Effects of Tai Chi on Stress and Cardiovascular Function in People with Coronary Heart Disease and/or Hypertension

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Dedication

This work is dedicated to my Grand Tai Chi Master Zhang Peijun (Beijing, China) for her compassion and generosity, inspirational encouragement, and infinite support for this doctoral project.

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Statement of Authentication

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Guo-Yan (Emily) Yang

Declarations

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Abbreviations

6MWT	6 Minute Walk Test
ACE	Angiotensin-Converting Enzyme
AE	Adverse Events
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ANZCTR	Australian New Zealand Clinical Trials Registry
ARBs	Angiotensin Receptor Blockers
BDI-II	Beck Depression Inventory-II
BMI	Body Mass Index
BUCM	Beijing University of Chinese Medicine
CABG	Coronary-Artery Bypass Grafting
CBT-I	Cognitive Behavioural Therapy for Insomnia
CCBs	Calcium Channel Blockers
CDC	Centers for Disease Control and Prevention
CENTRAL	Cochrane Central Register of Controlled Trials
CES-D	Center for Epidemiological Studies-Depression
CHD	Coronary Heart Disease
CHI	Cardiac Health Institute
CI	Confidence Interval
CNKI	China National Knowledge Infrastructure
CO	Carbon Monoxide
CONSORT	Consolidated Standards of Reporting Trials Statement
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reative Protein
CVD	Cardiovascular Disease
DALYs	Disability-Adjusted Life-Years
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition
ECG	Electrocardiogram
ET-1	Endothelin-1
FBG	Fasting Blood Glucose

FIQR	Revised Fibromyalgia Impact Questionnaire
G-CSF	Granulocyte Colony-Stimulating Factor
GLM	General Linear Model
GPx	Glutathione Peroxidase
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GZLM	Generalised Linear Model
H_2S	Hydrogen Sulphide
HDL-C	High-density Lipoprotein Cholesterol
HF	High Frequency
HF norm	Normalised High Frequency
HPA	Hypothalamic-Pituitary-Adrenal
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HRV	Heart Rate Variability
IL	Interleukin
ITT	Intention-to-Treat
IVUS	Intravascular Ultrasound
LDL-C	Low-density Lipoprotein Cholesterol
LF	Low Frequency
LF norm	Normalised Low Frequency
MAAS	Mindful Attention Awareness Scale
MacNew QLMI	MacNew Heart Disease Health-related Quality of Life Instrument
MD	Mean Difference
MI	Myocardial Infarction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MOS	Medical Outcomes Study
NCDs	Non-communicable Diseases
NF-$_k$B	Nuclear Factor-Kappa B
NHMRC	National Health and Medical Research Council
NICM	NICM Health Research Institute
NN	Normal-to-Normal
NO	Nitric Oxide

OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Intervention
PET	Positron Emission Tomography
PNN 50	Percentage of Successive R-R Intervals that Differ by More Than 50 milliseconds
POMS	Profile of Mood States
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register for Systematic Reviews
PSQI	Pittsburgh Sleep Quality Index
PSS-4	Perceived Stress Scale 4-Item
PSS-10	Perceived Stress Scale 10-Item
PSS-14	Perceived Stress Scale 14-Item
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Post-Traumatic Stress Disorder
PURE	Prospective Urban Rural Epidemiological
QoL	Quality of Life
RCT	Randomised Controlled Trial
REE	Resting Energy Expenditure
RMS SD	Square Root of the Mean Square of Successive R-R Interval Differences
RR	Relative Risk
SAE	Serious Adverse Event
SAS	Zung Self-Rating Anxiety Sale
SBP	Systolic Blood Pressure
SCL-R	Symptom Checklist-90-Revised
SCS-R	Revised Self-Compassion Scale
SD	Standard Deviation
SDS	Zung Self-Rating Depression Sale
SEBES	Self-Efficacy-Barriers to Exercise Scale
SF-12	12-Item Short Form Health Survey
SF-36	Medical Outcomes Study 36-Item Short Form Healthy Survey
SIBS-R	The Revised Spiritual Involvement and Beliefs Scale
SMD	Standardised Mean Difference
SOD	Superoxide Dismutase
SoF	Summary of Findings

SOP	Standardised Operating Procedures
SPARS	Severe Acute Respiratory Syndromes
SPS	Social Provision Scale
STAI	State and Trait Anxiety Inventory
TAS	Total Antioxidant Status
TCM	Traditional Chinese Medicine
TP	Total Power
VO_2max	Maximal Oxygen Intake
VO_2peak	Peak Oxygen Uptake
WHO	World Health Organization
WHOQOL-100	World Health Organization Quality of Life

Abstract

Introduction

Cardiovascular disease (CVD) is a group of disorders of the heart, vascular diseases of the brain and diseases of blood vessels. CVD is the number one cause of morbidity and mortality worldwide. Coronary heart disease (CHD) is the most common type of CVD. The risk factors of CVD included behavioural risk factors and other contributing cardiovascular factors. Hypertension is the leading cause of heart disease and stroke. It is well-established that stress, anxiety and depression are associated with the development of CVD and established CVD. Stress, anxiety and depression are frequently undertreated in CVD. Tai Chi may provide a treatment option for these conditions in the CVD population. The physical and psychological benefits of Tai Chi have been demonstrated in several studies in various populations, but few have investigated the effectiveness of Tai Chi on psychological stress, anxiety and depression in people with CVD.

Objectives

Three studies were conducted as part of this doctoral research: one systematic review, one randomised controlled trial and one qualitative sub-study of the trial, to answer the following research questions.

(1) What is the existing scientific evidence to support the effects of Tai Chi in improving psychological well-being and quality of life in patients with CVD and/or cardiovascular risk factors?

(2) What are the effects of Tai Chi on psychological stress, anxiety, depression and cardiovascular function in patients with CHD and/or hypertension?

(3) What are the perceptions of the trial participants on the facilitators and barriers to trial participation and adherence to Tai Chi intervention?

Methods

Three studies were conducted in this doctoral project. The first study is a systematic review of randomised controlled trials on Tai Chi for psychological well-being and quality of life in people with CVD and/or cardiovascular risk factors. Major English and Chinese language databases were searched. Data selection and extraction were conducted by two researchers independently. The methodological quality of included studies was assessed by the Cochrane risk of bias tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Statistical analyses were performed with Cochrane's Review Manager software (version 5.3). Data were summarised using mean difference (MD) with 95% confidence interval (CI) and presented in forest plots and 'Summary of Finding' tables.

The second study is a randomised controlled trial of Tai Chi in CVD participants. Participants (n=120) with CHD and/or hypertension were recruited from Beijing (n=80) and Sydney (n=40), and randomly assigned to the Tai Chi group (n=60) or waitlist control group (n=60). The Tai Chi group practiced a standardised 24-week Tai Chi intervention consisting of 2-hour Tai Chi class twice weekly for the first 12 weeks and once weekly for the rest 12 weeks. The primary outcome was psychological stress as measured by the Perceived Stress Scale-10 (PSS-10). The secondary outcomes included anxiety as measured by the *Zung* Self-Rating Anxiety Scale (SAS), depression as measured by the Beck Depression Inventory-II (BDI-II), cardiovascular function (including blood pressure, heart rate, heart rate variability, lipid and glucose profiles, and C-reactive protein), quality of life as measured by the 36-item Short Form Health Survey Questionnaire (SF-36) and physical fitness as measured by the 6-Minute Walk test (6MWT). All measures were assessed at baseline, week 12 and week 24.

The third study is a qualitative study using exit interviews with participants from the Tai Chi group who completed the study. Semi-structured interviews were chosen to allow in-depth interviews that encourage interviewees to answer pre-set open-ended questions or topics to be explored by the interviewer. Each semi-structured interview was guided by ten open-ended questions in English or Chinese (Mandarin). The interviews were audio-recorded, transcribed verbatim and imported into the NVivo (Version 11) software to facilitate coding and data analysis. Thematic analysis was chosen for analysing data in this study because it followed a standard procedure for conducting qualitative analysis to ensure clarity and rigour in process.

Results

The systematic review included 25 studies involving 2,084 participants with CVD and/or cardiovascular risk factors. The methodological quality of included studies was generally low to moderate. Only one study examined stress in people with CVD, reporting that an 8-week short-form Tai Chi program significantly decreased stress in people assessed by PSS-10 (MD -2.45, 95% CI: -3.06, -1.84). Individual studies found Tai Chi to be superior to control group in reducing other psychological measures such as depression, anxiety and improving mood. A meta-analysis of Tai Chi plus usual care versus usual care alone in decreasing depression found no significant difference. However, meta-analyses did find that Tai Chi significantly improved quality of life in all domains of the SF-36 including physical functioning (MD: 5.47, 95%CI: 0.66, 10.28, I^2=84%), role limitation due to physical health (MD: 11.82, 95%CI: 8.26, 15.38, I^2=32%), role limitation due to emotional health (MD: 8.27, 95%CI: 5.56, 10.98, I^2=0%), energy/vitality (MD: 7.03, 95%CI: 1.92, 12.14, I^2=81%), mental health (MD: 7.86, 95%CI: 4.29, 11.44, I^2=48%), social functioning (MD: 9.81, 95%CI: 5.19, 14.42, I^2=68%), bodily pain (MD: 6.34, 95%CI: 2.45, 10.23, I^2=53%), and general health (MD: 10.04, 95%CI: 7.15, 12.93, I^2=27%) and the Minnesota Living with Heart Failure Questionnaire (scale from 0 to 105) (MD: -11.10, 95%CI: -15.52, -6.68, I^2=73%). No adverse events were reported.

In the randomised controlled trial, we conducted, Tai Chi led to a significant reduction in PSS-10 scores at week 24 (Mean, 10.44; 95% confidence interval (CI), 8.86 to 12.03) compared with the waitlist group (Mean, 11.71; 95% CI, 10.01 to 13.34) (P=0.009). Walking distance measured by the 6-minute walk test was significantly improved in the Tai Chi group compared to the waitlist group (P=0.001). Significant differences were also detected between the two groups in depression, diastolic blood pressure, and quality of life. The between-group differences in other secondary outcomes did not reach statistical significance. No severe adverse events related to Tai Chi were reported. The attendance rate at Tai Chi classes was 82.5% during the 24-week program. Retention of participants was high, with 102 (85%) of all 120 participants completing the study.

In the qualitative sub-study, 34 participants were interviewed. Facilitators and barriers were identified as the two major domains, and six key themes with 31 codes emerged under the two domains. Facilitators to trial participation and adherence to Tai Chi interventions were grouped into four themes: internal/external motivation, positive feelings, benefits of Tai Chi, and future practice. A major internal motivation was to improve health. Positive feelings had three sub-

themes: positive feelings toward Tai Chi, the project, and the learning experience. Tai Chi instructor(s) were crucial in motivating participants' adherence to Tai Chi. The participants identified the benefits of committing to a regular and sustained Tai Chi practice included improvements in psychological well-being, physical health, social life and daily life activities. Under the domain of barriers to participation and adherence, subjective and objective concerns were the two predominating themes. Subjective concerns included concern learning Tai Chi was difficult and that Tai Chi might harm their knees if not practiced properly. Objective concerns included time conflict, air pollution, laziness and a lack of group atmosphere.

Conclusion

Tai Chi may be effective to improve psychological stress, fitness and quality of life and appears safe to practice in people with CHD and/or hypertension. We found a 24-week standardised Tai Chi was beneficial and safe in improving psychological stress, and physical fitness in patients with CHD and/or hypertension compared with the waitlist control group. In addition, our systematic review demonstrated that Tai Chi is potentially effective in improving quality of life in people with CVD and/or CVD risk factors and is safe to practise in this population. However, there is still lack of strong, well-designed studies demonstrating the beneficial effects of Tai Chi on stress, depression, anxiety and mood disturbance. More high-quality randomised controlled trials exploring the beneficial effects of Tai Chi on psychological well-being and quality of life are warranted. A major facilitator to trial participation and adherence is to improve health and Tai Chi instructor(s) is also crucial in motivating participants' adherence to Tai Chi. Barriers are related to subjective and objective concerns of Tai Chi practice, such as the difficulty and safety to learn and practice, and time conflict. Future research may seek to evaluate these facilitators and barriers further to improve the study design, recruitment and implementation.

Chapter 1: Introduction

This chapter presents a general introduction of the research in this doctoral thesis. It provides an overview of the background to the research, describes the objectives and research questions, and the structure of the thesis.

1.1 Background to the Research

1.1.1 Cardiovascular disease

Cardiovascular disease (CVD) is a group of disorders of the heart, vascular diseases of the brain and diseases of blood vessels (World Health Organization, 2018a). CVD is the number one cause of morbidity and mortality worldwide. An estimated 17.7 million people died from CVDs in 2015, representing 31% of all global deaths (World Health Organization, 2017).

Although the mortality rates of CVDs have fallen substantially in many high-income countries over the last three decades, they remain a considerable disease burden on both the individuals and society as a whole. According to the American Heart Association, the total direct and indirect cost of CVDs in the US alone for 2016 was an estimated US$555 billion (American Heart Association, 2017). Furthermore, the morbidity rates of CVDs are increasing dramatically in developing countries (W. Chen et al., 2018).

1.1.2 Coronary Heart Disease

Coronary heart disease (CHD), also known as ischaemic heart disease, is the most common form of CVD. Of all mortality due to CVD, CHD is the leading cause of premature death. CHD is estimated to be responsible for 41.8% (7.4 million) of the 17.7 million deaths globally in 2015 (World Health Organization, 2017).

In recent years, the prevalence, incidence and mortality rates of CHD in high-income countries have decreased dramatically, however, the morbidity of CHD has increased in middle- and low-income countries. In developing countries, however, the prevalence of CHD continues to increase. The mortality rate due to CHD in developing countries increased between 2012 and 2015 from 93.17 to 110.91 per 100,000 in urban areas and 68.62 to 110.67 per 100, 000 in rural areas (Chen et al., 2018).

1.1.3 Hypertension

Hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels have persistently raised pressure (World Health Organization, 2018d). Hypertension is the most important preventable cause of heart disease and stroke (GBD 2015 Risk Factors Collaborators, 2016; Redon et al., 2016; Tzoulaki, Elliott, Kontis, & Ezzati, 2016).

Hypertension accounted for an estimated 2.043 million mortalities in China in 2010, accounting for 24.6% of all deaths in China (H. Li & Ge, 2014). In 2014-2015, six million adult Australians (34%) were hypertensive (Blood pressure $\geq$ 140/90 mmHg) or taking antihypertensive medication (Australian Bureau of Statistics, 2015). The Global Burden of Disease, Injuries, and Risk Factor study 2015 found that the rate of elevated systolic blood pressure (SBP) ($\geq$110-115 and $\geq$140mm Hg) increased substantially between 1990 and 2015 (GBD, 2015), and the all disability-adjusted life-years (DALYs) and deaths associated with SBP also increased (Forouzanfar et al., 2017).

1.1.4 Cardiovascular Risk Factors

There has been strong scientific evidence demonstrated that behavioural risk factors and other contributing risk factors are associated with the development and prognosis of CVD.

Behavioural risk factors include smoking, unhealthy diet, physical inactivity and harmful use of alcohol (Tzoulaki et al., 2016). These unhealthy lifestyle behaviours can cause metabolic/physiological changes in the body, leading to other cardiovascular risk factors, such as hypertension, overweight/obesity, hyperglycemia/diabetes, and dyslipidaemia.

Other contributing risk factors such as poverty, aging and psychological factors including stress, anxiety and depression. Aging is also a contributing cardiovascular risk factor for clinically significant atherosclerotic lesion formation (Head, Daunert, & Goldschmidt-Clermont, 2017).

Population aging accelerates the rapid increasing burden of CVDs. Stress, anxiety, depression and their relationship with CVDs are discussed in detail below.

1.1.5 Stress, Anxiety and Depression

Accumulated scientific evidence has addressed the association between psychosocial factors and CVD. Psychological risk factors such as stress, anxiety, and depression are known to play an important, and independent role, in the development of CVD and its complications.

Psychological risk factors, particularly depression, are associated with other risk factors, including educational level, sedentary lifestyle, smoking, unhealthy diet and reduced compliance with risk factor modification (Pogosova et al., 2017). Depression is independently associated with increased cardiovascular morbidity and mortality in patients with CHD (Baumeister, Hutter, & Bengel, 2011; Gan et al., 2014; Rugulies, 2002).

Anxiety is highly comorbid with depression and both are independently associated with increased risk of mortality in CHD patients (Watkins et al., 2013). A recent Cochrane systematic review of 35 studies with 10,703 patients with CHD, assessed the effectiveness of psychological interventions (alone or with cardiac rehabilitation) compared with usual care (including cardiac rehabilitation where available) (Richards et al., 2017). Psychological interventions significantly reduced cardiovascular mortality (relative risk: 0.79, 95% confidence interval [CI] 0.63 to 0.98) and improved depressive symptoms (standardised mean difference [SMD] -0.27, 95%CI -0.39 to -0.15), anxiety (SMD -0.24, 95% CI -0.38 to -0.09) and stress (SMD -0.56, 95% CI -0.88 to -0.24). However, the risk of bias in the studies included in the review reduced certainty around the findings.

1.1.6 Tai Chi Intervention

Tai Chi, also known as Tai Chi Chuan/Quan or Taiji, was developed by a famous martial artist Chen Wang-Ting towards the end of Ming Dynasty (17^{th} Century A.D.) (L. Gu & Shen, 2007). Chen Wang-Ting comprehensively incorporated the essence of Chinese folk and military martial arts, breathing and meditative techniques, Taoist philosophy of *yin* and *yang*, and traditional Chinese medicine theory (Tang & Gu, 2012). The main components of Tai Chi is traditionally described including movements, meditation and imagination, and deep/abdominal breathing (Tang & Gu, 2012). The aim being that practitioners gain both physical and psychological benefits from Tai Chi.

Tai Chi was reported for the first time as an intervention in a clinical study in 1958 in China, where a case series demonstrated the beneficial effects of Tai Chi on tuberculosis (D. Wang, 1958). In recent years, research on Tai Chi for health and well-being has flourished. Numerous studies have demonstrated various physical and psychological benefits of Tai Chi intervention, including potential improvements in stress, anxiety, depression, quality of life and cardiovascular function.

1.1.7 Knowledge Gap

Cardiac rehabilitation aims to provide comprehensive, long-term secondary prevention of CVDs and is an essential intervention offered to patients with heart disease. Cardiac rehabilitation programs include components of medical evaluation, physical activity, cardiac risk factor modification, health education, and counselling (Dalal, Doherty, & Taylor, 2015). In the past decades, strong evidence has accumulated to suggest that CR reduces mortality, morbidity, unplanned hospital admissions in addition to improvements in exercise capacity and quality of life (Anderson et al., 2016; Dalal et al., 2015; Dalal, Zawada, Jolly, Moxham, & Taylor, 2010; Long et al., 2018). Given these important benefits, CR has been recommended in many evidence-based international guidelines. Guidelines from the American College of Cardiology and the American Heart Association give a Class I recommendation for referral to cardiac rehabilitation for patient education in the hospital setting in all patients with recent coronary events or revascularization procedures (Antman et al., 2004).

Structured exercise has been identified as the core component to the successful treatment of cardiac rehabilitation programs (Anderson et al., 2016; Long et al., 2018). However, current practice guidelines consistently recommend “comprehensive rehabilitation” programs that should include sufficient psychological components to optimise cardiovascular risk reduction, foster healthy behaviours and compliance to these behaviours, reduce disability, and promote an active lifestyle (Balady et al., 2007; Dalal et al., 2015).

Cardiac rehabilitation delivery faces substantial challenges such as financially viability due to barriers such as consistent and appropriate referral (especially for women, the elderly, ethnic minorities, and low socioeconomic status populations), accessibility (transportation, number, and geographic distribution of cardiac rehabilitation programs) and affordability (lack of insurance coverage, high co-payments, and use of resource-intensive, inefficient and costly models) (Balady et al., 2011; Clark et al., 2015; Sandesara et al., 2015). As a result, utilisation of cardiac rehabilitation is relatively low. Participation rates in cardiac rehabilitation programs

following ST-elevation myocardial infarction (STEMI) is about 25-35% in western countries (Urbinati & Tonet, 2018). A large prospective audit in Australia and New Zealand found only 46% of eligible patients were documented as referred to CR and even fewer were discharged with sufficient secondary prevention (Redfern et al., 2014). Significant improvements are needed to provide cost-effective, patient-centred, comprehensive secondary prevention for patients with CVDs.

Tai Chi for people with CVD has a number of potential health benefits. A recent systematic review and meta-analysis of thirteen studies demonstrated that Tai Chi based cardiac rehabilitation led to improved aerobic endurance and quality of life, and reduced anxiety and depression in patients with CHD. Tai Chi may be a cost-effective option for patients with or at risk of CVD (T. Liu, Chan, Liu, & Taylor-Piliae, 2018). However, only few rigorously designed randomised controlled trials (RCTs) exist investigating the impacts of Tai Chi intervention in patients with CHD and/or hypertension, particularly on psychological stress, anxiety, depression and other neuropsychological outcomes.

The adherence to Tai Chi programs appears to be relatively high. A feasibility, qualitative study with 17 veterans with post-traumatic stress disorder (PTSD) found that 93.8% of participants reported feeling engaged and satisfied with the Tai Chi program (Niles et al., 2016). Another qualitative study evaluated the feasibility of using a pragmatic, community-based Tai Chi interventions to enhance recruitment and adherence in a RCT of Tai Chi for women with osteopenia (Fischer, Fugate-Woods, & Wayne, 2014). Facilitators that were found to improve trial participation and adherence included convenience of class locations and times, alternative learning modalities, quality of teaching, community and social support, and perceived health benefits, while barriers included time-related issues. However, less is known about the influential factors on trial participation and adherence to Tai Chi intervention during and after a RCT from the perspective of participants.

1.2 Objectives and Research Questions

This doctoral research aims to explore the impact of Tai Chi on psychological well-being and cardiovascular function in people with CHD and/or hypertension. Three studies were conducted as part of this doctoral research: a systematic review, a RCT and a qualitative sub-study of the RCT, to investigate the effects of Tai Chi in this population.

1.2.1 Systematic Review

The first research question of the doctoral research is "What is the existing scientific evidence to support the effects of Tai Chi in improving psychological well-being and quality of life in patients with CVD and/or cardiovascular risk factors?" To answer this question, a systematic review was conducted.

The primary objective of the systematic review was to explore the effectiveness and safety of Tai Chi on psychological stress in patients with CVD and/or cardiovascular risk factors in existing RCTs. The secondary objective was to explore the effectiveness and safety of Tai Chi on psychological factors including anxiety, depression, mood disturbance, self-esteem and quality of life in patients with CVD and/or cardiovascular risk factors.

The hypotheses of this systematic review were that Tai Chi is beneficial for the management of stress, anxiety, depression, mood disturbance, self-esteem and quality of life in patients with CVD and/or cardiovascular risk factors and safe to practice in this population.

1.2.2 Randomised Controlled Trial

The second research question of this doctoral research is "What are the effects of Tai Chi on psychological stress, anxiety, depression and cardiovascular function in patients with CHD and/or hypertension?" To answer this research question, an international multi-centre RCT was conducted.

The primary objective of this trial was to determine the effect of a 24-week Tai Chi intervention on psychological stress in patients with CHD and/or hypertension. The secondary objective was to investigate the effects of a 24-week Tai Chi intervention on anxiety, depression, cardiovascular function, quality of life, and fitness measures in patients with CHD and/or hypertension. In addition, a close observation of any adverse events as a result of Tai Chi practice was conducted to explore the safety of Tai Chi intervention in patients with CHD and/or hypertension.

The hypotheses of this trial were that a 24-week Tai Chi intervention is beneficial for reducing stress, anxiety, depression and improving cardiovascular function, quality of life, and physical fitness in patients with CHD and/or hypertension and safe to practice in this population.

1.2.3 Qualitative Sub-Study

The third research question of this doctoral thesis is "What are the perceptions of the trial participants on the facilitators and barriers to trial participation and adherence to Tai Chi intervention?" To answer this question, a qualitative sub-study was conducted as an exit interview, embedding into the RCT.

The primary objective of this qualitative sub-study was to explore the perceptions of participants on facilitators to trial participation and adherence during and after the randomized controlled trial. The secondary objective was to explore the perceptions of participants on barriers to trial participation and adherence during and after the randomized controlled trial.

The hypotheses of this qualitative sub-study were that from the perceptions of participants, we would identify valuable information about the facilitators and barriers to trial participation and adherence during and after the randomized controlled trial.

1.3 Structure of the Thesis

The thesis has seven chapters in total, introducing the background information and knowledge gaps, and presenting the results of three main studies: (1) a systematic review, (2) an international multi-centre RCT, and (3) a qualitative sub-study of the RCT.

Chapter 1 is a general introduction of the research in this doctoral thesis. It provides an overview of the background to the research, describes the objectives and research questions, and describes in more detail the structure of the thesis.

Chapter 2 presents a literature review on the history and current development of research on Tai Chi and cardiovascular disease, to provide a wider context of research. Since the qualitative exit interviews was a sub-study embedded in the RCT, the background of this topic is summarised briefly in Chapter 2 and described in detail in Chapter 6.

Chapter 3 outlines the systematic review to explore whether Tai Chi can improve psychological well-being and quality of life in patients with cardiovascular disease and/or cardiovascular risk factors. The protocol of this systematic review was registered in the International Prospective Register for Systematic Reviews (PROSPERO) (NO.: CRD42016042905) and published in BMJ Open. After an introduction of the background (Section 3.1) and methods (Section 3.2),

the results (Section 3.3) were presented including characteristics of the included studies, methodological quality, and effects of interventions. A discussion (Section 3.4) based on the findings including interpretation of the results and comparisons with previous studies is also provided.

Chapter 4 describes the RCT entitled 'The effects of Tai Chi on stress and cardiovascular function in patients with coronary heart disease and/or hypertension'. Objectives of the trial (Section 4.1), the methodology (Section 4.2) are presented in detail. The methodology presents the study design, participants, sample size calculation, recruitment and screening, randomisation, intervention, outcome measures, data collection, data management and statistical analysis.

Chapter 5 outlines the results and discussion RCT in detail. The results present enrolment, participant discontinuations, baseline characteristics of participants, and the effects of the Tai Chi intervention on the primary outcome measure (i.e. stress) and secondary outcome measures (i.e. anxiety, depression, blood pressure, heart rate, heart rate variability, lipid and glucose profile, C-reactive protein, quality of life, and 6-minute walk test). A discussion of the findings including interpretation of the results and comparisons with previous studies is also provided.

Chapter 6 presents the qualitative sub-study of the RCT. Similarly, after a brief introduction of the background, it provides an overview of the RCT and describes the methods of the qualitative sub-study in detail (Section 6.2). Section 6.3 presents the results, including characteristics of participants who completed the exit interview, and influential factors focusing on facilitators and barriers of trial participation and adherence to intervention. A discussion (Section 6.4) by comparing and contrasting the findings with that of previous literature is provided.

Chapter 7 consists of a general discussion of the doctoral thesis. It synthesises and summarises the main findings of the systematic review, the RCT and the qualitative sub-study of the trial. The strengths and weakness of the studies within the context of research in this area and further research directions are discussed. Based on the general discussion, a conclusion is drawn.

Chapter 2: Literature Review: Tai Chi, Coronary Heart Disease and Hypertension

This chapter presents a literature review on the history and current development of research on Tai Chi and cardiovascular disease, to provide a wider context of research. Since the qualitative exit interview was a sub-study embedded in the RCT, the background of this topic is summarised briefly in Chapter 2 and described in detail in Chapter 5.

2.1 Cardiovascular Disease (CVD)

2.1.1 Definition and Pathophysiology of CVD

CVD is the name of a group of disorders of the heart, vascular diseases of the brain and diseases of blood vessels (World Health Organization, 2018a), and includes:

(1) CVDs due to atherosclerosis
(2) Other CVDs:
    - rheumatic heart disease
    - congenital heart disease
    - cardiomyopathies
    - cardiac arrhythmias

Atherosclerosis, a complex pathological process of plaque building up in the wall of blood vessels, is the main pathological process contributing to CVDs. These plaques cause the inner surface of the blood vessels to become irregular and the lumen to become narrow, making it harder for blood to flow through. Eventually, the plaque can rupture, triggering the formation of a blood clot and resulting in a heart attack or stroke. The atherosclerosis develops over years triggered by different risk factors such as hypertension, raised lipid levels (Talbot, Delaney, Sandfort, Herrington, & McClelland, 2018), cigarette smoking (Z. Wang, Wang, & Wang,

2017), physical inactivity (Florido et al., 2018), unhealthy diet (Kern et al., 2017), alcohol consumption (Kwon et al., 2016), diabetes (Katakami, 2018), aging (Head et al., 2017), genetic disposition (Peterlin, Petrovic, & Peterlin, 2018) and psychological factors (Chrysohoou, Kollia, & Tousoulis, 2018).

Rheumatic heart disease results from an abnormal autoimmune response to a group A streptococcal infection in a genetically susceptible host caused by acute rheumatic fever, which can affect different organs and lead to irreversible cardiac valve damage and heart failure (Marijon, Mirabel, Celermajer, & Jouven, 2012). Congenital heart diseases are malformations of heart structures present at birth (Hunter, 2001). Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electric dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic (Braunwald, 2017; Maron et al., 2006). Cardiac arrhythmias are any abnormal heart rate or rhythm, characterized by irregular rhythm of heartbeat which could be either too slow (<60 beats/minute) or too fast (>100 beats/minute) (D. G. Fu, 2015). These CVDs are less common than CVDs caused by atherosclerosis such as CHD and strokes.

2.1.2 Prevalence and Disease Burden of CVD

CVDs are the number one cause of morbidity and mortality worldwide. According to World Health Organization (WHO), an estimated 17.7 million people died from CVDs in 2015, representing 31% of all global deaths (World Health Organization, 2017). Out of the 17.7 million CVD deaths, CHD and stroke were responsible for 7.4 million and 6.7 million deaths, respectively.

