. This was supported by the finding that Syndrome X patients who

reported a large social network suffered less psychological distress. Interestingly, although women with Syndrome X had a far higher incidence of hysterectomy than the other study groups, including the published national average [261], oestrogen levels and gynaecological history had little effect of the psychological health of any group participating in Study One. Similarly, although women with Syndrome X had a family history of CHD comparable to that of women with CHD, far greater than that of the control group, family history of CHD had little impact on the psychological morbidity of any group.

The findings from Study One reflect those of Ruggeri *et al* who found higher levels of anxiety and depression in a small group of men and women with Syndrome X [26]. However, a similar study by Corlando *et al* failed to identify increased psychological morbidity among women with Syndrome X [113]. In a separate study of patients who did not fulfil the full diagnostic criteria of Syndrome X, 58% of NCCP patients reported cardiac symptoms in at least one parent, and 21% in at least one sibling [213], thus reaffirming the high incidence of a family history of CHD found among the Syndrome X patients in Study One. Similarly, the findings from Study One confirm the findings of previous research, which suggested that postmenopausal women with Syndrome X have a high incidence of hysterectomy [83].

The cross-sectional nature of Study One and a potential patient selection bias should be acknowledged as study limitations. Nonetheless, Study One identified impaired psychological well-being along patients with Syndrome X in comparison to women with CHD and a healthy control, while also identifying a number of social factors

which may be important in the development and treatments of psychological morbidity in women with Cardiac Syndrome X.

7.2 Study Two: The Psychological Effect of Exercise Training in Healthy Postmenopausal Women

Study Two was undertaken as a pilot study to assess whether an exercise intervention would improve psychological morbidity in a group of healthy women of a similar age and background to those suffering from Cardiac Syndrome X. Previous studies of exercise as a treatment for psychological morbidity among middle-aged and older women were limited by methodological inconsistencies [286]. Such an investigation of the impact of exercise on the psychological parameters assessed during Study One had not previously been undertaken. Similarly, little research had been undertaken to explore the impact of the continuation or cessation of exercise on psychological health following a prescribed exercise regime.

Study participants were randomly assigned to one of two possible study conditions on completion of a six-week moderate intensity exercise program. There were significant improvements in all measures of psychological morbidity following six weeks of moderate intensity exercise among the women participating in the study, although there were only minor improvements in quality of life. Baseline analysis of psychological well-being in relation to various social and gynaecological parameters, including the incidence hysterectomy and HRT use, supported the findings of Study One. However, changes in almost all measures of psychological well-being were unrelated to any measure of physical activity or increased fitness. Participants who continued to exercise for a further six weeks maintained positive changes in

psychological well-being, while gaining improvements in quality of life, not shown among the participants requested to desist from any physical activity for the same six-week follow-up period. Therefore although changes in psychological well-being were unrelated to changes in physical fitness, further benefits were lost on the cessation of physical activity.

While the small sample size and relatively brief exercise intervention period should be identified as study limitations, the data from Study Two indicates that moderate intensity exercise does promote improvements in psychological well-being among a population of healthy women of a similar age to majority of women with Cardiac Syndrome X. Study Two was also able to demonstrate that in order to maintain improvements in psychological health and increased quality of life, physical activity and exercise should be maintained following the cessation of any prescribed exercise program. This is consistent with similar improvements in psychological well-being that have been identified following an exercise intervention in various patient populations [333-336], although methodological inconsistencies, a lack of suitable control and a failure to include any period of follow-up have clouded the impact of such results. Interestingly, changes in psychological well-being were engendered without concurrent changes in physical fitness. This adds to the ongoing debate regarding the necessity for physical activity to increase physical fitness in order to improve psychological well-being [286].

7.3 Study Three: Angina Frequency, Psychological Morbidity and Quality of Life in Women with Syndrome X: The Impact of Cardiac Rehabilitation

Study One identified underlying psychological morbidity in women with Syndrome X and Study Two illustrated that exercise improved the psychological well-being of similar aged healthy women. Building on the findings of both studies, Study Three sought to ascertain whether a standard eight-week cardiac rehabilitation exercise program would improve psychological morbidity and improve the quality of life in women with Cardiac Syndrome X. Cardiac rehabilitation was chosen as a platform for the exercise intervention in preference to the walking program employed in Study Two due to its group environment, availability, accessibility, referable nature and the structured supervision that is provided within the framework of each class.

The results from Study Three show significant reductions in psychological morbidity and improvements in quality of life among the women randomly assigned to eight-weeks of cardiac rehabilitation in comparison to a symptom diary control group. Following rehabilitation, patients had an improved physical ability and reduced symptom severity while gaining substantial improvements in a number of additional cardiovascular risk factors. In light of the findings from Study Two, all patients who had undergone rehabilitation were encouraged to continue exercising, and therefore many of the improvements in psychological morbidity and quality of life were maintained in this group at the time of the eight-week follow-up.

Although this is the first known study of cardiac rehabilitation in patients with Syndrome X, Eriksson *et al* [159] and Tyne-Lenne *et al* [160] had previously suggested that exercise may improve quality of life and exercise capacity in this patient

population. Cardiac rehabilitation has been shown to improve psychological morbidity and quality of life in CHD patients grouped on the basis of clinically high levels of psychological morbidity [381;384;385], as well as the general population of patients with CHD [156;157;374;379]. Cardiac rehabilitation was identified as an appropriate platform for the prescription of exercise in this patient population due to its design, validity, supervised structure and accessibility, for both patients and clinicians alike. A number of study limitations should be considered in future case-control studies of CR within this patient group, including a comparable physical assessment among the control group and similar measures of physiological parameters in both groups at follow-up. Nevertheless, Study Three has demonstrated that an existing treatment framework, under the referral remit of almost all clinicians and GPs, could be harnessed as a useful treatment for reducing psychological morbidity and improving quality of life in women with Cardiac Syndrome X.

7.4 Summary

The aims of this thesis were to explore the suggested psychological morbidity in women with the full diagnostic criteria for Cardiac Syndrome X, to explore the suggested link between menopause and Syndrome X, and to identity social or gynaecological factors which may be related to increased psychological morbidity in patients with Syndrome X. In addition, following the results from Study One the aims were expanded to identify and trial a treatment for the impaired psychological well-being and quality of life within such a population of women with Syndrome X. The three studies included in this thesis have fulfilled all of these aims. Exercise was identified as a potentially useful intervention among patient with Syndrome X on the basis of earlier preliminary studies[159;160]. However, the lack of thorough research

exploring the impact of exercise on the psychological well-being on women of a similar age to the majority of patients diagnosed with Syndrome X lead to the development of Study Two. The positive finding of Study Two, that exercise improved psychological morbidity and quality of life in postmenopausal women, enabled the exploration of a structured exercise program as a treatment for psychological morbidity in women with Cardiac Syndrome X.

The studies undertaken in this thesis have contributed to the existing knowledge regarding the psychology of Cardiac Syndrome X, exercise in postmenopausal women and the use of cardiac rehabilitation as a treatment for psychological and physiological morbidity in women with Cardiac Syndrome X. Cardiac rehabilitation may be a useful and effective treatment armamentarium for a patient population that currently has so few successful therapeutic options.

7.5 Future Research

7.5.1 Cardiac Rehabilitation, Exercise Intervention and Physical Activity

Building on the findings from Study Three, along with the earlier work of Eriksson *et al* [159] and Tyni-Lenne *et al* [160], further research should address both the physiological and psychological impact of exercise therapy in patients with Syndrome X. All studies of exercise so far undertaken have only included a female study population, and while women do constitute the majority of patients with Cardiac Syndrome X [7], a minority of the patient population are male. Further research should explore various exercise intensities, along with the frequency of exercise participation in order to refine and ascertain an optimal exercised-based intervention for the reduction of

physiological and psychological morbidity among the population of patients with Cardiac Syndrome X.

7.5.2 Improved Social Support

The findings from Study One, supported by the baseline analysis of Study Three suggest that social network size has a considerable impact on the psychological morbidity of women with Cardiac Syndrome X. Accordingly, Study Three was designed to include an exercise intervention that promoted social interaction by means of a hospital-based group exercise program. Support groups have promoted improvements in psychological morbidity among breast cancer survivors [151], chronic pain sufferers [153] and patients with CHD [154]. Therefore, it would be interesting to discover if improving social support through support group attendance could improve the higher levels of psychological morbidity noted among Syndrome X patients with a small social network.

7.5.3 Stress Reduction and Relaxation

Anecdotally, many Syndrome X patients participating in studies One and Three reported that they often experienced chest pain symptoms when under periods of acute or chronic stress. In one of the few psychological intervention studies using the full diagnostic criteria for Syndrome X, Cunningham *et al* [25] explored the affect of Transcendental Meditation (TM) on nine postmenopausal women with Syndrome X. Chest pain frequency and quality of life improved following the course of meditation, and while no direct measures of stress were reported, meditation is a recognised stress reduction technique. Stress reduction and relaxation therapy is currently encouraged as a self-administered technique for the treatment for many conditions, including

chronic diseases such has CHD [140], cancer [141] and those manifesting in chronic pain [142].

Autogenic training (AT) is a relaxation technique developed by a German neurologist Johannes Schultz during the 19th century. It is a hypnosis-based auto-suggestive healing method, which consists of six standard exercises aimed at relieving anger, tension and stress. The exercises are usually taught in small groups over a period of eight weeks, where patients control the feeling of warmth and heaviness, eventually gaining more and more control over autonomic functions. Subsequently, patients are encouraged to perform these exercises at home, two or three times a day, on a regular basis [416]. In a recent study of the impact of Autogenic Training on coronary angioplasty patients, patients randomly assigned to receive eight-weeks of AT demonstrated significantly reduced state and trait anxiety and improved quality of life compared with a usual care control [417]. Patients also experienced significantly lower diastolic blood pressure and pulse rate following AT than among the control group. Similar outcomes would be beneficial in patients with Cardiac Syndrome X.

8: References

1. Lopez AD,.Murray CC. The global burden of disease, 1990-2020. *Nat.Med.* 1998;4:1241-3.

2. Windecker S, Meyer BJ, Bonzel T, Fabian J , Heyndrickx G, Morice MC *et al.* Interventional cardiology in Europe 1994. Working Group Coronary Circulation of the European Society of Cardiology. *Eur.Heart J.* 1998;19:40-54.

3. Chilton RJ. Recent discoveries in assessment of coronary heart disease: impact of vascular mechanisms on development of atherosclerosis. *J.Am.Osteopath.Assoc.* 2001;101:S1-S5 .

4. Schachter M. The pathogenesis of atherosclerosis. *Int.J.Cardiol.* 1997;62 **Suppl 2**:S3-S7.

5. Tak T,.Gutierrez R. Comparing stress testing methods. Available techniques and their use in CAD evaluation. *Postgrad.Med.* 2004;115:61-70.

6. Hazards of cardiac catheterisation. *Lancet* 1968;2:547-9.

7. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. *J.Am.Coll.Cardiol.* 1986;7:479-83.

8. Kemp HG, Jr., Vokonas PS, Cohn PF, Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Report of a six year experience. *Am.J.Med.* 1973;54:735-42.

9. Arbogast R,.Bourassa MG. Myocardial function during atrial pacing in patients with angina pectoris and normal coronary arteriograms. Comparison with patients having significant coronary artery disease. *Am.J.Cardiol.* 1973;32:257-63.

10. Kemp HG, Jr. Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. *Am.J.Cardiol.* 1973;32:375-6.

11. Mayou R, Bryant B, Forfar C, Clark D. Non-cardiac chest pain and benign palpitations in the cardiac clinic. *Br.Heart J.* 1994;72:548-53.

12. Bello N,.Mosca L. Epidemiology of coronary heart disease in women. *Prog.Cardiovasc.Dis.* 2004;46:287-95.

13. Vodopiutz J, Poller S, Schneider B, Lalouschek J, Menz F, Stollberger C . Chest pain in hospitalized patients: cause-specific and gender-specific differences. *J.Womens Health (Larchmt.)* 2002;11:719-27.

14. Nijher G, Weinman J, Bass C, Chambers J. Chest pain in people with normal coronary anatomy. *BMJ* 2001;323:1319-20.

15. Newman S. The psychological perspective: a professional view. *Heart* 2003;89 **Suppl 2**:ii16-ii18.

16. Suzuki H, Matsubara H, Koba S, Murakami M, Takeyama Y, Katagiri T. Clinical characteristics and follow-up in patients with microvascular angina. *Circ.J.* 2002;66:691-5.

17. Cox ID, Schwartzman RA, Atienza F, Brown SJ, Kaski JC. Angiographic progression in patients with angina pectoris and normal or near normal coronary angiograms who are restudied due to unstable symptoms. *Eur.Heart J.* 1998;19:1027-33.

18. Reaven G. Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. *Circulation* 2002;**106**:286-8.

19. Kaski JC, Aldama G, Cosin-Sales J. Cardiac syndrome X. Diagnosis, pathogenesis and management. *Am.J.Cardiovasc.Drugs* 2004;**4**:179-94.

20. Thomas JJ. Reducing anxiety during phase I cardiac rehabilitation. *J.Psychosom.Res.* 1995;**39**:295-304.

21. Murray CJ,.Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;**349**:1498-504.

22. Cassano P,.Fava M. Depression and public health: an overview. *J.Psychosom.Res.* 2002;**53**:849-57.

23. Mayou RA, Bryant BM, Sanders D, Bass C, Klimes I, Forfar C. A controlled trial of cognitive behavioural therapy for non-cardiac chest pain. *Psychol.Med.* 1997;**27**:1021-31.

24. Peski-Oosterbaan AS, Spinhoven P, van Rood Y, van der Does JW, Bruschke AV, Rooijmans HG. Cognitive-behavioral therapy for noncardiac chest pain: a randomized trial. *Am.J.Med.* 1999;**106**:424-9.

25. Cunningham C, Brown S, Kaski JC. Effects of transcendental meditation on symptoms and electrocardiographic changes in patients with cardiac syndrome X. *Am.J.Cardiol.* 2000;**85**:653-5, A10.

26. Ruggeri A, Taruschio G, Loricchio ML, Samory G, Borghi A, Bugiardini R. [The correlation between the clinical characteristics and psychological status in syndrome X patients]. *Cardiologia* 1996;**41**:551-7.

27. Rosano, G. M. and Crea, F. Chest pain and myocardial ischemia in syndrome x: new pathogenetic hypothesis. Coronary Artery Disease 3, 559-604. 1992.

28. Cannon RO, III, Bonow RO, Bacharach SL, Green MV, Rosing DR, Leon MB *et al.* Left ventricular dysfunction in patients with angina pectoris, normal epicardial coronary arteries, and abnormal vasodilator reserve. *Circulation* 1985;**71**:218-26.

29. Opherk D, Schuler G, Wetterauer K, Manthey J, Schwarz F, Kubler W. Four-year follow-up study in patients with angina pectoris and normal coronary arteriograms ("syndrome X"). *Circulation* 1989;**80**:1610-6.

30. Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. *J.Am.Coll.Cardiol.* 1995;**25**:807-14.

31. Cannon RO, III, Leon MB, Watson RM, Rosing DR, Epstein SE. Chest pain and "normal" coronary arteries--role of small coronary arteries. *Am.J.Cardiol.* 1985;**55**:50B-60B.

32. Marroquin OC, Holubkov R, Edmundowicz D, Rickens C, Pohost G, Buchthal S *et al.* Heterogeneity of microvascular dysfunction in women with chest pain not attributable to coronary artery disease: implications for clinical practice. *Am.Heart J.* 2003;**145**:628-35.

33. Sax FL, Cannon RO, III, Hanson C, Epstein SE. Impaired forearm vasodilator reserve in patients with microvascular angina. Evidence of a generalized disorder of vascular function? *N.Engl.J.Med.* 1987;**317** :1366-70.

34. Cannon RO, III,.Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. *Am.J.Cardiol.* 1988;**61**:1338-43.

35. Buchthal SD, den Hollander JA, Merz CN, Rogers WJ, Pepine CJ, Reichek N *et al.* Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N.Engl.J.Med.* 2000;**342**:829-35.

36. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P *et al.* Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N.Engl.J.Med.* 2002;**346**:1948-53.

37. Rosano GM, Lindsay DC, Poole-Wilson PA. Syndrome X: an hypothesis for cardiac pain without ischaemia. *Cardiologia* 1991;**36**:885-95.

38. Crake T, Canepa-Anson R, Shapiro L, Poole-Wilson PA. Continuous recording of coronary sinus oxygen saturation during atrial pacing in patients with coronary artery disease or with syndrome X. *Br.Heart J.* 1988;**59**:31-8.

39. Rosano GM, Kaski JC, Arie S, Pereira WI, Horta P, Collins P *et al.* Failure to demonstrate myocardial ischaemia in patients with angina and normal coronary arteries. Evaluation by continuous coronary sinus pH monitoring and lactate metabolism. *Eur.Heart J.* 1996;**17**:1175-80.

40. Camici PG, Marraccini P, Lorenzoni R, Buzzigoli G, Pecori N, Perissinotto A *et al.* Coronary hemodynamics and myocardial metabolism in patients with syndrome X: response to pacing stress. *J.Am.Coll.Cardiol.* 1991;**17**:1461-70.

41. Kaski JC. Overview of gender aspects of cardiac syndrome X. *Cardiovasc.Res.* 2002;**53**:620-6.

42. Kaski JC. Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X). *Circulation* 2004;**109**:568-72.

43. Turiel M, Galassi AR, Glazier JJ, Kaski JC, Maseri A. Pain threshold and tolerance in women with syndrome X and women with stable angina pectoris. *Am.J.Cardiol.* 1987;**60**:503-7.

44. Cannon RO, III, Quyyumi AA, Schenke WH, Fananapazir L, Tucker EE, Gaughan AM *et al.* Abnormal cardiac sensitivity in patients with chest pain and normal coronary arteries. *J.Am.Coll.Cardiol.* 1990;**16**:1359-66.

45. Rosen SD, Paulesu E, Wise RJ, Camici PG. Central neural contribution to the perception of chest pain in cardiac syndrome X. *Heart* 2002;**87**:513-9.

46. Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM *et al.* mu-opioid receptor-mediated antinociceptive responses differ in men and women. *J.Neurosci.* 2002;**22**:5100-7.

47. Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM *et al.* Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science* 2001;**293**:311-5.

48. Fillingim, R. B. and Maixner, W. Gender differences in the responses to noxious stimuli. Pain Forum (4), 209-221. 1995.

49. Zubieta JK, Dannals RF, Frost JJ. Gender and age influences on human brain mu-opioid receptor binding measured by PET. *Am.J.Psychiatry* 1999;**156**:842-8.

50. Cannon RO, III. The sensitive heart. A syndrome of abnormal cardiac pain perception. *JAMA* 1995;**273**:883-7.

51. Kohlmann CW, Ring C, Carroll D, Mohiyeddini C, Bennett P. Cardiac coping style, heartbeat detection, and the interpretation of cardiac events. *Br.J.Health Psychol.* 2001;**6**:285-301.

52. Quyyumi AA, Cannon RO, III, Panza JA, Diodati JG, Epstein SE. Endothelial dysfunction in patients with chest pain and normal coronary arteries. *Circulation* 1992;**86**:1864-71.

53. Widlansky ME, Gokce N, Keaney JF, Jr., Vita JA. The clinical implications of endothelial dysfunction. *J.Am.Coll.Cardiol.* 2003;**42**:1149-60.

54. Egashira K, Inou T, Hirooka Y, Yamada A, Urabe Y, Takeshita A. Evidence of impaired endothelium-dependent coronary vasodilatation in patients with angina pectoris and normal coronary angiograms. *N.Engl.J.Med.* 1993;**328**:1659-64.

55. Kaski JC, Tousoulis D, Galassi AR, McFadden E, Pereira WI, Crea F *et al.* Epicardial coronary artery tone and reactivity in patients with normal coronary arteriograms and reduced coronary flow reserve (syndrome X). *J.Am.Coll.Cardiol.* 1991;**18**:50-4.

56. Zeiher AM, Drexler H, Wollschlager H, Just H. Endothelial dysfunction of the coronary microvasculature is associated with coronary blood flow regulation in patients with early atherosclerosis. *Circulation* 1991;**84**:1984-92.

57. Lekakis JP, Papamichael CM, Vemmos CN, Voutsas AA, Stamatelopoulos SF, Moulopoulos SD. Peripheral vascular endothelial dysfunction in patients with angina pectoris and normal coronary arteriograms. *J.Am.Coll.Cardiol.* 1998;**31**:541-6.

58. Kaski JC, Cox ID, Crook JR, Salomone OA , Fredericks S, Hann C *et al.* Differential plasma endothelin levels in subgroups of patients with angina and angiographically normal coronary arteries. Coronary Artery Disease Research Group. *Am.Heart J.* 1998;**136**:412-7.

59. Kaski JC, Elliott PM, Salomone O, Dickinson K, Gordon D, Hann C *et al.* Concentration of circulating plasma endothelin in patients with angina and normal coronary angiograms. *Br.Heart J.* 1995;**74**:620-4.

60. Newby DE, Flint LL, Fox KA, Boon NA, Webb DJ. Reduced responsiveness to endothelin-1 in peripheral resistance vessels of patients with syndrome X. *J.Am.Coll.Cardiol.* 1998;**31**:1585-90.

61. Hoffmann E, Assennato P, Donatelli M, Colletti I, Valenti TM. Plasma endothelin-1 levels in patients with angina pectoris and normal coronary angiograms. *Am.Heart J.* 1998;**135**:684-8.

62. Cox ID, Botker HE, Bagger JP, Sonne HS, Kristensen BO, Kaski JC. Elevated endothelin concentrations are associated with reduced coronary vasomotor responses in patients with chest pain and normal coronary arteriograms. *J.Am.Coll.Cardiol.* 1999;**34**:455-60.

63. Sader MA,.Celermajer DS. Endothelial function, vascular reactivity and gender differences in the cardiovascular system. *Cardiovasc.Res.* 2002;**53**:597-604.

64. Hayward CS, Kelly RP, Collins P. The roles of gender, the menopause and hormone replacement on cardiovascular function. *Cardiovasc.Res.* 2000;**46**:28-49.

65. Webb CM, Rosano GM, Collins P. Oestrogen improves exercise-induced myocardial ischaemia in women. *Lancet* 1998;**351**:1556-7.

66. Roque M, Heras M, Roig E, Masotti M, Rigol M, Betriu A *et al.* Short-term effects of transdermal estrogen replacement therapy on coronary vascular reactivity in postmenopausal women with angina pectoris and normal results on coronary angiograms. *J.Am.Coll.Cardiol.* 1998;**31**:139-43.

67. Matsuda K, Teragawa H, Fukuda Y, Ueda K, Higashi Y, Sakai K *et al.* Response of the left anterior descending coronary artery to acetylcholine in patients with chest pain and angiographically normal coronary arteries. *Am.J.Cardiol.* 2003;**92**:1394-8.

68. Kidawa M, Krzeminska-Pakula M, Peruga JZ, Kasprzak JD. Arterial dysfunction in syndrome X: results of arterial reactivity and pulse wave propagation tests. *Heart* 2003;**89**:422-6.

69. O'Rourke MF. Wave travel and reflection in the arterial system. *J.Hypertens.* 1999;**17 Suppl 5**:S45-S47.

70. Genest J,.Pedersen TR. Prevention of cardiovascular ischemic events: high-risk and secondary prevention. *Circulation* 2003;**107**:2059-65.

71. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N.Engl.J.Med.* 1997;**336**:973-9.

72. Cosin-Sales J, Pizzi C, Brown S, Kaski JC. C-reactive protein, clinical presentation, and ischemic activity in patients with chest pain and normal coronary angiograms. *J.Am.Coll.Cardiol.* 2003;**41**:1468-74.

73. Rosalki SB. C-reactive protein. *Int.J.Clin.Pract.* 2001;**55**:269-70.

74. Arroyo-Espliguero R, Mollichelli N, Avanzas P, Zouridakis E, Newey VR, Nassiri DK *et al.* Chronic inflammation and increased arterial stiffness in patients with cardiac syndrome X. *Eur.Heart J.* 2003;**24**:2006-11.

75. Hsueh WA,.Quinones MJ. Role of endothelial dysfunction in insulin resistance. *Am.J.Cardiol.* 2003;**92**:10J-7J.

76. Schiffrin EL. Beyond blood pressure: the endothelium and atherosclerosis progression. *Am.J.Hypertens.* 2002;**15**:115S-22S.

77. Modan M, Halkin H, Almog S, Lusky A, Eshkol A, Shefi M *et al.* Hyperinsulinemia. A link between hypertension obesity and glucose intolerance. *J.Clin.Invest* 1985;**75**:809-17.

78. Dean JD, Jones CJ, Hutchison SJ, Peters JR, Henderson AH. Hyperinsulinaemia and microvascular angina ("syndrome X"). *Lancet* 1991;**337**:456-7.

79. Botker HE, Moller N, Ovesen P, Mengel A, Schmitz O, Orskov H *et al.* Insulin resistance in microvascular angina (syndrome X). *Lancet* 1993;**342**:136-40.

80. Botker HE, Frobert O, Moller N, Christiansen E, Schmitz O, Bagger JP. Insulin resistance in cardiac syndrome X and variant angina: influence of physical capacity and circulating lipids. *Am.Heart J.* 1997;**134**:229-37.

81. Chauhan A, Foote J, Petch MC, Schofield PM. Hyperinsulinemia, coronary artery disease and syndrome X. *J.Am.Coll.Cardiol.* 1994;**23**:364-8.

82. Cavallo PP, Pacini G, Giunti S, Comune M , Conte MR, Cassader M *et al.* Microvascular angina (cardiological syndrome X) per se is not associated with hyperinsulinaemia or insulin resistance. *Eur.J.Clin.Invest* 2000;**30**:481-6.

83. Rosano GM, Collins P, Kaski JC, Lindsay DC, Sarrel PM, Poole-Wilson PA. Syndrome X in women is associated with oestrogen deficiency. *Eur.Heart J.* 1995;**16**:610-4.

84. Rosano GM, Peters NS, Lefroy D, Lindsay DC, Sarrel PM, Collins P *et al.* 17-beta-Estradiol therapy lessens angina in postmenopausal women with syndrome X. *J.Am.Coll.Cardiol.* 1996;**28**:1500-5.

85. Lee TM, Su SF, Lee YT, Tsai CH. Effect of estrogen on ventricular repolarization in menopausal patients with syndrome X and effects of nicorandil. *Am.J.Cardiol.* 1999;**84**:65-9.

86. Albertsson PA, Emanuelsson H, Milsom I. Beneficial effect of treatment with transdermal estradiol-17-beta on exercise-induced angina and ST segment depression in syndrome X. *Int.J.Cardiol.* 1996;**54**:13-20.

87. Sitges M, Heras M, Roig E, Duran M, Masotti M, Zurbano MJ *et al.* Acute and mid-term combined hormone replacement therapy improves endothelial function in post-menopausal women with angina and angiographically normal coronary arteries. *Eur.Heart J.* 2001;**22**:2116-24.

88. Adamson DL, Webb CM, Collins P. Esterified estrogens combined with methyltestosterone improve emotional well-being in postmenopausal women with chest pain and normal coronary angiograms. *Menopause.* 2001;**8**:233-8.

89. Rozenberg S, Fellemans C, Ham H. Opinion survey towards hormone replacement therapy in the prevention of coronary heart disease. *Maturitas* 2001;**38** :273-7.

90. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;**280**:605-13.

91. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321-33.

92. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;**362**:419-27.

93. Herrington DM, Reboussin DM, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE *et al.* Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N.Engl.J.Med.* 2000;**343**:522-9.

94. Kaski JC,.Valenzuela Garcia LF. Therapeutic options for the management of patients with cardiac syndrome X. *Eur.Heart J.* 2001;**22**:283-93.

95. Cannon RO, III, Quyyumi AA, Mincemoyer R, Stine AM, Gracely RH, Smith WB *et al.* Imipramine in patients with chest pain despite normal coronary angiograms. *N.Engl.J.Med.* 1994;**330**:1411-7.

96. Cox ID, Hann CM, Kaski JC. Low dose imipramine improves chest pain but not quality of life in patients with angina and normal coronary angiograms. *Eur.Heart J.* 1998;**19**:250-4.

97. Huffman JC,.Stern TA. The use of benzodiazepines in the treatment of chest pain: a review of the literature. *J.Emerg.Med.* 2003;**25**:427-37.

98. Jessurun GA, Hautvast RW, Tio RA, DeJongste MJ. Electrical neuromodulation improves myocardial perfusion and ameliorates refractory angina pectoris in patients with syndrome X: fad or future? *Eur.J.Pain* 2003;**7**:507-12.

99. Melzack R,.Wall PD. Pain mechanisms: a new theory. *Science* 1965;**150**:971-9.

100. Fabian E,.Varga A. [Effect of simvastatin therapy on endothelial function of hypercholesteremic patients with syndrome X]. *Orv.Hetil.* 2002;**143**:2067-71.

101. Kayikcioglu M, Payzin S, Yavuzgil O, Kultursay H, Can LH, Soydan I. Benefits of statin treatment in cardiac syndrome-X1. *Eur.Heart J.* 2003;**24**:1999-2005.

102. Lanza GA, Manzoli A, Bia E, Crea F, Maseri A. Acute effects of nitrates on exercise testing in patients with syndrome X. Clinical and pathophysiological implications. *Circulation* 1994;**90**:2695-700.

103. Radice M, Giudici V, Albertini A, Mannarini A. Usefulness of changes in exercise tolerance induced by nitroglycerin in identifying patients with syndrome X. *Am.Heart J.* 1994;**127**:531-5.

104. Radice M, Giudici V, Pusineri E, Breghi L, Nicoli T, Peci P *et al.* Different effects of acute administration of aminophylline and nitroglycerin on exercise capacity in patients with syndrome X. *Am.J.Cardiol.* 1996;**78** :88-92.

105. Nalbantgil I, Onder R, Altintig A, Nalbantgil S, Kiliccioglu B, Boydak B *et al.* Therapeutic benefits of cilazapril in patients with syndrome X. *Cardiology* 1998;**89**:130-3.

106. Ozcelik F, Altun A, Ozbay G. Antianginal and anti-ischemic effects of nisoldipine and ramipril in patients with syndrome X. *Clin.Cardiol.* 1999;**22** :361-5.

107. Montorsi P, Manfredi M, Loaldi A, Fabbiocchi F, Polese A, de Cesare N *et al.* Comparison of coronary vasomotor responses to nifedipine in syndrome X and in Prinzmetal's angina pectoris. *Am.J.Cardiol.* 1989;**63**:1198-202.

108. Sutsch G, Oechslin E, Mayer I, Hess OM. Effect of diltiazem on coronary flow reserve in patients with microvascular angina. *Int.J.Cardiol.* 1995;**52**:135-43.

109. Lanza GA, Colonna G, Pasceri V, Maseri A. Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X. *Am.J.Cardiol.* 1999;**84**:854-6, A8.

110. Stewart S, Murphy N, Walker A, McGuire A, McMurray JJ. The current cost of angina pectoris to the National Health Service in the UK. *Heart* 2003;**89**:848-53.

111. Beck, AT, Ward, CH, Mendelson, M, Mock, J, and Erbaugh, J. An Inventory for Measuring Depression. Archives of General Psychiatry 4, 53-63. 1964.

112. Hamilton, M. The assessment of anxiety states by rating. British Journal of Medical Psychology 32, 50-55. 1959.

113. Corlando A, Marraccini P, Gistri R, Lorenzoni R, Camici P. [Psychological and social aspects in women with syndrome X]. *G.Ital.Cardiol.* 1991;**21**:705-12.

114. Eysenck H.J. Mannual of the Maudsley Personality Inventory. London: University of London Press, 1959.

115. Pilowsky I,.Spence ND. Patterns of illness behaviour in patients with intractable pain. *J.Psychosom.Res.* 1975;**19**:279-87.

116. Atienza F, Velasco JA, Brown S, Ridocci F, Kaski JC. Assessment of quality of life in patients with chest pain and normal coronary arteriogram (syndrome X) using a specific questionnaire. *Clin.Cardiol.* 1999;**22**:283-90.

117. Lewin RJ. Improving quality of life in patients with angina. *Heart* 1999;**82**:654-5.

118. Lyons RA, Lo SV, Littlepage BN. Comparative health status of patients with 11 common illnesses in Wales. *J.Epidemiol.Community Health* 1994;**48**:388-90.

119. Zvolensky MJ, Eifert GH, Feldner MT, Leen-Feldner E. Heart-focused anxiety and chest pain in postangiography medical patients. *J.Behav.Med.* 2003;**26**:197-209.

120. Karlsson I, Rasmussen C, Ravn J, Thiis JJ, Pettersson G, Larsso PA. Chest pain after coronary artery bypass: relation to coping capacity and quality of life. *Scand.Cardiovasc.J.* 2002;**36**:41-7.

121. McKenna KT, McEniery PT, Maas F, Aroney CN, Bett JH, Cameron J *et al.* Percutaneous transluminal coronary angioplasty: clinical and quality of life outcomes one year later. *Aust.N.Z.J.Med.* 1994;**24**:15-21.

122. Mayou RA, Bass CM, Bryant BM. Management of non-cardiac chest pain: from research to clinical practice. *Heart* 1999;**81**:387-92.

123. Peski-Oosterbaan AS, Spinhoven P, van der Does AJ, Bruschke AV. Noncardiac chest pain: interest in a medical psychological treatment. *J.Psychosom.Res.* 1998;**45**:471-6.

124. Sand NP,.Juelsgaard P. [Syndrome X. Somatic and social prognosis of patients with angina pectoris and normal coronary arteriography]. *Ugeskr.Laeger* 1994;**156**:1131-6.

125. Cheng C, Wong WM, Lai KC, Wong BC, Hu WH, Hui WM *et al.* Psychosocial factors in patients with noncardiac chest pain. *Psychosom.Med.* 2003;**65**:443-9.

126. Potts SG,.Bass CM. Psychosocial outcome and use of medical resources in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. *Q.J.Med.* 1993;**86**:583-93.

127. Potts SG,.Bass CM. Psychological morbidity in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. *Psychol.Med.* 1995;**25**:339-47.

128. Potts SG, Lewin R, Fox KA, Johnstone EC . Group psychological treatment for chest pain with normal coronary arteries. *QJM.* 1999;**92**:81-6.

129. Eslick GD, Jones MP, Talley NJ. Non-cardiac chest pain: prevalence, risk factors, impact and consulting--a population-based study. *Aliment.Pharmacol.Ther.* 2003;**17**:1115-24.

130. Bass C, Wade C, Hand D, Jackson G. Patients with angina with normal or near normal coronary arteries: clinical and psychosocial state 12 months after angiography. *British Medical Journal* 1983;**287**:1505-8.

131. Clouse RE,.Carney RM. The psychological profile of non-cardiac chest pain patients. *Eur.J.Gastroenterol.Hepatol.* 1995;**7**:1160-5.

132. Ho KY, Kang JY, Yeo B, Ng WL. Non-cardiac, non-oesophageal chest pain: the relevance of psychological factors. *Gut* 1998;**43**:105-10.

133. Huffman JC,.Pollack MH. Predicting panic disorder among patients with chest pain: an analysis of the literature. *Psychosomatics* 2003;**44**:222-36.

134. Beitman BD, Mukerji V, Lamberti JW, Schmid L, DeRosear L, Kushner M *et al.* Panic disorder in patients with chest pain and angiographically normal coronary arteries. *Am.J.Cardiol.* 1989;**63**:1399-403.

135. Lantinga LJ, Sprafkin RP, McCroskery JH, Baker MT, Warner RA, Hill NE. One-year psychosocial follow-up of patients with chest pain and angiographically normal coronary arteries. *Am.J.Cardiol.* 1988;**62**:209-13.

136. Ketterer MW, Brymer J, Rhoads K, Kraft P, Kenyon L, Foley B *et al.* Emotional distress among males with "syndrome X". *J.Behav.Med.* 1996;**19**:455-66.

137. Ockene IS, Shay MJ, Alpert JS, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary arteriograms: a follow-up study of functional status. *N.Engl.J.Med.* 1980;**303**:1249-52.

138. Olson MB, Kelsey SF, Matthews K, Shaw LJ, Sharaf BL, Pohost GM *et al.* Symptoms, myocardial ischaemia and quality of life in women: results from the NHLBI-sponsored WISE Study. *Eur.Heart J.* 2003;**24**:1506-14.

139. Aikens JE, Zvolensky MJ, Eifert GH. Differential fear of cardiopulmonary sensations in emergency room noncardiac chest pain patients. *J.Behav.Med.* 2001;**24**:155-67.

140. Zamarra JW, Schneider RH, Besseghini I, Robinson DK, Salerno JW. Usefulness of the transcendental meditation program in the treatment of patients with coronary artery disease. *Am.J.Cardiol.* 1996;**77**:867-70.

141. Luebbert K, Dahme B, Hasenbring M. The effectiveness of relaxation training in reducing treatment-related symptoms and improving emotional adjustment in acute non-surgical cancer treatment: a meta-analytical review. *Psychooncology.* 2001;**10**:490-502.

142. Carroll D,.Seers K. Relaxation for the relief of chronic pain: a systematic review. *J.Adv.Nurs.* 1998;**27**:476-87.

143. Infante JR, Torres-Avisbal M, Pinel P, Vallejo JA, Peran F, Gonzalez F *et al.* Catecholamine levels in practitioners of the transcendental meditation technique. *Physiol Behav.* 2001;**72**:141-6.

144. Bujatti M,.Riederer P. Serotonin, noradrenaline, dopamine metabolites in transcendental meditation-technique. *J.Neural Transm.* 1976;**39**:257-67.

145. Lang R, Dehof K, Meurer KA, Kaufmann W . Sympathetic activity and transcendental meditation. *J.Neural Transm.* 1979;**44**:117-35.

146. Klimes I, Mayou RA, Pearce MJ, Coles L, Fagg JR. Psychological treatment for atypical non-cardiac chest pain: a controlled evaluation. *Psychol.Med.* 1990;**20**:605-11.

147. Peski-Oosterbaan AS, Spinhoven P, van Rood Y. Cognitive behavoural therapy for unexplained non-cardiac chest pain: a pilot study. *Behavioral Cognitive Psychotherapy* 1997;**25**:339-50.

148. Sanders, D, Bass, C. M., Mayou, R. A., Goodwin, S, Bryant, B. M., and Tyndel S. Non-cardiac chest pain: why was a brief intervention apparently ineffective? Psychol.Med. 27, 1033-1040. 1997.

149. Lewin RJ, Thompson DR, Elton RA. Trial of the effects of an advice and relaxation tape given within the first 24 h of admission to hospital with acute myocardial infarction. *Int.J.Cardiol.* 2002;**82**:107-14.

150. Barlow SH, Burlingame GM, Nebeker RS, Anderson E. Meta-analysis of medical self-help groups. *Int.J.Group Psychother.* 2000;**50**:53-69.

151. Targ EF,.Levine EG. The efficacy of a mind-body-spirit group for women with breast cancer: a randomized controlled trial. *Gen.Hosp.Psychiatry* 2002;**24**:238-48.

152. Adamsen L. 'From victim to agent': the clinical and social significance of self-help group participation for people with life-threatening diseases. *Scand.J.Caring.Sci.* 2002;**16**:224-31.

153. Subramaniam V, Stewart MW, Smith JF. The development and impact of a chronic pain support group: a qualitative and quantitative study. *J.Pain Symptom.Manage.* 1999;**17**:376-83.

154. Hildingh C, Segesten K, Bengtsson C, Fridlund B. Experiences of social support among participants in self-help groups related to coronary heart disease. *J.Clin.Nurs.* 1994;**3**:219-26.

155. Barlow DH. Anxiety and its disorders. New York: Gilford, 1988.

156. Yoshida T, Kohzuki M, Yoshida K, Hiwatari M, Kamimoto M, Yamamoto C *et al.* Physical and psychological improvements after phase II cardiac rehabilitation in patients with myocardial infarction. *Nurs.Health Sci.* 1999;**1**:163-70.