Due to encouraging advances in prevention and successful treatment of acute cardiovascular events, the mortality rates of CVDs have fallen substantially in many high-income countries over the last three decades (Bhatnagar, Wickramasinghe, Wilkins, & Townsend, 2016). However, CVDs remain a considerable disease burden on the individuals and society as a whole. More than 4.2 million Australians are affected by CVDs in 2014-2015, namely every one in six Australians are affected (Australian Bureau of Statistics, 2015). The total direct and indirect cost of CVDs in the US alone for 2016 was around US$555 billion, and is expected to increase significantly to $1.1 trillion by 2035 (American Heart Association, 2017).

On the other hand, the mortality and morbidity rates of CVDs are increasing dramatically in developing countries. China is the largest developing country in the world, with a land mass of

9.6 million km^2 and a population of more than 1.33 billion. In China, morbidity rates due to CVD are estimated at 290 million, and the mortality rate between 2005 and 2015 increased from 174 to 298 per 100,000 people in rural areas and 209 to 265 per 100,000 people in urban areas in 2015 (W. Chen et al., 2018). In India, CHD led to 17% of total deaths and 26% of adult deaths in 2001-2003, increasing to 23% of total and 32% of adult deaths in 2010-2013 (Gupta, Mohan, & Narula, 2016).

2.1.3 Strategies of Controlling CVD

The World Heart Federation, WHO, and the World Stroke Organization articulate three critical strategies: (1) surveillance and monitoring, (2) prevention and reduction of risk factors, and (3) improved management and health care through early detection and timely treatment (World Health Organization, World Heart Federation, & Organization., 2011). In the past three decades, both population-wide primary prevention and individual level healthcare intervention strategies such as tobacco and alcohol control (Gravely et al., 2017) and salt reduction in diet (Rafieifar et al., 2016) have been largely reported for their contributions to the substantial decrease in mortality of CVDs.

At the individual level, interventions need to be targeted to those at high cardiovascular risks (World Health Organization, 2017), such as hypertension, raised blood lipid and serum glucose to prevent first cardiovascular events. For secondary prevention of cardiovascular events in those with established CVDs, including diabetes, necessary treatment with medications including aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and statins may help prevent up to 75% recurrent vascular events and decrease mortality (World Health Organization, 2017).

The use of effective secondary prevention medications is low worldwide, but especially low in low-income countries and rural areas. For example, in high-income countries use of antiplatelet drugs is 62.0%, beta-blockers 40.0%, ACE inhibitors 49.8%, and statins 66.5%; compared to low-income countries: 8.8%, 9.7%, 5.2%, and 3.3%, respectively (Yusuf et al., 2011).

When diagnosed as acute myocardial infarction or stroke, costly high-technology interventions such as coronary artery bypass surgery and other types of vascular surgery may be required for treatment (Nagendran et al., 2018).

2.2 Coronary Heart Disease (CHD)

2.2.1 Definition and Pathophysiology of CHD

Coronary heart disease (CHD), also known as ischaemic heart disease, is the most common form of CVD. CHD is characterised by inflammation with extravasation of immune cells into the sub-endothelial space, leading to the formation and/or progression of atherosclerotic plaques and thickening of the coronary artery walls. CHD occurs when there is a reduced supply of blood and oxygen to the myocardium resulting from a restriction or occlusion to at least one of the coronary arteries. Coronary occlusion secondary to disruption of atherosclerotic plaque with subsequent thrombus formation is the most common cause of the life threatening acute coronary syndrome (i.e. unstable angina and myocardial infarction) and sudden death (Ambrose & Singh, 2015). Clinically, CHD may present as angina, myocardial infarction, sudden death, and consequent chronic heart failure (Henderson, 1996).

Any condition attributed to obstruction of the coronary arteries which reduces blood flow to the heart is known as acute coronary syndrome, including unstable angina and myocardial infarction. Stable angina is not acute but categorised within ischaemic heart disease.

The development and progression of atherosclerotic plaque is extremely complex and includes a combination of multiple pathological process (Koenig, 2001). In the past decades, coronary imaging such as intravascular ultrasound (IVUS), optical coherence tomography (OCT) and positron emission tomography (PET) has evolved as a valuable adjunct to angiography, allowing the process of atherogenesis, plaque destabilization, and other pathologic conditions to be detected and quantified directly (Evans, Tarkin, Chowdhury, Warburton, & Rudd, 2016; Sakamoto, Nagamatsu, Yamamoto, Kaikita, & Tsujita, 2018). Pathological studies have revealed that rupture of lipid-rich plaque, followed by thrombus formation, is the main mechanism of acute coronary occlusion in 70-80% of patients with acute coronary syndrome (Naghavi et al., 2003). The rupture of the thin fibrous cap allows platelets to contact the highly thrombogenic necrotic core.

2.2.2 Prevalence and Disease Burden of CHD

Of all cardiovascular causes of mortality, CHD is the leading cause of premature death. CHD was responsible for an estimated 41.8% (7.4 million) of the 17.7 million cardiovascular mortality in 2015 (World Health Organization, 2017).

The mortality from CHD in developed countries has decreased in recent years. Death rates attributable to CVD declined by 28.8% from 2003 to 2013, and the actual number of CVD deaths per year declined by 11.7% (Mozaffarian et al., 2016). In the US, around 15.5 million people aged 20 years or above have CHD, and the prevalence increases with age for both women and men (Mozaffarian et al., 2016). In developing countries, however, the prevalence of CHD continues to increase. For example, in China, the "China Cardiovascular Disease Report 2017" (W. Chen et al., 2018) reported that the mortality rate due to CHD increased between 2012 and 2015 from 93.17 to 110.91 per 100,000 in urban areas and 68.62 to 110.67 per 100, 000 in rural areas. In India, the absolute number of deaths from CHD increased from 0.62 million in 1990 to 0.78 million in 1995, 0.95 million in 2000, 1.01 million in 2005, and 1.13 million in 2010 (GBD 2013 Mortality Causes of Death Collaborators, 2015; Gupta et al., 2016).

2.2.3 Current Management of CHD

Current strategies for impacting risk factors associated with secondary events in patients with CHD include smoking cessation, controlling hypertension, abnormal lipid levels, obesity and diabetes, psychosocial interventions, physical activity, and cardiac rehabilitation. We divide them into non-pharmaceutical therapies, pharmaceutical treatment, and cardiac rehabilitation, which are described below.

2.2.3.1 Non-pharmaceutical therapies

There is strong evidence suggesting that cigarette smoking cessation after an acute coronary event results in decreased morbidity and mortality. A population-based cohort study of 1,521 patients with a first acute MI a hazard ratio of 0.60 (95%CI 0.43 to 0.75) for death among quitters after MI compared with persistent smokers (Gerber, Rosen, Goldbourt, Benyamini, & Drory, 2009). However, a recent systematic review of seven RCTs demonstrated that currently available smoking cessation therapies are limited in their efficacy in patients hospitalised after an acute coronary event (Franck, Filion, & Eisenberg, 2018).

Psychosocial interventions are part of secondary prevention to facilitate cardiovascular risk reduction. A recent Cochrane review involving 35 studies with 10,703 people with CHD found no evidence that psychological treatments had an effect on total mortality, the risk of revascularisation procedures, or on the rate of non-fatal MI (Richards et al., 2017). Psychosocial interventions did reduce the rate of cardiac mortality and prevalence of

psychological symptoms (depression, anxiety, or stress). The risk of bias of the studies included in the review did result in some uncertainty around these findings.

Regular moderate or vigorous physical activity has been recommended in clinical practice guidelines for secondary prevention of CHD (Smith et al., 2006; Task Force et al., 2013). Physical activity is associated with reduced CHD risk (Tanasescu et al., 2002). Using self-reported data of 15,486 patients from 39 countries with stable CHD who participated in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) (R. A. H. Stewart et al., 2017), it demonstrated that more physical activity was associated with lower all-cause mortality (unadjusted hazard ratio [HR]: 0.82; 95%CI: 0.79 to 0.85; adjusted HR: 0.90, 95%CI: 0.87 to 0.93) and cardiovascular mortality (unadjusted HR: 0.83, 95% CI: 0.80 to 0.87; adjusted HR: 0.92, 95%CI: 0.88 to 0.96) in patients with stable CHD during a median follow-up of 3.7 years.

Surgical operations are also performed to treat CHD, including coronary-artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), valve surgery, and heart transplantation. CABG is a procedure in which autologous arteries or veins are used as grafts to bypass coronary arteries that are partially or completely obstructed by atherosclerotic plaque. CABG offers significant improvement in survival and quality of life for appropriately selected patients with multivessel coronary artery disease, especially those with more advanced coronary artery disease (Alexander & Smith, 2016). PTCA requires sophisticated equipment and skilled personnel, including cardiothoracic surgical support in the event that emergency bypass surgery is necessary (Bucher, Hengstler, Schindler, & Guyatt, 2000; Landau, Lange, & Hillis, 1994). A meta-analysis involving 953 patients treated with PTCA and 951 with medical treatment from six RCTs demonstrated that angioplasty may lead to a greater reduction in angina in patients with CHD than medical treatment but at the cost of more coronary artery bypass grafting (Bucher et al., 2000). Heart valve surgery is to cure the problem or lengthen life by restoring the function of a damaged or faulty heart value. A heart transplant is an operation in which a failing, diseased heart is replaced with a healthier, donor heart, which is usually reserved for people who have tried medications or other surgeries, but their conditions have not sufficiently improved. However, surgical interventions for CHD are costly and not always readily accessible for everyone (Favarato et al., 2003).

2.2.3.2 Pharmaceutical treatment

For people with established CHD, optimal medication include aspirin, beta-blockers, ACE inhibitors, and statins for secondary prevention of cardiac events (Pitts et al., 2017; Protty, Lacey, Hayes, & Freeman, 2017).

Aspirin is the classical antiplatelet pharmacotherapy in patients with CVDs because of its well-established role in secondary prevention of myocardial infarction, stroke, and death from vascular causes and its widespread availability and affordability (Gargiulo et al., 2016). Two meta-analyses of RCTs demonstrated that low-dose aspirin reduces the morbidity and mortality in patients with acute coronary syndromes or previous myocardial infarction (MI) and confers a durable long-term benefit (Antithrombotic Trialists' Collaboration, 2002; Antithrombotic Trialists' Collaboration et al., 2009). Another systematic review and meta-analysis appraised the hazards inherent to aspirin withdrawal or non-compliance in people at risk for or with coronary artery disease (Biondi-Zoccai et al., 2006). It found that the non-adherence or withdrawal of aspirin was associated with a 3-fold increased risk of major adverse cardiovascular events. Despite these convincing findings, some patients may not be receiving antiplatelet medications because of valid contraindications such as bleeding risk (Parekh, Galloway, Hong, & Wright, 2013).

Beta-blockers reduce sympathetic nervous system activity through blockade of adrenergic receptor subtypes (Poirier & Tobe, 2014). Treatment with beta-blockers remains the standard of care for patients with coronary artery disease, especially in patients after MI. Nevertheless, beta-blockers are not without adverse effects and their tolerability is not ideal (Bangalore et al., 2012). According to a national evaluation of adherence to beta-blocker therapy, among 17,035 patients with commercial health insurance in the US, only 45% of patients were adherent to beta-blocker use for one year after acute MI (Kramer et al., 2006). Additionally, a longitudinal, observational study of 44,708 patients demonstrated that beta-blocker use was not associated with a lower incidence of cardiovascular events among individuals with a prior history of MI, among individuals with coronary artery disease but no MI history, or among individuals with risk factors only for atherosclerotic disease (Bangalore et al., 2012).

ACE inhibitors block the activation of the renin-angiotensin system and may reduce the progression of both heart failure and atherosclerosis and reduce the rates of death, myocardial infarction, stroke, revascularization, cardiac arrest, heart failure, complications related to diabetes and new cases of diabetes (Heart Outcomes Prevention Evaluation Study Investigators

et al., 2000; White, 2003). In a systematic review and meta-analysis involving 12,763 patients, long-term use of ACE inhibitors lowered rates of mortality, myocardial infarction, and hospital admission for heart failure in patients with left-ventricular dysfunction or heart failure with or without a recent myocardial infarct (Flather et al., 2000). The adverse effects of ACE inhibitors include dry cough (Ontarget Investigators et al., 2008), acute renal impairment or renal failure (Ritter, 2011), hyperkalaemia (Ritter, 2011), urticarial and angio-oedema (Ontarget Investigators et al., 2008), and fetal injury (Ritter, 2011).

Statins, also called HMG-CoA reductase inhibitors, are used to lower low-density lipoprotein (LDL), for the prevention of atherosclerotic conditions such as stroke, myocardial infarction or limb ischemia (Psaty & Weiss, 2014). However, the magnitude of the preventive effect of statins is controversial. A systematic review involving 6 studies for primary prevention and 5 for secondary prevention demonstrated that death was postponed between -5 and 19 days in primary prevention trials and between -10 and 27 days in secondary prevention trials (Kristensen, Christensen, & Hallas, 2015). Side effects of statins include muscle symptoms, increased risk of diabetes, liver inflammation, cataracts, decreased energy, sexual dysfunction, and exertional fatigue (Abramson, Rosenberg, Jewell, & Wright, 2013).

2.2.3.3 Cardiac rehabilitation

Cardiac rehabilitation programs are comprehensive interventions including components of medical evaluation, prescribed exercise, cardiac risk factor modification, health education, and psychological counselling (Dalal et al., 2015). Cardiac rehabilitation (and secondary prevention) programs are designed to limit the physiological and psychological effects of cardiac illness, reduce the risk of sudden death or re-infraction, control cardiac symptoms, stabilise or reverse the atherosclerotic process, and enhance the psychosocial and vocational status of selected cardiac patients (Dalal et al., 2015).

Exercise training is a core component of cardiac rehabilitation programs. Internationally, cardiac rehabilitation programs are implemented through various models and vary in intensity and duration. For example, leading cardiac rehabilitation societies in North America and Europe recommend that patients progress from moderate- to vigorous-intensity aerobic endurance exercise, with resistance training included as an important adjunct, and recommend electrocardiograph-monitored exercise stress tests, while those in the United Kingdom, Australia and New Zealand specify lower-intensity exercise and less technical assessment of functional capacity (Price, Gordon, Bird, & Benson, 2016).

There has been an increasing number of clinical studies demonstrating the beneficial health effects of cardiac rehabilitation programs in patients with CHD. One recent updated Cochrane systematic review and meta-analysis (Anderson et al., 2016) involving 63 studies with 14,486 participants evaluated the exercise-based cardiac rehabilitation for people with CHD. It confirmed that exercise-based cardiac rehabilitation reduces cardiovascular mortality (RR 0.74, 95% CI 0.64 to 0.86) and the risk of hospital admissions (RR 0.82, 95% CI 0.70 to 0.96) as well as improvement in quality of life.

Unfortunately, given the benefits associated with cardiac rehabilitation, utilization of cardiac rehabilitation by patients with CHD historically has been poor, especially in older women (Grace et al., 2016; Ruano-Ravina et al., 2016). Barriers to patient referral and subsequent program entry and adherence include (1) lack of recognition by healthcare providers as well as their patients and families of the value of secondary prevention; (2) economic and logistic considerations for those wishing to participate; and (3) limited opportunities for safe and effective, reduced-cost programming, such as home-based or community centre programs (M. A. Williams et al., 2002).

Additionally, a substantial proportion of patients have stress, anxiety and depression symptoms after CHD events, which are associated with other factors, including sedentary lifestyle, smoking, unhealthy diet and reduced compliance with risk factor modification, but are undertreated (Pogosova et al., 2017). The American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation consistently recommend "comprehensive rehabilitation" programs that should include other components to optimise cardiovascular risk reduction, foster healthy behaviours and compliance to these behaviours, reduce disability, and promote an active lifestyle (Balady et al., 2007).

2.3 Hypertension

2.3.1 Definition and Pathophysiology of Hypertension

According to the definition of WHO, hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels have persistently raised pressure (World Health Organization, 2018d). Blood pressure is the force of blood pushing against the walls of the arteries as the heart pumps blood, and hypertension happens when the force is too high (National Heart Lung and Blood Institute, 2018).

Hypertension is defined as a systolic blood pressure (the highest pressure in blood vessels and happens when the heart contracts or beats while pumping blood) equal to or above 140 mm Hg and/or diastolic blood pressure (the lowest pressure in blood vessels in between heart beats when the heart muscle relaxes) equal to or above 90 mm Hg. However, the definitions of hypertension for the diagnosis and management decisions vary between international guidelines (Messerli, Rimoldi, & Bangalore, 2018). Table 2.1 outlines current values for categorisation of clinical blood pressure in Australian adults (National Heart Foundation of Australia, 2016).

Table 2.1 Classification of clinic blood pressure in adults

Diagnostic category	**Systolic (mmHg)**		**Diastolic (mmHg)**
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High-normal	130-139	and/or	85-89
Grade 1 (mild) hypertension	140-159	and/or	90-99
Grade 2 (moderate) hypertension	160-179	and/or	100-109
Grade 3 (severe) hypertension	≥180	and/or	≥110
Isolated systolic hypertension	>140	and	<90

There are two main types of hypertension: primary and secondary hypertension. Primary, or essential, hypertension is the most common type of hypertension, which tends to develop over years as a person ages. Secondary hypertension is caused by another medical condition or use of certain medicines, which usually resolves after the causes are treated or removed.

2.3.2 Prevalence and Disease Burden of Hypertension

Hypertension is a high-risk health disorder and is the most important risk factor for CVD mortality and cardiovascular events (GBD 2015 Risk Factors Collaborators, 2016; Redon et al., 2016; Tzoulaki et al., 2016). Complications of hypertension account for 9.4 million annual CVD deaths worldwide every year (World Health Organization, 2013). In China, using data from the 2010 National Population Census as a denominator, it is estimated that the total number of people with hypertension is approximately 270 million (H. Li & Ge, 2014). Hypertension accounted for 2.043 million deaths in China in 2010, representing for 24.6% of all deaths (H. Li & Ge, 2014). In 2014-2015, 6 million Australians (34%) aged 18 years and

over were hypertensive (Blood pressure ≥ 140/90 mmHg) or taking antihypertensive medication (Australian Bureau of Statistics, 2015), and 4.1 million Australians had uncontrolled or untreated hypertension.

The rate of elevated systolic blood pressure (SBP) (≥110-115 and ≥140mm Hg) has increased substantially between 1990 and 2015, and the all disability-adjusted life-years (DALYs) and deaths associated with SBP has also increased (Forouzanfar et al., 2017). Results from the Global Burden of Disease (2015) suggest that an estimated 3.5 billion adults had SBP of at least 110 to 115 mm Hg and 874 million adults had SBP of 140 mm Hg or higher worldwide.

2.3.3 Current Management of Hypertension

There are significant health and economic gains from early detection, adequate treatment and good control of hypertension. Early detection of hypertension can minimise the risk of life-threatening complications such as heart attack, heart failure, stroke and kidney failure (World Health Organization, 2013). Despite huge efforts, the levels of awareness, treatment and control rates of hypertension remains low, especially in developing countries (Y. Li et al., 2017). A recent systematic analysis of data from 178 studies involving 2,901,464 participants covering 30 provinces of China shows that from 1999 to 2014, the overall rates of prevalence, treatment, and control of hypertension were 28.9%, 35.3% and 13.4% in China, respectively (Y. Wang et al., 2016).

Management of hypertension for each individual is determined by numerous factors including a thorough clinical investigation to identify the severity of hypertension, the associated clinical conditions and/or end-organ damage, as recommended by the National Heart Foundation of Australia in *Guideline for the Diagnosis and Management of Hypertension in Adults - 2016* (Gabb, Mangoni, & Arnolda, 2017).

2.3.3.1 Non-pharmaceutical therapies

Lifestyle modification is recommended for all patients with or without hypertension and regardless of drug therapy. Numerous trials using lifestyle interventions in patients with hypertension have shown reductions in blood pressure and a reduction in combined cardiovascular events and total mortality (Eriksson, Franks, & Eliasson, 2009; Folta et al., 2009).

Lifestyle modification includes controlling behaviour risk factors such as the consumption of food containing excessive sodium and saturated fat, inadequate consumption of wholegrain breads and cereals, vegetables and fruits, harmful levels of alcohol consumption, lack of

physical activity, and poor stress management. Controlling these behaviour risk factors assists with reducing blood pressure and contributes to reducing other CVD risk factors and improving general health (World Health Organization, 2013). Importantly, long-term adherence to lifestyle improvement may delay or prevent the onset of hypertension, contribute to the reduction of blood pressure in patients with hypertension already on therapy and, in some cases, reduce or abolish the need for antihypertensive therapy (Gabb et al., 2017).

2.3.3.2 Pharmaceutical treatment

Several guidelines for the management of hypertension in different clinical settings have been developed by many professional bodies to inform clinicians (Jarari et al., 2015).

Thiazide diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) are recommended as suitable first-line drugs for the treatment of hypertension, either as monotherapy or in some combinations (Carey & Whelton, 2018; Gabb et al., 2017). A 2015 meta-analysis involving 55 RCTs (195, 267 patients with hypertension) comparing drug classes with placebo demonstrated that blood pressure lowering is accompanied by significant reductions in the relative and absolute risk of stroke and major cardiovascular events, independent of the specific drug properties (Thomopoulos, Parati, & Zanchetti, 2015).

Combination therapy, defined as the use at least two antihypertensive drugs, is required in up to 50-70% of patients to achieve blood pressure targets (Gabb et al., 2017). It is widely accepted that combining two classes of antihypertensive drug lowers blood pressure more than doubling the dose of one drug. ACE inhibitors and CCBs are superior to diuretics combined with either an ACE inhibitor or a beta-blocker in their effects on various cardiovascular events and mortality (Dahlof et al., 2005; Jamerson et al., 2008).

Since treatment of hypertension is long term, the tolerability and safety of drugs is particularly important. However, all effective antihypertensive drugs have adverse effects. In general, after starting drug treatment, patients should be reviewed at 4-to 6-week intervals to evaluate adherence, adverse effects, tolerability and efficacy (Gabb et al., 2017).

2.4 Cardiovascular Risk Factors

Strong evidence exists to support the association between behavioural risk factors and other contributing risk factors, and the development and prognosis of CVDs.

2.4.1 Behavioural Risk Factors

Global comparative risk assessment studies have estimated that the major risk factors of CVD are related to lifestyle, including smoking, unhealthy diet, physical inactivity and harmful use of alcohol (Tzoulaki et al., 2016). These unhealthy lifestyle behaviours may lead to metabolic/physiological changes in the body, resulting in other contributing cardiovascular risk factors, such as high blood pressure, overweight/obesity, hyperglycemia/diabetes, and dyslipidaemia. As a result, coronary and cerebral blood vessel problems may happen due to atherosclerosis, a process developing over many years starting in childhood and manifesting as heart attacks and strokes in people of middle age (Kwon et al., 2016; Z. Wang et al., 2017).

Smoking regardless of cigarette type is a major risk factor of CVD (Munro, Tarone, Wang, & Blot, 2016). Evidence from large prospective cohort studies with regards to the beneficial effects of smoking cessation on CHD mortality has been largely reported (Kondo et al., 2011; Luksiene, Tamosiunas, Virviciute, & Radisauskas, 2017). A population-based cohort study collected data at the 31-year and 46-year follow-ups with a total of 5038 and 5974 individuals demonstrated that, smoking seems to be above all an independent risk factor for CVD in the working-age population (Keto et al., 2016).

Insufficient physical activity is one of the ten leading risk factors for global mortality. Physical activity is any bodily movement produced by the muscles which results in energy expenditure. Globally in 2010, 23% of adults aged 18 years and above were insufficiently active (World Health Organization, 2018f). Based on self-report data from the Australian Bureau of Statistics (ABS) 2014-2015 National Health Survey (NHS), over one in two Australian adults (56%) had insufficient physical activity (Australian Bureau of Statistics, 2015). In adults, participation in at least 150 minutes of moderate intensity physical activity each week (or equivalent) is estimated to reduce the risk of CHD by approximately 30% and the risk of diabetes by 27%, as recommended by WHO (World Health Organization, 2018g).

Alcohol consumption is responsible for more than 200 diseases and health conditions, including hypertension, myocardial infarction, cardiomyopathy, cardiac arrhythmia, and cirrhosis of the liver (World Health Organization, 2014). Annually alcohol consumption was responsible for 2.5 million deaths worldwide, accounting for 3.8% of all global deaths, and more than half of these deaths were due to CVDs, liver cirrhosis and cancer (World Health Organization, 2018c).

Unhealthy diet is also a modifiable behaviour risk factor of CVD. A considerable body of research reported on the nutritional background of atherosclerosis in general and particularly

CHD. High dietary intakes of saturated fat, trans-fat cholesterol and salt, and low intake of fruits, vegetables and fish are associated with the risks of CVD. In people at high risk of CVD, adherence to a Mediterranean diet is recommended. A Mediterranean diet is characterised by a high consumption of vegetables, fruits and healthy oil and moderate consumption of protein (Erwin et al., 2018; Torres-Pena et al., 2018; Widmer, Flammer, Lerman, & Lerman, 2015). A body of evidence supports population-wide salt intake reduction as recommended by current guidelines as an essential public health effort to prevent CVD (Aaron & Sanders, 2013; Kanzler, Hartmann, Gruber, Lammer, & Wagner, 2014).

Overweight or obesity is a risk factor of cardiovascular morbidity, mortality and total mortality by prospective epidemiological studies (Königstein et al., 2018). In 2010, overweight and obesity were estimated to cause 3.4 million deaths, 3.9% of years of life lost, and 3.8% of disability-adjusted life-years (DALYs) worldwide (Lim et al., 2012). The number of people overweight or obese has increased between 1980 and 2013 from 28.8% to 36.9% in men and from 29.8% to 38.0% in women and increased substantially in children and adolescents in both developed and developing countries (M. Ng et al., 2014).

Diabetes is a major risk factor of CVD. Dinesh Shah et al. (Dinesh Shah et al., 2015) used linked electronic health records from 1997 to 2010 to investigate the absolute and relative risks associated with type 2 diabetes in a cohort of in 1.92 million patients in England. Their findings demonstrated that type 2 diabetes was strongly positively associated with many types of CVDs. The risk of cardiovascular events is from two to three times higher in people with diabetes and the prognosis is poorer, compared with those without diabetes (Emerging Risk Factors Collaboration et al., 2010; Karayiannides, Lundman, Friberg, & Norhammar, 2018; Ofstad, Atar, Gullestad, Langslet, & Johansen, 2018). A 23-year follow-up study found lifestyle intervention for people with impaired glucose tolerance reduced incidence of cardiovascular and all-cause mortality and diabetes (G. Li et al., 2014).

The blood lipid profile includes low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. An increase in concentration of total cholesterol and LDL-C and a decrease in HDL-C is associated with raised risk of CVD (Mediene-Benchekor et al., 2001). The importance of lipid management for prevention of coronary and stroke events has been reported in many clinical studies (LIPID Study Group (Long-term Intervention with Pravastatin in Ischaemic Disease), 2002). One meta-analysis of randomised trials of statins in combination with other preventive strategies with 165,792

individuals shows that each 1 mmol/L (39mg/dL) decrease in LDL cholesterol equates to a reduction in relative risk for stroke of 21.1%, and intense reduction of LDL cholesterol by statins also significantly reduced the risk of recurrent major cardiovascular events (Amarenco & Labreuche, 2009). The side effects of statins include muscle symptoms, increased risk of diabetes, liver inflammation, cataracts, decreased energy, sexual dysfunction, and exertional fatigue (Abramson et al., 2013).

2.4.2 Other Contributing Risk Factors

Other contributing risk factors for CVDs, include family history, aging, gender, socioeconomic determinants and psychological wellbeing (Havranek et al., 2015; World Health Organization, 2017).

Detailed medical family history (hereditary factors) data have been proposed to be effective in identifying high-risk families for earlier detection, management of modifiable risk factors and targeted intervention (Kulshreshtha et al., 2015; R. R. Williams et al., 2001). Large population-based studies have found that most early cardiovascular events occur in families with a positive family history of CVD (R. R. Williams et al., 2001). Analysis of data from 1034 children found that children with familial hypercholesterolemia (FH) in the highest LDL-C and whose lipoprotein as >300 mg/L had a 1.7-times and 1.45-times higher incidence, respectively (Wiegman et al., 2003). A case-control study of 1091 male and 531 female aged 40-70 years found that family history of CHD is not only a strong risk factor for myocardial infarction in both sexes, but that its effect is synergistic with other cardiovascular risk factors as well (Leander, Hallqvist, Reuterwall, Ahlbom, & de Faire, 2001).

Aging is the dominant risk factor for clinically significant atherosclerotic lesion formation which is the results of a myriad of independent pathways and their complex interactions (Head et al., 2017). Population aging accelerates the rapid increasing burden of CVDs. European Union region currently experiences most advanced stage of demographic aging due to related net-migration rate changes (Jakovljevic et al., 2018). According to United Nations, in 2025 an estimated 44% of population worldwide will live in relatively aged countries, with at least 20% of the population aged 60 years or over (United Nations Department of Economic and Social Affairs Population Division, 2015).

Gender is an important determinant of cardiovascular risk, and men generally develop CVD earlier than women (Lyngbakken et al., 2016). A prospective population-based cohort study with 2888 participants during a follow-up of up to 20.1 years demonstrated that at age 55,

though men and women have similar lifetime risks of CVD (men: 67.1%; women: 66.4%), there are considerable differences in the first manifestation (Leening et al., 2014). The authors concluded that men and women are more likely to develop CHD as a first event (27.2%), while women are more like to have cerebrovascular disease (22.8%) or heart failure (14.9%) as their first event, although there manifestation appear most often at older ages (Leening et al., 2014).

Social determinants of CVD include socioeconomic position (encompassing wealth and income, education, employment/occupational status, etc.), race and ethnicity, social support, culture, access to medical care, and residential environments (Havranek et al., 2015). Overall, lower socioeconomic position in the United Sates is associated with a greater prevalence of CVD risk factors and a higher incidence of and mortality resulting from CVD (Havranek et al., 2015). The prevalence of hypertension in blacks in the United States is among the highest in the world (Benjamin et al., 2018). Additionally, evidence from the analysis of 8,492 individuals with self-reported CVDs from 21 countries enrolled in the PURE study demonstrated that use of medication for secondary prevention of CVDs is alarmingly low, especially in low-income countries, ranging from 0% in South Africa (95% CI: 0-1.7), Tanzania (0-3.6), and Zimbabwe (0-5.1), to 49.3% in Canada (44.4-54.3) (Murphy et al., 2018).