157. Grace SL, Abbey SE, Shnek ZM, Irvine J, Franche RL, Stewart DE. Cardiac rehabilitation I. review of psychosocial factors. *Gen.Hosp.Psychiatry* 2002;**24**:121-6.

158. Leaf DA,.Goldhaber J. Effects of physical exercise training in syndrome X. *Clin.Cardiol.* 1993;**16**:65-6.

159. Eriksson BE, Tyni-Lenne R, Svedenhag J, Hallin R, Jensen-Urstad K, Jensen-Urstad M *et al.* Physical training in Syndrome X: physical training counteracts deconditioning and pain in Syndrome X. *J.Am.Coll.Cardiol.* 2000;**36**:1619-25.

160. Tyni-Lenne R, Stryjan S, Eriksson B, Berglund M, Sylven C. Beneficial therapeutic effects of physical training and relaxation therapy in women with coronary syndrome X. *Physiother.Res.Int.* 2002;**7**:35-43.

161. Langford CP, Bowsher J, Maloney JP, Lillis PP. Social support: a conceptual analysis. *J.Adv.Nurs.* 1997;**25**:95-100.

162. Shumaker SA,.Bronwell A. Towards a theory of social support: Closing conceptual gaps. *Journal of Social Issues* 1984;**40**:11-33.

163. Woloshin S, Schwartz LM, Tosteson AN, Chang CH, Wright B, Plohman J *et al.* Perceived adequacy of tangible social support and health outcomes in patients with coronary artery disease. *J.Gen.Intern.Med.* 1997;**12**:613-8.

164. Barrera M. Distinctions between social support concepts, measures and models. *American Journal of Community Psychology* 1986;**14**:413-45.

165. Lemke S,.Moos RH. Validity of the Sheltered Care Environment Scale: conceptual and methodological issues. *Psychol.Aging* 1990;**5**:569-71.

166. Hupcey JE. Clarifying the social support theory-research linkage. *J.Adv.Nurs.* 1998;**27**:1231-41.

167. Heller K, Swindle RW, Jr., Dusenbury L. Component social support processes: comments and integration. *J.Consult Clin.Psychol.* 1986;**54**:466-70.

168. Cohen S, Syme SL. Issues in the study and application of social support. In Cohen S, Syme SL, eds. *Social Support and Health*, pp 3-22. Orlando, Florida: Academic Press, 1985.

169. Antonucci, T. C. Social support: Theoretical advances, recent findings and pressing issues. In Social Support: Theory, Research and Application. 21-37. 1985. Nijhoff, Boston.

170. Pedersen SS, Middel B, Larsen ML. The role of personality variables and social support in distress and perceived health in patients following myocardial infarction. *J.Psychosom.Res.* 2002;**53**:1171-5.

171. Kitamura T, Kijima N, Watanabe K, Takezaki Y, Tanaka E. Precedents of perceived social support: personality and early life experiences. *Psychiatry Clin.Neurosci.* 1999;**53**:649-54.

172. Kitamura T, Watanabe K, Takara N, Hiyama K, Yasumiya R, Fujihara S. Precedents of perceived social support: personality, early life experiences and gender. *Psychiatry Clin.Neurosci.* 2002;**56**:169-76.

173. Coyne JC,.DeLongis A. Going beyond social support: the role of social relationships in adaptation. *J.Consult Clin.Psychol.* 1986;**54**:454-60.

174. Rook KS. The negative side of social interaction: impact on psychological well-being. *J.Pers.Soc.Psychol.* 1984;**46**:1097-108.

175. Rook, K. S. and Dooley D. Applying social support research: Theoretical problems and future directions. Journal of Social Issues 41, 5-28. 1985.

176. Lesperance F,.Frasure-Smith N. Depression in patients with cardiac disease: a practical review. *J.Psychosom.Res.* 2000;**48**:379-91.

177. Wenger NK. Social support and coronary heart disease in women: the challenge to learn more. *Eur.Heart J.* 1998;**19**:1603-5.

178. House JS. Social isolation kills, but how and why? *Psychosom.Med.* 2001;**63**:273-4.

179. Brummett BH, Barefoot JC, Siegler IC, Clapp-Channing NE, Lytle BL, Bosworth HB *et al.* Characteristics of socially isolated patients with coronary artery disease who are at elevated risk for mortality. *Psychosom.Med.* 2001;**63**:267-72.

180. Anderson D, Deshaies G, Jobin J. Social support, social networks and coronary artery disease rehabilitation: a review. *Can.J.Cardiol.* 1996;**12**:739-44.

181. Frasure-Smith N,.Lesperance F. Coronary artery disease, depression and social support only the beginning. *Eur.Heart J.* 2000;**21**:1043-5.

182. Cohen S,.Wills TA. Stress, social support, and the buffering hypothesis. *Psychol.Bull.* 1985;**98**:310-57.

183. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. *N.Engl.J.Med.* 1984;**311**:552-9.

184. Barefoot JC, Brummett BH, Helms MJ, Mark DB, Siegler IC, Williams RB. Depressive symptoms and survival of patients with coronary artery disease. *Psychosom.Med.* 2000;**62**:790-5.

185. Horsten M, Mittleman MA, Wamala SP, Schenck-Gustafsson K, Orth-Gomer K. Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. The Stockholm Female Coronary Risk Study. *Eur.Heart J.* 2000;**21**:1072-80.

186. Dickens CM, McGowan L, Percival C, Douglas J, Tomenson B, Cotter L *et al.* Lack of a close confidant, but not depression, predicts further cardiac events after myocardial infarction. *Heart* 2004;**90**:518-22.

187. Lindsay GM, Smith LN, Hanlon P, Wheatley DJ. The influence of general health status and social support on symptomatic outcome following coronary artery bypass grafting. *Heart* 2001;**85**:80-6.

188. Sherman AM, Shumaker SA, Kancler C, Zheng B, Reboussin DM, Legault C *et al.* Baseline health-related quality of life in postmenopausal women with coronary heart disease: the Estrogen Replacement and Atherosclerosis (ERA) trial. *J.Womens Health (Larchmt.)* 2003;**12**:351-62.

189. Biggs AM, Aziz Q, Tomenson B, Creed F. Effect of childhood adversity on health related quality of life in patients with upper abdominal or chest pain. *Gut* 2004;**53**:180-6.

190. Knox SS, Siegmund KD, Weidner G, Ellison RC, Adelman A, Paton C. Hostility, social support, and coronary heart disease in the National Heart, Lung, and Blood Institute Family Heart Study. *Am.J.Cardiol.* 1998;**82**:1192-6.

191. Wiklund I, Sanne H, Vedin A, Wilhelmsson C. Psychosocial outcome one year after a first myocardial infarction. *J.Psychosom.Res.* 1984; **28**:309-21.

192. Itkowitz NI, Kerns RD, Otis JD. Support and coronary heart disease: the importance of significant other responses. *J.Behav.Med.* 2003;**26**:19-30.

193. Berkhuysen MA, Nieuwland W, Buunk BP, Sanderman R, Rispens P. Change in self-efficacy during cardiac rehabilitation and the role of perceived overprotectiveness. *Patient.Educ.Couns.* 1999;**38**:21-32.

194. Robinson KM,.Steele D. The relationship between health and social support in caregiving wives as perceived by significant others. *J.Adv.Nurs.* 1995;**21**:88-94.

195. Mansfield PK, Koch PB, Gierach G. Husbands' support of their perimenopausal wives. *Women Health* 2003;**38**:97-112.

196. Grace SL, Abbey SE, Shnek ZM, Irvine J, Franche RL, Stewart DE. Cardiac rehabilitation II. referral and participation. *Gen.Hosp.Psychiatry* 2002;**24**:127-34.

197. Glynn LM, Christenfeld N, Gerin W. Gender, social support, and cardiovascular responses to stress. *Psychosom.Med.* 1999;**61**:234-42.

198. Kirschbaum C, Klauer T, Filipp SH, Hellhammer DH. Sex-specific effects of social support on cortisol and subjective responses to acute psychological stress. *Psychosom.Med.* 1995;**57**:23-31.

199. Robles TF,.Kiecolt-Glaser JK. The physiology of marriage: pathways to health. *Physiol Behav.* 2003;**79**:409-16.

200. Berkman LF,.Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *Am.J.Epidemiol.* 1979;**109**:186-204.

201. Stroebe MS,.Stroebe W. Who suffers more? Sex differences in health risks of the widowed. *Psychol.Bull.* 1983;**93**:279-301.

202. Stroebe MS. New directions in bereavement research: exploration of gender differences. *Palliat.Med.* 1998;**12**:5-12.

203. Belle D. The stress of caring: Women as providers of social support. *Handbook of stress: Theoretical and clinical aspects*, pp 496-505. New York: Free Press, 1982.

204. Burda, P. C. and Vaux, A. The social support process in men: Overcoming sex-role obstacles. Human Relations 40, 31-43. 1987.

205. Vinokur, A. D and Vinokur-Kaplan, D. In sickness and in health: Patterns of social support and undermining in older married couples. Journal of Aging and Health 2, 215-241. 1990.

206. Barbee, A. P, Gulley, M. R, and Cunningham, M. R. Support seeking in close relationships. Journal of Social and Personal Relationships 7, 531-540. 1990.

207. Depner CE,.Ingersoll-Dayton B. Supportive relationships in later life. *Psychol.Aging* 1988;**3**:348-57.

208. Stokes JP,.Wilson DG. The inventory of socially supportive behaviors: dimensionality, prediction, and gender differences. *Am.J.Community Psychol.* 1984;**12**:53-69.

209. Edwards AC, Nazroo JY, Brown GW. Gender differences in marital support following a shared life event. *Soc.Sci.Med.* 1998;**46**:1077-85.

210. Xu Y,.Burleson BR. Effects of sex, culture and support type on perceptions of spousal support. *Human Communication Research* 2001;**27**:535-66.

211. Davidson, C, Frankle, S, and Davey Smith, G. The limits of lifestyle: re-assessing 'fatalism' in the popular culture of illness prevention. Soc.Sci.Med. 34, 675-685. 1992.

212. Eifert GH, Hodson SE, Tracey DR, Seville JL, Gunawardane K. Heart-focused anxiety, illness beliefs, and behavioral impairment: comparing healthy heart-anxious patients with cardiac and surgical inpatients. *J.Behav.Med.* 1996;**19**:385-99.

213. Aikens JE, Michael E, Levin T, Myers TC , Lowry E, McCracken LM. Cardiac exposure history as a determinant of symptoms and emergency department utilization in noncardiac chest pain patients. *J.Behav.Med.* 1999;**22**:605-17.

214. Eifert GH,.Forsyth JP. Heart-focused and general illness fears in relation to parental medical history and separation experiences. *Behav.Res.Ther.* 1996;**34**:735-9.

215. Eifert GH. Cardiophobia: a paradigmatic behavioural model of heart-focused anxiety and non-anginal chest pain. *Behav.Res.Ther.* 1992;**30**:329-45.

216. Flor, H., Birbaumer, N., and Turk, D. C. The psychobiology of pain. Advances in Behaviour Research and Therapy 12, 47-84. 1990.

217. Fredrikson M, Annas P, Fischer H, Wik G . Gender and age differences in the prevalence of specific fears and phobias. *Behav.Res.Ther.* 1996;**34**:33-9.

218. Hunt K, Davison C, Emslie C, Ford G. Are perceptions of a family history of heart disease related to health-related attitudes and behaviour? *Health Educ.Res.* 2000;**15**:131-43.

219. Hunt K, Emslie C, Watt G. Lay constructions of a family history of heart disease: potential for misunderstandings in the clinical encounter? *Lancet* 2001;**357**:1168-71.

220. Richards HM, Reid ME, Watt GC. Socioeconomic variations in responses to chest pain: qualitative study. *BMJ* 2002;**324**:1308.

221. Cohen M. First-degree relatives of breast-cancer patients: cognitive perceptions, coping, and adherence to breast self-examination. *Behav.Med.* 2002;**28**:15-22.

222. Smith BL, Gadd MA, Lawler C, MacDonald DJ, Grudberg SC, Chi FS *et al.* Perception of breast cancer risk among women in breast center and primary care settings: correlation with age and family history of breast cancer. *Surgery* 1996; **120**:297-303.

223. Thirlaway K, Fallowfield L, Nunnerley H, Powles T. Anxiety in women "at risk' of developing breast cancer. *Br.J.Cancer* 1996;**73**:1422-4.

224. Hailey BJ, Carter CL, Burnett DR. Breast cancer attitudes, knowledge, and screening behavior in women with and without a family history of breast cancer. *Health Care Women Int.* 2000;**21**:701-15.

225. Deeks AA. Psychological aspects of menopause management. *Best.Pract.Res.Clin.Endocrinol.Metab* 2003;**17**:17-31.

226. Ruiz P, I, Montero P, I, Hernandez-Aguado I. Associated factors to psychiatric morbidity in postmenopausal phases. *Maturitas* 1997;**28**:107-15.

227. Eagles JM,.Whalley LJ. Ageing and affective disorders: the age at first onset of affective disorders in Scotland, 1969-1978. *Br.J.Psychiatry* 1985;**147**:180-7.

228. Hallstrom T,.Samuelsson S. Mental health in the climacteric. The longitudinal study of women in Gothenburg. *Acta Obstet.Gynecol.Scand.Suppl* 1985;**130**:13-8.

229. Dennerstein L, Smith AM, Morse C. Psychological well-being, mid-life and the menopause. *Maturitas* 1994;**20**:1-11.

230. Dennerstein L, Lehert P, Burger H, Dudley E. Mood and the menopausal transition. *J.Nerv.Ment.Dis.* 1999;**187**:685-91.

231. Dennerstein L, Dudley EC, Guthrie JR. Predictors of declining self-rated health during the transition to menopause. *J.Psychosom.Res.* 2003;**54**:147-53.

232. Dennerstein L, Randolph J, Taffe J, Dudley E, Burger H. Hormones, mood, sexuality, and the menopausal transition. *Fertil.Steril.* 2002;77 **Suppl 4**:42-8.

233. Dennerstein L, Lehert P, Guthrie J. The effects of the menopausal transition and biopsychosocial factors on well-being. *Arch.Women Ment.Health* 2002;**5**:15-22.

234. Dennerstein L. Well-being, symptoms and the menopausal transition. *Maturitas* 1996;**23**:147-57.

235. Koster A, Eplov LF, Garde K. Anticipations and experiences of menopause in a Danish female general population cohort born in 1936. *Arch.Women Ment.Health* 2002; **5**:9-13.

236. Rostosky SS,.Travis CB. Menopause research and the dominance of the biomedical model 1984 - 1994. *Psychology of Women Quarterly* 1996;**20**:285-312.

237. Vanwesenbeeck I, Vennix P, van de WH. 'Menopausal symptoms': associations with menopausal status and psychosocial factors. *J.Psychosom.Obstet.Gynaecol.* 2001;**22**:149-58.

238. Becker D, Lomranz J, Pines A, Shmotkin D, Nitza E, BennAmitay G *et al.* Psychological distress around menopause. *Psychosomatics* 2001;**42**:252-7.

239. Morse CA, Dudley E, Guthrie J, Dennerstein L. Relationships between premenstrual complaints and perimenopausal experiences. *J.Psychosom.Obstet.Gynaecol.* 1998;**19**:182-91.

240. Cooke DJ. Social support and stressful life events during mid-life. *Maturitas* 1985;**7**:303-13.

241. Anarte MT, Cuadros JL, Herrera J. Hormonal and psychological treatment: therapeutic alternative for menopausal women? *Maturitas* 1998;**29**:203-13.

242. Khastgir G,.Studd J. Patients' outlook, experience, and satisfaction with hysterectomy, bilateral oophorectomy, and subsequent continuation of hormone replacement therapy. *Am.J.Obstet.Gynecol.* 2000;**183**:1427-33.

243. Kjerulff KH, Langenberg PW, Rhodes JC, Harvey LA, Guzinski GM, Stolley PD. Effectiveness of hysterectomy. *Obstet.Gynecol.* 2000;**95**:319-26.

244. Carlson KJ, Miller BA, Fowler FJ, Jr. The Maine Women's Health Study: I. Outcomes of hysterectomy. *Obstet.Gynecol.* 1994;**83**:556-65.

245. MacDonald SR, Klock SC, Milad MP. Long-term outcome of nonconservative surgery (hysterectomy) for endometriosis-associated pain in women <30 years old. *Am.J.Obstet.Gynecol.* 1999;**180**:1360-3.

246. Oates M,.Gath D. Psychological aspects of gynaecological surgery. *Baillieres Clin.Obstet.Gynaecol.* 1989;3:729-49.

247. Cagnacci A, Neri I, Tarabusi M, Volpe A , Facchinetti F. Effect of long-term local or systemic hormone replacement therapy on post-menopausal mood disturbances. Influences of socio-economic and personality factors. *Maturitas* 1999;**31**:111-6.

248. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. *JAMA* 2002;**287**:591-7.

249. Wiklund I, Karlberg J, Mattsson LA. Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: a double-blind placebo-controlled study. *Am.J.Obstet.Gynecol.* 1993;**168**:824-30.

250. Greendale GA, Reboussin BA, Hogan P, Barnabei VM, Shumaker S, Johnson S *et al.* Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet.Gynecol.* 1998;**92**:982-8.

251. Freedman MA. Quality of life and menopause: the role of estrogen. *J.Womens Health (Larchmt.)* 2002;**11**:703-18.

252. Lucock MP,.Morley S. The Health Anxiety Questionnaire. *British Journal of Health Psychology* 1996;**1**:137-50.

253. Zigmond AS,.Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr.Scand.* 1983;**67**:361-70.

254. Brugha TS, Bebbington P, Tennant C, Hurry J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol.Med.* 1985;**15**:189-94.

255. Brown GW, Harris TO. Social Origins of Depression. London: Tavistock, 1978.

256. Beck AT, Emery G, Greenberg R. Anxiety Disorders and Phobias: A Cognitive Perspective. New York : Basic Books, 2001.

257. Johnston M, Pollard B, Hennessey P. Construct validation of the hospital anxiety and depression scale with clinical populations. *J.Psychosom.Res.* 2000;**48**:579-84.

258. Kuijpers PM, Denollet J, Lousberg R, Wellens HJ, Crijns H, Honig A. Validity of the hospital anxiety and depression scale for use with patients with noncardiac chest pain. *Psychosomatics* 2003;**44**:329-35.

259. Ormel J, Kempen GI, Penninx BW, Brilman EI, Beekman AT, Van Sonderen E. Chronic medical conditions and mental health in older people: disability and psychosocial resources mediate specific mental health effects. *Psychol.Med.* 1997;**27**:1065-77.

260. Amiel-Lebigre F, Kovess V, Labarte S, Chevalier A. Symptom distress and frequency of life events. *Soc.Psychiatry Psychiatr.Epidemiol.* 1998;**33**:263-8.

261. Redburn JC,.Murphy MF. Hysterectomy prevalence and adjusted cervical and uterine cancer rates in England and Wales. *BJOG.* 2001;**108**:388-95.

262. Kennedy TM,.Jones RH. The epidemiology of hysterectomy and irritable bowel syndrome in a UK population. *Int.J.Clin.Pract.* 2000;**54**:647-50.

263. Patterns of use of hormone replacement therapy in one million women in Britain, 1996-2000. *BJOG.* 2002;**109**:1319-30.

264. Leventhal H, Nerenz D. The assessment of illness cognition. In Karoly P, ed. *Measurement Strategies in Health Psychology*, pp 517-54. New York: Wiley and Sons, 1985.

265. Bassan M. Cardiac syndrome X. *N.Engl.J.Med.* 2002;**347**:1377-9.

266. Bahrke MS,.Morgan WP. Anxiety reduction following exercise and meditation. *Cognitive Therapy and Research* 1978;**2**:323-33.

267. Ransford CP. A role for amines in the antidepressant effect of exercise: a review. *Med.Sci.Sports Exerc.* 1982;**14**:1-10.

268. Cramer SR, Nieman DC, Lee JW. The effects of moderate exercise training on psychological well-being and mood state in women. *J.Psychosom.Res.* 1991;**35**:437-49.