Stress, anxiety and depression are also important contributing factors to CVDs; their relationship with CVDs are discussed in detail below.

2.5 Stress, Anxiety, Depression and CVD

There is a large body of evidence addressing the association between psychosocial factors and CVD. A recent longitudinal study (Palacios, Khondoker, Mann, Tylee, & Hotopf, 2018) involved 803 patients with diagnosis of CHD and followed them up every 6 months for 3 years. This study demonstrated that symptoms of anxiety and depression are highly prevalent in patients with stable CHD. Another study assessed psychosocial stress and major cardiovascular events in patients with stable CHD by a questionnaire in 14,577 patients followed-up 3.7 years (Hagström et al., 2018). Psychological stress was associated with increased CVD mortality in patients with stable CHD.

A recent Cochrane systematic review involving 35 studies with 10,703 participants with CHD explored the effectiveness of psychological interventions for the management of CHD (Richards et al., 2017). Psychological interventions led to a significant reduction in cardiovascular mortality (relative risk 0.79, 95% CI 0.63 to 0.98) and improved depressive

symptoms (SMD -0.27, 95%CI -0.39 to -0.15), anxiety (SMD -0.24, 95% CI -0.38 to -0.09) and stress (SMD -0.56, 95% CI -0.88 to -0.24) in patients with CHD.

Psychological risk factors such as stress, anxiety, and depression are known to play a significant and independent role in the development of hypertension, CHD and its complications (Albus, 2010; Chida & Hamer, 2008; Korkmaz, Korkmaz, Yildiz, Gundogan, & Atmaca, 2017; Nekouei, Doost, Yousefy, Manshaee, & Sadeghei, 2014; Palagini et al., 2016; Player & Peterson, 2011; Wiltink et al., 2011). These psychological risk factors, especially depression, are associated with other risk factors, including educational level, sedentary lifestyle, smoking, unhealthy diet and reduced compliance with risk factor modification (Pogosova et al., 2017). The influence of depression in patients with CHD that independently associated with increased cardiovascular morbidity and mortality has been extensively documented (Baumeister et al., 2011; Gan et al., 2014; Rugulies, 2002). Previous research has focused on the role of anxiety in depression-related risks. Anxiety is highly comorbid with depression and both are independently associated with increased risk of mortality in CHD patients (Watkins et al., 2013). As a result, the American Heart Association has recommended that patients who positively screen for depression should be evaluated for the presence of anxiety (Lichtman et al., 2008).

2.5.1 Stress

2.5.1.1 Definition of stress

The implication of stress on the risk and prognosis of CHD has been established for over four decades (Jenkins, 1971, 1976; Kivimaki et al., 2006; Redmond et al., 2013; Richardson et al., 2012). There are a number of types of stress defined in the research setting, including work stress, environmental stress, marital stress, financial stress, stressful life events, stress symptoms (e.g., sleep difficulties) and other stressors (Katsarou, Triposkiadis, & Panagiotakos, 2013). Definitions of stress focus on two major components: (1) the “cause”, namely environmental stressors or stimuli, such as work environment and life events; and (2) the “effect”, namely subjective reaction to stress, such as stress appraisal and emotional response (Kopp et al., 2010). Broadly speaking, stress measured in research can be classified into three perspectives: (1) environmental, focusing on stressors or life events; (2) psychological, assessing subjective stress appraisal and affective reactions; and (3) biological, assessing the activation of the physiological systems involved in the stress response (E. H. Lee, 2012).

2.5.1.2 Stress and CVD

Reporting on stress and CVD, has primarily focused on work stress. Numerous studies have documented work stress as a high risk factor of CVD and CHD (Gallo, Bogart, Vranceanu, & Walt, 2004; Karasek, Collins, Clays, Bortkiewicz, & Ferrario, 2010; Siegrist, 2005) Work stress includes job strain or demand-control, effort-reward imbalance, over-commitment, organisational injustice, shift work, job insecurity, job satisfaction, and working hours (Backe, Seidler, Latza, Rossnagel, & Schumann, 2012; Glozier et al., 2013). One meta-analysis found that between 8.8 to 10.2% of CHD morbidity was attributed to work stress, whereby the total costs of CHD and mental disorders attributed to work stress exposure ranged from 1.8 to 3 billion euros in France in 2003 (Sultan-Taïeb, Chastang, Mansouri, & Niedhammer, 2013). Employees with work stress had an average of 50% higher risk of the development of CHD than those without work stress (Kivimaki et al., 2006). A meta-analysis found that the association between work stress and cardiovascular morbidity and mortality was stronger in patients under the age of 55 (Backe et al., 2012). Similarly, another study emphasised the importance of reducing work stress, and recommended that people work until 65 years old to prevent cardiovascular events (Munakata, 2014). A meta-analysis found that for first CHD event, work stress was associated with an increased relative risk of recurrent CHD events of 65% (J. Li, Zhang, Loerbroks, Angerer, & Siegrist, 2015). Compared with work stress, marital stress appears to affect women more strongly, and marital stress was associated with a 2.9-fold increased risk of recurrent events in patients with CHD (Orth-Gomer et al., 2000).

Both epidemiological and prospective studies have generated evidence to support the causal relationship between stress and CVD. Flaa et al. (2008) conducted a longitudinal follow-up study over 18 years examining the prognostic significance of individual differences in reactions to psychological stress, and found that stress-induces sympathetic nervous activity, indicating a possible causal factor in the development of essential hypertension (Flaa, Eide, Kjeldsen, & Rostrup, 2008). A large-scale cross-sectional study that investigated the relationship between the psychosocial work environment and CVD prevalence in 13,779 workers aged between 16 to 65, found that work stress and a lack of co-worker social support contributed to higher CVD prevalence (Johnson & Hall, 1988). Financial stress also increases the incidence of CVD and all-cause mortality, especially among men (Carlsson et al., 2014).

Prognosis for people with CHD and/or hypertension may be worsened by psychological stress. A qualitative study involving interviewees with CHD identified that cardiac events were significantly more prevalent among patients with both psychiatric problems and biological risk factors (Shoja Shafti, 2014). A meta-analysis of 43 studies showed that stress reduction

interventions as a psychological treatment in patients with acute myocardial infarction resulted in a 2-year reduction in mortality in men and event recurrence in all patients with CHD by 27% (Linden, Phillips, & Leclerc, 2007). An observational cohort study found that high stress was associated with three-fold increased risk in readmission rates within 30 days in patients with acute coronary syndrome, after adjustment for demographic and clinical factors and depression (Edmondson, Green, Ye, Halazun, & Davidson, 2014). A cohort study involving 4,204 patients with acute myocardial infarction found that patients with moderate/high stress had a higher two-year mortality compared with those with low stress (Arnold, Smolderen, Buchanan, Li, & Spertus, 2012).

2.5.1.3 Pathophysiological mechanisms

The pathophysiological mechanisms underlying the association between stress and CVD remain unclear. Explanations include both physiological and behavioural responses to stress (Inoue, 2014; Lagraauw, Kuiper, & Bot, 2015). Stress may result in impaired elevated fibrinogen (Siegrist, Peter, Cremer, & Seidel, 1997; Vrijkotte, van Doornen, & de Geus, 1999), exaggerated cardiovascular reactivity such as increased blood pressure (Djindjic et al., 2013), increased lipid profile (Cesana et al., 2003; Evolahti, Hultcrantz, & Collins, 2009; Steptoe & Willemsen, 2004; Vrijkotte, van Doornen, & de Geus, 2000; S. C. Yang, Chien, Tsai, Ho, & Chen, 2011), endothelial dysfunction (Ushakov, Ivanchenko, & Gagarina, 2016), lower heart rate variability (Hintsanen et al., 2007), elevated hypothalamic-pituitary-adrenal (HPA) axis biomarkers (Chandola, Heraclides, & Kumari, 2010), beta-receptor down-regulation (Vrijkotte, van Doornen, & de Geus, 2004), heightened acute inflammatory responsivity (Emeny et al., 2013; Hamer et al., 2006), platelet activation (Brydon, Magid, & Steptoe, 2006), and induction in other behaviour (e.g. physical inactivity) or psychological risks (e.g. increased anxiety) (Balog et al., 2003; Ushakov et al., 2016). The multiple factors mentioned above can affect the clinical courses and outcomes of people with cardiovascular disease.

2.5.2 Anxiety

2.5.2.1Definition of Anxiety

Anxiety has been defined as a stimulus, a trait, a motive and a drive. Anxiety can be differentiated into state anxiety which is an emotional condition at a period of time, and trait anxiety which is a personality characteristic (Allahverdipour, Asgharijafarabadi, Heshmati, & Hashemiparast, 2013). The prevalence of anxiety in CHD patients varies from 12.0% to 41.8% in men, and 21.5% to 63.7% in women (Pajak et al., 2013). Research has shown that anxiety

has a substantial effect on both the development of CHD as well as an increased risk of subsequent cardiovascular events (Kubzansky, Cole, Kawachi, Vokonas, & Sparrow, 2006; Player & Peterson, 2011).

2.5.2.2 Anxiety and CVD

Anxiety and the development of CVD has been reported in recent years. Two meta-analyses confirmed anxiety as an independent risk factor for the development of CHD in healthy subjects, as well as for a poorer prognosis among patients with established CHD (Roest, Martens, de Jonge, & Denollet, 2010; Roest, Martens, Denollet, & de Jonge, 2010). Large-scale prospective studies have demonstrated a significant link between anxiety and sudden cardiac death or cardiac events (Janszky, Ahnve, Lundberg, & Hemmingsson, 2010; Kawachi et al., 1994; Nabi et al., 2010). Anxiety is a strong, independent predictor of major cardiac events in patients with stable coronary disease (Frasure-Smith & Lesperance, 2008; Moser et al., 2011; Phillips, 2011; Strik, Denollet, Lousberg, & Honig, 2003). Furthermore, anxiety following a major cardiac event can impede recovery and is associated with both higher morbidity and mortality.

Anxiety has a significant negative relationship with functional status and quality of life in patients with CHD (Allahverdipour et al., 2013). Engebretson and colleagues (1999) found that CHD patients with a high level of anxiety had a significantly lower quality of life in comparison to those with a lower level.

Anxiety as a CVD risk factor has been found to be independent of depression or other psychological factors (Benninghoven et al., 2006; Frasure-Smith & Lesperance, 2008; B. J. Shen et al., 2008).

2.5.2.3 Pathological mechanisms

The precise pathological mechanisms underlying anxiety and CVD are unclear. Several studies have demonstrated a link between potential pathological mechanisms including autonomic dysfunction such as reduced baroreflex cardiac control (Watkins, Blumenthal, & Carney, 2002), dysregulation of the HPA axis (Merswolken, Deter, Siebenhuener, Orth-Gomer, & Weber, 2013), increased markers of inflammation (Steptoe, Wikman, Molloy, Messerli-Burgy, & Kaski, 2013), progression of atherosclerosis (Paterniti et al., 2001), impaired vagal control, decreased heart rate variability (Martens, Nyklicek, Szabo, & Kupper, 2008), risk of ventricular

arrhythmia (van den Broek et al., 2009; Watkins et al., 2006), elevated in the cardiac biomarker C-reactive protein (Bankier, Barajas, Martinez-Rumayor, & Januzzi, 2008, 2009), and unhealthy behaviours or lifestyle (Bonnet et al., 2005).

2.5.3 Depression

2.5.3.1 Definition of Depression

According to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), depression is the subjective experience of psychological and somatic symptoms (Davidson, 2012). Depression is related, not only to the incidence of CHD, but also to the prognosis of patients with established heart disease. Depression is associated with an increased risk of mortality in patients with CHD (Carney et al., 2016). Depression is also associated with poor medical prognosis in CHD patients.

2.5.3.2 Depression and CVD

The close association between depression and the development of CVD is well documented. A meta-analysis involving thirty prospective cohort studies with 893,850 participants (59,062 CHD cases) during a follow-up period ranging from 2 to 37 years demonstrated that depression is independently associated with a significantly increased risk of CHD (relative risk ([RR]: 1.30; 95% CI: 1.22-1.40) and MI (RR: 1.30; 95%CI: 1.18-1.44) (Gan et al., 2014).

The prevalence of depression is high in patients with CHD. Rates of major depressive disorder of approximately 15% to 30% have been reported in patients after acute myocardial infarction or coronary artery bypass grafts (Carney & Freedland, 2003; Thombs et al., 2006), and 20% to 40% of individuals have significant patient-reported depressive symptoms (Bush et al., 2005; Celano & Huffman, 2011). An analysis of longitudinal data from nationwide general practices in Germany (n=1072) involving 59,992 patients matched to 59,992 controls demonstrated that 21.8% of the CHD group and 14.2% of the control group were diagnosed with depression (Konrad, Jacob, Rapp, & Kostev, 2016). A meta-analysis found that consistent with the general population, the prevalence of major depression is 2-times greater in women than men with CHD (Shanmugasegaram, Russell, Kovacs, Stewart, & Grace, 2012).

Depression in CHD patients has been associated with significant increases in medical utilization, loss of productivity and functional disability (Egede, 2007; W. F. Stewart, Ricci, Chee, Hahn,

& Morganstein, 2003). The health care costs of outpatient care, emergency room and readmission during the first year following myocardial infarction in patients with elevated depressive symptoms were 41% higher than for those with few depressive symptoms (Frasure-Smith et al., 2000).

Depression may increase other cardiovascular risk factors in people with established CVD. A large survey interviewing 8966 CHD patients <80 years of age covering 22 European countries found that CHD patients with severe depressive symptoms had lower frequency of regular exercise and decreased likelihood of exercise intention (Prugger et al., 2017). A prospective cohort study following 667 patients with stable CHD for 5 years demonstrated that greater depressive symptoms are linked to a range of poorer lifestyle risk factors (less physical activity, lower medication adherence, higher body mass index, higher waist to hip ratio, worse sleep quality and smoking), predicting future declines in physical activity, medication adherence and sleep quality (Sin, Kumar, Gehi, & Whooley, 2016).

Large epidemiological studies have convincingly demonstrated that depression is a predictor for occurrence and recurrence of CHD. The relative risk of death in depressed patients within 18 months following a cardiac event is twice as likely than in patients without depression (Frasure-Smith, Lesperance, & Talajic, 1995). A meta-analysis showed that those with both premorbid and post-CHD depression have 1.5 to 2 times higher risk of mortality and cardiac morbidity (Y. W. Leung et al., 2012).

Depression is associated with diminished health-related quality of life (HRQoL) in patients with CHD. A systematic review with 11 studies (Dickens, Cherrington, & McGowan, 2012) found that depression predicts subsequent physical HRQoL and this association was not attributable to confounding effects of baseline HRQoL or the severity of the CHD.

2.5.3.3 Pathological mechanisms

The underlying mechanisms of the multiple pathophysiological pathways involved in the relationship between depression and CHD and hypertension and other CVDs are not yet fully understood; and further clarification is needed. A large body of evidence suggests that depression increases the risk of CVD morbidity and mortality due to psychological, behavioural and biological mechanisms. The hypothesized mechanisms include the link between depression and atherosclerosis through the pathways of inflammation and endothelium dysfunction

(Chrysohoou et al., 2018), HPA dysregulation and heightened cortisol response, autonomic nervous system dysfunction and inflammation (Davidson, 2012; J. T. Wang, Hoffman, & Blumenthal, 2011). For example, depressed patients have greater platelet aggregation, reduced heart rate variability, erectile dysfunction (Sulistyo, Andiarso, & Hariawan, 2016), and a higher level of inflammatory markers such as C-reactive protein (Burg, Martens, Collins, & Soufer, 2011; Gegenava, Gegenava, & Kavtaradze, 2011; Strike & Steptoe, 2004; Sunbul, Sunbul, & Gulec, 2017). Other hypothesized mechanisms include psychosocial factors such as social isolation and low perceived social support, as well as negative lifestyle and behavioural factors (Lie, Hernandez, Trout, Kleiman, & Bozzay, 2017; J. T. Wang et al., 2011). The psychological difficulties associated with depression also exacerbate negative lifestyle factors such as smoking, poor diet, sleep architecture disruption and sedentary lifestyle (Davidson, 2012; Doyle et al., 2014; Lina & Li, 2016). Medication adherence also has been identified as a potential mediator of the depression CHD relationship (J. T. Wang et al., 2011; Ziegelstein et al., 2000).

2.6 Tai Chi

2.6.1 Overview of Tai Chi

Tai Chi, also known as Tai Chi Chuan/Quan or Taiji, is variously described as a meditative or internal martial atrial art or a mind-body exercise that originated in China. Tai Chi was developed by a famous martial artist Chen Wang-Ting towards the end of Ming Dynasty (17th Century A.D.) (L. Gu & Shen, 2007). Chen Wang-Tingcomprehensively incorporated the essence of Chinese folk and military martial arts, breathing and meditative techniques, Taoist philosophy of *yin* and *yang*, and traditional Chinese medicine theory (Tang & Gu, 2012).

The characteristics of Tai Chi reflect traditional Chinese medicine theory. Firstly, according to traditional Chinese medicine, meridians are passageways for the flow of '*qi*' and 'blood', which are the two basic bodily fluids in Chinese medicine (D. Li, 1995). Meridians spread on the surface of the whole body vertically and horizontally, integrating the inside with the outside of the body and connecting the inner organs, joints and extremities. The movements of Tai Chi are required to be led by mind and '*qi*' and relax the whole body to help '*qi*' and 'blood' flow smoothly (Tang & Gu, 2012). Secondly, traditional Chinese medicine addresses the concept of holism, i.e. all body functions are under the complete state of one organism (G. R. Sun, 2008).

The practice of Tai Chi requires the combination of mind, body and breath. Through the adjustment of mind, body and breath, Tai Chi enhances the harmony of the whole body. Thirdly, traditional Chinese medicine places emphasis on personalised treatment. Tai Chi is often adjusted to suit individual's need through selecting different Tai Chi styles or forms, practicing in lower or higher postures, or at slower or quicker speed (L. Gu & Shen, 2007).

Traditionally, the main components of Tai Chi are movement, meditation and imagination, and deep/abdominal breathing (Tang & Gu, 2012). This enables practitioners to benefit both physically and psychologically from Tai Chi. Tai Chi movements consist of a sequence of slow, continuous, graceful movements with circular and spiral body movements, which are known as *forms*.

In the past decade, clinical researchers have investigated the multiple components of Tai Chi. Wayne et al. (2013) deconstructed the multiple components of Tai Chi as follows: (1) awareness, mindfulness, and focused attention; (2) intention, belief and expectation; (3) structural integration, dynamic form and function; (4) active relaxation; (5) strengthening and flexibility; (6) natural, freer breathing; (7) social support, interaction and community; (8) embodied spirituality, philosophy and ritual. These components may work independently and synergistically to generate benefits (Wayne et al., 2013).

Tai Chi was reported for the first time as an intervention in a clinical study in 1958. This, case series conducted in China investigated the beneficial effects of Tai Chi on tuberculosis (D. Wang, 1958). In 1988, the first RCT of Tai Chi was conducted to investigate the effect of Tai Chi in combination with Qigong in cardiac rehabilitation (Y. Sun et al., 1988). The intensity of Tai Chi is regarded as low to moderate, and can be easily adjusted to meet different requirements of intensity (L. Gu & Shen, 2007). Therefore, it is a feasible choice for individuals who are sedentary or have limited exercise capacity such as the cardiac population.

Research assessing the safety and physical and psychological benefits of Tai Chi in healthy population and various patient cohorts has grown in recent years. We reviewed 507 clinical studies of Tai Chi and found that Tai Chi clinical studies have been conducted in 20 countries worldwide covering various diseases/conditions such as hypertension, diabetes, heart failure, CHD, and depression (G. Yang et al., 2015).

2.6.2 Tai Chi Styles

Tai Chi was traditionally only practiced in the *Chen* family. It wasn't until Yang Lu-Chan learned Tai Chi from the 14th generation of *Chen* family and adapted the *Chen*-style into *Yang*-style that Tai Chi was taught in Beijing and promoted to other areas of China (Z. W. Fu, 1963). It was not until 1928 when Chen Fa-Ke was invited to Beijing to teach Tai Chi that *Chen*-style Tai Chi was recognized and practiced by a wider population. Today Tai Chi is widely practiced for its health benefits both in Eastern and Western countries. Other classical styles include *Wu, Wu/Hao*, and *Sun* styles that are all derived directly or indirectly from *Chen* style, based on the unique backgrounds of the practitioners and the changes of social environment. For example, *Sun*-style Tai Chi was developed by Sun Lu-Tang, who learned *Chen*-style Tai Chi when he was already an expert in other two traditional martial arts (i.e. *Xingyi* and *Bagua*). Therefore, we can see the impacts of *Xingyi* and *Bagua* in *Sun*-style Tai Chi movements.

Each classical style has its own forms. Therefore, the movements and characteristics of different styles vary. For example, within *Yang* style, there are different forms varying with respect to the number of movements and postures (e.g., 24-, 37-, 72-, 108-, and 150-movement forms), or the overall emphasis (e.g., health maintenance, martial skills, meditation and self-realization, competitive performing arts) (Wayne & Kaptchuk, 2008b). However, because all styles and forms are derived directly or indirectly from *Chen* style, the core principles and theories of them, such as balance, breathing, coordination, relaxation and concentration are similar.

After the foundation of People's Republic of China, to improve the overall health of the general public, the Chinese government promoted the generalisation of the five classical styles by simplifying these traditional Tai Chi forms and developing several competition forms based on them (Chen, Yang, Wu/Hao, Wu and Sun). In 1956, the General Administration of Sports of China issued a book titled 'Simplified Tai Chi' according to the classical Yang-style Tai Chi, which removed difficult and duplicate forms and simplified the 81 forms into 24 forms, which are currently the most popular styles worldwide (L. Gu & Shen, 2007). In addition, Tai Chi can be practiced with a partner in a more practical manner, which is called 'pushing hands' (2-person interactive practice). There are also variations of Tai Chi, which are practiced with weapons, such as a sword, knife, folding fan, wooden staff or spear.

Consequently, in clinical research, Tai Chi interventions may vary in type, form, training and practicing approach, frequency, duration, and intensity. Take the duration as an example, our previous comprehensive review (G. Yang et al., 2015) involving 507 clinical studies of Tai Chi

reported that the duration of a Tai Chi intervention varied from five days to three years and the most common duration was 12 weeks.

Regardless of specific style, form, or teaching and practicing approach, Tai Chi itself is inherently a complex intervention, composed of multiple components each of which have potentially independent and synergistic therapeutic value (Wayne & Kaptchuk, 2008a). As a result, it is more appropriate to view Tai Chi as a form of whole-systems research rather than a single ingredient. Hence, Tai Chi intervention in clinical research is commonly provided as a full-course dinner for participants. It often consists of starters (warm-up exercise), main courses (Tai Chi practice) and desserts (Cool-down exercise) in each training class.

2.6.3 Use of Tai Chi for Health Benefits

Increasing evidence underscores the psychological benefits of Tai Chi intervention for healthy individuals and clinically affected populations.

2.6.3.1 Tai Chi and Psychological Health

In the past decade, several systematic reviews and meta-analyses of clinical studies have demonstrated that Tai Chi intervention is potentially beneficial for various populations on a range of psychological outcomes.

For cancer survivors, one recent systematic review and meta-analysis summarized and critically evaluated the effects of Tai Chi and Qigong mind-body exercises on symptoms and quality of life (Wayne et al., 2018). The review of 22 studies including 15 RCTs evaluating 1283 participants, found that Tai Chi and Qigong was associated with significant improvement in fatigue, sleep difficulty, depression, and overall quality of life in cancer survivors.

For individuals with multiple sclerosis, a systematic review investigated the effects of Tai Chi on physical and psychological function (Taylor & Taylor-Piliae, 2017). The review included three RCTs and five quasi-experimental studies involving 193 participants with multiple sclerosis. The participants in the Tai Chi group had better balance, gait and flexibility, less fatigue and depression, and better quality of life after the intervention.

For students in higher education, a review of 76 non-randomised and RCTs found that Tai Chi is beneficial to reduce symptoms of depression and anxiety and improve interpersonal sensitivity of students in higher education (Webster, Luo, Krageloh, Moir, & Henning, 2016).

Several systematic reviews and meta-analyses have evaluated the overall effects of Tai Chi on psychological outcomes in various populations. A systematic review found Tai Chi statistically significant reduction in anxiety in 12 included clinical studies (Sharma & Haider, 2015). Although the results suggested that Tai Chi might be a promising modality for anxiety management, this review had some limitations. Only three English databases were searched, not all included studies used a randomised controlled design, some had small sample size, different outcome measurements for anxiety, and non-standardized Tai Chi interventions and durations. One 2014 systematic review and meta-analysis of 37 RCTs and five quasi-experimental studies with various populations found that Tai Chi had beneficial effects on a range of psychological well-being measures, including depression, anxiety, and general stress management (F. Wang et al., 2014). However, the authors concluded that in spite of the positive outcomes, the included studies had significant methodological limitations.

Another meta-analysis of four studies comparing Tai Chi with waitlist control groups on depressive symptoms, found that Tai Chi appeared to have a significant impact in reducing depressive symptoms (Chi, Jordan-Marsh, Guo, Xie, & Bai, 2013). Two of the included studies were assessed as being of high quality, while the remaining two studies were rated as moderate quality. The authors recommended future research with larger sample sizes, more clarity on trial design and the intervention, longer-term follow up, and concomitant economic evaluations to be conducted.

One 2010 systematic review and meta-analysis involving 40 non-randomised controlled trials, RCTs and observational studies found that 21 of 33 randomised and non-randomised controlled studies reported that regular Tai Chi practice significantly increased psychological well-being including reduction of stress, anxiety, and depression, and enhanced mood in community-dwelling healthy participants and in patients with chronic conditions (C. Wang et al., 2010). The seven observational studies reinforced the beneficial association between Tai Chi and psychological health. This review searched eight English and three Chinese databases and identified 29 psychological measurements, however, the authors concluded that definitive conclusions were still limited due to variation in designs, comparisons, heterogeneous outcomes and inadequate controls. Similarly, an earlier systematic review involving fifteen RCTs (eight were of high methodological quality) using Tai Chi as intervention and other forms of activities or waitlist as control, and found that Tai Chi was reported in 13 studies with a significant effect in the management of depression and anxiety (W. C. Wang et al., 2009).

Although there is a significant body of evidence suggesting the beneficial effects of Tai Chi on psychological outcomes in healthy, psychosocially affected and various pathological populations, there are few studies investigating the effects of Tai Chi on psychosocial outcomes in people with CVD, especially patients with CHD and/or hypertension. One recent systematic review and meta-analyses evaluated the effects of Tai Chi-based cardiac rehabilitation on aerobic endurance, psychosocial well-being and cardiovascular disease risk reduction for patients with CHD (T. Liu et al., 2018). Although it included thirteen non-randomised controlled trials and RCTs, only two studies reported the relationship between Tai Chi and psychosocial well-being as measured by Zung Self-rating Anxiety Scale (SAS) for anxiety and Zung Self-rating Depression Scale (SDS) for depression. Four of the six studies assessed QoL. The meta-analyses of these studies showed that Tai Chi group had a significantly lower level of anxiety and depression, and better quality of life, compared with non-active control groups. Additionally, the above six studies were assessed as high risk of bias.

2.6.3.2 Tai Chi and Cardiovascular Health

Over the past decade, prospective studies of Tai Chi have reported significant improvements in a wide range of cardiovascular parameters such as blood pressure, endothelial function, blood lipid profiles, heart rate response, heart rate variability, C-reactive protein and poor exercise capacity.

For the overall cardiovascular health, one recent systematic review and meta-analysis assessed the effect of Tai Chi on cardiorespiratory fitness for coronary disease rehabilitation (Y. L. Yang, Wang, Wang, Shi, & Wang, 2017). It included five studies-two RCTs and three non-randomised controlled trials with 291 patients with CHD. Meta-analyses of three studies showed that compared to other types of low- or moderate-intensity exercise, Tai Chi significantly improved VO_2max. Although one study showed that Tai Chi seemed less effective at improving VO_{2max} as compared to high-intensity exercise. A previous systematic review and meta-analysis assessed the effect of Tai Chi on cardiorespiratory fitness in healthy adults included 20 studies with 1868 participants (G. Zheng, Li, et al., 2015). The study designs were two RCTs, eight non-randomised controlled trials, three self-controlled trials and seven cohort studies; the majority of them were of low methodological quality. Tai Chi had positive effect on blood pressure, heart rate, stroke volume, cardio output, lung capacity, and cardiorespiratory endurance.

For the management of cardiovascular risk factors, a 2014 Cochrane systematic review comprehensively searched RCTs of Tai Chi lasting at least three months involving healthy adults or adults at high risk of CVD to evaluate the effects of Tai Chi for primary prevention of CVD (Hartley, Flowers, Lee, Ernst, & Rees, 2014). The authors identified no long-term trials examining Tai Chi for the primary prevention of CVD, and found that despite some beneficial effects of Tai Chi suggested by 13 small trials (1520 participants) and three ongoing trials, the results were not consistent across all studies and no conclusions could be drawn as to the effectiveness of Tai Chi on CVD risk factors. Another meta-analysis of RCTs evaluated the effect of Tai Chi on blood lipid profiles (X. Pan et al., 2016). Six studies involving 445 participants found that the Tai Chi group was superior to the control group in lowering blood triglyceride and total cholesterol level, but no differences was found in blood LDL-C and HDL-C. Two previous systematic reviews (M. S. Lee, Lee, Kim, & Ernst, 2010; Yeh, Wang, Wayne, & Phillips, 2008) evaluated the effect of Tai Chi for lowering blood pressure. The authors found beneficial effects of Tai Chi in reduction of blood pressure, but the conclusion was not definitive.

For patients with CHD, one 2011 systematic review found that Tai Chi may improve serum lipid profiles, lower blood pressure and heart rate in patients with CHD (Dalusung-Angosta, 2011). However, this review identified limited evidence by searching Medline/PubMed and the Cochrane Library database for clinical trials or RCTs published in English between 1985 and 2008, and all but one of the included studies used a small sample size ($n \leq 100$).