269. Schwarz L,.Kindermann W. Changes in beta-endorphin levels in response to aerobic and anaerobic exercise. *Sports Med.* 1992;**13**:25-36.

270. Chaouloff F. Physical exercise and brain monoamines: a review. *Acta Physiol Scand.* 1989;**137**:1-13.

271. Paluska SA,.Schwenk TL. Physical activity and mental health: current concepts. *Sports Med.* 2000;**29**:167-80.

272. Lee IM,.Skerrett PJ. Physical activity and all-cause mortality: what is the dose-response relation? *Med.Sci.Sports Exerc.* 2001;**33**:S459-S471.

273. Eliot RS, Forker AD, Robertson RJ. Aerobic exercise as a therapeutic modality in the relief of stress. *Adv.Cardiol.* 1976;**18**:231-42.

274. Bachmann GA,.Grill J. Exercise in the postmenopausal woman. *Geriatrics* 1987;**42**: 75.

275. Ransford HE,.Palisi BJ. Aerobic exercise, subjective health and psychological well-being within age and gender subgroups. *Soc.Sci.Med.* 1996;**42**:1555-9.

276. Woade, A. Girl Power. The Flora Light Challenge for Running 2004 , 15-16. 2004. **The London Marathon.**

277. McTiernan A, Stanford JL, Daling JR, Voigt LF. Prevalence and correlates of recreational physical activity in women aged 50-64 years. *Menopause.* 1998;**5**:95-101.

278. Dearden JS,.Sheahan SL. Counseling middle-aged women about physical activity using the stages of change. *J.Am.Acad.Nurse Pract.* 2002;**14**:492-7.

279. Evenson KR, Wilcox S, Pettinger M, Brunner R, King AC, McTiernan A. Vigorous leisure activity through women's adult life: the Women's Health Initiative Observational Cohort Study. *Am.J.Epidemiol.* 2002;**156**:945-53.

280. US Department of Health and Human Services. Physical activity and health: a report of the Surgeon General. 1996. Atlanta, GA, National Centre for Chronic Disease Prevention and Health Promotion.

281. De B, I,.Sallis J. Relative contribution of psychosocial variables to the explanation of physical activity in three population-based adult samples. *Prev.Med.* 2002;**34**:279-88.

282. McAuley E, Bane SM, Rudolph DL, Lox CL. Physique anxiety and exercise in middle-aged adults. *J.Gerontol.B Psychol.Sci.Soc.Sci.* 1995;**50**:229-35.

283. Spink KS. Relation of anxiety about social physique to location of participation in physical activity. *Percept.Mot.Skills* 1992; **74**:1075-8.

284. Ransdell LB, Wells CL, Manore MM, Swan PD, Corbin CB. Social physique anxiety in postmenopausal women. *J.Women Aging* 1998;**10**:19-39.

285. Salmon P. Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. *Clin.Psychol.Rev.* 2001;**21**:33-61.

286. Byrne A,.Byrne DG. The effect of exercise on depression, anxiety and other mood states: a review. *J.Psychosom.Res.* 1993;**37**:565-74.

287. Petruzzello SJ,.Landers DM. State anxiety reduction and exercise: does hemispheric activation reflect such changes? *Med.Sci.Sports Exerc.* 1994;**26**:1028-35.

288. Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety. *Med.Sci.Sports Exerc.* 2001;**33**:S587-S597.

289. Fox KR. The influence of physical activity on mental well-being. *Public Health Nutr.* 1999;**2**:411-8.

290. Craft, L. L. and Landers D.M. The effect of exercise on clinical depression and depression resulting from mental illness: A meta analysis. Journal of Sport and Exercise Psychology 20, 339-357. 1998.

291. Courneya KS, Friedenreich CM, Sela RA, Quinney HA, Rhodes RE, Handman M . The group psychotherapy and home-based physical exercise (group-hope) trial in cancer survivors: physical fitness and quality of life outcomes. *Psychooncology.* 2003;**12**:357-74.

292. Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO. The DOSE study: a clinical trial to examine efficacy and dose response of exercise as treatment for depression. *Control Clin.Trials* 2002;**23**:584-603.

293. Peterson RA, Headen SW. Profile of mood states. In Keyser DJ, Sweetlands R.C., eds. *Test Critiques*, pp 522-9. Kansas City : Westport, 1984.

294. McIntyre CW,.Watson D. The effect of social interaction, exercise and test stress on positive and negative affect. *Bulletin of the Psychonomics Society* 1990;**28**:141-3.

295. Tuson KM, Sinyor D, Pelletier LG. Acute exercise and possitive affect: An investigation of psychological processes leading to affective change. *International Journal of Sports Psychology* 1995;**26**:138-59.

296. Morgan WP, Brown DR, Raglin JS, O'Connor PJ, Ellickson KA. Psychological monitoring of overtraining and staleness. *Br.J.Sports Med.* 1987;**21**:107-14.

297. Mondin GW, Morgan WP, Piering PN, Stegner AJ, Stotesbery CL, Trine MR *et al.* Psychological consequences of exercise deprivation in habitual exercisers. *Med.Sci.Sports Exerc.* 1996;**28**:1199-203.

298. Aidman, E. V and Woollard, S. The influence of self-reported exercise addiction on acute emotional and physiological responses to brief exercise deprivation. Psychology of Sport and Exercise. 2002.

299. Petruzzello SJ, Jones AC, Tate AK. Affective responses to acute exercise: a test of opponent-process theory. *J.Sports Med.Phys.Fitness* 1997;**37**:205-12.

300. Kennedy MM,.Newton M. Effect of exercise intensity on mood in step aerobics. *J.Sports Med.Phys.Fitness* 1997;**37**:200-4.

301. Frazier SE,.Nagy S. Mood state changes of women as a function of regular aerobic exercise. *Percept.Mot.Skills* 1989;**68**:283-7.

302. Hale BS,.Raglin JS. State anxiety responses to acute resistance training and step aerobic exercise across eight weeks of training. *J.Sports Med.Phys.Fitness* 2002;**42**:108-12.

303. DiLorenzo TM, Bargman EP, Stucky-Ropp R, Brassington GS, Frensch PA, LaFontaine T. Long-term effects of aerobic exercise on psychological outcomes. *Prev.Med.* 1999;**28**:75-85.

304. Blumenthal JA, Williams RS, Needels TL, Wallace AG. Psychological changes accompany aerobic exercise in healthy middle-aged adults. *Psychosom.Med.* 1982;**44**:529-36.

305. King AC, Taylor CB, Haskell WL. Effects of differing intensities and formats of 12 months of exercise training on psychological outcomes in older adults. *Health Psychol.* 1993;**12**:292-300.

306. Perrig-Chiello P, Perrig WJ, Ehrsam R, Staehelin HB, Krings F. The effects of resistance training on well-being and memory in elderly volunteers. *Age Ageing* 1998;**27**:469-75.

307. Blumenthal JA, Babyak MA, Moore KA, Craighead WE, Herman S, Khatri P *et al.* Effects of exercise training on older patients with major depression. *Arch.Intern.Med.* 1999;**159**:2349-56.

308. Babyak M, Blumenthal JA, Herman S, Khatri P, Doraiswamy M, Moore K *et al.* Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom.Med.* 2000;**62**:633-8.

309. Oman RF,.King AC. The effect of life events and exercise program format on the adoption and maintenance of exercise behavior. *Health Psychol.* 2000;**19**:605-12.

310. Herman S, Blumenthal JA, Babyak M, Khatri P, Craighead WE, Krishnan KR *et al.* Exercise therapy for depression in middle-aged and older adults: predictors of early dropout and treatment failure . *Health Psychol.* 2002;**21**:553-63.

311. McAuley E, Blissmer B, Marquez DX, Jerome GJ, Kramer AF, Katula J. Social relations, physical activity, and well-being in older adults. *Prev.Med.* 2000;**31** :608-17.

312. McAuley E,.Rudolph DL. Physical activity, aging and psychological well-being. *J.Ag.Phys.Act* 1995;**3**:67-96.

313. Lennox SS, Bedell JR, Stone AA. The effect of exercise on normal mood. *J.Psychosom.Res.* 1990;**34**:629-36.

314. Norris R, Carroll D, Cochrane R. The effects of aerobic and anaerobic training on fitness, blood pressure, and psychological stress and well-being. *J.Psychosom.Res.* 1990;**34**:367-75.

315. Moses J, Steptoe A, Mathews A, Edwards S. The effects of exercise training on mental well-being in the normal population: a controlled trial. *J.Psychosom.Res.* 1989;**33**:47-61.

316. Katula JA, Blissmer BJ, McAuley E. Exercise intensity and self-efficacy effects on anxiety reduction in healthy, older adults. *J.Behav.Med.* 1999;**22**:233-47.

317. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol.Rev.* 1977;**84**:191-215.

318. O'Leary A. Self-efficacy and health. *Behav.Res.Ther.* 1985;**23**:437-51.

319. McAuley E, Bane SM, Mihalko SL. Exercise in middle-aged adults: self-efficacy and self-presentational outcomes. *Prev.Med.* 1995;**24**:319-28.

320. Butki BD, Rudolph DL, Jacobsen H. Self-efficacy, state anxiety, and cortisol responses to treadmill running. *Percept.Mot.Skills* 2001;**92**:1129-38.

321. Doyne EJ, Chambless DL, Beutler LE. Aerobic exercise as a treatment for depression in women. *Behavioral Therapy* 1983;**14**:434-40.

322. Doyne EJ, Ossip-Klein DJ, Bowman ED, Osborn KM, McDougall-Wilson IB, Neimeyer RA. Running versus weight lifting in the treatment of depression. *J.Consult Clin.Psychol.* 1987;**55**:748-54.

323. Bhui K,.Fletcher A. Common mood and anxiety states: gender differences in the protective effect of physical activity. *Soc.Psychiatry Psychiatr.Epidemiol.* 2000;**35**:28-35.

324. Williams P,.Lord SR. Effects of group exercise on cognitive functioning and mood in older women. *Aust.N.Z.J.Public Health* 1997;**21**:45-52.

325. Slaven L,.Lee C. Mood and symptom reporting among middle-aged women: the relationship between menopausal status, hormone replacement therapy, and exercise participation. *Health Psychol.* 1997;**16**:203-8.

326. Hunter M,.O'Dea I. An evaluation of a health education intervention for mid-aged women: five year follow-up of effects upon knowledge, impact of menopause and health. *Patient.Educ.Couns.* 1999;**38**:249-55.

327. Slaven L,.Lee C. Psychological effects of exercise among adult women: The impact of menopausal status. *Psychology and Health* 1995;**9**:297-303.

328. van der PG, Bernards N, Meijman TF, Heijnen CJ. The effect of depressive symptomatology on plasma cortisol responses to acute bicycle exercise among post-menopausal women. *Psychiatry Res.* 1999;**85**:113-7.

329. Maroulakis E,.Zervas Y. Effects of aerobic exercise on mood of adult women. *Percept.Mot.Skills* 1993;**76**:795-801.

330. Blanchard CM, Courneya KS, Laing D. Effects of acute exercise on state anxiety in breast cancer survivors. *Oncol.Nurs.Forum* 2001;**28**:1617-21.

331. Guthrie JR, Smith AM, Dennerstein L, Morse C. Physical activity and the menopause experience: a cross-sectional study. *Maturitas* 1994;**20**:71-80.

332. Bartholomew JB,.Linder DE. State anxiety following resistance exercise: the role of gender and exercise intensity. *J.Behav.Med.* 1998;**21**:205-19.

333. Grant S, Todd K, Aitchison TC, Kelly P , Stoddart D. The effects of a 12-week group exercise programme on physiological and psychological variables and function in overweight women. *Public Health* 2004;**118**:31-42.

334. Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *J.Clin.Oncol.* 2003;**21**:1660-8.

335. Pinto BM, Clark MM, Maruyama NC, Feder SI. Psychological and fitness changes associated with exercise participation among women with breast cancer. *Psychooncology.* 2003;**12**:118-26.

336. Castro CM, Wilcox S, O'Sullivan P, Baumann K, King AC. An exercise program for women who are caring for relatives with dementia. *Psychosom.Med.* 2002;**64**:458-68.

337. Norvell N, Martin D, Salamon A. Psychological and physiological benefits of passive and aerobic exercise in sedentary middle-aged women. *J.Nerv.Ment.Dis.* 1991; **179**:573-4.

338. Labbe EE, Welsh MC, Delaney D. Effects of consistent aerobic exercise on the psychological functioning of women. *Percept.Mot.Skills* 1988;**67**:919-25.

339. Burnham TR,.Wilcox A. Effects of exercise on physiological and psychological variables in cancer survivors. *Med.Sci.Sports Exerc.* 2002;**34**:1863-7.

340. Annesi JJ. Effects of minimal exercise and cognitive behavior modification on adherence, emotion change, self-image, and physical change in obese women. *Percept.Mot.Skills* 2000;**91**:322-36.

341. Lee RE, Goldberg JH, Sallis JF, Hickmann SA, Castro CM, Chen AH. A prospective analysis of the relationship between walking and mood in sedentary ethnic minority women. *Women Health* 2001;**32**:1-15.

342. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C *et al.* Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995;**273**:402-7.

343. Cox KL, Gorely TJ, Puddey IB, Burke V, Beilin LJ. Exercise behaviour change in 40 to 65-year-old women: The SWEAT Study (Sedentary Women Exercise Adherence Trial). *Br.J.Health Psychol.* 2003;**8**:477-95.

344. Rippe JM, Ward A, Porcari JP, Freedson PS. Walking for health and fitness. *JAMA* 1988;**259**:2720-4.

345. Asikainen TM, Miilunpalo S, Oja P, Rinne M, Pasanen M, Vuori I. Walking trials in postmenopausal women: effect of one vs two daily bouts on aerobic fitness. *Scand.J.Med.Sci.Sports* 2002;**12**:99-105.

346. Jakicic JM, Wing RR, Butler BA, Robertson RJ. Prescribing exercise in multiple short bouts versus one continuous bout: effects on adherence, cardiorespiratory fitness, and weight loss in overweight women. *Int.J.Obes.Relat Metab Disord.* 1995;**19**:893-901.

347. Coleman KJ, Raynor HR, Mueller DM, Cerny FJ, Dorn JM, Epstein LH. Providing sedentary adults with choices for meeting their walking goals. *Prev.Med.* 1999;**28**:510-9.

348. Murphy M, Nevill A, Neville C, Biddle S , Hardman A. Accumulating brisk walking for fitness, cardiovascular risk, and psychological health. *Med.Sci.Sports Exerc.* 2002;**34**:1468-74.

349. King AC, Haskell WL, Taylor CB, Kraemer HC, DeBusk RF. Group- vs home-based exercise training in healthy older men and women. A community-based clinical trial. *JAMA* 1991;**266**:1535-42.

350. Brown MA, Goldstein-Shirley J, Robinson J, Casey S. The effects of a multi-modal intervention trial of light, exercise, and vitamins on women's mood. *Women Health* 2001;**34**:93-112.

351. Morgan WP. Affective beneficence of vigorous physical activity. *Med.Sci.Sports Exerc.* 1985;**17**:94-100.

352. Petruzzello SJ, Landers DM, Hatfield BD, Kubitz KA, Salazar W. A meta-analysis on the anxiety-reducing effects of acute and chronic exercise. Outcomes and mechanisms. *Sports Med.* 1991;**11**:143-82.

353. Schwarz L,.Kindermann W. Beta-endorphin, adrenocorticotropic hormone, cortisol and catecholamines during aerobic and anaerobic exercise. *Eur.J.Appl.Physiol Occup.Physiol* 1990;**61**:165-71.

354. Dunn AL,.Dishman RK. Exercise and the neurobiology of depression. *Exerc.Sport Sci.Rev.* 1991;**19**:41-98.

355. Brosse AL, Sheets ES, Lett HS, Blumenthal JA. Exercise and the treatment of clinical depression in adults: recent findings and future directions. *Sports Med.* 2002;**32**:741-60.

356. Boutcher SH,.Landers DM. The effects of vigorous exercise on anxiety, heart rate, and alpha activity of runners and nonrunners. *Psychophysiology* 1988;**25**:696-702.

357. Hatfield BD,.Landers DM. Psychophysiology in exercise and sport research: an overview. *Exerc.Sport Sci.Rev.* 1987;**15**:351-87.

358. Stewart AL, Hays RD, Ware JE, Jr. The MOS short-form general health survey. Reliability and validity in a patient population. *Med.Care* 1988;**26**:724-35.

359. Marquis P, Fayol C, Joire JE. Clinical validation of a quality of life questionnaire in angina pectoris patients. *Eur.Heart J.* 1995;**16**:1554-60.

360. Watson EK, Firman DW, Baade PD, Ring I. Telephone administration of the SF-36 health survey: validation studies and population norms for adults in Queensland. *Aust.N.Z.J.Public Health* 1996;**20**:359-63.

361. Mosca L, Grundy SM, Judelson D, King K, Limacher M, Oparil S *et al.* Guide to Preventive Cardiology for Women. *Circulation* 1999;**99**:2480-4.

362. Horgan J, Bethell H, Carson P, Davidson C, Julian D, Mayou RA *et al.* Working party report on cardiac rehabilitation. *Br.Heart J.* 1992;**67**:412-8.

363. Lear SA,.Ignaszewski A. Cardiac rehabilitation: a comprehensive review. *Curr.Control Trials Cardiovasc.Med.* 2001;**2**:221-32.

364. Rehabilitation of patients with cardiovascular disease: Report of the WHO expert committee. 270. 1964. World Health Organisation. WHO Technical Report Series.

365. National service framework for Coronary Heart Disease. 2000. London, DoH London.

366. Hevey D, Brown A, Cahill A, Newton H, Kierns M, Horgan JH. Four-week multidisciplinary cardiac rehabilitation produces similar improvements in exercise capacity and quality of life to a 10-week program. *J.Cardiopulm.Rehabil.* 2003;**23**:17-21.

367. Campbell NC, Grimshaw JM, Rawles JM, Ritchie LD. Cardiac rehabilitation in Scotland: is current provision satisfactory? *J.Public Health Med.* 1996;**18**:478-80.

368. Jolly K, Lip GY, Sandercock J, Greenfield SM, Raftery JP, Mant J *et al.* Home-based versus hospital-based cardiac rehabilitation after myocardial infarction or revascularisation: design and rationale of the Birmingham Rehabilitation Uptake Maximisation Study (BRUM): a randomised controlled trial [ISRCTN72884263]. *BMC.Cardiovasc.Disord.* 2003;**3**:10.

369. Kugler J, Dimsdale JE, Hartley LH, Sherwood J. Hospital supervised vs home exercise in cardiac rehabilitation: effects on aerobic fitness, anxiety, and depression. *Arch.Phys.Med.Rehabil.* 1990;**71**:322-5.

370. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K *et al.* Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am.J.Med.* 2004;**116**:682-92.

371. Linden W. Psychological treatments in cardiac rehabilitation: review of rationales and outcomes. *J.Psychosom.Res.* 2000;**48**:443-54.

372. Turner SC, Bethell HJ, Evans JA, Goddard JR, Mullee MA. Patient characteristics and outcomes of cardiac rehabilitation. *J.Cardiopulm.Rehabil.* 2002;**22**:253-60.

373. O'Callaghan WG, Teo KK, O'Riordan J, Webb H, Dolphin T, Horgan JH. Comparative response of male and female patients with coronary artery disease to exercise rehabilitation. *Eur.Heart J.* 1984;**5**:649-51.

374. Marchionni N, Fattirolli F, Fumagalli S, Oldridge N, Del Lungo F, Morosi L *et al.* Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial infarction: results of a randomized, controlled trial. *Circulation* 2003;**107**:2201-6.

375. Dugmore LD, Tipson RJ, Phillips MH, Flint EJ, Stentiford NH, Bone MF *et al.* Changes in cardiorespiratory fitness, psychological wellbeing, quality of life, and vocational status following a 12 month cardiac exercise rehabilitation programme. *Heart* 1999;**81**:359-66.

376. Shephard RJ,.Franklin B. Changes in the quality of life: a major goal of cardiac rehabilitation. *J.Cardiopulm.Rehabil.* 2001;**21**:189-200.