For patients with chronic heart failure, a systematic review and meta-analysis evaluating the effects of Tai Chi identified eleven trials with 656 patients (Ren et al., 2017). The review found that Tai Chi could improve the distance walking within 6 minutes, quality of life, and left ventricular ejection fraction and may reduce B-type natriuretic peptide and heart rate. Another recent meta-analysis also searched major English and Chinese databases to evaluate evidence from RCTs of Tai Chi for patients with chronic heart failure (Q. Gu et al., 2017). It included thirteen RCTs, and also found that Tai Chi induced significant improvement in 6-minute walking distance, quality of life, left ventricular ejection fraction, and B-type natriuretic peptide. Two previous systematic reviews also found Tai Chi may improve exercise capacity and quality of life in patients with chronic heart failure (S. M. Ng et al., 2012; L. Pan, Yan, Guo, & Yan, 2013).

For patients with stroke and stroke risk factors, one systematic review and meta-analysis summarised the evidence of Tai Chi and Qigong for the primary prevention of stroke (Lauche

et al., 2017). It included 21 trials involving 1604 patients with hypertension, hyperlipidaemia, diabetes, overweight or obesity, or metabolic syndrome, and found significant benefits of Tai Chi/Qigong over no intervention for hypertension, the homeostatic model assessment index, and fasting blood glucose, and for the body mass index compared with exercise controls. However, the risk of bias was unclear or high for the majority of included trials, and heterogeneity between trials was high. Another previous systematic review including 36 studies with 2393 participants with stroke found similar results (G. Zheng, Huang, et al., 2015).

For patients with type 2 diabetes, one systematic review and meta-analysis of RCTs found that the existing evidence is not convincing enough to suggest that Tai Chi is effective for managing patients with type 2 diabetes, because a limited number of studies and inconsistent results (M. S. Lee, Jun, Lim, & Lim, 2015). The authors found that compared with sham exercise, one study demonstrated that Tai Chi may be not effective in lowering fasting blood glucose or HbA1c; compared with anti-diabetic medication, a meta-analysis of five studies favoured Tai Chi on fasting blood glucose; compared with standard care alone, Tai Chi in combination with standard care showed positive effects on HbA1c and fasting blood glucose; compared with no treatment, a meta-analysis of four studies showed positive effects of Tai Chi on HbA1c. Previous systematic reviews demonstrated similar results (M. S. Lee, Choi, Lim, & Ernst, 2011; Yan, Gu, & Pan, 2013).

2.6.3.3 Tai Chi and Quality of Life

A range of clinical studies has demonstrated the beneficial effects of Tai Chi in improving health-related quality of life in healthy individuals and patients with difference disorders/conditions, such as patients with cancer (Wayne et al., 2018; Yan, Pan, Zhang, Sun, & Cui, 2014; Zeng, Luo, Xie, Huang, & Cheng, 2014), multiple sclerosis (Taylor & Taylor-Piliae, 2017; Zou et al., 2017), perimenopausal syndrome (Y. Wang, Shan, Li, Yang, & Shan, 2017), Parkinson's disease (R. Song et al., 2017), chronic heart failure (Q. Gu et al., 2017; L. Pan et al., 2013; Ren et al., 2017), chronic obstructive pulmonary disease (W. Wu et al., 2014), and type 2 diabetes (M. S. Lee et al., 2011).

Furthermore, in cardiac populations research into quality of life outcomes seems to be more extensive than other psychosocial outcome measures, as well as physical outcomes. Three systematic reviews and meta-analyses evaluated the effect of Tai Chi in patients with chronic heart failure (Q. Gu et al., 2017; L. Pan et al., 2013; Ren et al., 2017). Their results consistently

demonstrated that Tai Chi can significantly improve quality of life in patients with chronic heart failure.

2.6.3.4 Tai Chi and Physical Fitness

Tai Chi has been widely believed to have beneficial effects on physical fitness. Our previous comprehensive review involving available clinical studies on Tai Chi found that a large body of research reported Tai Chi resulted in improvements in balance and prevention of falls, mobility and postural stability, muscle strength, flexibility, and exercise capacity (G. Yang et al., 2015).

One systematic review and meta-analysis involving five trials has demonstrated positive effects of Tai Chi on improving the spine dimension of bone mineral density in patients with perimenopausal syndrome (Y. Wang, W. Shan, et al., 2017). For students in higher education, a comprehensive review involving 72 clinical studies with 9263 participants showed that Tai Chi could increase their flexibility, lung capacity, balance, 800/1000m run time (Webster et al., 2016). For patients with chronic obstructive pulmonary disease, a systematic review and meta-analysis involving eleven RCTs with 824 patients demonstrated that compared with the non-exercise group, Tai Chi group demonstrated significant improvements in walking distance of the six-minute walking test (6MWT), and greater reductions in St George's Respiratory Questionnaire and Chronic Respiratory Disease Questionnaire (W. Wu et al., 2014).

Tai Chi-based cardiac rehabilitation significantly improved aerobic endurance compared with both active and non-active control interventions, as well as psychosocial well-being, among patients with CHD (T. Liu et al., 2018). Another recent systematic review found in their meta-analysis of seven trials demonstrated that Tai Chi could significantly improve the walking distance in 6MWT using the random-effects model (Ren et al., 2017). Similar beneficial effects of Tai Chi on 6MWT were found in another systematic review on Tai Chi for patients with chronic heart disease (Q. Gu et al., 2017).

2.6.3.5 Other health benefits

Our 2015 review of existing clinical evidence found that Tai Chi is beneficial for health promotion or preservation, balance control or fall prevention, and for the management of physical and mental health covering 93 diseases/conditions (G. Yang et al., 2015). The top 10 diseases/conditions investigated in clinical studies on Tai Chi is as follows: hypertension,

diabetes, osteoarthritis, osteoporosis or osteopenia, breast cancer, heart failure, chronic obstructive pulmonary disease (COPD), CHD, schizophrenia, and depression (G. Yang et al., 2015).

2.6.4 Mechanisms of Action of Tai Chi in CVD

The underlying mechanisms on how Tai Chi works for people with CVD and cardiovascular risk factors remains largely unclear. Fortunately, with the advances in neuroimaging technologies, new clues have been provided for understanding the underlying mechanisms of the beneficial effects of Tai Chi. Possible effects of Tai Chi included induced modulation of brain morphology, functional homogeneity and connectivity, regional activity and macro-scale network activity on health from available literature, and identified possible links between the alterations in brain and beneficial effects of Tai Chi, such as improved motor functions, pain perception, metabolic profile, cognitive functions, mental health and sleep quality (Yu et al., 2018).

Other possible explanations are summarised and analysed below.

2.6.4.1 Psychological Health

Nuclear factor-kappa B (NF-$_k$B) signalling is an important mediator of the antineurogenic and behavioural actions of stress and depressive behaviours (Koo, Russo, Ferguson, Nestler, & Duman, 2010). investigated meditation effects of Tai Chi on NF-$_k$B signalling in 26 lonely older adults. In an RCT of 26 lonely older adults, the Tai Chi group had significantly decreased the levels of stress and increased NF-$_k$B levels, and change in psychological stress was correlated with change in NF-$_k$B activation, compared with control group who received a health education only (Black et al., 2014). This finding indicates that Tai Chi-induced reduction in stress may attenuate increase in NF-$_k$B activation.

Another potential mechanism may be related to the link between inflammation and depression. Inflammation could produce depression in vulnerable individuals by lowering plasma tryptophan and diminishing brain serotonin activity, and low serotonin function may compromise mechanisms involved in maintaining recovery from depression (Cowen & Browning, 2015). A Korea RCT investigated the effects of Tai Chi on serotonin, nicotine dependency, depression and anger in 38 hospitalized alcohol-dependent patients (Oh & Kim, 2016). This study found that the experimental group after 8-week Tai Chi practice significantly

increased blood serotonin level (P=0.001) and reduced nicotine dependency, symptoms of depression and anger, compared with control group who followed only the routine hospital rehabilitation program. It suggests that alternation of blood serotonin level might be involved in the mechanism behind Tai Chi-induced depression management.

Additionally, increased levels of pro-inflammatory marker C-reactive protein (CRP) are associated with the development of depression (Kohler-Forsberg et al., 2017; B. M. Song et al., 2015). A cross-sectional and prospective analyses of data from 73,131 men and women aged 20 to 100 years also suggested that elevated levels of CRP are associated with increased risk for psychological distress and depression (Wium-Andersen, Orsted, Nielsen, & Nordestgaard, 2013). The effects of Tai Chi in reducing inflammatory markers and CRP in trial where 73 older adults with major depression were randomised to either tai chi and medication or education and medication (Lavretsky et al., 2011). The Tai Chi plus medication group showed greater reduction of depressive symptoms and to achieve a depression remission, as well as significantly greater improvements in quality of life and cognitive function, and decline in inflammatory markers and CRP. Reduction in inflammatory markers and CRP might be part of the underlying mechanism of how Tai Chi improved psychological distress and depression.

2.6.5.2 Cardiovascular Health

Oxidative stress has been known with at least two critical roles within the cell, the generation of cellular damage and the involvement in several signalling pathways in its balanced normal state (Cervantes Gracia, Llanas-Cornejo, & Husi, 2017), which is associated with CVD development via endothelial dysfunction (Nair & Gongora, 2017; Nosalski, McGinnigle, Siedlinski, & Guzik, 2017; Paneni, Diaz Canestro, Libby, Luscher, & Camici, 2017). A quasi-randomised controlled study with 55 elderly Mexican individuals (Rosado-Pérez, Santiago-Osorio, Ortiz, & Mendoza-Núñez, 2012) found that after six months of daily training in Tai Chi the experimental group exhibited a statistically significant decrease in glucose levels, total cholesterol, LDL-C and systolic blood pressure, as well we an increase in superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity and total antioxidant status (TAS) compared with the control group, Reducing oxidative stress might be involved in the underlying mechanism of Tai Chi.

Endothelin-1 (ET-1) and circulating hormones play important roles in maintaining cardiovascular function. A study with 44 subjects demonstrated that the change in ET-1 and

triglyceride was significant after 3-month of Tai Chi training in the Tai Chi group (Lu & Kuo, 2013; Mao & Sha, 2006).

It is also reported in a 3-arm study involving patients with essential hypertension (Tai Chi group, n=24; hypertensive group, n=16; healthy control group, n=16) demonstrated that 12 weeks of Tai Chi practice significantly increased the plasma nitric oxide (NO), carbon monoxide (CO) and hydrogen sulphide (H_2S) levels and lowered blood pressure (X. Pan, Zhang, & Tao, 2015). Correlations were observed in this study between changes of blood pressure and changes in these gaseous signalling molecules.

In addition, one study analysed data of Tai Chi practitioners (n=19) and Tai Chi-naive participants (n=13), and found that Tai Chi performance led to acute decreases in sympathetic activity which could not be explained by physical activity alone (Motivala, Sollers, Thayer, & Irwin, 2006).

Depression is associated with increased CRP levels in patients with CVD (Y. Wang, Y. Z. Zhen, et al., 2017), and elevated CRP levels are associated with increased risk for psychological distress and depression (Wium-Andersen et al., 2013) and the development of depression (Kohler-Forsberg et al., 2017; B. M. Song et al., 2015). One recent RCT involving women aged 35 to 50 years at increased risk of CVD demonstrated that compared with waitlist group, 8-week Tai Chi intervention decreased granulocyte colony-stimulating factor (G-CSF), which was also observed 2-month post intervention, indicating that Tai Chi may help down-regulate pro-inflammatory cytokines associated with underlying CVD risks including interferon gamma, tumour necrosis factor, interleukin (IL)-8 and IL-4 (Robins, Elswick, Sturgill, & McCain, 2016). Therefore, the management of the cardiovascular risk factors of depression, elevated inflammatory markers and CRP levels might be involved in mechanisms behind the beneficial effects of Tai Chi for cardiovascular health.

2.6.4.3 Physical Fitness

Physical inactivity has been widely investigated as a behaviour risk factor for CVD. A meta-analysis and its updated analyses (Taylor-Piliae, 2008; Taylor-Piliae & Froelicher, 2004) estimated the effect of Tai Chi in improving aerobic capacity expressed as peak oxygen uptake (VO_2peak) (mL x kg (-1) x min (-1)). The findings demonstrated that large significant effects of Tai Chi on aerobic capacity were found for subjects enrolled in the cross-sectional studies in both women and men aged 55 years or older when comparing with sedentary subjects. Additionally, one recent three-arm RCT involving 374 middle-aged Chinese subjects found that

Tai Chi practice consumed a smaller amount of energy metabolism but produced similar health benefits as self-paced brisk walking, by having higher effects on resting energy expenditure (REE) and improving maximal oxygen intake (VO_2max) and REE-kilocalorie expenditure (Hui, Xie, Woo, & Kwok, 2016).

In addition, one study with 40 elderly individuals demonstrated that the Tai Chi group after 16 weeks of practice showed a 19.9% increase in muscle strength of the knee flexors ($P<0.01$) (J. X. Li, Xu, & Hong, 2009), indicating the beneficial effects of Tai Chi in improving postural stability and proprioception of knee and ankle (J. X. Li, Xu, & Hong, 2008) in old people. Similar findings have been reported in a 48-week, single-blind, RCT involving 269 women aged 70 years or older (Greenspan, Wolf, Kelley, & O'Grady, 2007). It demonstrated that compared with wellness education group, Tai Chi group reported significant improvements in their physical dimension and ambulation categories. Furthermore, one study with 28 elder adults found that Tai Chi group was superior to resistance training group in increasing serum parathyroid hormone at 12 weeks, and reducing the urinary calcium level at 24 weeks, indicating that Tai Chi is beneficial for bone metabolism (C. L. Shen et al., 2007). Therefore, the impacts in musculoskeletal system might be part of the underlying mechanism of Tai Chi-induced improvements in balance, strength, and flexibility.

2.7 Summary

CVD is the leading cause of morbidity and mortality worldwide, which remains a heavy disease burden both on the individual and society. CHD is the most common forms of CVD. Hypertension is the most important preventable cause of heart disease and stroke around the world. Despite huge efforts, the levels of awareness, treatment and control rates of hypertension remain extremely low. Psychological risk factors such as stress, anxiety, and depression are known to play a significant and independent role in the development of hypertension, CHD and its complications. However, a substantial proportion of patients after CHD events suffering stress, anxiety and depression symptoms are undertreated.

Cardiac rehabilitation programs are “comprehensive” interventions including components of medical evaluation, prescribed exercise, cardiac risk factor modification, health education, and psychological counselling. Exercise training is a core component of cardiac rehabilitation programs. Exercise-based cardiac rehabilitation program reduces cardiovascular mortality and

the risk of hospital admissions as well as improvement in QoL (Anderson et al., 2016). Unfortunately, there is a lack of standardised cardiac rehabilitation programs to manage psychological risk factors such as stress, anxiety and depression. In addition, effective implementation of cardiac rehabilitation after acute coronary syndrome, coronary revascularisation, and heart failure has remained suboptimal, with overall participation rates <50% over recent decades despite international recommendations (Dalal et al., 2015).

Tai Chi could be a promising exercise option for patients with CHD declining cardiac rehabilitation programs, considering the multiple components and characteristics of Tai Chi and results from related clinical studies (Salmoirago-Blotcher et al., 2017). Several systematic reviews and meta-analyses have demonstrated the potential physical and psychological benefits of Tai Chi, including improving stress, anxiety, depression, quality of life and cardiovascular function. However, these findings are often inconclusive and should be interpreted cautiously, given the methodological limitations, variations across included trials in study design, outcomes and small sample size.

Nevertheless, there is a lack of RCTs investigating the effects of Tai Chi on the management of stress, anxiety and depression in patients with CHD and/or hypertension. Herein, a robust investigation into this area is needed to provide a comprehensive overview and reliable evidence of the effect and safety of Tai Chi in patients with CHD and/or hypertension, to formulate relevant recommendations for patients, healthcare professionals and researchers.

The doctoral project is designed to explore the impact of Tai Chi on psychological well-being and cardiovascular function in patients with CHD and/or hypertension. This doctoral project consists of three studies: a systematic review, a RCT and a qualitative sub-study of the RCT.

Chapter 3: Does Tai Chi Improve Psychological Well-being and Quality of Life in Patients with Cardiovascular Disease and/or Cardiovascular Risk Factors? A Systematic Review

This chapter consists of a systematic review exploring whether Tai Chi can improve psychological well-being and quality of life in patients with cardiovascular disease and/or cardiovascular risk factors. After a brief introduction of the background and methods, the results are presented in detail including characteristics and methodological quality of the included studies and effects of interventions. This follows with a discussion of the findings, including an interpretation of the results and comparisons with previous studies. The reporting of this systematic review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Appendix 1).

3.1 Introduction

3.1.1 Rationale

The rational of this systematic review is provided in detail in Chapter 2. To speak briefly, cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, which remains a heavy disease burden both on the individual and society. The major cardiovascular risk factors are related to unhealthy lifestyle behaviours, which may lead to other cardiovascular risk factors such as hypertension, overweight/obesity, hyperglycemia/diabetes, and dyslipidaemia (Tzoulaki et al., 2016). Other contributing risk factors of CVDs include family history, aging, gender, socioeconomic determinants and psychological wellbeing (Havranek et al., 2015; World Health Organization, 2017). Psychological risk factors such as stress, anxiety, and depression are known to play a significant and independent role in the development of CVD. In addition, a substantial proportion of patients with CVD suffering from stress, anxiety and depression symptoms are undertreated. Tai Chi is a promising option for patients with CVD

and/or cardiovascular risk factors, considering the multiple components and characteristics of Tai Chi.

In recent years, an increasing number of studies have demonstrated the beneficial effects of Tai Chi on mental health, however, however, it remains unknown on Tai Chi for psychological well-being and quality of life (QoL) in people with or at risk of CVD. Five systematic reviews (Chi et al., 2013; Sharma & Haider, 2015; C. Wang et al., 2010; F. Wang et al., 2014; W. C. Wang et al., 2009) involving various populations have reported the beneficial effects of Tai Chi on well-being, but none focused on people with or at risk of CVD. One recent systematic review (T. Liu et al., 2018) evaluated the effects of Tai Chi-based rehabilitation on aerobic endurance, psychosocial well-being and cardiovascular disease risk reduction for patients with CHD, but patients with other CVDs were not included. Another ten systematic reviews (Dalusung-Angosta, 2011; M. S. Lee et al., 2010; Lin, Lin, & Lien, 2013; Nery et al., 2014; S. M. Ng et al., 2012; L. Pan et al., 2013; J. Wang et al., 2013; Yeh, Wang, Wayne, & Phillips, 2009; Yeh, Wang, et al., 2008; G. Zheng, Li, et al., 2015) have evaluated Tai Chi for cardiovascular population, but only physical outcomes were assessed rather than psychological outcomes and quality of life.

3.1.2 Objectives

To address the above gap in literature, the current systematic review of randomised controlled trials is designed to explore the effectiveness and safety of Tai Chi for psychological well-being and quality of life in people with CVD and/or cardiovascular risk factors.

3.2 Methods

3.2.1 Protocol and Registration

The protocol of this systematic review was registered in the the International Prospective Register for Systematic Reviews (PROSPERO) (NO.: CRD42016042905) and has been published in BMJ Open (G. Yang et al., 2017).

3.2.2 Eligibility Criteria

Type of study

We included only parallel RCTs and first phase data and outcomes of randomised cross-over trials.

Type of participants

We included participants aged 40 years or older with a diagnosis of a cardiovascular disease (such as coronary heart disease, stroke, heart failure, myocardial infarction and hypertension) or with cardiovascular risk factors (including hypertension, diabetes, and/or dyslipidaemia). No gender limitation was applied.

Type of intervention

Any types of Tai Chi were eligible for inclusion, regardless of the forms (such as 24-form, 54-form, 83-form Tai Chi), or styles (such as Chen, Yang, Wu and Sun style). The duration should be at least one month with a frequency at least once per week.

Type of control

No treatment, waitlist control, sham control, other forms of exercise, and conventional medical treatments were eligible types of control. For conventional medical treatments, conventional medications recommended by current internationally accepted clinical guidelines are eligible. These controls are appropriate to explore the effectiveness of Tai Chi and possibly available according to our previous review (G. Yang et al., 2015). Comparisons also included a co-intervention if applied in all arms.

Type of outcome

The primary outcomes were psychological status of stress measured by validated instruments, such as the Perceived Stress Scale (PSS), Depression Anxiety Stress Scale (DASS), and Standard Stress Scale (SSS). The secondary outcomes were other measures of psychological status including anxiety, depression, mood disturbance, self-esteem and quality of life, and adverse events.

3.2.3 Information Sources

We conducted electronic searches from the following major English and Chinese databases from inception to 31st March 2018: Cochrane Heart Review Group Specialised Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Library (2018, Issue 1), MEDLINE (from 1946), EMBASE (from 1947), PubMed (from 1966), Sino-Med database (from 1978), China National Knowledge Infrastructure (CNKI, from 1979), VIP Journal Integration Platform (VJIP, from 1989), and Wanfang Data Chinese database (from 1985).

We searched grey literature from the following databases and sources from their inception to 31st March 2018: CNKI database, the System for Information on Grey Literature (OpenSIGLE) (opensigle.inist,fr), the Healthcare Management Information Consortium (HMIC) (www.ovid.com/site/catalog/DataBase/99.jsp?top=2&mid=3&bottom=7&subsection=10), the National Technical Information Service (www.ntis.gov) and the PsycEXTRA (www.apa.org/psycextra).

We also searched the following trials registers to identify unpublished data to 31st March 2018 from completed trials: Current Controlled Trials (www.controlled-trials.com), US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov), Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), and the World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch). Additional clinical trials were also identified by searching the reference lists of relevant studies.

3.2.4 Literature Search

We searched for relevant RCTs regardless of publication status (e.g. published, unpublished, in press, or in progress). The English searching terms include “Tai Chi”, “Tai Chi Chuan”, “Tai Chi Chih”, “ta’i chi”, “Tai Ji Quan”, “taijiquan”, “cardiovascular disease”, “coronary heart disease”, “stroke”, “heart failure”, “hypertension”, “high blood pressure”, “diabetes”, “dyslipidaemia”, “high cholesterol”, "randomised controlled trial", "randomized controlled trial", "controlled clinical trial", "randomly", "clinical", "trial", "random", "randomised" and "randomized". The Chinese searching terms include “*Tai_ji* (Tai Chi)”, “*Tai_ji_chuan* (Tai Chi)”, “Xin_xue_guan_bing (cardiovascular disease)”, “Gao_xue_ya (hypertension)”, “Tang_niao_bing (diabetes)”, “Gao_xue_zhi (dyslipidaemia)” and “*sui_ji* (randomized)”. Examples of detailed search strategies for one English database and one Chinese database are available in Table 3.1. We applied a similar strategy for other electronic databases.

Table 3.1 Search strategies

Database	Number	Search items
PubMed	#1	[Title/Abstract] (“Tai Chi” OR “Tai ji” OR “Tai Chi Chih” OR “Ta’i chi” OR “taichi” OR “tai chi chuan” OR “taichi chuan” OR “taiji” OR “Tai Ji Quan” OR “taijiquan” OR “martial arts”)

	#2	[Title/Abstract] ("cardiovascular disease" OR "coronary heart disease" OR "stroke" OR "heart failure" OR "hypertension" OR "high blood pressure" OR "diabetes" OR "dyslipidaemia" OR "high cholesterol")
	#3	[All fields] ("randomized controlled trial" OR "randomised controlled trial" OR "controlled clinical trial" OR "randomly" OR "clinical" OR "trial" OR "random" OR "randomised" OR "randomized")
	#4	#1 and #2 and 3#
CNKI	#1	[Abstract] ("*Tai_ji*" (Tai Chi) OR "*Tai_ji_quan*" (Tai Chi)
	#2	[Abstract] ("*Xin_xue_guan_bing*" (cardiovascular disease) OR "Guan_xin_bing" (coronary heart disease) OR "Zhong_feng" (stroke) OR "Nao_zu_zhong" (stroke) OR "Xin_shuai" (heart failure) OR "*Gao_xue_ya*" (hypertension) OR "*Tang_niao_bing*" (diabetes) OR "*Gao_xue_zhi*" (dyslipidaemia)
	#3	[All fields] ("*sui_ji*" (randomized or randomised))
	#4	#1 and #2 and 3#

Note: CNKI, China National Knowledge Infrastructure.

3.2.5 Study Selection

Two authors (GYY and WYL) selected studies independently. Search results were merged from different sources using Endnote X9.2 reference management software. We removed the duplicate records of the same report (i.e. records reporting the same journal title, volume and pages). Two authors (GYY and WYL) screened titles and abstracts to remove obviously irrelevant reports independently. We retrieved full texts of all potentially relevant reports and linked together multiple reports of the same study if any. We examined full-text reports for compliance of studies with eligibility criteria. We also corresponded with investigators, where appropriate, to request further information, such as missing methods information or results. Two authors (GYY and WYL) had discussions to make final decisions on study inclusion. Any disagreement about the selection of studies was resolved by discussion, and another author arbitrated when necessary (NK).

3.2.6 Data Collection

Two authors (GYY and WYL) extracted the data from the included trials independently using a pre-defined data extraction form (Appendix 2) developed from the recommendation of the

Cochrane Collaboration (Cochrane Training, 2017). Any disagreements were resolved by discussion with a third author (NK).

The extracted data included: (1) publication information: authors, country, year of publication; (2) study designs: method of random number generation and allocation concealment, blinding methods; (3) participants: sample size, characteristics of participants (e.g. age, gender, duration of disorder, and severity of disorder); (4) intervention: type and/or form of Tai Chi, details of treatment and control; and (5) outcome data: outcomes measures, data from previously specified outcomes. In case of missing data or unclear information, we contacted the original authors to clarify.

3.2.7 Risk of Bias Assessment

To assess the validity of included studies, we emphasize the risk of bias in the results (The risk that they will overestimate or underestimate the true intervention effect) (Higgins & Green, 2011). We used the risk of bias tool recommended by the Cochrane Collaboration (Higgins & Green, 2011). This is a specific tool comprising a judgement and a support for the judgement for each item. The following items of bias for each study included in this review were assessed:

- Selection bias (random sequence generation and allocation concealment)-whether: the allocation sequence was random; the allocation sequence was adequately concealed; baseline differences between intervention groups suggest a problem with the randomisation process;
- Detection bias (blinding of outcome assessment)-whether: the method of measuring the outcome was inappropriate; measurement or ascertainment of the outcome could have differed between intervention groups; outcome assessors were aware of the intervention received by study participants;
- Attrition bias (incomplete outcome data-whether: data for this outcome were available for all, or nearly all, participants randomised; (if applicable) there was evidence that the result was not biased by missing outcome data; (if applicable) missingness in the outcome was likely to depend on its true value (e.g. the proportions of missing outcome data, or reasons for missing outcome data, differ between intervention groups));
- Reporting bias (selective reporting)-whether: the trial was analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis; the numerical result being assessed is likely to have been selected, on the basis

of the results, from multiple outcome measurements within the outcome domain; the numerical result being assessed is likely to have been selected, on the basis of the results, from multiple analyses of the data; and

- Other bias-any important concerns about bias not addressed in the above domains.

We did not report performance bias, considering the difficulty to blind the participants and personnel in Tai Chi study. For each item, there are three potential bias judgements: 'low risk', 'high risk', or 'unclear risk'. A clinical trial that met all criteria was judged as having a low risk of bias, a trial that met none of the criteria was judged as having a high risk of bias, and a trial with insufficient information to judge was classified as unclear risk of bias. Any disagreements were resolved by discussion, with involvement a third author (NK) where necessary.

3.2.8 Grading the Quality of Evidence

Systematic reviews of the effects of healthcare provide essential, but not sufficient information for making well informed decisions. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach provides a system for rating quality of evidence and strength of recommendations that is explicit, comprehensive, transparent, and pragmatic (Guyatt et al., 2008). GRADE is increasingly being adopted by many international organisations.

We assessed the quality of evidence in relation to each outcome included in the 'Summary of findings' (SoF) tables using the evidence grading system with GRADEPro GDT application developed by the GRADE collaboration (Guyatt et al., 2008).

One reviewer (GY) initially applied the GRADE system and then discussed the quality of evidence ratings for each outcome with another member of the review team (NK). We reached final decisions on the ratings through discussion and consensus.

The GRADE classifies the quality of evidence into four levels:

- High quality: further research is very unlikely to change our confidence in the estimate of effect;
- Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;

- Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- Very low quality: any estimate of effect is very uncertain (Guyatt et al., 2008).

Evidence based on RCTs begins as high quality evidence, and we took the following factors into account when deciding whether or not to downgrade the quality of evidence in relation to each outcome: study limitations, inconsistency of results, imprecision, indirectness of evidence, and reporting bias (Guyatt et al., 2008).

- Study limitations: Risk of bias can differ across outcomes when, for instance, each outcome is informed by a different subset of studies. Study limitation in randomised trials include: lack of allocation concealment, lack of blinding, incomplete accounting of patients and outcome events, selective outcome reporting, and other limitations (i.e. stopping early for benefit, use of invalidated outcome measures, carryover effects in crossover trial, and recruitment bias in cluster-randomised trials) (Guyatt, Oxman, Vist, et al., 2011).
- Inconsistency: GRADE suggests rating down the quality of evidence if large inconsistency (heterogeneity) in study results remains after exploration of a priori hypotheses that might explain heterogeneity. Judgement of the extent of heterogeneity is based on similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2 (Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou, et al., 2011).
- Imprecision: GRADE's primary criterion for judging precision is to focus on the 95% confidence interval (CI) around the difference in effect between intervention and control for each outcome. If the optimal information size (OIS) criterion is not met, rate down for imprecision, unless the sample size is very large (at least 200 and perhaps 4000 patients). If the OIS criterion is met and the 95% CI excludes no effect (i.e. CI around RR excludes 1.0) precision adequate. If OIS is met, and CI overlaps no effect (i.e. CI includes RR of 1.0) rate down if CI fails to exclude important benefit or important harm (Guyatt, Oxman, Kunz, Brozek, et al., 2011).
- Indirectness: quality of evidence decreases when substantial differences exist between the population, the intervention, the comparison, or the outcomes measured in relevant research studies and those under consideration in a guideline or systematic review

(Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter, et al., 2011).