377. Rafanelli C, Roncuzzi R, Finos L, Tossani E, Tomba E, Mangelli L *et al.* Psychological assessment in cardiac rehabilitation. *Psychother.Psychosom.* 2003;**72**:343-9.

378. Cossette S, Frasure-Smith N, Lesperance F. Clinical implications of a reduction in psychological distress on cardiac prognosis in patients participating in a psychosocial intervention program. *Psychosom.Med.* 2001;**63**:257-66.

379. Johnston M, Foulkes J, Johnston DW, Pollard B, Gudmundsdottir H. Impact on patients and partners of inpatient and extended cardiac counseling and rehabilitation: a controlled trial. *Psychosom.Med.* 1999;**61**:225-33.

380. Parent N,.Fortin F. A randomized, controlled trial of vicarious experience through peer support for male first-time cardiac surgery patients: impact on anxiety, self-efficacy expectation, and self-reported activity. *Heart Lung* 2000;**29**:389-400.

381. Lavie CJ,.Milani RV. Prevalence of anxiety in coronary patients with improvement following cardiac rehabilitation and exercise training. *Am.J.Cardiol.* 2004;**93**:336-9.

382. Lavie CV,.Milani RV. Impact of aging on hostility in coronary patients and effects of cardiac rehabilitation and exercise training in elderly persons. *Am.J.Geriatr.Cardiol.* 2004;**13**:125-30.

383. Maines TY, Lavie CJ, Milani RV, Cassidy MM, Gilliland YE, Murgo JP. Effects of cardiac rehabilitation and exercise programs on exercise capacity, coronary risk factors, behavior, and quality of life in patients with coronary artery disease. *South.Med.J.* 1997;**90**:43-9.

384. Milani RV, Lavie CJ, Cassidy MM. Effects of cardiac rehabilitation and exercise training programs on depression in patients after major coronary events. *Am.Heart J.* 1996;**132**:726-32.

385. Milani RV,.Lavie CJ. Prevalence and effects of cardiac rehabilitation on depression in the elderly with coronary heart disease. *Am.J.Cardiol.* 1998;**81**:1233-6.

386. Dracup K, Moser DK, Marsden C, Taylor SE, Guzy PM. Effects of a multidimensional cardiopulmonary rehabilitation program on psychosocial function. *Am.J.Cardiol.* 1991;**68**:31-4.

387. Lavie CJ,.Milani RV. Effects of cardiac rehabilitation, exercise training, and weight reduction on exercise capacity, coronary risk factors, behavioral characteristics, and quality of life in obese coronary patients. *Am.J.Cardiol.* 1997;**79**:397-401.

388. Seki E, Watanabe Y, Sunayama S, Iwama Y , Shimada K, Kawakami K *et al.* Effects of phase III cardiac rehabilitation programs on health-related quality of life in elderly patients with coronary artery disease: Juntendo Cardiac Rehabilitation Program (J-CARP). *Circ.J.* 2003;**67**:73-7.

389. Izawa K, Hirano Y, Yamada S, Oka K, Omiya K, Iijima S. Improvement in physiological outcomes and health-related quality of life following cardiac rehabilitation in patients with acute myocardial infarction. *Circ.J.* 2004;**68**:315-20.

390. Oldridge N, Gottlieb M, Guyatt G, Jones N, Streiner D, Feeny D. Predictors of health-related quality of life with cardiac rehabilitation after acute myocardial infarction. *J.Cardiopulm.Rehabil.* 1998;**18**:95-103.

391. McKelvie RS, Teo KK, Roberts R, McCartney N, Humen D, Montague T *et al.* Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). *Am.Heart J.* 2002;**144**:23-30.

392. Hawkes AL, Nowak M, Speare R. Short Form-36 Health Survey as an evaluation tool for cardiac rehabilitation programs: is it appropriate? *J.Cardiopulm.Rehabil.* 2003;**23**:22-5.

393. Oldridge N. Assessing health-related quality of life: is it important when evaluation the effectiveness of cardiac rehabilitation? *J.Cardiopulm.Rehabil.* 2003;**23**:26-8.

394. O'Rourke A, Lewin B, Whitecross S, Pacey W. The effects of physical exercise training and cardiac education on levels of anxiety and depression in the rehabilitation of coronary artery bypass graft patients. *Int.Disabil.Stud.* 1990;**12**:104-6.

395. O'Farrel P, Murray J, Huston P, LeGrand C, Adamo K. Sex differences in cardiac rehabilitation. *Can.J.Cardiol.* 2000;**16**:319-25.

396. Lavie CJ, Milani RV, Cassidy MM, Gilliland YE. Effects of cardiac rehabilitation and exercise training programs in women with depression. *Am.J.Cardiol.* 1999;**83**:1480-3, A7.

397. Kennedy MD, Haykowsky M, Daub B, Van Lohuizen K, Knapik G, Black B. Effects of a comprehensive cardiac rehabilitation program on quality of life and exercise tolerance in women: A retrospective analysis. *Curr.Control Trials Cardiovasc.Med.* 2003;**4**:1.

398. Lavie CJ,.Milani RV. Benefits of cardiac rehabilitation and exercise training in elderly women. *Am.J.Cardiol.* 1997;**79**:664-6.

399. Lavie CJ,.Milani RV. Effects of cardiac rehabilitation and exercise training programs in patients > or = 75 years of age. *Am.J.Cardiol.* 1996;**78**:675-7.

400. Allen JK, Becker DM, Swank RT. Factors related to functional status after coronary artery bypass surgery. *Heart Lung* 1990;**19**:337-43.

401. Moore SM, Ruland CM, Pashkow FJ, Blackburn GG. Women's patterns of exercise following cardiac rehabilitation. *Nurs.Res.* 1998;**47**:318-24.

402. Moore SM, Dolansky MA, Ruland CM, Pashkow FJ, Blackburn GG. Predictors of women's exercise maintenance after cardiac rehabilitation. *J.Cardiopulm.Rehabil.* 2003;**23**:40-9.

403. Blanchard CM, Rodgers WM, Courneya KS, Daub B, Black B. Self-efficacy and mood in cardiac rehabilitation: should gender be considered? *Behav.Med.* 2002;**27**:149-60.

404. King KM, Humen DP, Smith HL, Phan CL, Teo KK. Psychosocial components of cardiac recovery and rehabilitation attendance. *Heart* 2001;**85**:290-4.

405. Turner SC, Evans JA, Bethell HJ, Goddard J. Psychological assessments for cardiac rehabilitation patients. *Int.J.Cardiol.* 2003;**92**:201-7.

406. Clarke DE, Walker JR, Cuddy TE. The role of perceived overprotectiveness in recovery 3 months after myocardial infarction. *J.Cardiopulm.Rehabil.* 1996;**16**:372-7.

407. Younger J, Marsh KJ, Grap MJ. The relationship of health locus of control and cardiac rehabilitation to mastery of illness-related stress. *J.Adv.Nurs.* 1995;**22**:294-9.

408. Singh SJ, Morgan MD, Scott S, Walters D , Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992;**47**:1019-24.

409. Eifert GH, Thompson RN, Zvolensky MJ, Edwards K, Frazer NL, Haddad JW *et al.* The cardiac anxiety questionnaire: development and preliminary validity. *Behav.Res.Ther.* 2000;**38**:1039-53.

410. Brown K. A review to examine the use of SF-36 in cardiac rehabilitation. *Br.J.Nurs.* 2003;**12**:904-9.

411. Altman D. Practical Statistics for Medical Research. London: Chapman and Hall, 1991.

412. Fillingim RB,.Edwards RR. The association of hormone replacement therapy with experimental pain responses in postmenopausal women. *Pain* 2001;**92**:229-34.

413. Oldridge N, Streiner D, Hoffmann R, Guyatt G. Profile of mood states and cardiac rehabilitation after acute myocardial infarction. *Med.Sci.Sports Exerc.* 1995;**27**:900-5.

414. Carhart RL, Jr.,.Ades PA. Gender differences in cardiac rehabilitation. *Cardiol.Clin.* 1998;**16**:37-43.

415. Gilbody SM, House AO, Sheldon TA. Routinely administered questionnaires for depression and anxiety: systematic review. *BMJ* 2001;**322**:406-9.

416. Kanji N. Autogenic Training. Complementary Therapies in Medicine 5, 162-167. 1997.

417. Kanji N, White AR, Ernst E. Autogenic training reduces anxiety after coronary angioplasty: a randomized clinical trial. *Am.Heart J.* 2004;**147**:E10.

9: Appendices

Appendix A: Study One informed consent documents for all three study populations.

Royal Brompton & Harefield NHS Trust & National Heart and Lung Institute

FORM OF CONSENT *ADULT PATIENT*

TITLE OF PROJECT:

Depression, health anxiety and oestrogen levels in patients with Syndrome X.

EXPLANATION OF PROJECT:

We would like to invite you to participate in the above study. 20% of patients who have chest pain and an angiogram (an x-ray of the heart) are found have no blockages in the arteries of their heart (coronary arteries), and the majority of these patients are women. This commonly referred to as Syndrome X. Most women who suffer from Syndrome X are postmenopausal or have low oestrogen levels. We would like to see whether there is a link between oestrogen levels and anxiety and depression in women suffering from Syndrome X, and compared with women who have furring up of their coronary arteries (coronary artery disease) and women who suffer from neither. We would also like to investigate whether the amount of social support (from friends and family) and number of other life events (such as illness, bereavement etc) affects the likelihood of suffering from Syndrome X.

You will be asked to fill in 4 questionnaires which will measure your levels of anxiety and depression, along with your quality of life. You will also be asked to fill in other questions concerning your family background and domestic circumstances, along with questions about your medical history. These questionnaires will take no longer than 30 minutes to complete. Please answer all the questions. The answers you give will only be used for the purpose of this study and will held in the strictest confidence. We will inform your GP of your participation in this study if you wish.

A 7 ml blood sample (approximately 1 tablespoonful) will be taken for measurement of your oestrogen level. No HIV or genetic tests will be performed. The blood samples will then be distroyed. Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected.

Signed by the person in charge of the Project _____ Date _____

The Ethics Committee of the Royal Brompton & Harefield NHS Trust/National Heart & Lung Institute has approved the above statement.
Signed by the Chairman/Representative of the Committee _____ Date _____

DOCTOR'S DECLARATION

I have explained the project to the Participant as outlined above in the presence/absence* of a Witness**

Signed _____ Date _____ Time _____

* delete as appropriate **every effort should be made to give the explanation in the presence of witness

Royal Brompton & Harefield NHS Trust & National Heart and Lung Institute

FORM OF CONSENT *ADULT VOLUNTEER*

TITLE OF PROJECT:

Depression, health anxiety and oestrogen levels in patients with Syndrome X.

EXPLANATION OF PROJECT:

We would like to invite you to participate in the above study. 20% of patients who have chest pain and an angiogram (an x-ray of the heart) are found have no blockages in the arteries of their heart (coronary arteries), and the majority of these patients are women. This commonly referred to as Syndrome X. Most women who suffer from Syndrome X are postmenopausal or have low oestrogen levels. We would like to see whether there is a link between oestrogen levels and anxiety and depression in women suffering from Syndrome X, and compared with women who have furring up of their coronary arteries (coronary artery disease) and women who suffer from neither. We would also like to investigate whether the amount of social support (from friends and family) and number of other life events (such as illness, bereavement etc) affects the likelihood of suffering from Syndrome X.

As a person who suffers from neither Syndrome X or coronary artery disease, we would like you to participate so that we can compare answers given by healthy people to those of patients who suffer with the above heart conditions. You will be asked to fill in 4 questionnaires which will measure your levels of anxiety and depression, along with your quality of life. You will also be asked to fill in other questions concerning your family background and domestic circumstances, along with questions about your medical history. These questionnaires will take no longer than 30 minutes to complete. Please answer all the questions. The answers you give will only be used for the purpose of this study and will held in the strictest confidence. We will inform your GP of your participation in this study if you wish. A 7 ml blood sample (approximately 1 tablespoonful) will be taken for measurement of your oestrogen level. No HIV or genetic tests will be performed. The blood samples will then be distroyed. Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected.

Signed by the person in charge of the Project _____ Date _____

The Ethics Committee of the Royal Brompton & Harefield NHS Trust/National Heart & Lung Institute has approved the above statement.
Signed by the Chairman/Representative of the Committee_____ Date _____

DOCTOR'S DECLARATION

I have explained the project to the Participant as outlined above in the presence/absence* of a Witness**

Signed _____ Date _____ Time _____

NOTES FOR PATIENTS

1. Please do not hesitate to ask the Doctor any questions you may have about this project before you decide whether you wish to participate.
2. If you decide, now or at any other stage, that you no longer wish to participate in the project, this will not in any way prejudice your future treatment.
3. If you decide to take part in this project, you will be given a copy of this form for your information.

FORM OF CONSENT

(for use by adult patients undergoing investigations connected with clinical research)

I, _____ of _____

_____

give my consent to undergo the research procedures described overleaf. The nature, purpose and possible consequences have been fully explained to me.

Signed _____ Date_____

** **WITNESS** (See Note 1)

I am satisfied that the procedures have been fully explained to the Patient. The Patient has given consent in my presence.

Name of Witness _____ Position _____

Address_____

Signed _____ Date _____

1. **WITNESS: Wherever possible, a witness should be present whilst the doctor/sponsor explains the procedures to the patient. If this is impractical, complete the "Doctor's Declaration" accordingly. In the case of a patient, the witness should not be a doctor if the sponsor is a doctor. If the witness is a nurse, he or she must be a ward sister or senior nurse in charge of the ward who is not undertaking a post-basic course.
2. SAFE-KEEPING OF THIS FORM: In the case of a patient, a copy of this signed form must be kept in the patients case-notes, and the sponsor should retain a copy for subsequent examination if required by the Ethics Committee.

Appendix B: Study One Syndrome X patient information sheet.

Patient Information Sheet

We would like to invite you to participate in the above study. 20% of patients who have chest pain and an angiogram (an x-ray of the heart) are found have no blockages in the arteries of their heart (coronary arteries), and the majority of these patients are women. This is commonly referred to as Syndrome X. Most women who suffer from Syndrome X are postmenopausal or have low oestrogen levels. We would like to see whether there is a link between oestrogen levels and anxiety and depression in women suffering from Syndrome X, compared with women who have furring up of their coronary arteries (coronary artery disease) and women who suffer from neither. We would also like to investigate whether the amount of social support (from friends and family) and number of other life events (such as illness, bereavement etc) affects the likelihood of suffering from Syndrome X.

You will be asked to fill in 4 questionnaires which will measure your levels of anxiety and depression, along with your quality of life. You will also be asked to complete other questions concerning your family background and domestic circumstances, along with questions about your medical history. These questionnaires will take no longer than 30 minutes to complete. Please answer all the questions. The answers you give will only be used for the purpose of this study and will held in the strictest confidence. We will inform your GP of your participation in this study if you wish.

A 7 ml blood sample (approximately 1 tablespoonful) will be taken for measurement of your oestrogen level. No HIV or genetic tests will be performed. The blood samples will then be destroyed.

Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected.

Appendix C: Study One CHD patient information sheet.

The Hearts and Minds Study

CHD Patient Information Sheet

We would like to invite you to participate in the above study. 20% of patients who have chest pain and an angiogram (an x-ray of the heart) are found have no blockages in the arteries of their heart (coronary arteries), and the majority of these patients are women. This commonly referred to as Syndrome X. Most women who suffer from Syndrome X are postmenopausal or have low oestrogen levels. We would like to see whether there is a link between oestrogen levels and anxiety and depression in women suffering from Syndrome X, and compared with women who have furring up of their coronary arteries (coronary artery disease) and women who suffer from neither. We would also like to investigate whether the amount of social support (from friends and family) and number of other life events (such as illness, bereavement etc) affects the likelihood of suffering from Syndrome X.

As a person who suffers from coronary artery disease, we would like you to participate so that we can compare your answers to those of patients who suffer with Syndrome X. You will be asked to fill in 4 questionnaires which will measure your levels of anxiety and depression, along with your quality of life. You will also be asked to fill in other questions concerning your family background and domestic circumstances, along with questions about your medical history. These questionnaires will take no longer than 30 minutes to complete. Please answer all the questions. The answers you give will only be used for the purpose of this study and will held in the strictest confidence. We will inform your GP of your participation in this study if you wish.

A 7 ml blood sample (approximately 1 tablespoonful) will be taken for measurement of your oestrogen level. No HIV or genetic tests will be performed. The blood samples will then be distroyed.

Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected.

Appendix D: Study One participant eligibility questionnaire.

The Hearts and Minds Study

Name:

Address:

Date of Birth:

When was your last menstrual period (age or year)?.....

Do you suffer from Syndrome X? Yes / No / Unknown

Have you ever had a heart attack? Yes / No / Unknown

Do you suffer from high blood pressure? Yes / No / Unknown

Do you suffer from high cholesterol? Yes / No / Unknown

Have you ever suffered from angina? Yes / No / Unknown

If yes, how many times per week? .....

Do you suffer from any medical conditions? Yes / No / Unknown

If yes, please indicate below:

.....

.....

.....

Which afternoons are the most convenient for a research appointment (please circle all that apply):

Monday Tuesday Wednesday Thursday Friday

Please return your completed form in the envelope provided.

Thank you!

Appendix E: Study One healthy control group information sheet.

The Hearts and Minds Study

Volunteer Information Sheet

We would like to invite you to participate in the above study. 20% of patients who have chest pain and an angiogram (an x-ray of the heart) are found have no blockages in the arteries of their heart (coronary arteries), and the majority of these patients are women. This commonly referred to as Syndrome X. Most women who suffer from Syndrome X are postmenopausal or have low oestrogen levels. We would like to see whether there is a link between oestrogen levels and anxiety and depression in women suffering from Syndrome X, and compared with women who have furring up of their coronary arteries (coronary artery disease) and women who suffer from neither. We would also like to investigate whether the amount of social support (from friends and family) and number of other life events (such as illness, bereavement etc) affects the likelihood of suffering from Syndrome X.

As a person who suffers from neither Syndrome X nor coronary artery disease, we would like you to participate so that we can compare answers given by healthy people to those of patients who suffer with the above heart conditions. You will be asked to fill in 4 questionnaires which will measure your levels of anxiety and depression, along with your quality of life. You will also be asked to fill in other questions concerning your family background and domestic circumstances, along with questions about your medical history. These questionnaires will take no longer than 30 minutes to complete. Please answer all the questions. The answers you give will only be used for the purpose of this study and will held in the strictest confidence. We will inform your GP of your participation in this study if you wish.

A 7 ml blood sample (approximately 1 tablespoonful) will be taken for measurement o f your o estrogen l evel. No HIV or genetic tests will be performed. The blood samples will then be distroyed.

Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected.

Appendix F: The additional questions relating to the chest pain patients and normal volunteers participating in Study One.

Date of Birth:

When was your last menstrual period (age or year)?.....

Do you still have your womb? Yes / No / Unknown

If no, how old were you when you had a hysterectomy?.....

Do you still have you ovaries? Yes / No / Unknown

If no, how old were you when you had them removed?.....

Are you currently taking HRT? Yes / No / Unknown

If yes, for how long?.....

Do you suffer from high blood pressure? Yes / No / Unknown

Do you suffer from high cholesterol? Yes / No / Unknown

Have you ever had a heart attack? Yes / No / Unknown

Have you ever suffered from Angina? Yes / No / Unknown

If yes, for how long?.....

Do you smoke? Yes / No How many per day?.....

Have you ever undergone any of the following procedures:

Treadmill ECG test	Yes / No / Unknown	Date:.....
Cardiac echo / ultrasound	Yes / No / Unknown	Date:.....
Thallium scan	Yes / No / Unknown	Date:.....
Angiogram	Yes / No / Unknown	Date:.....
Angioplasty	Yes / No / Unknown	Date:.....
Bypass surgery	Yes / No / Unknown	Date:.....

Have you ever been admitted to hospital? If yes, please list the reason and the year of admission (or your age at the time of admission):

.....

.....

.....

.....

Please list below any medical conditions you currently suffer from, along with the date the conditions began:

.....

.....

.....

.....

.....

.....

.....

Please list below any medications you are currently taking along with the date you began taking them:

.....

.....

.....

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.....

.....

.....

Has anyone in your family ever suffered from heart disease or a heart attack? If so, please indicate your relationship to them and the age at they became ill:

.....

.....

.....

.....

.....

.....

Date of Birth:

When was your last menstrual period (age or year)?.....

Do you still have your womb? Yes / No / Unknown

If no, how old were you when you had a hysterectomy?.....

Do you still have you ovaries? Yes / No / Unknown

If no, how old were you when you had them removed?.....

Are you currently taking HRT? Yes / No / Unknown

If yes, for how long?.....

Do you suffer from high blood pressure? Yes / No / Unknown

Do you suffer from high cholesterol? Yes / No / Unknown

Have you ever suffered from Angina? Yes / No / Unknown

Do you smoke? Yes / No How many per day?.....

Have you ever been admitted to hospital? If yes, please list the reason and the year of admission (or your age at the time of admission):

.....

.....

.....

.....

Please list below any medical conditions you currently suffer from, along with the date the conditions began:

.....

.....

.....

.....

Please list below any medications you are currently taking along with the date you began taking them:

.....

.....

.....

Has anyone in your family ever suffered from heart disease or a heart attack? If so, please indicate your relationship to them and the age at they became ill:

.....

.....

.....

Appendix G: The Health Anxiety Questionnaire.

Please answer **ALL** the questions, circling **ONE** response for each question.

1. Do you ever worry about your health?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

2. Are you ever worried that you might get a serious illness in the future?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

3. Does the thought of serious illness scare you?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

4. When you notice an unpleasant feeling in your body, do you tend to find it difficult to think of anything else?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

5. Do you ever examine your body to find whether there is something wrong?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

6. If you have an ache or pain do you worry that it might be caused by a serious illness?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

7. Do you ever find it difficult to keep worries about your health out of your mind?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

8. When you notice an unpleasant feeling in your body, do you worry about it?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

9. When you wake up in the morning do you find you very soon begin to worry about your health?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

10. When you hear of a serious illness or the death of someone you know, does it ever make you more concerned about your own health?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

11. When you read or hear about an illness on TV or radio does it ever make you think you may be suffering from that illness?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

12. When you experience unpleasant feelings in your body, do you tend to ask friends and family about them?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

13. Do you tend to read up about illness and disease to see if you may be suffering from one?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

14. Do you ever feel afraid of new which reminds you of death (such as funerals, obituary notices)?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

15. Do you ever feel afraid that you may die soon?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

16. Do you ever feel afraid that you may have cancer?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

17. Do you ever feel afraid that you may have heart disease?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

18. Do you ever feel afraid that you may have any other serious illness?

If so, which one?.....

19. Have your bodily symptoms stopped you from working during the past 6 months or so?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

20. Do your bodily symptoms stop you from concentrating on what you are doing?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

21. Do your bodily symptoms stop you from enjoying yourself?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

22. When you experience unpleasant feelings in your body, do you ever worry that it might be caused by a serious illness?
a) Not at all or rarely
b) Sometimes
c) Often
d) Most of the time

Appendix H: The Hospital Anxiety and Depression Scale.

Please answer **ALL** the questions, circling **ONE** response for each question.

I feel tense or 'wound up':
a) Most of the time
b) A lot of the time
c) From time to time, occasionally
d) Not at all

I still enjoy the things I used to enjoy:
a) Definitely as much
b) Not quite so much
c) Only a little
d) Hardly at all

I get a sort of frightened feeling as if something awful is about to happen:
a) Very definitely and quite badly
b) Yes, but not too badly
c) A little, but it doesn't worry me
d) Not at all

I can laugh and see the funny side of things:
a) As much as I always could
b) Not quite so much now
c) Definitely not so much now
d) Not at all.

Worrying thoughts go through my mind:
a) A great deal of the time
b) A lot of the time
c) From time to time but not too often
d) Only occasionally

I feel cheerful
a) Not at all
b) Not often
c) Sometimes
d) Most of the time

I can sit at ease and feel relaxed
a) Definitely
b) Usually
c) Not often
d) Not at all

I feel as if I am slowed down
a) Nearly all the time
b) Very Often
c) Sometimes
d) Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach:
a) Not at all
b) Occasionally
c) Quite often
d) Very often

I have lost interest in my appearance:
a) Definitely
b) I don't take as much care as I should
c) I may not take quite as much care
d) I take as much care as ever

I feel restless as if I have to be on the move:
a) Very much indeed
b) Quite a lot
c) Not very much
d) Not at all

I look forward with enjoyment to things:
a) As much as I ever did
b) Rather less than I used to
c) Definitely less than I used to
d) Hardly at all

I get sudden feelings of panic
a) Very often indeed
b) Quite often
c) Not very often
d) Not at all

I can enjoy a good book, radio or TV programme:
a) Often
b) Sometimes
c) Not often
d) Very seldom

Appendix I: The List of Threatening Experiences.

We would like to ask you some questions about personal situations that you may have encountered since you have become concerned about your heart. Although some of these things are personal and of a sensitive nature, it would help a great deal if you would answer them. Please answer **ALL** the questions.

Since you first became concerned about your heart have you experienced any of the following:

1. Serious illness or injury to yourself?	Yes / No
2. Serious illness or injury to a close relative?	Yes / No
3. The death of s first-degree relative, including a child or spouse?	Yes / No
4. The death of a close family friend or second degree relative?	Yes / No
5. Separation due to marital difficulties?	Yes / No
6. Broken off a steady relationship?	Yes / No
7. A serious problem with a close friend, neighbour or relative?	Yes / No
8. Been unemployed / seeking work for more than one month?	Yes / No
9. Been sacked from your job?	Yes / No
10. A major financial crisis?	Yes / No
11. Problems with the police and court appearances?	Yes / No
12. Had something valuable lost or stolen?	Yes / No

Appendix J: Demographic Information Scale.

Please answer **ALL** the questions

Have you ever been (please circle as many as apply to you): Married
Separated
Divorced
Widowed
Single

How many people live with you? Please give details below

Relationship (i.e. husband, sister) Occupation / School

.....
.....
.....
.....
.....

Are you in contact with other relatives? How often? Please list below:

Relative (i.e. aunts, grandchildren)	**In contact by telephone (i.e. once a week)**	**Visiting (i.e. once a week)**

Can you tell us about any friends or acquaintances you see regularly, including neighbours or workmates? Please list them below, giving an indication of how often you are in touch with them.

Relationship (ie friend, neighbour)	**In contact by telephone (i.e. once a week)**	**Visiting (i.e. once a week)**

If you had a problem of some sort, who would be the first person you would want to discuss it with?

.....

How often are you in contact with this person?.....

Appendix K: Study Two Informed Consent Document.

Royal Brompton & Harefield NHS Trust & National Heart and Lung Institute

FORM OFCONSENT *ADULT VOLUNTEER*

TITLE OF PROJECT:

The Psychological Effect of Exercise Training in Postmenopausal Women.

EXPLANATION OF PROJECT:

We would like to invite you to participate in the above study. Exercise has been shown to have a beneficial effect on mood and quality of life in many groups of people, from the very young to the very old, healthy and infirm. However, few studies have been performed which look at the impact of exercise on the psychological health of postmenopausal women.

As you have consented to participate in the study entitled: Effect Of Exercise Training On Cardiovascular Risk Factors And Endothelium-Dependent Vasomotion In Postmenopausal Women under the care of Dr Pornpat Chandrruangphen, we would like to invite you to participate in our study which will explore the psychological effect of the exercise program you will be undertaking. You will be asked to complete a collection of 5 questionnaires, 3 times over the course of the study, which will measure your levels of anxiety, depression and quality of life. You will complete the first collection of questionnaires when you consent to take part in the study, when you will also be asked about your medical history and domestic circumstances. The questionnaires will be administered for a second time when you have completed the 6 weeks of exercise as instructed by Dr Chandrruangphen, and for a third time 6 weeks after you have completed the exercise program. The questionnaires will take no longer than 30 minutes to complete on each occasion. The answers you give will be anonymised and held in the strictest confidence.

Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected. Your participation in Dr Chandrruangphens study entitle: Effect Of Exercise Training On Cardiovascular Risk Factors And Endothelium-Dependent Vasomotion In Postmenopausal Women will also be unaffected. We will inform your GP of your participation in this study if you wish.

Signed by the person in charge of the Project _____ Date _____

The Ethics Committee of the Royal Brompton & Harefield NHS Trust/National Heart & Lung Institute has approved the above statement.
Signed by the Chairman/Representative of the Committee_____ Date _____

DOCTOR'S DECLARATION

I have explained the project to the Participant as outlined above in the presence/absence* of a Witness**

Signed _____ Date _____ Time _____

* delete as appropriate **every effort should be made to give the explanation in the presence of witness

Appendix L: The SF-36 Quality of Life Scale.

This survey asks for your views about your health. This information will help us keep track of how you feel and how well you are able to do your usual activities.

Please answer **every question** by marking the answer as indicated you are unsure about how to answer a question, give the best answer you can.

1. In general would you say your health is:

	(circle one)
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Compared to **one year ago,** how would you rate your health in general now?

	(circle one)
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same as one year ago	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

Activities	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
Moderate activities, such as moving a table, pushing a vacuum cleaner or playing golf	1	2	3
Lifting or carrying groceries	1	2	3
Climbing several flights of stairs	1	2	3
Climbing one flight of stairs	1	2	3
Bending, kneeling or stooping	1	2	3
Walking more than a mile	1	2	3
Walking half a mile	1	2	3
Walking one hundred yards	1	2	3
Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	Yes	No
Cut down on the amount of time you spend on work or other activities	1	2
Accomplish less than you would like	1	2
Were limited in the kind of work or other activities	1	2
Had difficulty performing work or other activities (for example, it took extra effort)	1	2

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	Yes	No
Cut down on the amount of time you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Didn't do work or other activities as carefully as usual	1	2

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with friends, family, neighbours or groups?

(circle one)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during **the past 4 weeks**?

(circle one)

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

	(circle one)
Not a bit.....	1
A little bit.....	2
Moderately.....	3
Quite a bit.....	4
Extremely.....	5

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes the closest to the way you have been feeling.

   How much of the time during the **past 4 weeks** –

(circle one number on each line)

	All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
Did you feel full of life?	1	2	3	4	5	6
Have you bee a very nervous person?	1	2	3	4	5	6
Have you felt so down in the dumps that nothing could cheer you?	1	2	3	4	5	6
Have you felt calm and peaceful?	1	2	3	4	5	6
Did you have a lot of energy?	1	2	3	4	5	6
Have you felt downhearted and low?	1	2	3	4	5	6
Did you feel worn out?	1	2	3	4	5	6
Have you been a happy person?	1	2	3	4	5	6
Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?

	(circle one)
All of the time.....	1
Most of the time.....	2
Some of the time.....	3
A little of the time.....	4
None of the time.....	5

11. How TRUE or FALSE is each of the following statements for you?

(circle one number on each line)

	Definitely true	**Mostly true**	**Don't know**	**Mostly false**	**Definitely false**
I seem to get ill more easily than other people	1	2	3	4	5
I am as healthy as anybody I know	1	2	3	4	5
I expect my health to get worse	1	2	3	4	5
My health is excellent	1	2	3	4	5

Appendix M: The additional questions asked of volunteers participating in Study Two.

Date of birth.....Age.....
What is/was your occupation?.....
What is/was your husbands occupation (if applicable)? .....
.....

When was your last menstrual period (age or year)?.....
Do you still have your womb? Yes / No / Unknown
If no, how old were you when you had a hysterectomy?.....

Why did you have a hysterectomy?.....
.....
Do you still have you ovaries? Yes / No / Unknown
If no, how old were you when you had them removed?.....

When you went through the menopause, did you experience any of the following symptoms? If yes, please indicate the severity of your symptoms:

	None	Mild	Moderate	Severe
Hot flushes				
Night sweats				
Heat intolerance				
Sleep disturbance				
Vaginal dryness				
Mood swings				
Periods of low mood, the 'blues'				
Loss of concentration				

Did you attend a menopause clinic or gynaecologist for advice or information relating to your menopausal symptoms? Yes / No / Unknown

Are you currently taking HRT? Yes / No / Unknown
If yes, for how long?.....
If no, have you ever taken HRT, and for how long?.....
.....
What is/was the name of your HRT?.....

Do you smoke? Yes / No How many per day?.....

Do you currently partake in exercise? Yes / No
If yes, please describe the exercise you do and how often you do it:.....
.....
.....
.....

Have you ever been admitted to hospital? If yes, please list the reason and the year of admission (or your age at the time of admission):

.....
.....
.....
.....
.....
.....
.....

Please list below any medical conditions you currently suffer from, along with the date the conditions began:

.....
.....
.....
.....
.....
.....
.....

Please list below any medications you are currently taking along with the date you began taking them:

.....
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.....
.....

Appendix N: Study Three Informed Consent Document.

Royal Brompton & Harefield NHS Trust & National Heart and Lung Institute

FORM OF CONSENT *ADULT PATIENT*

TITLE OF PROJECT:

Angina Frequency, Psychological Morbidity and Quality of Life in Women with Syndrome X.

EXPLANATION OF PROJECT:

We would like to invite you to participate in the above study. 20% of patients who have chest pain and an angiogram (an x-ray of the heart) are found have no blockages in the arteries of their heart (coronary arteries), and the majority of these patients are women. This is commonly referred to as Syndrome X. Most women who suffer from Syndrome X suffer frequent chest pain and as a result, we have found that they have higher levels of health worry and anxiety. This often means that patients with Syndrome X have an impaired quality of life.

Cardiac rehabilitation is currently offered to patients with heart disease or who have had a heart transplant, as it has been shown to improve fitness, reduce the frequency and severity of chest-pain and improve quality of life. As a patient who suffers from Syndrome X, we would like to invite you to participate in our study which will evaluate the effectiveness of cardiac rehabilitation as a new treatment for Syndrome X.

If you agree to participate in the study, you will be asked to complete four questionnaires that will measure your levels of anxiety and depression, along with your quality of life. You will also be asked to fill in other questions concerning your medical history and domestic circumstances. You will then be randomly assigned to 8 weeks of twice weekly cardiac rehabilitation classes based at the Harefield Hospital or 8 weeks of symptom monitoring to act as a control group. The control group will be used as a comparison group to assess whether or not patients symptoms, quality of life or psychological health is affected by cardiac rehabilitation. You will have an equal chance of being assigned to either group. Throughout the 8 weeks of cardiac rehabilitation or symptom monitoring you will be asked to complete a daily angina, physical activity and symptom diary. You will be guided through a sample day of the diary before you begin the study to help you complete it accurately.

If you are assigned to the rehabilitation group, you will undergo an assessment by a physiotherapist at Harefield who will establish your level of fitness and symptom severity. This will enable the classes and level of activity to be tailor made to your ability. The hour and a half long classes will be made up of cardiovascular exercises, such as using an exercise bike, active rest periods, stretches and relaxation. You will take part in the general rehabilitation classes, which are made up of patients suffering from all kinds of heart conditions, fitness levels and abilities. Following the 8 weeks of rehabilitation you will be asked to repeat the pre-rehabilitation assessment to measure any improvement in your physical fitness and level of ability.

If you are assigned to the symptom monitoring group, you will be asked to carry on your everyday life as normal. You should not increase the amount of exercise you do during this time. At the completion of the study you will be able to participate in a cardiac rehabilitation program should you wish to.

You will then be asked to return to the Brompton for a further visit to return your diary and repeat the questionnaires you completed during your first visit. 8 weeks after this appointment, you will be sent a further set of identical questionnaires in order to assess any long term impact of cardiac rehabilitation, which you should complete at home and return by post.

The questionnaires will take no longer than 30 minutes to complete. The answers you give will be held in the strictest confidence and only used for the purposes of this study. Performing any form of exercise increases your risk of exercise related injury, such as sprains. However, every effort will be made to minimise any risk of injury through constant supervision while exercising. Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected. We will inform your GP of your participation in this study if you wish.

Signed by the person in charge of the Project _____ Date _____

The Ethics Committee of the Royal Brompton & Harefield NHS Trust/National Heart & Lung Institute has approved the above statement.
Signed by the Chairman/Representative of the Committee_____ Date _____

DOCTOR'S DECLARATION

I have explained the project to the Participant as outlined above in the presence/absence* of a Witness**

Signed _____ Date _____ Time _____

* delete as appropriate **every effort should be made to give the explanation in the presence of witness

Appendix O: Study Three Informed Consent Document – Active Patients.

Royal Brompton & Harefield NHS Trust & National Heart and Lung Institute

FORM OF CONSENT *ADULT PATIENTS ACTIVE*

TITLE OF PROJECT:

Angina Frequency, Psychological Morbidity and Quality of Life in Women with Syndrome X.

EXPLANATION OF PROJECT:

We would like to invite you to participate in the above study. 20% of patients who have chest pain and an angiogram (an x-ray of the heart) are found have no blockages in the arteries of their heart (coronary arteries), and the majority of these patients are women. This is commonly referred to as Syndrome X. Most women who suffer from Syndrome X suffer frequent chest pain and as a result, we have found that they have higher levels of health worry and anxiety. This often means that patients with Syndrome X have an impaired quality of life.

As a patient with Syndrome X who currently takes part in more than 2 periods of planned exercise per week, we would like to invite you to participate in our study which will explore the affect of exercise on the physical and psychological health of women with Syndrome X. If you agree to participate in the study, you will be asked to complete four questionnaires that will measure your levels of anxiety and depression, along with your quality of life. You will also be asked to fill in other questions concerning your medical history and domestic circumstances. We would like to compare your responses with those of Syndrome X patients who take no regular exercise. Patients who take no planned exercise will also be randomly assigned to 8 weeks of twice weekly cardiac rehabilitation classes based at the Harefield Hospital or 8 weeks of symptom monitoring, in order to evaluate the effectiveness of exercise as a new treatment for Syndrome X.

The study will take place during a single study visit at the Royal Brompton Hospital. The questionnaires will take no longer than 30 minutes to complete. The answers you give will be held in the strictest confidence and only used for the purposes of this study. Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected. We will inform your GP of your participation in this study if you wish.

Signed by the person in charge of the Project _____ Date _____

The Ethics Committee of the Royal Brompton & Harefield NHS Trust/National Heart & Lung Institute has approved the above statement.
Signed by the Chairman/Representative of the Committee_____ Date _____

DOCTOR'S DECLARATION
I have explained the project to the Participant as outlined above in the presence/absence* of a Witness**

Signed _____ Date _____ Time _____

Appendix P: Study Three symptom monitoring diary.

Syndrome X

Cardiac Rehabilitation Study

Symptom Severity Scale:

1 = Mild symptoms

2 = Discomforting symptoms

3 = Distressing symptoms

4 = Horrible symptoms

5 = Excruciating symptoms

Symptom Diary Example:

Monday….. Symptom and time:……Severity……. ……Severity……. ……Severity…….
Tuesday….. Symptom and time:……Severity……. ……Severity……. ……Severity…….
Wednesday…… Symptom and time:……Severity……. ……Severity……. ……Severity…….

Week 1:

Monday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Tuesday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Wednesday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Thursday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Friday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Saturday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Sunday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....

Week 8:

Monday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Tuesday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Wednesday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Thursday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Friday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Saturday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....
Sunday..... Symptom and time:.....Severity..... .....Severity..... .....Severity.....

Appendix Q: Study Three patient information sheet.

Angina Frequency, Quality of Life and Cardiac Rehabilitation in Women with Syndrome X.

EXPLANATION OF PROJECT:

We would like to invite you to participate in the above study. 20% of patients who have chest pain and an angiogram (an x-ray of the heart) are found have no blockages in the arteries of their heart (coronary arteries), and the majority of these patients are women. This is commonly referred to as Syndrome X. Most women who suffer from Syndrome X suffer frequent chest pain and as a result, we have found that they have higher levels of health worry and anxiety. This often means that patients with Syndrome X have an impaired quality of life.