- Publication bias: publication bias should be suspected when available evidence comes from a number of small studies, most of which have been commercially funded. The most popular approach based on examination of the pattern of data is the funnel plot (Guyatt, Oxman, Montori, et al., 2011). If a funnel plot is not appropriate to use because there are less than 10 studies included in the meta-analysis, the extent to which we are uncertain about the magnitude of the effect due to selective publication of studies would be considered by considering the following factors: study design, study size, lag bias, and search strategy (Guyatt, Oxman, Montori, et al., 2011).

Our review included only RCTs and we downgraded the evidence for each outcome from high quality by one level if we considered that there was a serious limitation in relation to a particular factor or by two levels if we considered there was a very serious limitation.

3.2.9 Synthesis of Results

We summarised data using mean difference (MD) with 95% CI for continuous outcomes. Clinical heterogeneity was assessed according to the characteristics of the included studies and the participants, details of the intervention or control, and types of outcome measurements. We assessed statistical heterogeneity by using the I^2 statistic. As recommended by the Cochrane Collaboration (Higgins & Green, 2011), the statistical heterogeneity was regarded as substantial if the I^2 statistic was greater than 50%, and considerable if I^2 statistic was greater than 75%.

We performed statistical analyses with Cochrane's Review Manager software (version 5.3). We pooled data if the I^2 statistic was less than 75% and the clinical heterogeneity among trials was deemed acceptable. We used random-effects model to conduct the meta-analysis unless the I^2 statistic was less than 25%. We did not perform funnel plots to detect publication bias because there were no more than 10 included trials in each meta-analysis.

3.2.10 Additional Analysis

We performed subgroup data analysis for patients with cardiovascular risks or CVDs.

3.3 Results

3.3.1 Study Selection

We initially identified 534 relevant English and Chinese articles, from which 97 were excluded as duplicates. We screened the remaining abstracts and 81 full text articles for potentially relevant data. Finally, 56 studies were excluded because of no relevant outcomes, not randomised study and duplication. A total of 25 studies met the inclusion criteria (Barrow, Bedford, Ives, O'Toole, & Channer, 2007; Caminiti et al., 2011; Ding, Wang, Wang, & Gong, 2013; Han, Huang, Li, & Chen, 2010; Lam, Dennis, Diamond, & Zwar, 2008; X. Liu, Miller, Burton, Chang, & Brown, 2013; Meng, 2014; X. Pan, 2016; Robins et al., 2016; Sang, Liu, Lang, Tian, & Zhang, 2015; H. Song, 2013; F. Sun & Sun, 2014; J. Sun & Buys, 2015; Tsai et al., 2003; Tsang, Orr, Lam, Comino, & Singh, 2007; H. Wang, 2014; P. Wang, Han, & Liang, 2009; X. Wang, Zhang, Ding, & Jiang, 2013; F. Wu, Song, Bao, Xiang, & Jia, 2010; Yao, Li, & Ma, 2010; Yeh et al., 2011; Yeh et al., 2004; Yeh et al., 2013; E. Zhang, 2014; S. Zhang & Chen, 2011). The selection procedure is shown in a PRISMA Flow Diagram (Figure 3.1).

3.3.2 Study Characteristics

Of the included studies, 11 were published in English and 14 in Chinese published between year 2003 and 2016. The studies were conducted in 5 countries including China, the United Kingdom, the United States, Italy and Australia. The sample size of the included studies ranged from16 to 300, making a total of 2,084 participants. There were 864 participants with cardiovascular disease (including coronary heart disease, myocardial infarction, chronic heart failure or symptomatic heart failure), and 1220 with cardiovascular risk factors (including documented borderline hypertension or hypertension, impaired glucose metabolism or type 2 diabetes). Table 3.2 shows the main characteristics of the included 25 studies.

There are various comparisons in the included 25 studies, including Tai Chi versus waitlist, Tai Chi versus education, Tai Chi plus usual care versus usual care, Tai Chi versus sedentary life control, Tai Chi plus health education versus health education, Tai Chi versus health education, Tai Chi plus usual care versus aerobic exercise plus usual care, Tai Chi plus usual care versus health education plus usual care, Tai Chi plus diet guidance and usual care versus diet guidance and usual care, Tai Chi versus non-exercise-related activity. The ‘usual care’ is defined as conventional medical care.

Figure 3.1 PRISMA Flow Diagram Applied to Search Results
(From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097)

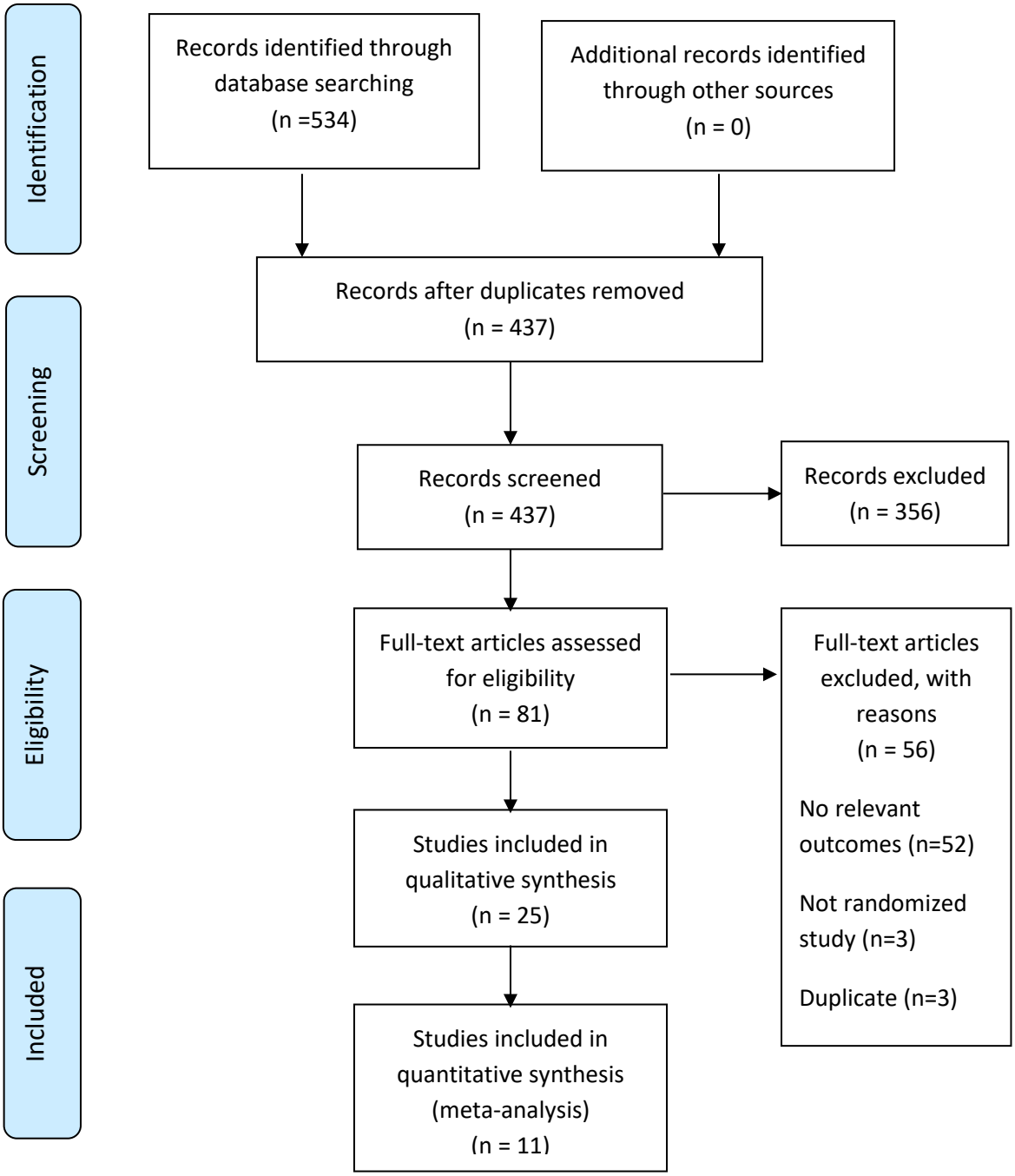


Table 3.2 Characteristics of included studies on Tai Chi for CVD and/or risk factors

Study ID	Disease/ condition	Sample size	Intervention	Duration (weeks)	Control	Lost to follow up (No. (%))	Outcome measures
Barrow DE 2007	Symptomatic heart failure	65	Wu Chian Chuan style Tai Chi, twice 55-min sessions weekly + Usual medical care	16	Usual medical care	13/65 (20%) in total; I: 7/32 (21.8%); C: 6/33 (18.1%)	Safety; mood (SCL-R); QoL (MLHF)
Caminiti G 2011	Chronic heart failure	60	A modified 10-form Yang style Tai Chi, three 50-min sessions weekly + Endurance Training + Usual medical care	12	Endurance Training: three 50-min sessions weekly + Usual medical care	3/60 (5.0%) in total; I: 0; C: 3/30 (10.0%)	Safety; QoL (MacNewQLMI)
Ding FM 2013	Acute myocardial infarction after PCI	90	42-form Chen style Tai Chi, at least five 60-min sessions per week + Behaviour guidance + Usual medical care + Jogging	24	Control 1: Behaviour guidance + Usual medical care; Control 2: Jogging	NR	QoL (SF-36)
Han QY 2010	Cardiovascular risk factor-hypertension	60	24 simplified Yang style Tai Chi, 45-60 minutes per session, 1-2 sessions daily + Usual medical care	240	Usual medical care	2/60 (3.3%) in total; I: 0; C: 2/30 (6.6%)	Safety, QoL (SF-36)
Lam P 2008	Cardiovascular risk factor-Type 2 diabetes	53	Tai Chi for Diabetes (a 12-movement hybrid from Sun and Yang styles), two 1-hour classes weekly for 12 weeks and then once weekly for a further 12 weeks	24	Wait list	10/53 (18.8%)	QoL (SF-36)
Liu X 2013	Cardiovascular risk factor-Elevated	41	Kai Mai Tai Chi, three 90-min sessions weekly + Usual medical care	12	Usual medical care	NR	QoL (MOS SF36)

	blood glucose or diabetes						
Study ID	**Disease/ condition**	**Sample size**	**Intervention**	**Duration (weeks)**	**Control**	**Lost to follow up (No. (%))**	**Outcome measures**
Meng E 2014	Cardiovascular risk factor- Type 2 diabetes	200	Tai Chi + Health education + Diet guidance + Usual medical care	12	Health education + Dietary guidance + Usual medical care	NR	QoL (SF-36)
Pan XF 2016	Chronic heart failure	61	24 simplified Yang style Tai Chi, one 30-min session daily + Health education + Diet guidance + Usual medical care	24	Health education + Diet guidance + Usual medical care	NR	QoL (SF-36)
Robins JL 2016	At increased risk for cardiovascular disease	96	Specially designed short-form Tai Chi, one 60-minute session weekly & home practice 15 minutes most days of the week	8	Wait list	33/96 (34.3%) in total; I: 16/47 (34.0%); C: 17/49(34.6%)	Stress (PSS), SIBS-R; depression (CES-D), social support (SPS), mindfulness (MAAS), self-compassion (SCS-R)
Sang L 2015	Chronic heart failure	100	Specially designed Tai Chi program, one 15-minute session daily + Usual medical care	12	Usual medical care	NR	QoL (MLHF)
Song HN 2013	Cardiovascular risk factor- Impaired glucose metabolism	80	24 simplified Yang style Tai Chi, one 50-min session daily + Health education	12	Health education	NR	Depression (SDS), anxiety (SAS), QoL (WHOQOL-100)

Study ID	Disease/ condition	Sample size	Intervention	Duration (weeks)	Control	Lost to follow up (No. (%))	Outcome measures
Sun F 2014	Cardiovascular risk factor- Hypertension	90	24 simplified Yang style Tai Chi, one 2-hour session daily	8	Health education	10/90 (11.1%) in total; I: 7/45 (15.5%); C: 3/45 (6.6%)	Depression (SDS), anxiety (SAS)
Sun J 2015	Cardiovascular risk factor- Hypertension	300	Tai Chi in group 3 hours & 2 hours home practice weekly	48	Active controls: non-exercise-related activities such as reading	35/300 (11.6%) in total; I: 14/150 (9.3%); C: 20/150 (13.3%)	QoL (SF-12)
Tsai JC 2003	Cardiovascular risk factor- Documented borderline hypertension	88	108-form Yang style Tai Chi, three 50-min sessions weekly	12	A sedentary life control: usual lifestyle behaviours including eating habits and previous sedentary life pattern	12/88 (13.6%), losses were equally divided between the groups.	Safety; state and trait anxiety (STAI)
Tsang T 2007	Cardiovascular risk factor- Type 2 diabetes	38	Tai Chi for Diabetes (a 12-movement hybrid from Sun and Yang styles), twice 1-hour sessions weekly	16	Sham exercise (e.g. seated calisthenics & gentle stretching)	1/38 (2.6%) in total; I: 1/18 (5.5%); C: 0	Safety; QoL (SF-36)
Wang HP 2014	Cardiovascular risk factor- Type 2 diabetes	70	24 simplified Yang style Tai Chi, five 40-min sessions weekly + Diet guidance + Usual medical care	8	Dietary guidance + Usual medical care	NR	Mood (SCL-90)
Wang P 2009	Cardiovascular risk factor- Type 2 diabetes	64	24 simplified Yang style Tai Chi, 45-60 minutes per session, 5-7 sessions weekly + Health education + Usual medical care	24	Health education + Usual medical care	0	QoL (SF-36)
Wang XK 2013	Acute myocardial infarction after PCI	60	42-form Chen style Tai Chi, five 60-min sessions weekly + Behaviour guidance + Usual medical care	24	Behaviour guidance + Usual medical care	NR	QoL (SF-36)

Study ID	Disease/ condition	Sample size	Intervention	Duration (weeks)	Control	Lost to follow up (No. (%))	Outcome measures
Wu F 2010	Cardiovascular risk factor-Type 2 diabetes	40	24 simplified Yang style Tai Chi, 60-min per session, >3 sessions weekly + Usual medical care	24	Usual medical care	NR	QoL (SF-36)
Yao CD 2010	Chronic heart failure	150	42-form Chen style Tai Chi, 5-15 minutes per session (30 minutes per session after the first month), >5 sessions weekly + Life style guidance + Usual medical care	24	Life style guidance + Usual medical care	NR	QoL (MLHF)
Yeh GY 2004	Chronic heart failure	30	5-form simplified Yang-style Tai Chi, twice 60-min sessions weekly & home practice >3 times weekly + Usual medical care + Dietary guidance + General exercise advice	12	Usual medical care + Dietary guidance + General exercise advice	0	Safety; QoL (MLHF)
Yeh GY 2011	Chronic heart failure	100	5-form simplified Yang-style Tai Chi, twice 60-min sessions weekly & home practice >3 times weekly + Usual medical care + General exercise advice	12	Usual medical care + General exercise advice + Health education	4/100 (4.0%) in total; I: 1/50 (2.0%); C: 3/50 (6.0%)	Safety; mood (POMS), psychosocial functioning (CESI); QoL (MLHF)
Yeh GY 2013	Heart failure with preserved ejection fraction	16	5-form simplified Yang-style Tai Chi, twice 60-min sessions weekly & home practice >3 times weekly + Usual medical care + General exercise advice	12	Usual medical care + General exercise advice + Aerobic exercise, twice 1-hour weekly	0	Safety; mood (POMS), self-efficacy (SEBES); QoL (MLHF)
Zhang EM 2014	Cardiovascular risk factor-	40	24 simplified Yang style Tai Chi, 60-min per session	14	Usual medical care	NR	Depression (SDS)

	Type 2 diabetes with depression (SDS>40)		+ Usual medical care		+ Walking (80-100 steps/min)		
Zhang SQ 2011	Acute myocardial infarction after PCI	132	42-form Chen style Tai Chi, 5-15 minutes per session (30-min session after the first month), > 5 sessions weekly + Behaviour guidance + Usual medical care	48	Behaviour guidance + Usual medical care	NR	QoL (MLHF)

Abbreviations: PCI=percutaneous coronary intervention; QoL=Quality of life; STAI=state and anxiety inventory; PSS=the Perceived Stress Scale; CES-D =the Center for Epidemiological Studies-Depression; MOS=Medical Outcomes Study; SPS=the revised Social Provision Scale; MAAS=the Mindful Attention Awareness Scale; SCS-R=the revised Self-Compassion Scale; SIBS-R=the revised Spiritual Involvement and Beliefs Scale; MLHFQ=the Minnesota Living with Heart Failure questionnaire; WHOQOL-100=the World Health Organization Quality of Life; SAS=Zung Self-Rating Anxiety Scale; SCL-90=Symptom Chelist-90; SCL-R= Symptom Chelist-90-Revised; POMS=the Profile of Mood States; SEBES= the Self-Efficacy-Barriers to Exercise Scale.

Various Tai Chi styles and forms were used. The majority of studies (15/25, 60.0%) applied Yang style, and the most popular one was 24-form Simplified Yang style (8/25, 32.0%). Most studies used a modified or simplified Tai Chi program (16/25, 64.0%), including 24-form Simplified Yang style (8/25, 32.0%), 5-form Simplified Yang style (3/25, 12.0%), a modified 10-movement Yang style (1/25, 4.0%), Tai Chi for Diabetes (a 12-movement hybrid from Sun and Yang styles) (2/25, 8.0%) and specially designed Tai Chi program (2/25, 8.0%). Two studies did not report the specific Tai Chi style/form used (Meng, 2014; J. Sun & Buys, 2015).

Twenty-three studies (23/25, 92.0%) reported that participants practiced Tai Chi programs in group classes, while two studies (H. Wang, 2014; F. Wu et al., 2010) did not reported the practice method. The group classes were guided and supervised by a professional Tai Chi instructor (Caminiti et al., 2011; Han et al., 2010; X. Liu et al., 2013; F. Sun & Sun, 2014; Tsai et al., 2003; P. Wang et al., 2009; Yeh et al., 2011; Yeh et al., 2004; Yeh et al., 2013) an experienced trainer/investigator (Barrow et al., 2007; Robins et al., 2016; J. Sun & Buys, 2015; Tsang et al., 2007) or an exercise physiologist (Orr, Tsang, Lam, Comino, & Singh, 2006; F. Wu et al., 2010). In addition, for three studies, a physician (Yeh et al., 2004), a trained cardiac rehabilitation nurse (Barrow et al., 2007) or a healthcare provider (Sang et al., 2015) was also in attendance. Heart rate, blood pressure or electrocardiogram (ECG) of participants were monitored in nine studies to measure exercise intensity (Han et al., 2010; X. Pan, 2016; Tsai et al., 2003; P. Wang et al., 2009; X. Wang et al., 2013; F. Wu et al., 2010; Yao et al., 2010; E. Zhang, 2014; S. Zhang & Chen, 2011).

Nine studies (9/25, 36.0%) (Barrow et al., 2007; Han et al., 2010; X. Liu et al., 2013; X. Pan, 2016; Robins et al., 2016; J. Sun & Buys, 2015; Yeh et al., 2011; Yeh et al., 2004; Yeh et al., 2013) encouraged or required home practice in addition to their group class, five of which (X. Liu et al., 2013; Robins et al., 2016; Yeh et al., 2011; Yeh et al., 2004; Yeh et al., 2013) provided a videotape/DVD to participants demonstrating the Tai Chi practice to support home practice.

Tai Chi programs varied from 5 to 120 minutes per session, and 60 minutes per session was the duration in 50% of the 26 studies. In two studies (Yao et al., 2010; S. Zhang & Chen, 2011), the time of each session gradually increased from 5-15 minutes (learning the movements for the first 4 weeks) to 30 minutes (maintenance practice).

The frequency varied from two to fourteen sessions weekly (2 sessions daily); two and three sessions weekly were the most common frequencies, accounting for 26.9% and 19.2% respectively. The duration varied from 8 to 240 weeks, and the most common duration was 12 weeks (9/25, 36.0%), followed by 24 weeks (7/25, 28.0%). Tai Chi intervention was used in combination with usual medical care in 19 studies (19/25, 76.0%).

Amongst the 25 studies, the reported outcomes include physical performance, safety, psychological outcomes, and quality of life. Psychological well-being outcomes included stress, state and trait anxiety, depression, social support, mindfulness and self-compassion, mood, and self-efficacy and psychosocial functioning. Health-related quality of life was assessed using five different general or disease-specific instruments, including 12-Item Short Form Health Survey (SF-12), the World Health Organization Quality of Life (WHOQOL-100), and the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), the MacNew Heart Disease Health-related Quality of Life Instrument (MacNew QLMI), and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Table 3.3 lists the details of the Tai Chi intervention used in the included studies.

Table 3.3 Tai Chi intervention applied in the included studies

Study ID	Disease/ condition	Tai Chi intervention				
		Style & Form	**Instruction provider**	**Components**	**Timing (min/session; times/week)**	**Duration (weeks)**
Barrow DE 2007	Symptomatic heart failure	Wu Chian Chuan style	A trained Tai Chi trainer, with a trained cardiac rehabilitation nurse also in attendance.	(1) Group class: Chi Kung (20 mins) for relaxation, stillness of mind & mood; rest period (5 mins); Tai Chi (20 mins); cool down (5 mins). The practice was gradually increased, reaching full potential on week 8. (2) Home practice encouraged.	50 min/session; twice/week & home practice	16
Caminiti G 2011	Chronic heart failure	A modified 10-form Yang-style	An experienced Tai Chi instructor	Group class: warm up (10 mins), Tai Chi (30 mins), & cool down (10 mins). Week 1-8 learned the movements. Week 9-12 practiced the complete sequence, in the same speed. A trained cardiac rehabilitation therapist also in attendance.	50 min/session; three times/week	12
Ding FM 2013	Acute myocardial infarction after PCI	42-form Chen style	NR	Group class: a warm-up exercise (15 mins), Tai Chi practice (30 mins), and cool down exercise (15 mins).	60 min/session; at least five times per week	24
Han QY 2010	Hypertension	24 simplified Yang-style	A professional Tai Chi instructor	(1) Prior to class: introduce the importance & methods of Tai Chi practice; (2) Group class: warm up (10-15 mins), Tai Chi (20-30 mins), and cool down (5 mins), focusing on the movements, breathing and mind/consciousness. Target heart rate was monitored.	45-60 min/session; 7-14 (1-2 sessions daily) times per week	240
Lam P 2008	Type 2 diabetes	Tai Chi for Diabetes (a 12-movement hybrid from Sun and Yang styles)	NR	Group class: Tai Chi program	60 min/session; twice/week for week 1-12 and once/week for week 13-24	24
Liu X 2013	Elevated blood glucose or diabetes	Kai Mai Tai Chi	A Tai Chi/Qigong instructor	(1) Group class: Tai Chi intervention; (2) Home practice: a video/DVD was provided.	90 min/session; three times/week and home practice	12

Study ID	Disease/ condition	Tai Chi intervention				
		Style & Form	**Instruction provider**	**Components**	**Timing (min/session; times/week)**	**Duration (weeks)**
Liu X 2013	Elevated blood glucose or diabetes	Kai Mai Tai Chi	A Tai Chi/Qigong instructor	(1) Group class: Tai Chi intervention; (2) Home practice: a video/DVD was provided.	90 min/session; three times/week and home practice	12
Meng E 2014	Type 2 diabetes	Tai Chi	NR	NR	NR	12
Pan XF 2016	Chronic heart failure	24 simplified Yang-style	NR	(1) Tai Chi practice in the morning. The intensity could be adjusted based on the target heart rate. Target heart rate = resting heart rate + resting heart rate x (60%-80%). ECG was provided to monitor patients' status; (2) Home practice: heart rate monitored.	30 min/session; seven times/week	24
Robins JL 2016	At increased risk for CVD	Specially designed short-form program	The principal investigator who has 16 years of experience in designing and implementing tai chi interventions	(1) Group class: a warm-up exercise on breathing and balance; Tai Chi were taught in a sequence focusing on skills in balancing, focused breathing, gentle physical posturing and movement, and consciousness for relaxation; (2) Home practice: a DVD was provided.	60 min/session; once/week and 15-minute home practice daily	8
Sang L 2015	Chronic heart failure	Specially designed program	Health care providers in attendance	Group class: Tai Chi. Health care providers were also in attendance.	15 min/session; seven times /week	12
Song HN 2013	Impaired glucose metabolism	24 simplified Yang-style	NR	Practiced Tai Chi till the heart rate reached >100 times/min for 10 min.	50 min/session; seven times/week	12
Sun F 2014	Hypertension	24 simplified Yang-style	A professional Tai Chi instructor	Group class: practice in comfortable and quiet environment, focusing on correct movements, breathing skills and the mind/consciousness.	120 min/session; seven times/week	8
Sun J 2015	Hypertension	Tai Chi	An experienced trainer	(1) Group class: a variety of meditation techniques including breathing, balance, flexibility, concentration, calming, and stress-reduction techniques; (2) Home practice	90 min/session; twice/week and 120-minute home practice	48

Study ID	Disease/ condition	Tai Chi intervention				
		Style & Form	**Instruction provider**	**Components**	**Timing (min/session; times/week)**	**Duration (weeks)**
Tsai JC 2003	Documented borderline hypertension	108-form Yang style	A qualified master & a Tai Chi instructor	(1) Prior to participation: learned Tai Chi from a qualified master; (2) Group class: Tai Chi practice, including warm-up exercises (10 mins), Tai Chi practice at same speed (30 mins), and a cool-down exercise (10 mins). Heart rates were monitored by an ECG telemeter. Blood pressure was monitored too.	50 min/session; three times/week	12
Tsang T 2007	Type 2 diabetes	Tai Chi for Diabetes (a 12-movement hybrid from Sun and Yang styles)	An investigator extensively trained	Group class: a specific warm-up exercises for the whole body (10 mins); Tai Chi in its entirety (45 mins). involving breathing techniques and visualization; cool-down exercises (5 mins).	60 min/session; twice/week	
Wang HP 2014	Type 2 diabetes	24 simplified Yang-style	NR	Group class: Patients could progress at their own pace and intensity.	40 min/session; five times/week	8
Wang P 2009	Type 2 diabetes	24 simplified Yang style	A professional Tai Chi instructor	(1) Prior to class: nurses and volunteers introduced the purpose, importance and methods of Tai Chi practice; (2) Group class: Tai Chi program (45-60 mins), including a warm-up exercise, Tai Chi practice, and cool down exercise, focusing on the movements, breathing and mind or consciousness. The intensity could be adjusted based on the target heart rate. Target heart rate = resting heart rate + resting heart rate x (50%-70%).	45-60 min/session; 5-7 times/week	24
Wang XK 2013	Acute myocardial infarction after PCI	42-form Chen style	NR	Group class: Week 1-4 learned the sequence; Week 5-24 maintained practice: warm up (15 mins), Tai Chi (30 mins), and cool down (15 mins). Heart rate, blood pressure & ECG were monitored before, during & after class.	60 min/session; five times/week	24

Study ID	Disease/ condition	Tai Chi intervention				
		Style & Form	**Instruction provider**	**Components**	**Timing (min/session; times/week)**	**Duration (weeks)**
Wu F 2010	Type 2 diabetes	24 simplified Yang-style	A physiologist with Tai Chi teaching experience	Group class: Practiced Tai Chi before breakfast till the heart rate reached 130-140 times /min.	60 mins/session; at least three times/week	24
Yao CD 2010	Chronic heart failure	42-form Chen style	NR	Group class: Week 1-4 learned the complete sequence; Week 5-24 maintained practice: a complete set of Tai Chi (30 mins). The intensity could be adjusted based on the target heart rate. Target heart rate = resting heart rate + resting heart rate *(10%-20%). ECG telemeter was provided to monitor patients' status.	5-15 min/session (30 mins per session after week 4); at least five times/week	24
Yeh GY 2004	Chronic heart failure	5 simplified Yang-style	An experienced Tai Chi instructor, with a physician also in attendance	(1) Group class: warm up (i.e. weight shifting, arm swinging, gentle stretches, visualization techniques, and traditional breathing), focusing on releasing tension in the physical body, incorporating mindfulness and imagery into movement, increasing awareness of breathing, and promoting overall relaxation of body & mind; 5-form simplified Tai Chi. Chairs were provided, and patients could progress at their own pace. (2) Home practice: videotape provided.	60 min/session; twice/week and at least three times of home practice per week	12
Yeh GY 2011	Chronic heart failure	5 simplified Yang-style	1 or 2 certified and experienced instructors (6 total study instructors with average experience of 20 years)	(1) Group class: a warm-up exercise (i.e. weight shifting, arm swinging, gentle stretches, visualization techniques and tractional breathing methods), focusing on releasing tension in the body, incorporating mindfulness and imagery into movement, increasing awareness of breathing, and promoting overall relaxation of body and mind; 5 simplified Tai Chi movements. Chairs were provided for resting, and patients could progress at their own pace. (2) Home practice: videotape provided.	60 min/session; twice/week & at least three times of home practice per week	12

Study ID	Disease/ condition	Tai Chi intervention				
		Style & Form	**Instruction provider**	**Components**	**Timing (min/session; times/week)**	**Duration (weeks)**
Yeh GY 2013	Heart failure with preserved ejection fraction	5-form simplified Yang-style	An experienced instructor	(1) Group class: warm up (i.e. weight shifting, arm swinging, gentle stretches, visualization techniques & traditional breathing), focusing on releasing tension in the physical body, incorporating mindfulness and imagery into movement, increasing awareness of breathing, and promoting overall relaxation of body & mind; 5-form simplified Tai Chi. Chairs were provided. Patients could progress at their own pace. (2) Home practice: videotape provided.	60 min/session; twice/week and at least three times of home practice per week	12
Zhang EM 2014	Type 2 diabetes with depression (SDS>40)	24 simplified Yang-style	NR	Group class: a warm-up exercise (5 mins); Tai Chi practice (50-60 mins) with background music under guidance in breathing, balance and flexibility; cool down exercises (5 mins). Week 1-2 learned the complete sequence; week 3-5 practiced single movements; week 6-8 practiced the complete sequence, focusing on the combination of mind, qi and body; week 9-14 competitive practice. The intensity could be adjusted based on heart rate. The target heart rate = (220 -Age) x (65~85%) + resting heart rate.	60 min/session; NR the times per week	14
Zhang SQ 2011	Acute myocardial infarction after PCI	42-form Chen style	NR	Group class: Week 1-4 learned the movements; Week 5-48 maintained practice: a complete set of Tai Chi (30 mins). Adjusted intensity based on the target heart rate. Target heart rate = resting heart rate + resting heart rate x (10%-20%). ECG telemeter was provided to monitor patients' status.	5-15 min/session (30 mins per session after week 4); at least five times per week	48

Note: NR, not reported; min, minute.