Cardiac rehabilitation is currently offered to patients with heart disease or who have had a heart transplant, as it has been shown to improve fitness, reduce the frequency and severity of chest-pain and improve quality of life. As a patient who suffers from Syndrome X, we would like to invite you to participate in our study which will evaluate the effectiveness of cardiac rehabilitation as a new treatment for Syndrome X.

If you agree to participate in the study, you will be asked to complete four questionnaires that will measure your levels of anxiety and depression, along with your quality of life. You will also be asked to fill in other questions concerning your medical history and domestic circumstances. You will then be randomly assigned to 8 weeks of once weekly cardiac rehabilitation classes based at the Harefield Hospital or 8 weeks of symptom monitoring to act as a control group. The control group will be used as a comparison group to assess whether or not patients symptoms, quality of life or psychological health is affected by cardiac rehabilitation. You will have an equal chance of being assigned to either group. Throughout the 8 weeks of cardiac rehabilitation or symptom monitoring you will be asked to complete a daily angina, physical activity and symptom diary. You will be guided through a sample day of the diary before you begin the study to help you complete it accurately.

If you are assigned to the rehabilitation group, you will undergo an assessment by a physiotherapist at Harefield who will establish your level of fitness and symptom severity. This will enable the classes and level of activity to be tailor made to your ability. The hour and a half long classes will be made up of cardiovascular exercises, such as using an exercise bike, active rest periods, stretches and relaxation. You will take part in the general rehabilitation classes, which are made up of patients suffering from all kinds of heart conditions, fitness levels and abilities. Following the 8 weeks of rehabilitation you will be asked to repeat the pre-rehabilitation assessment to measure any improvement in your physical fitness and level of ability.

If you are assigned to the symptom-monitoring group, you will be asked to carry on your everyday life as normal. You should not increase the amount of exercise you do during this time. At the completion of the study you will be able to participate in a cardiac rehabilitation program should you wish to.

You will then be asked to return to the Brompton for a further visit to return your diary and repeat the questionnaires you completed during your first visit. 8 weeks after this appointment, you will be sent a further set of identical questionnaires in order to assess any long term impact of cardiac rehabilitation, which you should complete at home and return by post.

The questionnaires will take no longer than 30 minutes to complete. The answers you give will be held in the strictest confidence and only used for the purposes of this study. Performing any form of exercise increases your risk of exercise related injury, such as sprains. However, every effort will be made to minimise any risk of injury through constant supervision while exercising. Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected. We will inform your GP of your participation in this study if you wish.

Appendix R: Study Three participant eligiblity questionnaire.

Cardiac Rehabilitation and Syndrome X

Name:

Address: **Phone:**

Date of Birth:

Do you suffer from Syndrome X? Yes / No / Unknown

Do you suffer from angina or chest discomfort / tightness? Yes / No / Unknown

If yes, how many times per week? .....

Do you suffer from any medical conditions that prevent you from exercising? Yes / No / Unknown

If yes, please give details:.....

.....

How long can you walk at an average pace without having to stop for a rest (minutes / hours)?.....

.....

How far can you walk in that time (yards / miles)?.....

.....

How long do you walk for on an average day (minutes / hours)?.....

.....

Are you currently taking part in an exercise program, e.g. swimming, keep-fit class, etc? Yes / No

If yes, please state the type of exercise, how many times per week you take part and how long each session lasts:.....

.....

.....

Are you currently taking part in any other research? Yes / No

Please return your completed form in the freepost envelope provided.

Thank you!

Appendix S: Study Three patient information sheet - Active.

Angina Frequency, Quality of Life and Cardiac Rehabilitation in Women with Syndrome X – Active Patients.

EXPLANATION OF PROJECT:

We would like to invite you to participate in the above study. 20% of patients who have chest pain and an angiogram (an x-ray of the heart) are found have no blockages in the arteries of their heart (coronary arteries), and the majority of these patients are women. This is commonly referred to as Syndrome X. Most women who suffer from Syndrome X suffer frequent chest pain and as a result, we have found that they have higher levels of health worry and anxiety. This often means that patients with Syndrome X have an impaired quality of life.

As a patient with Syndrome X who currently takes part in more than 2 periods of planned exercise per week, we would like to invite you to participate in our study which will explore the affect of exercise on the physical and psychological health of women with Syndrome X. If you agree to participate in the study, you will be asked to complete four questionnaires that will measure your levels of anxiety and depression, along with your quality of life. You will also be asked to fill in other questions concerning your medical history and domestic circumstances. We would like to compare your responses with those of Syndrome X patients who take no regular exercise. Patients who take no planned exercise will also be randomly assigned to 8 weeks of twice weekly cardiac rehabilitation classes based at the Harefield Hospital or 8 weeks of symptom monitoring, in order to evaluate the effectiveness of exercise as a new treatment for Syndrome X.

The study will take place during a single study visit at the Royal Brompton Hospital. The questionnaires will take no longer than 30 minutes to complete. The answers you give will be held in the strictest confidence and only used for the purposes of this study. Please understand that you need not take part in this study if you do not wish to. If you do take part, you may withdraw at any time, and need give no reason for doing so. If you choose not to take part, or if you withdraw, your normal care and treatment will be unaffected. We will inform your GP of your participation in this study if you wish.

Appendix T: Cardiac Anxiety Questionnaire.

Please answer **ALL** the questions, circling **ONE** response for each question.

	Never	Rarely	Some-times	Often	Always
I pay attention to my heart beat	0	1	2	3	4
I avoid physical exertion	0	1	2	3	4
My racing heart wakes me up at night	0	1	2	3	4
Chest pain/discomfort wakes me up at night	0	1	2	3	4
I take it easy as much as possible	0	1	2	3	4
I check my pulse	0	1	2	3	4
I avoid exercise or other physical work	0	1	2	3	4
I can feel my heart in my chest	0	1	2	3	4
I avoid activities that make my heart beat faster	0	1	2	3	4
If a test comes out normal, I still worry about my heart	0	1	2	3	4
I feel safe being around a hospital, doctor or other medical facility	0	1	2	3	4
I avoid activities that make me sweat	0	1	2	3	4
I worry that doctors do not believe my symptoms are real	0	1	2	3	4

When I have chest discomfort or when my heart is beating fast:

	Never	Rarely	Some-times	Often	Always
I worry that you may have a heart attack	0	1	2	3	4
I have difficulty concentrating on anything else	0	1	2	3	4
I get frightened	0	1	2	3	4
I like to be checked out by a doctor	0	1	2	3	4
I tell my family or friends	0	1	2	3	4

Appendix U: The additional questions asked of Cardiac Syndrome X patients participating in Study Three.

Date of birth.....Age.....
What is/was your occupation?.....
What is/was your husbands occupation (if applicable)? .....
.....

Do you suffer from high blood pressure? Yes / No / Unknown
Do you suffer from high cholesterol? Yes / No / Unknown
Have you ever suffered from Angina (chest pain / tightness)? Yes / No / Unknown
If yes, for how long?.....
If yes, how many times a week?.....
When were you diagnosed with Syndrome X?.....

When was your last menstrual period (age or year)?.....
Do you still have your womb? Yes / No / Unknown
If no, how old were you when you had a hysterectomy?.....

Why did you have a hysterectomy?.....
.....
Do you still have you ovaries? Yes / No / Unknown
If no, how old were you when you had them removed?.....

When you went through the menopause, did you experience any of the following symptoms? If yes, please indicate the severity of your symptoms:

	None	**Mild**	**Moderate**	**Severe**
Hot flushes				
Night sweats				
Heat intolerance				
Sleep disturbance				
Vaginal dryness				
Mood swings				
Periods of low mood, the 'blues'				
Loss of concentration				

Did you attend a menopause clinic or gynaecologist for advice or information relating to your menopausal symptoms? Yes / No / Unknown

Are you currently taking HRT? Yes / No / Unknown
If yes, for how long?.....
If no, have you ever taken HRT, and for how long?.....
.....
What is/was the name of your HRT?.....
Do you smoke? Yes / No How many per day?.....

Do you currently partake in exercise? Yes / No
If yes, please describe the exercise you do and how often you do it:.....
.....
.....
.....
.....

Have you ever been admitted to hospital? If yes, please list the reason and the year of admission (or your age at the time of admission):
.....
.....
.....
.....
.....

Please list below any medical conditions you currently suffer from, along with the date the conditions began:
.....
.....
.....
.....
.....
.....

Please list below any medications you are currently taking along with the date you began taking them:
.....
.....
.....
.....
.....
.....

Has anyone in your family ever suffered from heart disease or a heart attack? If so, please indicate your relationship to them and the age at they became ill:
.....
.....
.....

10: Publications

European Heart Journal (2004) 25, 1695–1701

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Clinical research

Distinct psychosocial differences between women with coronary heart disease and cardiac syndrome X☆

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KEYWORDS
Syndrome X;
Coronary heart disease;
Women;
Psychology

Aims To compare the impact of oestrogen, gynaecological history, social support, life events and family history of CHD on psychosocial morbidity in syndrome X, CHD patients and healthy controls.

Methods and Results 100 female syndrome X (60 ± 9 years), 100 female CHD (65 ± 9 years) and 100 healthy female volunteers (61 ± 10 years) completed the hospital anxiety and depression scale (HADS), health anxiety questionnaire (HAQ), a demographic information scale, life events scale, family history of CHD, menopausal, menstrual and gynaecological history. A 17β-oestradiol sample was taken. Syndrome X patients had higher levels of life interference ($p < 0.05$) and HADS anxiety ($p < 0.05$) than CHD patients, and higher levels of all HADS and HAQ scales than controls ($p < 0.01$). Syndrome X patients with a large social network had lower HADS anxiety ($p < 0.05$), health worry ($p < 0.05$), life interference ($p < 0.01$) and total HAQ ($p < 0.01$). Social network ($p = 0.003$), divorced/separated or widowed status ($p = 0.005$), HRT ($p = 0.008$) and HADS anxiety score ($p < 0.001$) accounted for 41.9% of the variance in HAQ scores in syndrome X. Oestrogen was unrelated to the HADS or HAQ for any group.

Conclusion Syndrome X patients suffered higher levels of psychological morbidity in comparison to CHD patients and controls. Life events and social network size were related to health anxiety, general anxiety and depression in women with syndrome X.
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Introduction

In spite of an excellent prognosis, cardiac syndrome X is associated with debilitating symptomology, ineffective therapeutic interventions and a poor quality of life. First termed cardiac syndrome X by Kemp,[1] the triad of angina pectoris, a positive exercise test for myocardial

☆ The study was undertaken at the Department of Cardiac Medicine, National Heart and Lung Institute, Imperial College London.

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ischaemia and angiographically smooth coronary arteries continues to perplex clinicians.

At the present time, there is no common agreement on the exact cause of the symptoms associated with syndrome X. Suggested mechanisms include coronary microvascular dysfunction ('microvascular angina'),[2] perfusion abnormalities,[3] a generalised disorder of vascular function,[4] hormonal irregularities,[5] early signs of abnormal left ventricular function,[6] insulin resistance,[7] or abnormal visceral pain perception.[8] It has also been suggested that at the time of angiography, patients with syndrome X have 'sensitive hearts'[9] while a central, rather than peripheral, locus for the pain sensation has also been proposed.[10] What is recognised however, is the disabling affect of the symptoms that rob patients of their quality of life.

Cardiac syndrome X occurs most commonly, but not exclusively, in postmenopausal women which has led many to question the role of ovarian hormones in the pathogenesis of the condition. Preliminary investigations have identified a possible link between the development of syndrome X and oestrogen deficiency,[5] while 17β-oestradiol reduced angina frequency[11] and esterified oestrogen improved quality of life in postmenopausal women with syndrome X.[12] Suggested mechanistic pathways include its role as a vasodilator[13] and as an analgesic pertaining to an increased pain sensitivity in women.[14]

Although syndrome X is most commonly found in postmenopausal women, no rigorous, large-scale psychosocial studies have focussed on this population. Psychosocial investigations using the full diagnostic criteria for syndrome X are limited, as previous studies have included a wide range of patients with non-cardiac chest pain. Such samples include patients without angiography,[15] without a positive exercise test for myocardial ischaemia[16] or with abnormal or partially occluded coronary arteries.[17,18] Imipramine, an analgesic with independent antidepressant effect, has been shown to reduce chest pain symptoms in patients with normal or near normal coronary arteries,[19] while physical symptom have been associated with psychiatric morbidity in patients with non-cardiac chest pain.[20] Studies using the full diagnostic criteria are limited by their relatively small sample size, but have suggested higher levels of neuroticism and anxiety in syndrome X than confirmed coronary disease,[21] which may be related to psychosocial factors.[22] Others have found that relaxation and stress reduction lead to fewer incidence of chest pain in syndrome X patients.[23] However, the same is also true for patients with CHD[24] along with many other conditions and disorders with related chronic pain.[25] Previous studies have not examined a lack of social support, recent life events and family history of heart disease as possible reasons for increased anxiety in syndrome X patients.

Therefore, we hypothesised that women with syndrome X would have higher levels of general anxiety, depression and greater worry about their health than both CHD patients and healthy controls, and that a family history of CHD, reduced social support, experience of stressful life events, oestrogen depletion and gynaecological history could account for this. In order to test this hypothesis, we enrolled a large group of female syndrome X patients and compared them to age-matched female CHD patients and healthy controls.

Methods

Consecutive female syndrome X patients aged <80 years with chest pain, positive exercise test for myocardial ischaemia and angiographically smooth coronary arteries were recruited from the Women's Heart Clinic at the Royal Brompton & Harefield NHS Trust, a specialised clinic for syndrome X patients. Age-matched female coronary heart disease (CHD) patients aged <80 years with angiographically proven disease (>50% stenosis in one or more major coronary arteries) including angioplasty, coronary artery bypass grafting and myocardial infarction were recruited from the Outpatients Department at the Royal Brompton & Harefield NHS Trust. CHD patients were also taken from the recent cardiac catheterisation lists and approached to participate by mail. Female age-matched healthy volunteers with no previous history of chronic illness were recruited from the nursing and ancillary staff of the Royal Brompton & Harefield NHS Trust and from associated women's groups. CHD patients and controls were recruited from a population within the age-range of the syndrome X patients. All participants gave written informed consent using the consent form approved by the Royal Brompton & Harefield NHS Trust Ethics Committee.

All study visits took place in a quiet, private room where the project was fully explained and any questions answered. The participants were then guided through, and asked to complete, a number of questionnaires (see Experimental measures) which the participants either completed in the clinic or took home and returned by post. Participants were requested to complete the questionnaires alone. Questionnaires were made anonymous by using identification numbers and kept confidentially. Patients also gave a blood sample, which was analysed for 17β-oestradiol, measured by standard radioimmunoassay (Abbott IMX System, Abbott Diagnostics, Berkshire, UK).

Experimental measures

The health anxiety questionnaire[26] (HAQ) is comprised of four sub-scales, which measures health worry and preoccupation, fear of illness and death, reassurance-seeking behaviour and interference with life. Developed and validated in medical, psychiatric and healthy volunteers, the 22 questions have a four-point Likert scale response format.

The hospital anxiety and depression scale[27] (HADS) measures clinically significant anxiety and depression in general medical patients. The 14-item questionnaire is split into two sub-scales (anxiety and depression) using a four-point Likert scales response format, with a score of 11 or more on either scale described as clinically significant anxiety or depression. The scale does not include somatic items (e.g., pain), which may result from physical illness. It has been validated with both outpatients and inpatients, and is used extensively in studies with non-psychiatric clinical populations.

The list of threatening experiences[28] is a widely used list of 12 life events which have been shown to have a marked or moderated effect on psychological well-being. Each of the 12 experience questions has a yes/no response format, the total number of events were recorded and classified into three groups: no events, one or two events and three or more events.

A demographic information scale[29] was used to assess social support and isolation by recording the patients living circumstances, frequency of contact with friends and relatives and size of social network.

Additionally, participants were asked to complete questions regarding their menopausal status, menstrual and gynaecological history, including details of hormone therapy, hysterectomy and last menstrual period, along with any known family history of CHD, their current medications and previous life-long hospitalisations pertaining to their heart or general admission. Hospital admissions for childbirth were disregarded.

Statistics

The data were analysed using Pearson's correlation co-efficient, *t*-tests, ANOVA and Tukey *post hoc* tests; overall comparisons of categorical data were performed using Chi-square. Data that did not fulfil the requirements for parametric testing were analysed using the Mann–Whitney test. Statistical significance level was set at $p < 0.05$. The study was performed as an independent-subjects design, using two-tailed tests. *Post hoc* tests were used only following a significant main effect, thus reducing the chance of Type I errors. Data are expressed as means ± SD unless otherwise stated. The first set of analyses compared the three groups of subjects; syndrome X, CHD and healthy controls. The second set of analyses included only the syndrome X patients and sought to identify the social and medical variables that were associated with anxiety, depression and health anxiety scores. The sample size is based on previous large-scale studies of patients with syndrome X[30] and non-cardiac chest pain.[15]

Multiple regression analysis with mean substitution for missing variables was used to identify the variables most closely associated with health anxiety in syndrome X patients. The total HAQ score was the dependent variable; this was normally distributed as assessed by histogram. The following were entered as independent variables: age, marital status (as two dummy variables), the use of HRT, history of hysterectomy, oestrogen level, size of social network (large or small), family history of coronary heart disease under the age of 60 years and number of life events (as 0, 1 –2, 3+), HADS anxiety score and HADS depression score. Constant variance of the residuals was assessed by inspecting the normal probability plots which fitted a straight line. The linearity assumption was assessed for anxiety and depression scores by examining the quadratic relationship; there was negligible difference in R^2 between linear and quadratic equations. The results for the final model are shown in Table 3.

Results

Demographics

100 Female syndrome X patients (60 ± 9 years), 100 female CHD patients (65 ± 9 years) and 100 healthy age-matched female volunteers (61 ± 10 years) participated in the study. No syndrome X or CHD patient refused to participate in the project. Age of onset for syndrome X patients (54 ± 8 years) was significantly younger than for CHD patients (60 ± 9 years) ($p < 0.001$). However, there was no significant difference in duration of chest pain between the syndrome X (6 ± 5 years) and CHD (5 ± 5 years) patients. Seventy-two percent of syndrome X patients were married or living as married, in comparison with 60% of CHD patients and healthy volunteers (ns).

Hospital anxiety and depression scale

Syndrome X patients recorded significantly higher anxiety scores (7.17 ± 3.9) than both CHD patients (5.9 ± 3.7, $p < 0.05$) and healthy controls (4.9 ± 3.1, $p < 0.01$). Syndrome X and CHD patients both had higher depression scores (5.0 ± 3.2 and 4.9 ± 3.5, respectively) than the healthy controls (2.8 ± 2.2, $p < 0.01$). Clinical levels of anxiety (>11) were found in 16% of syndrome X patients compared with 10% of CHD patients and 5% of healthy controls ($p < 0.05$). Similar number of syndrome X and CHD patients had clinical levels of depression (9% and 7%, respectively) while no subject in the control group was clinically depressed.

Health anxiety questionnaire

Both syndrome X and CHD patients had higher total HAQ scores than controls ($p < 0.01$) (Table 1). Syndrome X and CHD patients had significantly higher scores than healthy controls on the scales measuring health worry and preoccupation ($p < 0.001$), fear of illness ($p < 0.01$) and life interference ($p < 0.001$). Syndrome X patients had significantly higher scores than the CHD patients on the interference with life scale ($p < 0.05$).

Family history of CHD

Sixty-six percent of syndrome X patients reported some family history of CHD, compared to 65% of CHD patients and 48% of controls ($p < 0.05$). Thirty-four percent of both the CHD and syndrome X patient groups reported a sibling or parent with CHD before the age of 60 compared to 9% of controls ($p < 0.001$). No measure of family history of CHD was significantly associated with HADS anxiety or depression or HAQ health anxiety scores for any group.

Social contact

Data regarding patients' social network were split into two categories: patients who reported having no friends or a small social network (six or fewer friends) and patients with a large social network (seven or more friends). There were no differences between syndrome X, CHD patients and healthy controls in the size of social network (56%, 55% and 47%, respectively with a small social network, $p = 0.42$). No differences were found between the three groups in the frequency of contact with friends, either by phone or in person.