3.3.2 Methodological Quality

We contacted the corresponding authors by emails to clarify unclear or missing information in the papers, and the response rate was low (4/25, 16%). Accordingly, only two studies were rated as low risk of bias in all six items, and the majority were rated as unclear risk of bias. The methodological quality of the included studies was generally poor.

Although all included studies mentioned 'randomised', only nine studies (Caminiti et al., 2011; Lam et al., 2008; X. Liu et al., 2013; X. Pan, 2016; Tsang et al., 2007; Yeh et al., 2011; Yeh et al., 2004; Yeh et al., 2013; E. Zhang, 2014) reported the specific methods for sequence generation, including 'random number table', and 'computer-generated allocation method'. Three studies (Lam et al., 2008; Tsang et al., 2007; Yeh et al., 2004) reported the allocation concealment, in which two studies (Tsang et al., 2007; Yeh et al., 2004) reported their specific method by using 'a sealed, sequentially numbered, opaque envelope'. Five studies (Lam et al., 2008; J. Sun & Buys, 2015; Tsai et al., 2003; Yeh et al., 2011; Yeh et al., 2013) reported that the blinding of outcome assessors. We did not report performance bias, considering the difficulty to blind the participants and personnel in Tai Chi study. Thirteen studies (Barrow et al., 2007; Caminiti et al., 2011; Han et al., 2010; Lam et al., 2008; Robins et al., 2016; F. Sun & Sun, 2014; J. Sun & Buys, 2015; Tsai et al., 2003; Tsang et al., 2007; P. Wang et al., 2009; Yeh et al., 2011; Yeh et al., 2004; Yeh et al., 2013) reported information about participants lost to follow up, from which the average drop-out rate was 11.6%. Figure 3.2 and 3.3 illustrate the summary of risk of bias of the included studies.

Figure 3.2 Risk of bias graph of the included trials.

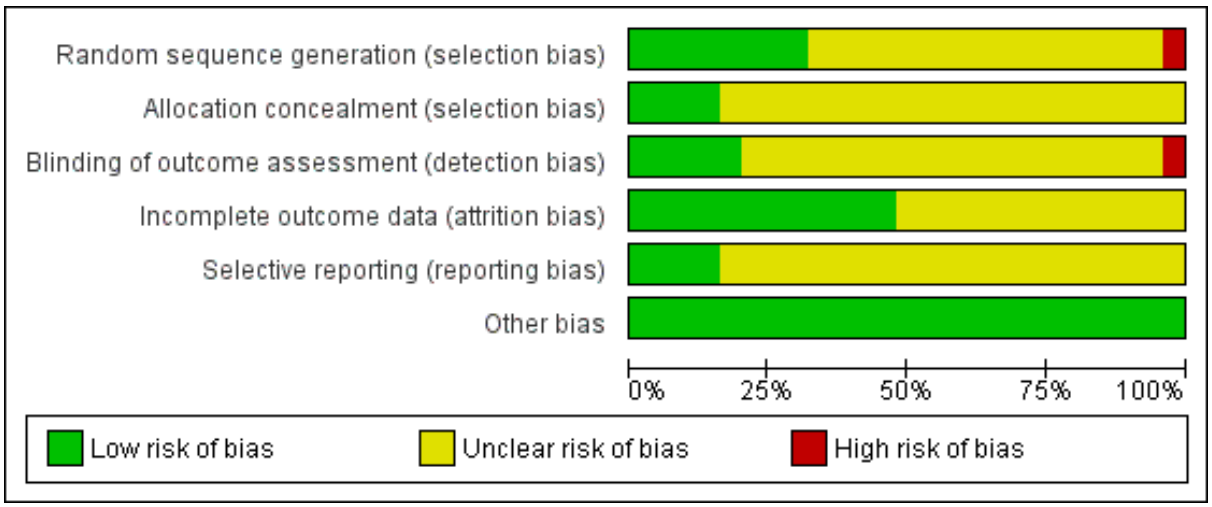


Figure 3.3 Risk of bias summary of included trials.

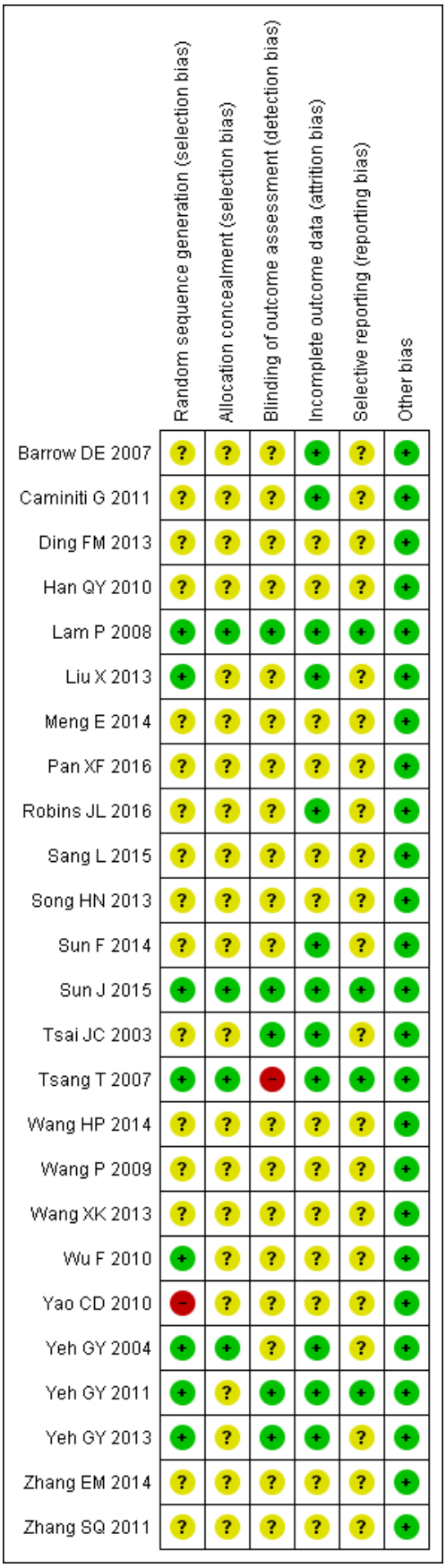


Table 3.4 Effect estimates of Tai Chi program for psychological well-being and quality of life in people with or at risk of CVD

Outcomes and comparisons	Effect estimate (MD, 95% CI)	No. of participants (studies)	Study ID
Stress			
Tai Chi program versus Waitlist			
Assessed with PSS-10	-2.45 [-3.06, -1.84] *	59 (1 RCT)	Robins JL2016
Depression			
Tai Chi program versus Waitlist			
Assessed with CES-D	-6.05 [-6.79, -5.31] *	59 (1 RCT)	Robins JL 2016
Tai Chi program versus Education			
Assessed with SDS	-2.06 [-4.09, -0.03] *	80 (1 RCT)	Sun F 2014
Tai Chi program + Usual care versus Usual care			
Assessed with SDS	-1.99 [-6.08, 2.09] Δ	120 (2 RCTs)	Zhang EM 2014, Song HN 2013
Anxiety			
Tai Chi program versus Sedentary life control			
Assessed with STAI:			
STAI -Trait Anxiety	-7.00 [-9.88, -4.12] *	76 (1 RCT)	Tsai JC 2003
STAI -State Anxiety	-6.20 [-8.95, -3.45] *	76 (1 RCT)	Tsai JC 2003
Tai Chi program + Health education versus Health education			
Assessed with SAS	-4.72 [-8.26, -1.18] *	80 (1 RCT)	Song HN 2013
Tai Chi program versus Health education			
Assessed with SAS	-6.21 [-8.26, -4.16] *	80 (1 RCT)	Sun F 2014
Mood			
Tai Chi program + Usual care versus Usual care + Aerobic exercise			
Assessed with POMS:			
POMS-Total mood disturbance	2.60 [-9.18, 14.38]	16 (1 RCT)	Yeh GY 2013
POMS-Depression	-0.70 [-3.20, 1.80]	16 (1 RCT)	Yeh GY 2013

Outcomes and comparisons	Effect estimate (MD, 95% CI)	No. of participants (studies)	Study ID
Tai Chi program + Usual care versus Usual care + Health education			
Assessed with POMS	-	100 (1 RCT)	Yeh GY 2011
Tai Chi program +Diet guidance + Usual care versus Diet guidance + Usual care			
Assessed with SCL-90:			
SCL-90-Anxiety	-0.41 [-0.63, -0.19] *	70 (1 RCT)	Wang HF 2014
Quality of life			
Tai Chi program + Health education versus Health education			
Assessed with WHOQOL-100	10.41 [4.54, 16.28] *	80 (1 RCT)	Song HN 2013
Tai Chi program + Usual care versus Usual care + Health education			
Assessed with MLHFQ	-	100 (1 RCT)	Yeh GY 2011
Tai Chi program versus Non-exercise-related activity			
Assessed with SF-12:		266 (1 RCT)	Sun J 2015
Physical functioning	3.36 [-0.61, 7.33]		
Role limitation due to physical health	12.52 [8.62, 16.42] *		
Role limitation due to emotional health	5.15 [0.81, 9.49] *		
Energy/Vitality	9.33 [4.39, 14.27] *		
Mental health	5.54 [1.02, 10.06] *		
Social functioning	4.99 [0.80, 9.18] *		
Bodily pain	14.04 [9.20, 18.88] *		
General health	-7.84 [-13.56, -2.12]		
Tai Chi program + Usual care versus Usual care			
Assessed with SF-36:		359 (4 RCTs)	Wu F 2010, Meng E 2014, Han QY 2010, Pan XF 2016
Physical functioning	5.47 [0.66, 10.28] Δ*		
Role limitation due to physical health	11.82 [8.26, 15.38] Δ*		
Role limitation due to emotional health	8.27 [5.56, 10.98] Δ*		
Energy/Vitality	7.03 [1.92, 12.14] Δ*		

Outcomes and comparisons	Effect estimate (MD, 95% CI)	No. of participants (studies)	Study ID
Mental health	7.86 [4.29, 11.44] Δ*		
Social functioning	9.81 [5.19, 14.42] Δ*		
Bodily pain	6.34 [2.45, 10.23] Δ*		
General health	10.04 [7.15, 12.93] Δ*		
Assessed with MLHFQ	-11.10 [-15.52, -6.68] Δ*	428 (5 RCTs)	Sang L 2015, Yao CD 2010, Zhang SQ 2011, Yeh GY 2013, Yeh GY 2004

Abbreviations: CI, confidence interval; *, the effect estimate favours experimental group; Δ, result from Meta-analysis; -, the study reported median scores of instruments. PSS-10, Perceived Stress Scale 10-item; CES-D, Centre for Epidemiological Studies-Depression; SDS, Zung Self-Rating Depression Sale; STAI, State and Trait Anxiety Inventory; SAS, Zung Self-Rating Anxiety Scale; POMS, Profile of Mood States; SCL-90, Symptom Checklist-90-Revised; WHOQOL-100, World Health Organization Quality of Life; MLHFQ, Minnesota Living with Heart Failure Questionnaire; SF-12, 12-Item Short Form Health Survey; SF-36, 36-Item Short Form Health Survey.

3.3.3 Effects of Interventions

The effect estimates of Tai Chi for psychological well-being and quality of life in people with or at risk of CVD were shown in the Table 3.4.

3.3.3.1 Primary Outcome: Stress

One study (Robins et al., 2016) conducted in the USA reported the effects of Tai Chi on stress in 96 women with cardiovascular risk by Perceived Stress Scale 10-item (PSS-10) (Range of possible scores: 0-40; higher scores reflect higher levels of perceived stress). Compared with the waitlist control group, the specially designed 8-week short-form Tai Chi program was superior in decreasing the perceived stress (MD -2.45, 95% CI: -3.07, -1.83) at 16 weeks (2 months following the intervention). Table 3.5 shows the summary of finding of this study.

3.3.3.2 Other psychological well-being outcomes

Anxiety

Anxiety was reported in one study (Tsai et al., 2003) conducted in Taiwan measured by the State and Trait Anxiety Inventory (STAI). The STAI contains 20 items each on trait (scale from 20-80) and state anxiety (scale from 20-80); higher scores indicate higher level of anxiety. The Tai Chi group had significantly lower scores on both state and trait anxiety compared with the sedentary life control group in patients with cardiovascular risks (documented borderline hypertension) at week 12. Table 3.4 shows the effect estimates of this study.

Two other studies (H. Song, 2013; F. Sun & Sun, 2014) involving participants with cardiovascular risks (i.e. hypertension and impaired glucose metabolism) conducted in mainland China reported anxiety measured by Zung Self-Rating Anxiety Scale (SAS) (scale from 20-80); higher scores indicate higher level of anxiety. Compared with health education, Song HN et al. (H. Song, 2013) favoured Tai Chi program plus health education group in decreasing SAS scores, and Sun F et al. (F. Sun & Sun, 2014) found also Tai Chi group was superior in reducing anxiety symptoms.

Table 3.5 Summary of findings: Tai Chi versus waitlist group for stress and depression in people with CVD and/or CVD risk factors

Outcomes	**Anticipated absolute effects*** (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)
	Risk with Waitlist	**Risk with Tai Chi Program**		
Stress assessed with: **PSS-10** Scale from: 0 to 40 [Worse]	The mean stress score as measured by PSS-10 was **15**.	MD **2.45 unit lower** (3.06 lower to 1.84 lower)	59 (1 RCT)	⨁⨁◯◯ LOW [a]
Depression assessed with: **CES-D** Scale from: 0 to 60 [Worse]	The mean depression score as measured by CES-D was **12**.	MD **6.05 unit lower** (6.79 lower to 5.31 lower)	59 (1 RCT)	⨁⨁◯◯ LOW [a]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **MD:** Mean difference; **CVD:** cardiovascular disease; **PSS-10:** Perceived Stress Scale 10-item; **CES-D:** Centre for Epidemiological Studies-Depression.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

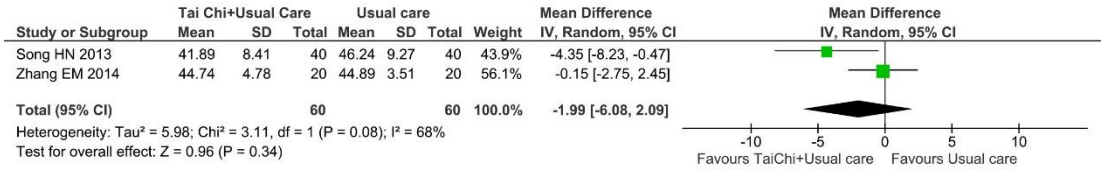
Explanations
a. Unclear risk of bias in respect to randomization, concealment, blinding of outcome assessors, and selective reporting.

Depression

One study (Robins et al., 2016) measured depression using the Center for Epidemiological Studies-Depression (CES-D) (scale from 0-60, with high scores indicating greater depressive symptoms). The specially designed 8-week short-form Tai Chi program significantly decreased depressive symptoms scores at week 8 compared with the waitlist control group. Table 3.5 shows the summary of finding of this outcome.

Three studies (H. Song, 2013; F. Sun & Sun, 2014; E. Zhang, 2014) conducted in China assessed depression with Zung Self-Rating Depression Sale (SDS) (scale from 20-80). Meta-analysis of two studies (H. Song, 2013; E. Zhang, 2014) involving participants with type 2 diabetes or impaired glucose metabolism showed no significant difference between a 24 Simplified Tai Chi program plus usual care and usual care alone in decreasing depression (Figure 3.4). Table 3.6 shows the summary of findings of this meta-analysis. Another study (F. Sun & Sun, 2014) involving 80 participants with hypertension also reported that there was no significant difference in decreasing depression between the 24 Simplified Tai Chi group and health education group at week 8.

Figure 3.4 Forest plot of Tai Chi plus usual care compare with usual care for SDS



Mood

Changes in mood in respect to Tai Chi reported in two studies (Yeh et al., 2011; Yeh et al., 2013) conducted in the USA using the Profile of Mood States (POMS). One study (Yeh et al., 2013) involving 16 participants with heart failure with preserved ejection fraction found no significant differences in mood measured by POMS between a 5-Simplified Tai Chi Program plus usual care and usual care alone group. The other study (Yeh et al., 2011) involving 100 participants with chronic heart failure reported significant improvement in median scores on POMS in total mood disturbance, depression and vigour subscales. One study (H. Wang, 2014) assessed mood using Symptom Checklist-90-Revised (SCL-R) in 35 elderly people with

diabetes and found there was a significant difference in anxiety of SCL-R scores between Tai Chi plus usual care and usual care group.

Self-esteem

No studies reported this outcome.

3.3.3.3 Quality of life

Twenty-two studies (21/25, 84.0%) reported the changes in quality of life. Thirteen studies used general quality of life questionnaires, including the SF-12, the SF-36, and the WHOQOL-100. The disease-specific MLHFQ was used in seven studies involving patients with chronic heart failure or acute myocardial infarction after percutaneous coronary intervention (PCI). One study applied the MacNew QLMI.

One study (J. Sun & Buys, 2015) found there were significant differences in both physical and mental total scores of SF-12 between Tai Chi and non-exercise related activity control groups. Another study (H. Song, 2013) reported significant differences between Tai Chi program plus health education group and health education alone group in quality of life measured by the total score of WHOQOL-100.

Compared with usual medical care alone, a meta-analysis of four studies (Han et al., 2010; Meng, 2014; X. Pan, 2016; F. Wu et al., 2010) in which quality of life assessed using SF-36 found a significant between-group difference in favour of Tai Chi program plus usual care in all domains of SF-36, including physical functioning (MD: 5.47, 95%CI: 0.66, 10.28, I^2=84%), role limitation due to physical health (MD: 11.82, 95%CI: 8.26, 15.38, I^2=32%), role limitation due to emotional health (MD: 8.27, 95%CI: 5.56, 10.98, I^2=0%), energy/vitality (MD: 7.03, 95%CI: 1.92, 12.14, I^2=81%), mental health (MD: 7.86, 95%CI: 4.29, 11.44, I^2=48%), social functioning (MD: 9.81, 95%CI: 5.19, 14.42, I^2=68%), bodily pain (MD: 6.34, 95%CI: 2.45, 10.23, I^2=53%), and general health (MD: 10.04, 95%CI: 7.15, 12.93, I^2=27%). One small study (X. Liu et al., 2013) reported not the scores but the mean between-group differences for each domain of SF-36, and found statistically significant improvements in favour of Tai Chi group in four domains including physical functioning, role physical, bodily pain and vitality ($p<0.05$).

Compared with sham exercise or waitlist group respectively, two small studies (Lam et al., 2008; Tsang et al., 2007) found that Tai Chi group was not superior in any domains of SF-36.

Table 3.6 shows the summary of findings of two meta-analyses on QoL assessed by SF-36 and MLFHQ. Figure 3.5 present the forest plot of Tai Chi in combination with usual care compared with usual medical care alone for SF-36.

Subgroup Analysis

We performed subgroup analyses of SF-36 for patients with CVDs or cardiovascular risks. In patients with cardiovascular risks (i.e. hypertension or type 2 diabetes), compared with usual care alone, a subgroup meta-analysis of three studies (Han et al., 2010; Meng, 2014; F. Wu et al., 2010) in which quality of life assessed using SF-36 found a significant between-group difference in favour of Tai Chi plus usual conventional care in only six domains of SF-36, including role limitation due to physical health (MD: 9.70, 95%CI: 5.95, 13.46, I^2=0%), role limitation due to emotional health (MD: 8.50, 95%CI: 4.68, 12.32, I^2=20%), energy/vitality (MD: 4.81, 95%CI: 0.99, 8.63, I^2=40%), mental health (MD: 7.86, 95%CI: 4.29, 11.44, I^2=48%), social functioning (MD: 10.79, 95%CI: 3.94, 17.65, I^2=78%), and general health (MD: 9.96, 95%CI: 5.16, 14.76, I^2=51%), but not the domains of physical functioning (MD: 4.44, 95%CI: -0.99, 9.87, I^2=82%) and bodily pain (MD: 5.19, 95%CI: -0.02, 10.40, I^2=51%). In the individual study (X. Pan, 2016) involving patients with chronic heart failure, compared with usual medical care alone, the Tai Chi plus usual care was supervior in all domains of SF-36. The heterogeneity could not be explained by the differences of participants.

Table 3.6 Summary of findings: Tai Chi program + usual care versus usual care for quality of life and depression in people with CVD and/or cardiovascular risk factors

Outcomes	**Anticipated absolute effects*** (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)
	Risk with Usual Care	**Risk with Tai Chi Program + Usual Care**		
QoL - Physical functioning assessed with: **SF-36** from: 0 to 100 [Better]	Physical functioning Mean range: **78-90**	MD **5.47 unit higher** (0.66 higher to 10.28 higher)	359 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b]
QoL - Role limitation due to physical health assessed with: SF-36 Scale from: 0 to 100 [Better]	Role limitation due to physical health Mean range: **58-78**	MD **11.82 unit higher** (8.26 higher to 15.38 higher)	359 (4 RCTs)	⨁⨁◯◯ LOW [a]
QoL - Role limitation due to emotional health assessed with: **SF-36** Scale from: 0 to 100 [Better]	Role limitation due to emotional health Mean range: **34-82**	MD **8.27 unit higher** (5.56 higher to 10.98 higher)	359 (4 RCTs)	⨁⨁◯◯ LOW [a]
QoL - Energy/Vitality assessed with: **SF-36** Scale from: 0 to 100 [Better]	Energy/Vitality Mean range: **57-76**	MD **7.03 unit higher** (1.92 higher to 12.14 higher)	359 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b]
QoL - Mental health assessed with: **SF-36** Scale from: 0 to 100 [Better]	Mental health Mean range: **64-75**	MD **7.86 unit higher** (4.29 higher to 11.44 higher)	359 (4 RCTs)	⨁⨁◯◯ LOW [a]
QoL - Social functioning assessed with: **SF-36** Scale from: 0 to 100 [Better]	Social functioning Mean range: **66-86**	MD **9.81 unit higher** (5.19 higher to 14.42 higher)	359 (4 RCTs)	⨁⨁◯◯ LOW [a]
QoL - Bodily pain assessed with: **SF-36** Scale from: 0 to 100 [Better]	Bodily pain Mean range: **67-80**	MD **6.34 unit higher** (2.45 higher to 10.23 higher)	359 (4 RCTs)	⨁⨁◯◯ LOW [a]

Outcomes	Anticipated absolute effects* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)
	Risk with Usual Care	**Risk with Tai Chi Program + Usual Care**		
QoL - General health assessed with: **SF-36** Scale from: 0 to 100 [Better]	General health Mean range: **56-69**	MD **10.04 unit higher** (7.15 higher to 12.93 higher)	359 (4 RCTs)	⨁⨁◯◯ LOW [a]
QoL assessed with: **MLHFQ** Scale from: 0 to 105 [Worse]	MLHFQ Mean range: **28-52**	MD **11.1 unit lower** (15.52 lower to 6.68 lower)	428 (5 RCTs)	⨁⨁◯◯ LOW [c]
Depression assessed with: **SDS** Scale from: 20 to 80 [Worse]	SDS Mean range: **45-46**	MD **1.99 unit lower** (6.08 lower to 2.09 higher)	120 (2 RCTs)	⨁⨁◯◯ LOW [d]

Abbreviation: QoL, Quality of life.

Explanations

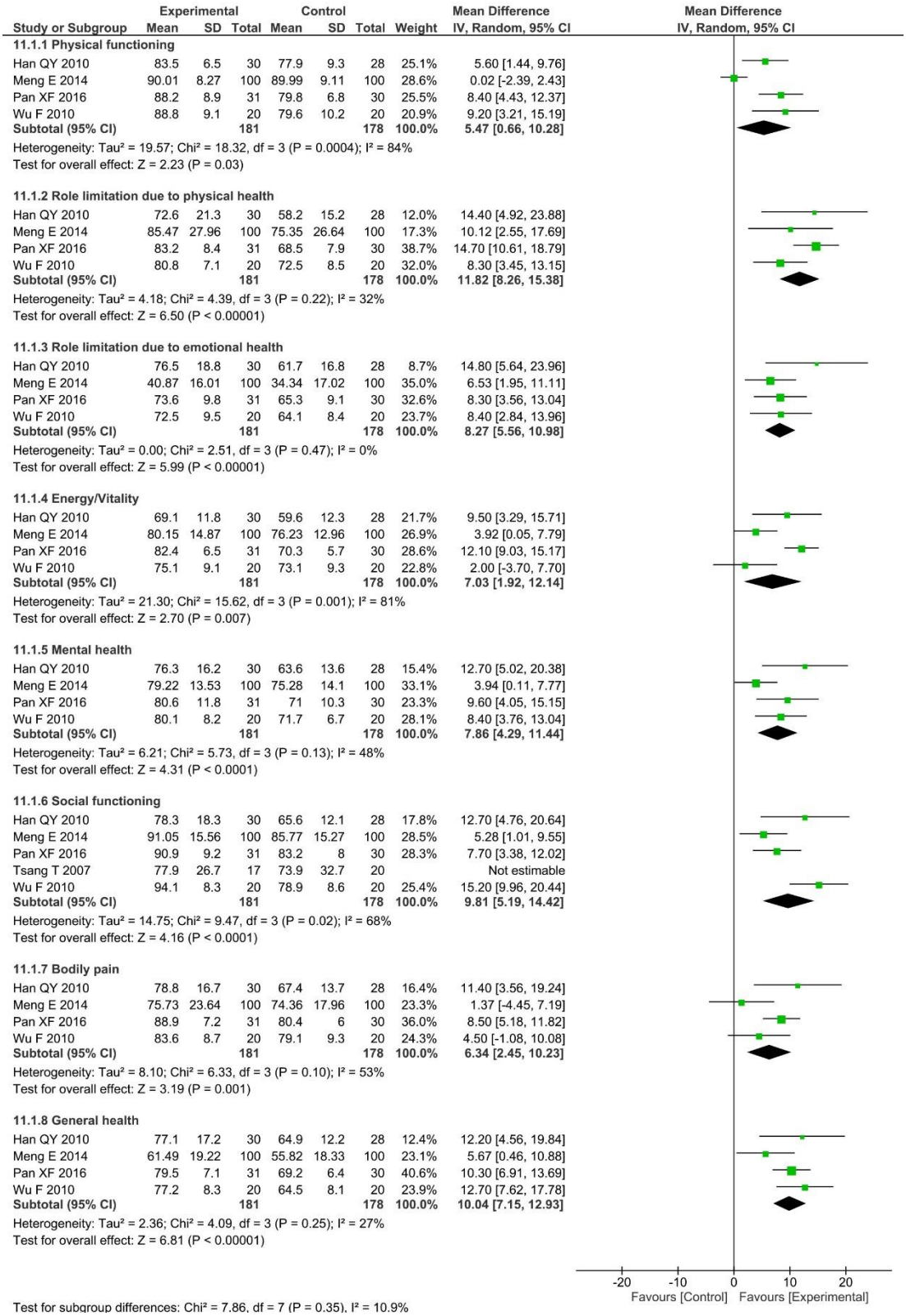
a. Downgraded the risk of bias by 2 levels because three of the four studies in the meta-analysis have unclear risk of bias in randomisation, allocation concealment, blinding of outcome assessor, incomplete reporting and selective reporting. Any other limitations related to inconsistency, indirectness and imprecision were negligible.

b. Downgraded the risk of bias by 1 level because a large heterogeneity was found among the included studies under this outcome.

c. Downgraded the risk of bias by 2 levels because three of the five studies in the meta-analysis have unclear risk of bias in randomisation, allocation concealment, blinding of outcome assessor, incomplete reporting and selective reporting. Any other limitations related to inconsistency, indirectness and imprecision were negligible.

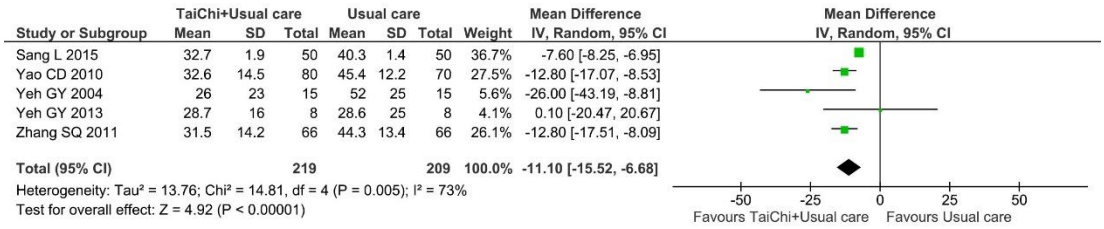
d. Downgraded the risk of bias by 2 levels because both studies in the meta-analysis have unclear risk of bias in randomisation, allocation concealment, blinding of outcome assessor, incomplete reporting, and selective reporting. Any other limitations related to inconsistency, indirectness and imprecision were negligible.

Figure 3.5 Forest plot of Tai Chi in combination with usual care compared with usual care alone for SF-36



Compared with usual medical care alone, a meta-analysis of five studies (Sang et al., 2015; Yao et al., 2010; Yeh et al., 2004; Yeh et al., 2013; S. Zhang & Chen, 2011) showed that there was a significant difference in MLHFQ total scores in favour of Tai Chi in combination with usual care group (MD: -11.10, 95%CI: -15.52, -6.68, I^2=73%) (Table 3.6; Figure 3.6).

Figure 3.6 Forest plot of Tai Chi in combination with usual care compared with usual care for MLHFQ



One individual study (Barrow et al., 2007) reported a 15-point change of MLHFQ in the Tai Chi program plus usual medical care group and the between-group difference was statistically significant (P<0.001). Another individual study (Yeh et al., 2011) also reported Tai Chi group experienced a significantly improved median MLHFQ score more than the education group (P=0.04). One study (Caminiti et al., 2011) reported the QoL measured by MacNew QLMI and found no significant difference between Tai Chi program plus usual medical care group and usual medical care alone.

3.3.3.4 Safety

Eight studies (8/25, 32.0%) involving patients with type 2 diabetes, hypertension, chronic heart failure or symptomatic heart failure reported safety information. No adverse events occurred related to Tai Chi intervention.

However, five studies observed adverse events during the study period, including 7 deaths in the control group (Barrow et al., 2007; Han et al., 2010; Yeh et al., 2011), 1 death in the intervention group (Barrow et al., 2007), 11 hospitalizations due to heart failure exacerbation/angina/shortness (3 in the Tai Chi group and 8 in the control group) (Yeh et al., 2011; Yeh et al., 2004), 2 arrhythmias in the Tai Chi group (Yeh et al., 2011), 2 cases of syncope in control group (Yeh et al., 2011), 3 falls (2 in the Tai Chi group and 1 in the control group) (Yeh et al., 2011), 3 cases of worsening heart failure (1 in the Tai Chi group and 2 in the control

group) (Barrow et al., 2007; Caminiti et al., 2011) and 2 cases of worsening co-morbidities in the control group (Barrow et al., 2007).

3.4 Discussion

3.4.1 Summary of Evidence

This systematic review included 25 eligible RCTs on Tai Chi for people with CVD and/or cardiovascular risk factors. Tai Chi seems potentially effective in improving quality of life in people with CVD and/or cardiovascular risk factors. The meta-analyses demonstrated that Tai Chi in combination with usual medical care significantly improved all domains of the SF-36 and the MLHFQ scores.

The sub-group analyses of SF-36 for people with CVDs are consistent with the main findings. However, the sub-group analyses of SF-36 for people with cardiovascular risk factors found a significant between-group difference in favour of Tai Chi plus usual medical care in only six domains of SF-36, but not the domains of physical functioning and bodily pain. The possible reason why Tai Chi plus usual medical care was not superior in improving the two domains of SF-36 is related to baseline characteristics of the participants. Two of the three studies in the sub-group analyses involved patients with type 2 diabetes and the high scores of these two domains of SF-36 at baseline limited the space of change after intervention.

Our findings support previous literature on Tai Chi for quality of life. One systematic review and meta-analysis involving seven trials on Tai Chi for patients with heart failure found that the Tai Chi group had significantly lower scores of the MLHFQ than that of the control group (Ren et al., 2017).

Our findings related to SF-36 and MLHFQ may achieve the clinical significance. There is still no consensus on the minimal important difference (MID) and minimal clinically important difference (MCID) of SF-36 in patients with cardiovascular risk factors or CVDs. A systematic review of MID and MCID in health-related quality of life demonstrated that MID for SF-36 in patients with pulmonary fibrosis ranged from 2 to 4 points and in patients with prostate cancer ranged from 6 for mental health to 14 for role physical (Jayadevappa, Cook, & Chhatre, 2017). In our review, we found significant between-group differences in all domains of SF-36 in favour of Tai Chi in combination with usual medical care and the mean difference ranged from 5.47

to 11.82 points. In addition, the subgroup analysis of SF-36 in patients with cardiovascular risks found the between-group mean difference ranged from 4.44 to 10.79 points. Accordingly, our findings related to Tai Chi for SF-36 may achieve the clinical significance. For MLHFQ, a meta-analysis of disease-specific health-related quality of life questionnaires for heart failure demonstrated that interventions with small expected effects such as exercise programs produced small score changes and interventions expected to produce large effects such as medications produced large score changes (Garin et al., 2009). A study exploring the minimal detectable change (MDC) and MCID of the MLHFQ found that the MDC ranged from 7.27 to 16.96 and the MCID related to "somewhat better" ranged from 3.59 to 19.14 points (Gonzalez-Saenz de Tejada et al., 2019). In our review, we found a significant difference in MLHFQ total scores in favour of Tai Chi in combination with usual care and the mean difference was 11.10 points. Accordingly, our findings related to Tai Chi for MLHFQ may achieve the clinical significance.

There is still a lack of strong, well-designed studies that demonstrate unequivocally the beneficial effects of Tai Chi in decreasing stress, depression, anxiety, and mood disturbance in this population. Individual studies with various measurements found statistically significant differences between the Tai Chi and the control groups in decreasing stress, depression, anxiety and mood disturbance. Considering the clinical heterogeneity, we did not pool the data together. However, a meta-analysis of two studies showed Tai Chi in combination with usual care was not superior to the usual care alone in decreasing depression.

Tai Chi appears safe to practice for people with CVD and/or cardiovascular risk factors. No adverse events related to Tai Chi were reported in included studies. However, only 32.0% of 25 included studies reported safety information. The low reporting rate of safety was consistent with findings of previous reviews. Wayne et al. (2014) systematically assessed the frequency and quality of adverse events reported in RCTs on Tai Chi, and only 33% of the 153 included RCTs reported adverse events information (Wayne, Berkowitz, Litrownik, Buring, & Yeh, 2014). Similarly, our previous bibliometric review found that only 20.7% of 507 included studies reported safety information (G. Yang et al., 2015). Although Tai Chi was unlikely to result in serious adverse events, it might be associated with minor musculoskeletal aches and pains (Wayne et al., 2014).

3.4.2 Limitations

The general methodological quality of these studies was poor to moderate. Poor reporting allows authors to escape scrutiny of any weak aspects of their trials (Schulz, Altman, & Moher, 2010), and may limit critically appraisal important aspects of a trial. In this systematic review, we classified a certain item of risk of bias as unclear if a trial with insufficient information to judge and downgrade the quality of evidence using GRADE criteria. We recommend researchers follow the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement (Schulz et al., 2010) and its extension for non-pharmacologic treatments (Boutron, Altman, Moher, Schulz, & Ravaud, 2017) to improve the research transparency. In addition, due to the nature of Tai Chi, blinding of both participants and researchers to the interventions is hard to be feasible, so the included studies might have high risk of performance bias.

Secondly, the results of these individual studies may not achieve clinical significance. Three studies (H. Song, 2013; F. Sun & Sun, 2014; E. Zhang, 2014) used SDS (scale from: 20-80) to assess depression. Previous studies with cardiovascular disease have often used a cut-off index score of 50 as a definition of clinical depression (Parissis et al., 2008; Pihl, Jacobsson, Fridlund, Stromberg, & Martensson, 2005; Shiotani et al., 2002). However, only in one (H. Song, 2013) study the mean SDS scores of the Tai Chi and control groups at baseline were above 50. Although Sun and Sun (2014) found that the Tai Chi group was superior in reducing SDS scores (F. Sun & Sun, 2014), it may not achieve clinical significance because the baseline SDS scores of both groups were around 30 (Jayadevappa et al., 2017; Garin et al., 2009; Gonzalez-Saenz de Tejada et al., 2019).

Thirdly, we did not perform subgroup analyses to exploring the effectiveness of different Tai Chi styles. Therefore, the findings could not provide a specific recommendation based on Tai Chi styles/forms. However, because all styles and forms are derived directly or indirectly from *Chen* style, the core principles and theories of them, such as balance, breathing, coordination, relaxation and concentration are similar.

3.4.3 Conclusions

Tai Chi appears an effective and safe intervention to improve quality of life in people with CVD and/or cardiovascular risk factors. It remains uncertain whether Tai Chi is beneficial for the management of stress, depression, anxiety, and mood disturbance in this population. Stronger,

better designed studies assessing Tai Chi for psychological well-being and quality of life as primary outcomes in people with CVD and/or cardiovascular risk factors are warranted.

Chapter 4: Methods of the Randomised Controlled Trial

This chapter describes the objectives and methodology of a RCT exploring the effects of Tai Chi on stress and cardiovascular function in patients with coronary heart disease and/or hypertension. The protocol of the trial has been registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au) (Trial ID: ACTRN12616001204437). The methodology section presents the study design, participants, sample size calculation, recruitment and screening, randomisation, intervention, outcome measures, data collection, statistical analysis and data management. The reporting of this study is in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (Appendix 3).

4.1 Introduction

4.1.1 Background

The detailed background of this study is presented in Chapter 2.

4.1.2 Objectives

The primary objective of this study is to determine the effect of a 24-week Tai Chi intervention on psychological stress in patients with CHD and/or hypertension.

The secondary objective is to investigate the effect of a 24-week Tai Chi intervention on anxiety, depression, cardiovascular function (including blood pressure, heart rate, heart rate variability (HRV), blood lipid profiles, blood glucose profiles and CRP, QoL and physical fitness outcome measures in patients with CHD and/or hypertension.

4.2 Methods

4.2.1 Trial Design

This was a prospective, randomised, international multi-centre, controlled trial designed to investigate the effect of a standardised Tai Chi intervention on psychological stress and cardiovascular function. The primary outcome was psychosocial status of stress measured by the Perceived Stress Scale 10-item (PSS-10). Secondary outcomes included psychosocial status of anxiety measured by Zung Self-Rating Anxiety Scale (SAS), and depression measured by Beck Depression Inventory-II (BDI-II), cardiovascular function (including blood pressure, heart rate, HRV, blood lipid profiles, blood glucose profiles, and CRP), quality of life measured by SF-36, and physical fitness using 6 Minute Walk Test (6MWT). A semi-structured exit interview was also conducted to explore participants' perceptions on facilitators and barriers to trial participation and adherence during and after the randomized controlled trial (see Chapter 5).

Participants with CHD and/or hypertension were randomly assigned into the Tai Chi group who participated in a 24-week Tai Chi intervention, comprising of a 12-week intensive intervention and 12-week sustained intervention or the waitlist control group. The study was conducted in two locations: Sydney, Australia, and Beijing, China. All study procedures complied with Good Clinical Practice guidelines and approval by local human research ethics committees from both the Western Sydney University (Ethics approval number: H11189) and Beijing University of Chinese Medicine (Ethics approval number: 2015BZHYLL0233) before trial commencement.

4.2.2 Participants

Inclusion Criteria:

(1) ≥40 years of age, regardless of gender;

(2) With documented diagnosis of CHD (myocardial infarction, angina or revascularization) with severity of angina class I to II according to the Canadian Cardiovascular Society functional classification, and/or with established diagnosis of hypertension according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al., 2003)*;*

(3) Ability to perform prescribed Tai Chi program;

(4) Willing to complete the 24-week Tai Chi intervention;

(5) Not practicing Tai Chi in the past 6 months;

(6) Ability to speak and read Chinese or English fluently;

(7) Willing to sign a written informed consent.

Exclusion Criteria:

(1) Pregnancy

(2) Previous or current psychological disorders not associated with depression or anxiety

(3) End stage congestive heart failure

(4) Permanent bed-bound status

(5) Unstable abdominal, thoracic or cerebral aneurysm

(6) Acute myocarditis, pericarditis, pulmonary embolus or pulmonary infarction

(7) Significant limitation of physical activity for reasons other than CHD

(8) Participation in a clinical trial for an experimental drug within the last 30 days before the study

4.2.3 Sample Size Calculation

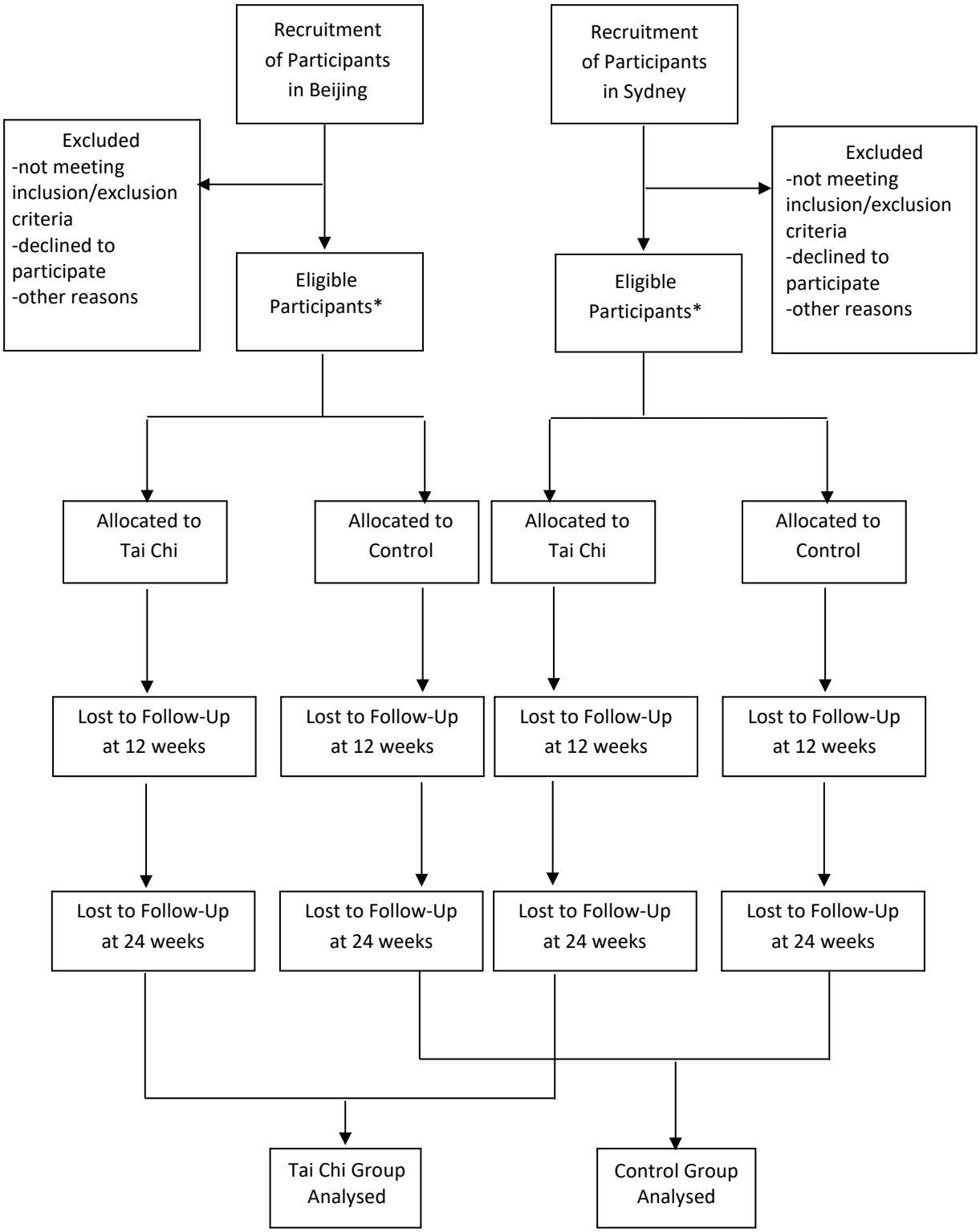
The current study is an exploratory randomized controlled trial focusing primarily on the effect of Tai Chi on stress in patients with CHD or hypertension. There are no preliminary data on which to base a sample size calculation. A previous study evaluated the effect of a 12-week Tai Chi intervention on psychobiological stress response in 70 healthy men and women. This study found that the Tai Chi participants exhibited a significantly lower increase in perceived stressfulness (P=0.006) and maintained a higher level of calmness (P=0.019) in response to psychosocial stress measured by PSS-10 (Nedeljkovic, Ausfeld-Hafter, Streitberger, Seiler, & Wirtz, 2012) compared with the waitlist group. The formula we used for sample size calculation is as follows: $n=2[(a+b)^2\delta^2]/\Delta^2$. In this formula, 'n' stands for the sample size in each of the groups, 'δ' stands for standard deviation, 'Δ' stands for the difference in effect size, 'a' stands for conventional multiplier for alpha of 0.05, 'b' stands for conventional multiplier for power of 0.80. Based on an alpha of 0.05, sample size estimates indicated that we would be able to detect a difference in stress between 3 to 4 with a sample size of 50 participants per group, based on standard deviation estimates of 6 to 7 at a power of 0.80. As no previous research was available on which to base the standard deviation estimates, the estimates should be considered vague approximations. Hence, 100 participants is a conservative estimate to detect a statistically significant result. An attrition rate of 20% is expected during the study; consequently, a total of 120 patients were recruited.

4.2.4 Recruitment and Screening

Patients were recruited from Beijing, China and Sydney, Australia. In Beijing, the target number of participants was 80. Potential participants were recruited from Changying Community Health Service Centre in Chaoyang District. Ono experienced doctors from Changying Community Health Service Centre assisted in the screening and assessment of participants. The principal investigator was in charge of all promotion activities and preparation of advertisements. Two research assistants from the Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine (BUCM) assisted the patient recruitment. Prior to recruitment, an introduction activity was held by the Changying Community Health Service focusing on Tai Chi and information about the study conducted as a health education program for the community residents, particularly potential participants. Residents were informed about this study through notice boards and Health Service Centre websites. Potential participants who expressed interest in participating were contacted by phone. Participants were identified through newsletter advertisements and community bulletins. Interested persons also were encouraged to contact the study investigator for further information and to determine eligibility. If subjects meet the eligibility criteria, they were invited for a baseline evaluation.

In Sydney, the target number of participants was 40. Potential participants were recruited from the Cardiac Health Institute (CHI) and Buddhist Compassion Relief Tzu Chi Foundation Australia. These participants were identified through poster advertisements placed in CHI and Tzu Chi Foundation. Potential community groups were also used to identify participants through newsletter advertisements and community bulletins. Additional participants were identified through advertisements placed on Western Sydney University's website and in local newspapers. Once participants were identified, they underwent a brief telephone interview to provide preliminary details about the study as well as to assess eligibility for basic inclusion/exclusion criteria and accessibility to the test site for screening. Figure 4.1 shows the flow diagram of the trial.

Figure 4.1 - CONSORT Flow Diagram in Protocol



Note: CONSORT, Consolidated Standards of Reporting Trials statement, which is used worldwide to improve the reporting of randomized, controlled trials. *Eligible participants were randomly assigned to either the Tai Chi intervention group or the wait list control group. The allocation ratio was 1:1. Participants recruited in Beijing and Sydney were randomly assigned separately. Two independent statisticians generated the random allocation sequence using SPSS (version 24.0, SPSS Inc. statistics) software.

Then a suitable day and time for a screening session were advised to potential participants. Following this, the participant information sheet and an appointment letter detailing the arranged time and date, the location and any additional information to bring were sent via email and/or post.

At the screening session, participants were provided with an information sheet. A brief introduction of the aim and methodology of the study were also provided orally if possible. Participants were required to provide written informed consent before the screening procedure begins and were invited and encouraged to ask questions throughout the recruitment procedure and whilst the study is in progress.

4.2.5 Randomisation

After eligibility assessments, eligible participants were randomly assigned to either the Tai Chi intervention group or the wait list control group. The allocation ratio was 1:1. Participants recruited in Beijing and Sydney were randomly assigned separately. Two independent statisticians generated the random allocation sequence using SPSS (version 24.0, SPSS Inc. statistics) software.

Allocation concealment was achieved by an independent third party using sequentially numbered, sealed, and opaque envelopes. Randomisation envelopes were opened sequentially only when a participant met the eligibility criteria, provided informed consent, and participant details were written on the envelope.

4.2.6 Intervention

4.2.6.1 Tai Chi intervention

The Tai Chi group practiced a standardised Tai Chi program specially designed for patients with CVDs over a period of 24 weeks. The Tai Chi program consists of a 12-week *intensive* Tai Chi intervention period and a following *sustained* Tai Chi intervention period over 12 weeks. In the *intensive* period, each Tai Chi class lasted 2 hours, twice per week for 12 weeks; while in the *sustained* period, each Tai Chi class also lasted 2 hours, but once per week for the following 12 weeks. All the classes were held in spacious rooms. Participants were monitored for potential adverse events during Tai Chi practice. Attendance was recorded by the Tai Chi instructor in each class and tracked the reasons for missed sessions.

Figure 4.2 shows the main components of the Tai Chi program, including walking, meditation, 13-form Thumping Techniques, standing posture, and 13-form Chen-style Tai Chi. The 13-

form Thumping Techniques were derived from meridian/channel theories of traditional Chinese medicine. The 13-form Chen-style Tai Chi was modified from the classical 83-form Chen-style Tai Chi. In addition, in the classes, Tai Chi history, theories and principles were also introduced. Each Tai Chi class consists of: (1) 10 minutes of walking, (2) 10 minutes of meditation, (3) 20 minutes of 13-form Thumping Techniques, (4) 20 minutes of break and question-and-answer session, (5) 10 minutes of standing postures, and (6) 50 minutes of Tai Chi practice. Participants learned the entire sequence by the end of the 12th week, and the entire sequence was repeated in the following weeks. An outline procedure of the standardised Tai Chi program over 24 weeks is shown in Appendix 4.

Figure 4.2 Main components of the 24-week standardised Tai Chi program.

All Tai Chi classes were held by the principal investigator or a Tai Chi master Zhang Peijun who has more than 30 years of Tai Chi teaching experience. The principal investigator is a qualified Tai Chi instructor who has learned Tai Chi in Beijing from Master Tian Qiutian and Master Zhang Peijun since 2006 and is a member of Beijing Huacheng Martial Arts Association. To ensure that the two instructors applied a standardised teaching protocol, the principal investigator completed the required instructor training in Beijing prior to initiation of the intervention classes. The Tai Chi classes in Sydney recruitment centre started after the completion of that in Beijing recruitment centre, where Master Zhang Peijun served as the primary instructor and the principal investigator was a teaching assistant. In addition, all sessions in Sydney recruitment centre were reported regularly by the principal investigator to Master Zhang Peijun and timely feedback were received throughout the study to ensure proper instruction. Furthermore, two training sessions were delivered by Master Zhang Peijun via videoconferencing to the participants in Tai Chi group.

Participants were encouraged to maintain their routine physical activity, but not to begin new additional training. Participants were required to practice at least three other days per week at home. Printed handbooks containing instructional pictures and written descriptions of the Tai

Chi intervention and DVDs were provided to facilitate home practice. Tai Chi instructors reminded participants in class to practice the program daily. A WeChat group (a social media communication application developed by Tencent) was set up to promote timely feedbacks between participants and instructors to support home practice. A self-report patient diary for recording the home practice sessions were required to be completed by participants weekly (see Appendix 5).

4.2.6.2 Waitlist Control

Participants assigned to the waitlist control group were asked to maintain their routine physical activities, but not to begin any new exercise programs during the study.

These participants were offered an equivalent 12-week intensive Tai Chi intervention and 12-week sustained Tai Chi intervention at the termination of the study provided the Tai Chi intervention in the treatment is proved to be safe (no severe adverse events directly associated with Tai Chi).

4.2.7 Outcome Measures

4.2.7.1 Primary Outcome Measure

The primary outcome of this study is stress. The implication of stress on the development and prognosis of CHD has been established for over four decades (Jenkins, 1971, 1976; Kivimaki et al., 2006; Redmond et al., 2013; Richardson et al., 2012). Tai Chi could be a promising exercise option for relieving stress in patients with CHD and/or hypertension, however evidence to support this is generally lacking. To address the knowledge gap about Tai Chi for stress in patients with CHD and/or hypertension, stress is chosen as the primary outcome of this study.

- Perceived Stress Scale 10-item (PSS-10) (see Appendix 6)

The PSS-10 was applied to measure stress in this study, because of its high internal consistency, reliability, factorial validity and hypothesis validity of both English and Chinese version in this population. The PSS designed by Cohen and colleagues is the most commonly used tool to measure perceived stress, with the original scale containing 14 items. The PSS was modified by Cohen and Williamson to a 10-item, 5-point Likert scale (0, never; 4, very often), with possible scores ranging from 0 to 40. A higher score indicates more perceived stress.

The high internal consistency, reliability, factorial validity and hypothesis validity of the PSS in CHD patients were reported in a review where 19 articles were identified on psychometric evaluation of PSS (E. H. Lee, 2012). High internal consistency of the Chinese version of PSS has also been reported (r=0.90) (S. Lee & Crockett, 1994). One study reported adequate test-retest reliability and construct validity of the PSS among Chinese women (Z. Wang, J. Chen, et al., 2011). Another study applied the PSS-10 to assess the perceived stress change among ethnic Chinese people with cardiovascular disease risk factors following a 12-week Tai Chi exercise also found similar results (Taylor-Piliae, Haskell, Waters, & Froelicher, 2006). The satisfactory psychometric properties of all three Chinese version of PSS (PSS-14, PSS-10 and PSS-4) have been confirmed by testing in 1,860 Chinese cardiac patients (D. Y. Leung, Lam, & Chan, 2010).

4.2.7.2 Secondary Outcome Measures

The secondary outcomes of this study include psychological well-being (including anxiety and depression), cardiovascular function (including blood pressure, heart rate, heart rate variability (HRV), blood lipid profiles, blood glucose profiles and CRP), QoL and physical fitness. As discussed in Chapter 2, these outcomes are associated with the development and prognosis of CHD and its complications. Tai Chi is potentially beneficial for improving these outcomes. However, little is known about the benefits of Tai Chi for these outcomes in patients with CHD and/or hypertension. To address the knowledge gap in existing literature, these secondary outcomes and the following outcomes measures were applied in this study.

Psychological status

- Zung Self-Rating Anxiety Scale (SAS) (see Appendix 7)

SAS is a self-report instrument that measures levels of anxiety in patients who have anxiety-related symptoms. The SAS has 20 questions. Each question is scored using a 4-point scale, from ‘none of the time’ to ‘most of the time’. There are 15 increasing anxiety level questions and 5 decreasing anxiety questions.

The high reliability and validity of the English version of SAS and its Chinese version has been reported (F. Wang, 1994). Researchers have widely used the Chinese version of SAS among Chinese population in various trials (Y. W. Liu & Tsui, 2014; Luo et al., 2013; Shi, Liu, Wang, & Wang, 2015; G. Wang et al., 2013; K. Zhang et al., 2013).

- Beck Depression Inventory-II (BDI-II) (see Appendix 8)

The BDI-II is a 21-item self-report rating inventory that measures the existence and severity of symptoms of depression, which is in line with the depression criteria of the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV). This study used the revised edition of the BDI and BDI-1A. Each of the 21 items is a list of four statements arranged in increasing severity about a particular symptom of depression, except for two items (16 and 18) where seven points are provided to indicate either an increase or decrease of appetite and sleep. Each item is assigned a score of 0-3, with 3 indicating the most severe symptoms. A cumulative score is determined by adding the scores of the individual items. The total score can range from 0 to 63.

The BDI-II is a reliable and well-validated measure for depression in adults (Jaksic, Ivezic, Jokic-Begic, Suranyi, & Stojanovic-Spehar, 2013; Krefetz, Steer, Gulab, & Beck, 2002; Osman, Kopper, Barrios, Gutierrez, & Bagge, 2004; Steer, Ball, Ranieri, & Beck, 1997). The reliability and validity of the Chinese version of BDI has also been confirmed in previous studies (Shek, 1990; Y. P. Wang, Andrade, & Gorenstein, 2005; Y. X. Zhang, Wang, & Qian, 1990; Y. P. Zheng, Wei, Goa, Zhang, & Wong, 1988). The validity of a Chinese version of the BDI-II for use with Chinese community adolescents based on the cross-validated factor structure has been tested (Byrne, Stewart, & Lee, 2004). Findings related to internal consistency reliability, stability over 6 months, and associations with relevant external criteria and provided strong support for the valid use of Chinese version of BDI-II. Wang Z. and colleagues evaluated that reliability and validity of the Chinese version of BDI-II in 142 patients with depression, and confirmed the valid use of Chinese version of BDI-II (Z. Wang, C. Yuan, et al., 2011).

Cardiovascular function

- Blood Pressure and Heart Rate

Blood pressure and heart rate are two important measurements of overall heart health. All blood pressure and heart rate measurements were calculated using automatic sphygmomanometers, designed for professional use.

Brachial blood pressure was taken following a 5-minute rest period. This has been done with an automatic sphygmomanometer whilst the participant was sitting comfortably. Blood pressure was measured three times consecutively and a mean result obtained.

- Heart Rate Variability (HRV)

HRV reflects the modulation of cardiac function by autonomic and other physiological systems (Hamaad, Lip, & MacFadyen, 2004). Abnormalities in HRV have been reported in various settings of ischaemic heart disease, and the most important current application of HRV analysis is in post-infarction phase where abnormal HRV indicates an increased risk of cardiac mortality (Huikuri, 1995). Most studies involving patients with stable CHD or patients with a recent acute coronary event have found that HRV was lower in depressed patients than in their counterparts with no depression (Carney & Freedland, 2009; Harris, Sommargren, Stein, Fung, & Drew, 2014; Stapelberg, Hamilton-Craig, Neumann, Shum, & McConnell, 2012).

The SphygmoCor HRV System was used to conduct HRV measurement (SphygmoCor, AtCor Medical Pty, Sydney, Austrialia). The SphygmoCor HRV System is a sophisticated system for non-invasively assessing the Autonomic Nervous System (ANS) based on HRV analysis. HRV analysis is based on measuring variability in intervals between the R-R intervals. The system uses a 3-lead electrocardiogram (ECG) connected to the electronics module to non-invasively record a continuous 10-minute ECG waveform. After a 5-minute rest with regular and calm breathing pattern, participants were asked to lay in a supine resting position in a quiet room with a stable room temperature. Participants remained awake, whilst the SphygmoCor system captured data.

The SphygmoCor HRV system provides HRV time and frequency domain parameters. Time domain measures are the means and standard deviations of R-R intervals recorded by the continuous ECG, where normal-to-normal (NN) intervals represent all the R-R intervals. Key parameters of time domain measures include: heart rate, RMS SD (m/s) (the square root of the man squared differences of successive NN intervals; estimate of the short-term components of HRV, HRV Index and PNN50 (%) (the proportion of RR intervals having a difference of >50 msec; is virtually independent of circadian rhythms).