Syndrome X patients who reported a small social network (six or fewer friends) had significantly higher levels of HADS depression ($p < 0.05$), HAQ health worry ($p < 0.01$), interference with life ($p < 0.01$) and total HAQ score ($p < 0.01$) than those who reported a large social network (Fig. 1). CHD patients with a small social

Table 1 The median and interquartile range of the health anxiety questionnaire (HAQ) sub-scales for all three groups

	Health worry	Fear of illness	Reassurance-seeking	Interference with life	Total HAQ score
Syndrome X	5.0 (4)	4.0 (3)	1.0 (2)	3.0 (3)	13.5 (10)
CHD	4.0 (5)	4.0 (4)	1.0 (2)	2.5 (3)*	14.0 (11)
Control	3.0 (4)**,***	3.0 (3)**,***	1.0 (2)	1.0 (1)**,***	8.0 (9)**,***

Data are expressed as median (interquartile range).
* $p = <0.05$ compared with syndrome X.
** $p = <0.01$ compared with syndrome X.
*** $p = <0.01$ compared with CHD.

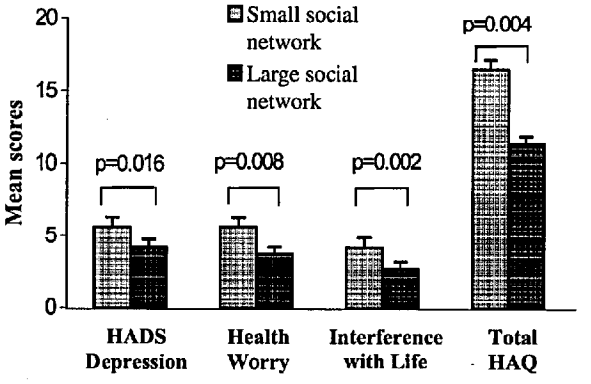


Fig. 1 The effect of social network size on the HADS and HAQ scores of syndrome X patients.

network also had higher levels of HADS depression (5.2 ± 3.4 vs. 3.8 ± 3.5, $p < 0.05$) and interference with life (3.5 ± 2.5 vs. 2.1 ± 2.1, $p < 0.01$) than those with a large social network. There were no differences in the HADS or HAQ scores of control group on the basis of their social network. Number or frequency of contact with relatives, either by telephone or visiting was unrelated to sub-scales of the HADS and HAQ for any group.

Life events

There was no significant difference between the number of life events (expressed as none, one to two and three or more,) experienced by syndrome X, CHD patients and controls. Syndrome X patients who reported three or more stressful life events had higher general anxiety (8.8 ± 4.6 vs. 5.7 ± 2.9 and 6.6 ± 3.2, $p < 0.01$), reassurance-seeking (1.72 ± 1.4 vs. 0.8 ± 0.8 and 1.25 ± 0.9, $p < 0.01$) and total HAQ score (17.1 ± 10.7 vs. 11.7 ± 5.6 and 12.7 ± 7.3, $p < 0.05$), while CHD patients who reported three or more life events had higher general anxiety (6.9 ± 3.8 vs. 5.7 ± 3.7 and 3.2 ± 2.1, $p < 0.01$), depression (5.5 ± 3.6 vs. 4.4 ± 3.3 and 2.8 ± 3.3, $p < 0.05$) and total HAQ score (15.9 ± 8.1 vs. 13.3 ± 7.5 and 10.1 ± 6.7, $p < 0.05$). No differences were found among the controls.

Gynaecological factors

Forty-five percent of syndrome X patients had undergone hysterectomy in comparison with 39% of CHD patients and 24% of controls ($p < 0.01$). Sixty-seven percent of syndrome X patients were prescribed hormone replacement therapy compared to 29% each of CHD patients and controls ($p < 0.001$). No difference in the number of patients having undergone oophorectomy was found. Syndrome X and CHD patients experienced their last menstrual period (LMP) at a significantly younger age than controls ($p < 0.001$), however, there was no difference in the age at hysterectomy between the three groups. A history of hysterectomy or current HRT use had no effect on the various scales of the HADS or HAQ for any group.

Oestrogen plasma levels

The independent laboratory range for oestrogen was lowered from a minimum detectable level of <37 to <18 pmol/l during the study. Therefore, patients whose level was found to be less than <37 pmol/l were re-coded as 36 pmol/l for the purpose of standardizing the analysis. 17β-oestradiol samples were not recorded for 2% of syndrome X patients, 12% of CHD patients and 6% of controls due to laboratory or phlebotomy difficulties.

Syndrome X patients had higher 17β-oestradiol levels (199.9 ± 218.3 pmol/l) than CHD patients (112.2 ± 168.2 pmol/l) and controls (137 ± 190.3 pmol/l, $p < 0.01$). However, there were no differences in the levels of plasma oestrogen of the syndrome X, CHD patients or healthy controls when the three groups were compared on the basis of HRT use. Oestrogen level was unrelated to any measure of the HADS or HAQ for any of the three groups. The number of years elapsed since the last menstrual period was also unrelated to either measure within the HADS or HAQ for any group.

Medications, hospitalisations and illness

Syndrome X patients underwent their first cardiac admission at a significantly younger age (51.8 ± 11.2 years) than CHD patients (59.9 ± 10.1 years, $p < 0.001$), whereas CHD patients had a greater number of cardiac admissions (1.6 ± 1.28) than patients with syndrome X (0.85 ± 1.28, $p < 0.001$). There were no differences between the three groups concerning number of non-cardiac admissions. Syndrome X patients took fewer cardiovascular medications (2.1 ± 1.7) than CHD patients (4.21 ± 4.9, $p < 0.001$), while CHD patients took more non-cardiovascular medications than patients with syndrome X

Table 2 Percentage of patients with concomitant medical conditions and cardiovascular risk factors

	Syndrome X (%)	CHD (%)	Controls (%)	Significance
Current smokers	11	11	15	0.630
Hypertension	33	58	25	0.001
Hypercholesterolaemia	26	68	9	0.001
Respiratory	17	14	11	0.474
Gastric/abdominal	20	16	14	0.511
Neurological	15	7	7	0.087
Endocrinological	16	32	4	0.001
Musculoskeletal	33	29	23	0.287
Other	17	16	13	0.716

($p < 0.05$) and healthy controls ($p < 0.001$). The prevalence of cardiovascular risk factors and concomitant illness in all three groups is illustrated in Table 2.

Multivariable analysis

The second part of our hypothesis concerned the possible reasons for high levels of health anxiety in syndrome X patients. In the multiple regression analysis, a small social network ($p = 0.003$), divorced/separated or widowed status ($p = 0.005$), not taking Hormone Replacement Therapy ($p = 0.008$) and a high HADS anxiety score ($p < 0.001$) emerged as the variables independently associated with health anxiety score. They accounted for 41.9% of the variance (Table 3).

Discussion

In this carefully matched study, syndrome X patients had significantly higher levels of anxiety and felt their health interfered more with their everyday lives than CHD patients and controls. Both syndrome X and CHD patients had much higher levels of health anxiety and were significantly more depressed than controls, suggesting a greater concern about their respective illnesses. However, the higher level of general anxiety (as measured by the HADS) found in syndrome X patients cannot be accounted for by the presence of chest pain, as patients in the CHD and syndrome X groups suffered similar symptoms. This is an important new finding, as previous studies have attributed higher levels of anxiety in patients with non-cardiac chest pain to the anxiety and depression associated with all chronic medical conditions.[31]

Syndrome X patients had a similar sized social network with a similar frequency of contact as CHD patients and healthy controls. However, syndrome X patients who reported having a large social network were significantly less anxious and depressed, and had lower levels of health related anxiety than those who reported having a small social network. The size of social network had less impact on measures of health related anxiety in CHD patients, and no effect on the psychological health of controls. It therefore appears that a larger support network moderates the levels of depression and health anxiety experienced by patients with syndrome X. Both syndrome X and CHD patients were adversely affected by threatening life events, experiencing increased health anxiety when exposed to three or more life events. However, depression was linked to life events in women with CHD, whereas reassurance was related to life events in women with syndrome X. This may reflect previous research linking depression and CHD,[32] while highlighting the relationship between syndrome X patients and reassurance-seeking behaviour.

Both CHD and syndrome X patients had a similar number of first degree relatives who had developed CHD

Table 3 Results of multiple regression analysis showing the variables most closely associated with total health anxiety questionnaire (HAQ) score

	Non-standardised β co-efficient	Standard error	Standardised co-efficient	Significance
Constant	2.193	3.266		0.50
Age	−0.022	0.035	0.058	0.52
Single	2.010	1.492	0.115	0.18
Divorced, widowed, separated	−1.980	0.694	−0.246	0.005
Hormone replacement therapy	1.654	0.694	0.224	0.019
Oestrogen level	−0.001	0.001	−0.036	0.69
Hysterectomy	−0.238	0.638	−0.034	0.71
Social network size	−0.956	0.308	−0.276	0.003
Stressful life events	0.599	0.397	0.131	0.13
Family history of coronary heart disease in person (<60 years)	−0.165	0.621	−0.023	0.79
Anxiety score	0.349	0.086	0.396	<0.001
Depression score	0.104	0.106	0.097	0.33

before the age of 60, but a strong positive family history of CHD was unrelated to psychological morbidity in any group. Eifert et al.,[33] suggested that direct exposure to heart disease is more likely in patients with chest pain and angiographically smooth coronary arteries than heart disease patients or normal controls, whereas our study identified an almost identical pattern of family history of CHD in the syndrome X and CHD patients. A strong positive family history of CHD may be relevant in the physiological development of syndrome X, but appears to have little effect on the psychological health of the three groups under investigation in this study.

Our study confirms the finding that postmenopausal women with syndrome X have a higher incidence of hysterectomy.[5] Previous studies have reported an average hysterectomy prevalence of 17.4% in British women aged 40–80 years[34] and of 13.6% in a British urban community sample.[35] The higher frequency of hysterectomy found in healthy volunteers in this study (24%) may reflect regional variation, as previous large-scale studies have noted countrywide differences in HRT use and hysterectomy.[36] The greater number of syndrome X patients prescribed HRT may reflect the impact of previous studies advocating the use of HRT as a treatment regime in syndrome X,[11] as the frequency of HRT use in the CHD and control group (29%) reflects the previously documented national average (33%).[36] Hysterectomy and HRT use was unrelated to depression or general anxiety in patients with syndrome X. In the multivariable analysis, not taking HRT was associated with increased health anxiety, though this result must be treated with caution as the univariate result was only at a borderline level of significance ($p = 0.055$). Recent studies such as women's health initiative (WHI)[37] and heart and estrogen/progestin replacement study (HERS)[38] have raised serious concerns regarding the safety of HRT. The administration of HRT and its role for symptomatic relief should therefore be under review.

Evidence to support the suggested oestrogen depletion in syndrome X patients was not found. Oestrogen depletion may be a factor in the development of syndrome X, and therefore a sample taken at the time of diagnosis may be a more accurate marker of possible cause. As our sample only included patients who had been diagnosed with syndrome X for more than one year, this was outside the remit of the current study. An exploration of menopausal symptomology and reason for hysterectomy in women with syndrome X is also worthy of further study.

Syndrome X patients were on average eight years younger than CHD patients at the time of diagnosis, a finding which reflects in the general age disparity between the syndrome X and CHD patients. While every care was taken to age-match the groups as closely as possible, due to the differences in aetiology and age at onset in the two conditions, exact age-matching was not possible. We did not find age was related to levels of anxiety, depression or health anxiety, so this slight age discrepancy cannot explain our findings.

This study has drawn attention to a number of psychosocial factors which should be addressed in order to manage and treat patients with cardiac syndrome X more effectively. As syndrome X patients with small social networks suffer higher levels of psychological morbidity, future research should target treatments involving social interaction, such as support groups and group therapy. Many patients report increased pain frequency and severity during periods of stress, including the cumulative effect of a number of adverse life events, suggesting that a programme of stress identification, management and reduction may also play an important role in the treatment of syndrome X. Research into transcendental meditation and cognitive behavioural therapy should be extended in order to assess their effectiveness and reliability as psychological treatments for syndrome X, as previous small-scale studies have gained positive results.[16,23,39]

Our findings may also impact upon research into the modification of illness behaviour through the adjustment of health beliefs, a strategy which has had little success in patients with syndrome X.[40] Leventhal et al.,[41] described a number of factors they believed predicted illness behaviour, and while health beliefs were noted, social factors such as social support, modelling behaviour and heritability were all implicated in the formation of health behaviours. It could be argued therefore, that the social environment identified in the current study should be incorporated into any future studies relating to the modification illness behaviours in syndrome X, including the adjustment of health beliefs.

Study limitations

The cross-sectional design, sample selection methods used and self-response questionnaire format used during this study may be identified as limiting factors. The limitations of our chosen questionnaires were recognised, along with those of others previously used in similar research, but were implemented as the most appropriate for the study. The control group and a number of the CHD patients were recruited into the study on the basis of their response to a request for volunteers, which may have resulted in selection bias on the basis of previous psychological morbidity or increased health awareness. In an attempt to reduce bias, patients and volunteers were recruited from similar clinics, the same hospital referral area and physical location. No control subject had ever suffered chest pain, however the possibility that some controls may have suffered from subclinical CHD should be noted.

Recent discussions in the medical press [42] have shown that cardiologists and internists continue to dismiss women with syndrome X. The psychosocial and gynaecological components associated with syndrome X will therefore continue to be misunderstood. Treatment modalities that address these elements of the condition may result in clinical improvement of some patients with this syndrome. Until such psychosocial factors as those identified in this study are recognised within the dichotomous pathology of this debilitating condition, we will be no closer to finding a useful and effective treatment armamentarium for patients with cardiac syndrome X.

References

1. Kemp Jr HG, Vokonas PS, Cohn PF et al. The anginal syndrome associated with normal coronary arteriograms. Report of a six year experience. *Am J Med* 1973;54:735–42.
2. Cannon III RO, Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol* 1988;61:1338–43.
3. Panting JR, Gatehouse PD, Yang GZ et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002;346:1948–53.
4. Sax FL, Cannon III RO, Hanson C et al. Impaired forearm vasodilator reserve in patients with microvascular angina. Evidence of a generalized disorder of vascular function. *N Engl J Med* 1987;317:1366–70.
5. Rosano GM, Collins P, Kaski JC et al. Syndrome X in women is associated with oestrogen deficiency. *Eur Heart J* 1995;16:610–4.
6. Cannon III RO, Bonow RO, Bacharach SL et al. Left ventricular dysfunction in patients with angina pectoris, normal epicardial coronary arteries, and abnormal vasodilator reserve. *Circulation* 1985;71:218–26.
7. Dean JD, Jones CJ, Hutchison SJ et al. Hyperinsulinaemia and microvascular angina ("syndrome X"). *Lancet* 1991;337:456–7.
8. Shapiro LM, Crake T, Poole-Wilson PA. Is altered cardiac sensation responsible for chest pain in patients with normal coronary arteries? Clinical observation during cardiac catheterisation. *Br Med J [Clin Res Ed]* 1988;296:170–1.
9. Cannon III RO. The sensitive heart. A syndrome of abnormal cardiac pain perception. *JAMA* 1995;273:883–7.
10. Rosen SD, Paulesu E, Wise RJ et al. Central neural contribution to the perception of chest pain in cardiac syndrome X. *Heart* 2002;87:513–9.
11. Rosano GM, Peters NS, Lefroy D et al. 17-beta-Estradiol therapy lessens angina in postmenopausal women with syndrome X. *J Am Coll Cardiol* 1996;28:1500–5.
12. Adamson DL, Webb CM, Collins P. Esterified estrogens combined with methyltestosterone improve emotional well-being in postmenopausal women with chest pain and normal coronary angiograms. *Menopause* 2001;8:233–8.
13. Rosano GM, Lindsay DC, Poole-Wilson PA. Syndrome X: an hypothesis for cardiac pain without ischaemia. *Cardiologia* 1991;36:885–95.
14. Turiel M, Galassi AR, Glazier JJ et al. Pain threshold and tolerance in women with syndrome X and women with stable angina pectoris. *Am J Cardiol* 1987;60:503–7.
15. Mayou RA, Bass CM, Bryant BM. Management of non-cardiac chest pain: from research to clinical practice. *Heart* 1999;81:387–92.
16. Peski-Oosterbaan AS, Spinhoven P, van Rood Y et al. Cognitive-behavioral therapy for noncardiac chest pain: a randomized trial. *Am J Med* 1999;106:424–9.
17. Potts SG, Bass CM. Psychological morbidity in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. *Psychol Med* 1995;25:339–47.
18. Potts SG, Lewin R, Fox KA et al. Group psychological treatment for chest pain with normal coronary arteries. *QJM* 1999;92:81–6.
19. Cannon III RO, Quyyumi AA, Mincemoyer R et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994;330:1411–7.
20. Bass C, Cawley R, Wade C et al. Unexplained breathlessness and psychiatric morbidity in patients with normal and abnormal coronary arteries. *Lancet* 1983;1:605–9.
21. Ruggeri A, Taruschio G, Loricchio ML et al. The correlation between the clinical characteristics and psychological status in syndrome X patients. *Cardiologia* 1996;41:551–7.
22. Corlando A, Marraccini P, Gistri R et al. Psychological and social aspects in women with syndrome X. *G Ital Cardiol* 1991;21:705–12.
23. Cunningham C, Brown S, Kaski JC. Effects of transcendental meditation on symptoms and electrocardiographic changes in patients with cardiac syndrome X. *Am J Cardiol* 2000;85:653–5.. A10.
24. Ornish D, Scherwitz LW, Doody RS et al. Effects of stress management training and dietary changes in treating ischemic heart disease. *JAMA* 1983;249:54–9.
25. Luebbert K, Dahme B, Hasenbring M. The effectiveness of relaxation training in reducing treatment-related symptoms and improving emotional adjustment in acute non-surgical cancer treatment: a meta-analytical review. *Psychooncology* 2001;10:490–502.
26. Lucock MP, Morley S. The health anxiety questionnaire. *Br J Health Psychol* 1996;1:137–50.
27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
28. Brugha TS, Bebbington P, Tennant C et al. The list of threatening experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol Med* 1985;15:189–94.
29. Brown GW, Harris TO. *Social origins of depression*. London: Tavistock; 1978.
30. Kaski JC, Rosano GM, Collins P et al. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. *J Am Coll Cardiol* 1995;25:807–14.
31. Ormel J, Kempen GI, Penninx BW et al. Chronic medical conditions and mental health in older people: disability and psychosocial resources mediate specific mental health effects. *Psychol Med* 1997;27:1065–77.
32. Lesperance F, Frasure-Smith N. Depression in patients with cardiac disease: a practical review. *J Psychosom Res* 2000;48:379–91.
33. Eifert GH, Forsyth JP. Heart-focused and general illness fears in relation to parental medical history and separation experiences. *Behav Res Ther* 1996;34:735–9.
34. Redburn JC, Murphy MF. Hysterectomy prevalence and adjusted cervical and uterine cancer rates in England and Wales. *BJOG* 2001;108:388–95.
35. Kennedy TM, Jones RH. The epidemiology of hysterectomy and irritable bowel syndrome in a UK population. *Int J Clin Pract* 2000;54:647–50.
36. Patterns of use of hormone replacement therapy in one million women in Britain, 1996–2000. *BJOG* 2002;109:1319–30.
37. Rossouw JE, Anderson GL, Prentice RL et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA* 2002;288:321–33.
38. Hulley S, Grady D, Bush T et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and estrogen/progestin replacement study (HERS) research group. *JAMA* 1998;280:605–13.
39. Mayou RA, Bryant BM, Sanders D et al. A controlled trial of cognitive behavioural therapy for non-cardiac chest pain. *Psychol Med* 1997;27:1021–31.
40. Sanders D, Bass CM, Mayou RA et al. Non-cardiac chest pain: why was a brief intervention apparently ineffective?. *Psychol Med* 1997;27:1033–40.
41. Leventhal H, Nerenz D. The assessment of illness cognition. In: Karoly P, editor. *Measurement strategies in health psychology*. New York: Wiley; 1985. p. 517–54.
42. Bassan M. Cardiac syndrome X. *N Engl J Med* 2002;347:1377–9.