Spectral analysis of a series of successive R-R intervals provides the frequency domain analysis. This technique separates the heart rate spectrum into various components and quantifies sympathetic and vagal influences on the heart. Key parameters of frequency domain measures include: Total Power (ms^2) (reflecting all cyclic components of HRV), High Frequency (HF) (generally representing parasympathetic activity and is therefore generally considered to be a marker of vagal activity), Low Frequency (LF) is influenced by both sympathetic and

parasympathetic activity, and the ratio of HF: LF (representing the balance of parasympathetic and sympathetic activity).

- C - Reactive Protein (CRP)

CRP is a well-accepted systemic marker of inflammation (Pepys & Hirschfield, 2003). Modestly elevated baseline levels of CRP are associated with the long-term risk of CHD, whilst the changes in CRP following myocardial infarction are associated with death and cardiac complications (Abd et al., 2011; Casas, Shah, Hingorani, Danesh, & Pepys, 2008; Strang & Schunkert, 2014). A meta-analysis found that early increased plasma CRP moderately correlates to long-term risk of recurrent cardiovascular events or death, and may be a valuable prognostic indicator in patients after acute coronary syndromes (He, Tang, Ling, Chen, & Chen, 2010).

In Beijing, blood samples were taken from participants by suitably qualified nurses and couriered to Changying Community Health Service Centre Pathology Laboratories where pathology testing was conducted.

In Sydney, the participants were asked to visit a local Laverty Pathology Laboratory where pathology testing was conducted.

- Lipid Profile and Glucose Profile

The lipid profile (primarily low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, elevated low-density lipoprotein cholesterol (LDL-C), and elevated total cholesterol) are important factors in CHD (McCullough, 2005). The relationship between low-density lipoprotein cholesterol (LDL-C) and CHD event rates has been well established (O'Keefe, Cordain, Harris, Moe, & Vogel, 2004).

Blood collection procedures for this outcome measure are identical to that of C-reactive protein described above.

Quality of life (QoL)

- Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (see Appendix 9)

QoL is a patient-important outcome. We used SF-36 to measure QoL in this study considering that SF-36 is a generic outcome measure designed to examine functional health and well-being

from the patient's point of view. It is a practical, reliable and valid measure of physical and mental health that can be completed in five to ten minutes.

The SF-36 includes the following eight health concepts: (1) physical functioning; (2) role limitations because of physical health problems; (3) bodily pain; (4) social functioning; (5) general mental health (psychological distress and psychological well-being); (6) role limitations because of emotional problems; (7) vitality (energy/fatigue); and (8) general health perceptions. Answers to each question are scored (some items need to be recoded). These scores are then summed to produce raw scale scores for each health concept which are then transformed to a 0-100 scale.

The reliability and validity of the Chinese version of SF-36 has also been confirmed in previous studies (P. Wang, Chen, Yang, & Wu, 2015; R. Wang et al., 2011; Xiao et al., 2016; Y. Zhang, Qu, Lun, Guo, & Liu, 2012), and SF-36 has been widely by Chinese researchers to measure quality of life in patients with CHD or hypertension (S. Gu, Hu, & Dong, 2016; W. Ma et al., 2010; R. Wang et al., 2009).

Physical fitness

- 6-Minute Walk Test (6MWT)

The 6MWT was used to measure the physical exercise capacity and fitness of participants because it addresses physical activity, a modifiable risk factor for secondary prevention of CHD. It is a widely used valid test among the CHD population. The 6MWT measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway.

In this study, the 6MWT was measured with a measuring wheel. At least two practice walks were administered (with adequate time for rest and recovery) prior to recording measurements. Participants were instructed prior to the test to wear comfortable clothing and shoes and to use their typical walking aid during the test if appropriate. The American Thoracic Society (American Thoracic Society, 2002) recommends an indoor, 30-meter corridor or walkway with cones placed at the beginning and end of the 30-meter boundary to indicate turns. In the literature, the corridor distance across studies varies, which is likely due to the need to use what is readily available. In this study, the walking course was 30 metres in length.

Compliance

Participants were asked to complete a weekly diary documenting their practice at home. Their attendance of each Tai Chi class was also documented by the instructor and the attendance rate was calculated at the end of study.

Other Assessments

Participants were asked to complete a weekly diary documenting the changes with regards to medication use, diet, exercise and negative behaviours such as alcohol consumption and smoking to assess potential confounding variables (see Appendix 10).

4.2.7.3 Safety Measures

The standardised Tai Chi intervention is specifically tailored to the target individuals with CHD and/or hypertension. Tai Chi instructors of this trial are appropriately qualified and experienced. All Adverse Events (AE) were recorded and signed off by the principal investigator. During home practice, all potential adverse events were recorded in diaries by the participants. If there is a Serious Adverse Event (SAE), the participant contacted the principal investigator (contact details were provided on Participant Information Sheets). SAEs were immediately reported to local Human Research Ethics Committees in accordance with the guidelines.

All outcome assessments in this study are non-invasive, except blood lipid profile and C-reactive protein. Blood samples were taken from participants by trained and qualified nurses in Beijing and Sydney recruitment centres respectively, and couriered to pathology laboratories for testing.

4.2.7.4 Exit Interview

Semi-structured exit interviews were conducted as a qualitative sub-study of this RCT with participants from Tai Chi group who completed the study. The objective of the exit interviews was to explore participants' perceptions on factors influencing trial participation and adherence to Tai Chi intervention during and after the RCT. Ten core questions were asked in the exit interviews in Chinese or English. Transcripts were recorded, transcribed and imported into the NVivo version 11 software for coding and analysis. The detailed methods and results of the qualitative sub-study were described in Chapter 5.

4.2.8 Data Collection

All assessment procedures and data collection were adhered to our pre-defined standardised operating procedures (SOPs). Data were collected at baseline, mid-treatment and post-treatment

sessions on week 0, 12 and 24 of the study. Data collection in Beijing was performed by the principal investigator and two research assistants. In Sydney data collection was performed by the principal investigator.

We collected data of psychological stress, anxiety, depression and quality of life, using printed psychometric questionnaires including PSS-10, SAS, BDI-II and SF-36, respectively. Blood samples were taken by two trained and qualified nurses in Beijing and Sydney respectively, and pathology tests conducted by Changying Community Health Service Centre in Beijing and the Laverty Pathology in Sydney, respectively. Data of heart rate and heart rate variability were collected using proprietary software employed by equipment manufacturers for the SphygmoCor system. The 6MWT distanced was collected with a measuring wheel.

We had a record of identified information to be able to monitor safety of participants, such as determine which participants experience adverse events, as well as which intervention group the participant has been allocated to. Coded information was used for data collection of pathology testing.

Table 4.1 presents the time-points of data collection and assessment procedures.

Table 4.1 Assessment procedures and Time-points.

Outcome Measure/Action	**Week -2**	**Week 0**	**Week 12**	**Week 24**
Screening (medical history, randomization, inclusion, exclusion, consent forms)	x			
Psychosocial status				
Perceived Stress Scale 10-item (PSS-10)		x	x	x
Zung Self-Rating Anxiety Scale (SAS)		x	x	x
Beck Depression Inventory-II (BDI-II)		x	x	x
Cardiovascular function				
Blood pressure		x	x	x
Heart rate		x	x	x
Heart rate variability		x	x	x
Lipid and glucose profile		x	x	x

C-creative protein		x	x	x
Quality of life				
36-item Short Form Health Survey (SF-36)		x	x	x
Physical fitness				
6-Minute Walk test (6MWT)		x	x	x
Compliance				
Participant diary (to be completed daily)		x	x	x
Attendance rate (to be completed weekly)		x	x	x
Exit interview				x

4.2.9 Statistical Analysis

SPSS software (version 25.0, SPSS Inc. statistics) was used to perform data analyses. The significance level was set at a *P* value of less than 0.05. All statistical testing was 2-sided.

Demographic characteristics and medical history of participants were described using means and standard deviations (SD) for continuous variables, and frequencies and percentages for categorical variables. Baseline comparisons between the two groups were performed using *t*-tests analyses for continuous variables and chi-square tests for categorical variables.

In the current study, a mixed linear model was used to assess differences between the two groups in the primary outcome for repeated measurements. The effects of the intervention and time points were considered as fixed effects, with treatment effects represented as interaction effects (time*group), while the participants were regarded as random effects. Normality was confirmed following the analyses. The general linear mixed model models for group means as fixed effect while simultaneously modelling for individual subject variables as random effects (Krueger & Tian, 2004). Compared with repeated measures ANOVA, the mixed model has the strength of accommodating missing data points in longitudinal datasets (Krueger & Tian, 2004). Furthermore, rather than treating time as a categorical variable, the mixed model is capable of treating time as either a continuous variable or a categorical variable or both (Krueger & Tian, 2004).

Similarly, we also analysed the main secondary outcomes using linear mixed effects models with interaction tests. Normality was confirmed by examining the distribution of residuals

following the analyses. When there was significant skewness of data, we performed log transformation or winsorising to dealing with outliers.

The secondary outcome CRP were categorized into binary data based on the original laboratory reports of <4.0 mg/L or ≥4.0 mg/L, because the standard of laboratory reports from Beijing and Sydney were different. According to the Australian Bureau of Statistics, the test reference range for normal CRP levels is <5.0 mg/L, while CRP levels >10.0 mg/L are indicative of an acute infection or inflammation (Australian Bureau of Statistics, 2014). However, the Centers for Disease Control and Prevention (CDC) and the AHA recommended that: low risk, <1.0 mg/L; average risk, 1.0-3.0 mg/L; and high risk, >3.0 mg/L; if the CRP level is >10 mg/L, then the test should be repeated and the patient examined for sources of infection or inflammation (G. L. Myers et al., 2004). Therefore, CRP was analysed using the generalised linear model (GZLM) with a binary logistic model. The effects of the intervention and time points were considered as fixed effects, with treatment effects represented as interaction effects (time*group), and the participants were regarded as random effects.

Once significant differences among the means between the Tai Chi and waitlist control groups were determined, one-way ANCOVA analysis was conducted to determine the response at week 12 and week 24. Partial η^2 represents the proportion of the variation which could be explained by the predictor variable after correcting for all other predictors in the model. Effect size was calculated by Cohen's $d = \frac{M1-M2}{SD}$ (Cohen, 1988). Cohen (1988) suggested that d=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size (Cohen, 1988). Subgroup analyses was also conducted for these outcomes by breaking down the sample size into subset of participants with or without hypertension.

We also conducted intention-to-treat (ITT) analyses for these outcomes, in which all participants as originally allocated after randomisation were included, assuming no improvements for missing data. All tests were 2-sided. A *P* value of less than 0.05 was considered as statistically significant.

4.2.10 Data Management

During the PhD project, data were recorded in participant source document files and an electronic database. Electronic data were stored on a hard drive, on a password-protected computer with backups on portable hard disc drives kept in a locked cabinet in the NICM Health Research Institute (NICM) which is only accessible to researchers directly involved in the

project. Specific requests for access to the data by any other person would be considered after formal application to the PhD supervisor.

Participants were not given their individual results. However, they were given the overall group results through a workshop which they were invited to after completion of the study. Any incidental findings on a participant's results were communicated to the participant and communicated to their local doctor via letter when needed.

Information on all participants was maintained in a locked filing cabinet within the NICM, along with other documents related to the clinical trial, for a period of 15 years. All participant paper files and electronic data files would be deleted or destroyed after 15 years as per the National Statement on Ethical Conduct in Human Research (2007-Update May 2015) issued by the National Health and Medical Research Council (NHMRC) (National Health and Medical Research Council, Australan Research Council, & Australian Vice-Chancellors' Committee, 2015).

Chapter 5: Results and Discussion of the Randomised Controlled Trial

This chapter describes a results and discussion of the RCT exploring the effects of Tai Chi on stress and cardiovascular function in patients with coronary heart disease and/or hypertension. The results section presents the enrolment, participant discontinuations, baseline characteristics, and the effects of the Tai Chi intervention on the primary outcome measure (i.e. stress) and secondary outcome measures (i.e. anxiety, depression, blood pressure, heart rate, heart rate variability, lipid and glucose profile, C-reactive protein, quality of life, and 6-minute walk test). A discussion for the findings including interpretation of the results and comparisons with previous studies is also provided. The reporting of this study is in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (Appendix 3).

5.1 Results

5.1.1 Participant Flow

Eighteen participants (15.0%) out of the 120 recruited withdrew from the study over 24 weeks, including 15 (15/18, 83.3%) participants at the 12-week assessment and 3 (3/18, 16.7%) participants at the 24-week assessment. There was no significant difference between the two groups with regards to the lost to follow-up rates over 24 weeks (P=0.306), using a Chi-square test. The reasons of participant discontinuations were presented in Table 5.1.

Table 5.1 Reasons for withdrawal over 24 weeks (n=18)

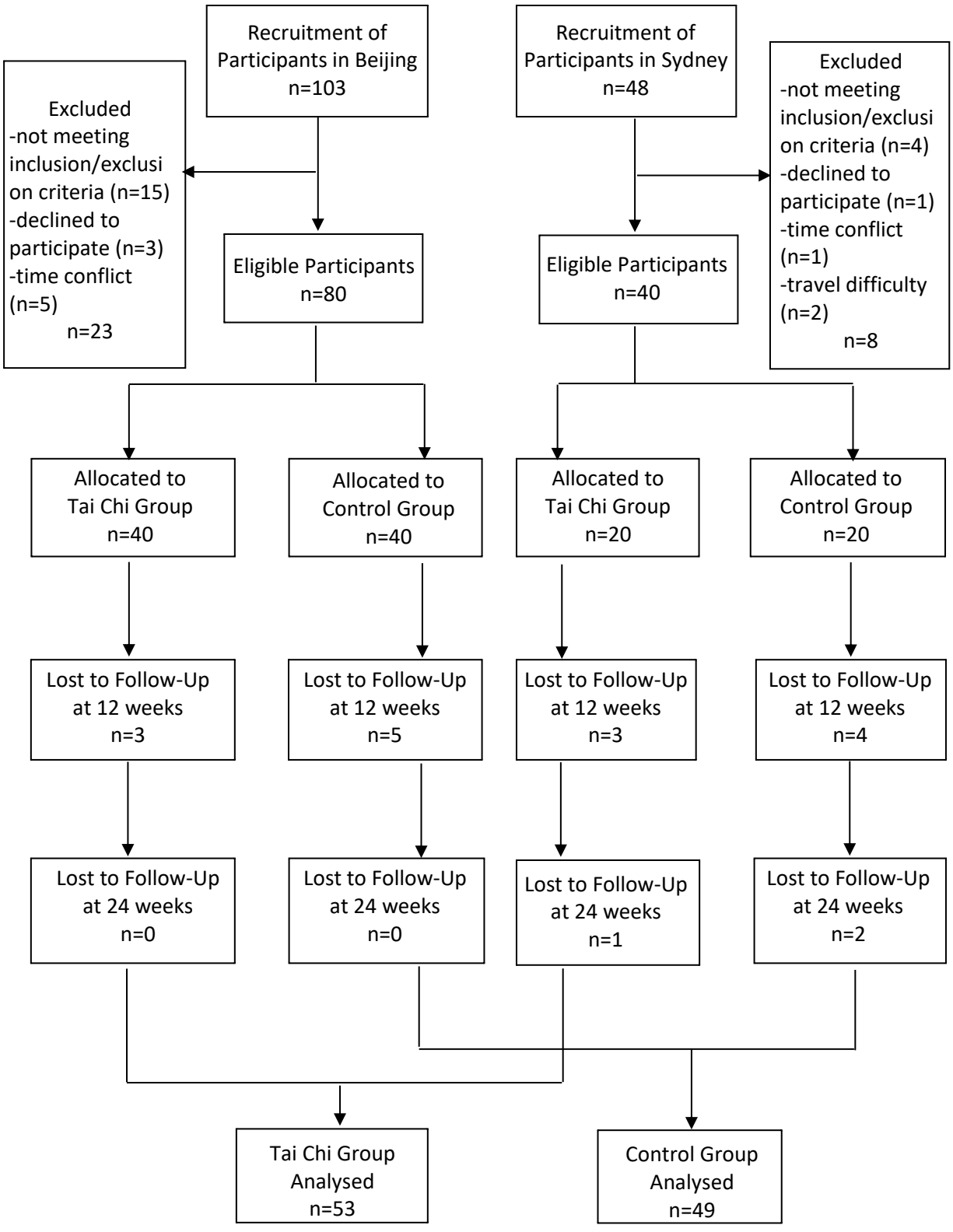
Reasons for Withdrawal	Tai Chi Group		Waitlist Group	
	Week 0-12	Week 13-24	Week 0-12	Week 13-24
Family and domestic responsibility	3	0	4	0

Travel difficulty	1	0	3	0
Cancer diagnosis	0	0	2	0
Participation in an intensive stroke rehabilitation program	1	0	0	0
Tiny fracture of rib bone	1	0	0	0
Subtotal	**6**	**0**	**9**	**0**
Work transferred to overseas	0	0	0	1
Pace-maker installation surgery	0	1	0	0
Loss of interest in Tai Chi	0	0	0	1
Subtotal	**0**	**1**	**0**	**2**
Total	**7**		**11**	

As shown in Table 5.1, among the eighteen participants withdrew from the study over 24 weeks, seven were from the Tai Chi group and eleven were from the waitlist group. The reasons for participant discontinuations include: (1) family and domestic responsibility (3 participants in Tai Chi group and 4 in waitlist group); (2) difficulties to travel to the recruitment site (1 in Tai Chi group and 3 in waitlist group); (3) work transferred to overseas (1 in waitlist group); (4) cancer diagnosis during the study (2 in waitlist group); (5) time conflict due to participation in an intensive stroke rehabilitation program (1 in Tai Chi group); (6) pace-maker installation surgery (1 in Tai Chi group); (7) loss of interest in Tai Chi (1 in waitlist group); and (8) tiny fracture of rib bone (1 in Tai Chi group) during the 24-week waiting period.

The CONSORT Flow Chart is illustrated in Figure 5.1.

Figure 5.1 CONSORT Flow Diagram



Note: CONSORT, Consolidated Standards of Reporting Trials statement, which is used worldwide to improve the reporting of randomized, controlled trials.

5.1.2 Recruitment

The recruitment in Beijing started in August 2015 and finished in November 2015. In Sydney the recruitment commenced August 2016 and closed in January 2017. During these periods, a total of 151 participants were screened including 103 in Beijing and 48 in Sydney recruitment centres. At the screening session, participants were provided with an information sheet outlining the details of the trial and a copy of written informed consent form. The aims, methodology, potential risks and requirements of the study were discussed with the participants. Participants were encouraged to ask questions throughout the screening session. Participants were required to sign the informed consent form before the screening procedure begins.

One hundred and twenty participants met the criteria, of which 80 (80/120, 66.7%) participants were from Beijing recruitment centre and 40 (40/120, 33.3%) from Sydney recruitment centre. Eligible participants were randomly assigned to either Tai Chi group (n=60) or the wait-list control group (n=60). The allocation ratio was 1:1. Randomisation was carried out separately in the two recruitment centres. An independent statistician generated the random allocation sequence by SPSS software (version 25.0, SPSS Inc. statistics). Allocation concealment was achieved by using sequentially numbered, sealed, and opaque envelopes.

The last patient completed the study in November 2017. Out of the 120 participants, 102 (85.0%) completed the study. Of the 102 participants who completed the study, 53 (52.0%) were in the Tai Chi group (37 in Beijing centre and 16 in Sydney centre), and 49 (48.0%) were in the waitlist control group (35 in Beijing centre and 14 in Sydney centre).

5.1.3 Baseline Data

5.1.3.1 Demographic Characteristics

No statistical difference was identified in demographic characteristics including age, sex, body-mass index (BMI), education, smoking and alcohol consumption, except the occupation status between the Tai Chi and waitlist control groups ($P>0.05$). The demographic characteristics of the 120 participants are shown in Table 5.2.

Table 5.2 Demographic characteristics of the study participants.

Variable	Tai Chi Group (n=60)	Waitlist Group (n=60)	*P* value
Age, mean±SD, y	65.08±6.38	63.55±9.01	0.284
Female, n (%)	37(61.7)	36(60.0)	0.852
Body-mass index (BMI)*, mean±SD, kg/m^2	25.63±2.60	25.33±2.81	0.545
Higher education, n (%)	29(48.3)	32(53.3)	0.584
Retired, n(%)	56(93.3)	48(80.0)	0.032
Smoker, n (%)	9(15.0)	10(16.7)	0.803
Regular alcohol drinker, n (%)	1(1.7)	6(10.0)	0.114

Abbreviation: *BMI: The body-mass index is the weight in kilograms divided by the square of the height in meters; y, year; n, number.

The mean age of participants in the two groups was similar, 65.08 ±6.38 years in the Tai Chi group and 63.55±9.01 years in the waitlist control group. There was no significant difference between the two groups in age (*P*=0.284).

Out of the 120 participants, 73 (60.8%) were women. The proportion of female participants in both groups was balanced at baseline, 37 (61.7%) participants in the Tai Chi group and 36 (60.0%) in the waitlist control group. No significant difference was identified between the two groups (*P*=0.852).

All the 120 participants were Chinese descent. The number of participants who possess higher education qualifications in the two groups was similar (*P*=0.584). There were 29 (48.3%) participants in the Tai Chi group had a higher education qualification compared to 32 (53.3%) in the waitlist control group.

There were more retirees in the Tai Chi groups (56/60, 93.3%) than in the waitlist group (48/60, 80.0%). The difference reached statistical significance (*P*=0.032).

Smoking was reported in only a few participants in both groups. The proportion of non-smokers in both groups are very similar (*P*=0.803), 51 (85.0%) participants in the Tai Chi group and 50 (83.3%) in the waitlist control group. Majority of the participants reported alcohol consumption

not on a regular base, 59 (98.3%) in the Tai Chi group and 54 (90.0%) in the waitlist group. No significant differences were identified between the two groups (*P*=0.114).

5.1.3.2 Medical History

Out of the 120 participants randomised, 107 (89.2%) had hypertension (53 in Tai Chi group and 54 in waitlist control group), 31 (25.8%) had CHD (14 in Tai Chi group and 17 in waitlist control group), and 18 (15.0%) had both hypertension and CHD (7 in Tai Chi group and 11 in waitlist group). At baseline, there was no statistical difference between the two groups in medical history (*P*>0.05), including family history of CVDs and current disease and medication status (see Table 5.3).

Table 5.3 Medical history between the Tai Chi and waitlist groups at baseline

Variable	Tai Chi Group (n=60)	Waitlist Group (n=60)	*P* value
Has family history of CVD, n (%)	55(91.7)	59(98.3)	0.207*
Disease, n (%)[a]			
Hypertension	53(88.3)	54(90.0)	0.769
CHD	14(23.3)	17(28.3)	0.532
Both hypertension and CHD	7(11.7)	11(18.3)	0.306
Self-reported coexisting disease, n (%)[b]			
Diabetes or hyperglycaemia	13(21.7)	9(15.0)	0.345
High cholesterol	10(16.7)	13(21.7)	0.487
Stroke	1(1.7)	3(5.0)	0.619*
Depression	2(3.3)	2(3.3)	1.000*
Current medication taken, n (%)[c]			
Medication taken for hypertension	42(70.0)	48(80.0)	0.206
Medication taken for cholesterol	22(36.7)	21(35.0)	0.849
Medication taken for CHD	14(23.3)	15(25.0)	0.831
Medication taken for diabetes or hyperglycaemia	10(16.7)	6(10.0)	0.283
Medication for depression	2(3.3)	2(3.3)	1.000*
Dietary supplements or herbal medicine	6(10.0)	4(6.7)	0.509
Nil	4(6.7)	5(8.3)	1.000*

Abbreviation: CVD, cardiovascular disease; CHD, coronary heart disease; n, number.

*Fisher's exact test.
[a] Some participants had both hypertension and CHD.
[b] Some patients self-reported more than one coexisting diseases/conditions.
[c] Some participants self-reported more than one medication taken.

No significant difference was identified between the two groups in self-reported coexisting diseases and/or conditions (P>0.05). Out of 120 participants, 22 participants (22/120, 18.3%) had diabetes or hyperglycaemia (13/60, 21.7% in Tai Chi group; 9/60, 15.0% in waitlist group), 23 (23/120, 19.2%) had high cholesterol (10/60, 16.7% in Tai Chi group; 13/60, 21.7% in waitlist group), 4 (4/120, 3.3%) had stroke (1/60, 1.7% in Tai Chi group; 3/60, 5.0% in waitlist group), and 4 (4/120, 3.3%) had depression (2/60, 3.3% in Tai Chi group; 2/60, 3.3% in waitlist group).

5.1.4 Primary Outcome Measure: Stress

Baseline assessment

The baseline comparison of mean PSS-10 scores of participants in the Tai Chi and waitlist control groups were presented in Table 5.4.

Table 5.4 Baseline comparisons of PSS-10 scores between the two groups.

Variable	Tai Chi Group (n=60)	Waitlist Group (n=60)	*P* value
PSS-10, mean ± SD, score	12.73±6.08	11.55±6.18	0.292

Abbreviation: PSS-10, the Perceived Stress Scale 10-item; SD, standard deviation.

PSS-10 is the most commonly used tool for measuring perceived stress. PSS-10 score ranges from 0 to 40, with higher score indicating more perceived stress. At baseline, the mean PSS-10 scores of participants in the Tai Chi and waitlist control groups were 12.73±6.08 and 11.55±6.18, respectively. There was no significant difference between the two groups (P=0.292).

Week 12

The comparison of PSS-10 scores at baseline, 12 and 24 weeks between the Tai Chi and waitlist groups are presented in Table 5.5.

Table 5.5 Stress as measured by PSS-10 in the Tai Chi and waitlist groups at baseline, week 12 and 24.

	Tai Chi Group		Waitlist Group	
	No.	Mean (95% CI)	No.	Mean (95% CI)
Baseline	60	12.73 (11.21, 14.25)	60	11.55 (10.03, 13.07)
Week 12	54	10.38 (8.81, 11.97)	51	12.46 (10.85, 14.07)
Week 24*	53	10.44 (8.86, 12.03)	49	11.71 (10.08, 13.34)

Note: PSS-10, the Perceived Stress Scale 10-item. PSS-10 score ranges from 0 to 40, with higher score indicating more perceived stress. CI, confidence interval. *Using a mixed linear model, the Tai Chi group demonstrated a significantly greater reduction in PSS-10 scores over 24 weeks (*P*=0.009).

The mean PSS-10 score in the Tai Chi group decreased from 12.73 (95% CI: 11.21 to 14.25) at baseline to 10.38 (95% CI: 8.81 to 11.97) at week 12, while the mean stress score of the waitlist group had a slight increase from 11.55 (95% CI: 10.03 to 13.07) at baseline to 12.46 (95% CI: 10.85 to 14.07) at week 12. The Tai Chi group was superior to the waitlist group in decreasing PSS-10 mean scores at week 12; the differences reached statistical significance (*P*=0.006).

In the ITT analysis, we included all participants originally randomised, assuming no improvements for missing data. Similarly, significant differences in PSS-10 mean scores were identified between the two groups at week 12 (*P*=0.018), favouring the Tai Chi group.

In summary, the above analyses consistently suggested that Tai Chi intervention resulted in a statistically significant decrease of the mean scores of PSS-10 over 12 weeks, compared with the waitlist group.

Week 24

The Tai Chi group demonstrated a greater reduction in PSS-10 scores over 24 weeks (mean, 10.44; 95%CI, 8.86 to 12.03) compared with the waitlist group (mean, 11.71; 95%CI, 10.08 to 13.34). There were statistically significant differences between the two groups in PSS-10 at week 24 (*P*=0.009). The residuals of PSS-10 scores were normally distributed after checking

the histogram of residuals. The stress as measured by PSS-10 of the Tai Chi group and waitlist group at baseline, week 12 and 24 was illustrated in Figure 5.2.

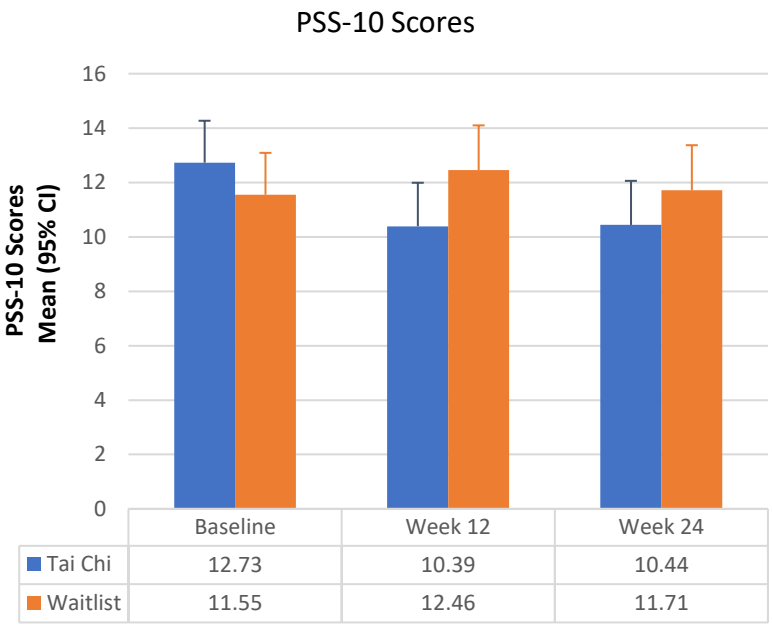


Figure 5.2 Changes in Perceived Stress Scale 10-item (PSS-10) score change over 24 weeks. The error bars indicate 95% confidence intervals (CI). Using a linear mixed model, there was a significant difference over 24 weeks between the Tai Chi and waitlist control group in stress level as measured by PSS-10 (a linear mixed model: *P*=0.009), favouring Tai Chi group.

As shown in Figure 5.2, the mean PSS-10 score in Tai Chi group decreased from 12.73 (95% CI: 11.21 to 14.25) at baseline to 10.38 (95% CI: 8.81 to 11.97) at week 12 and maintained at a similar level at week 24 (mean 10.44; 95% CI: 8.86 to 12.03). In contrast, the mean PSS-10 score of the waitlist group increased from 11.55 (95% CI: 10.03 to 13.07) at baseline to 12.46 (95% CI: 10.85 to 14.07) at week 12 and to 11.71 (95% CI: 10.08 to 13.34) at week 24, compared with baseline data.

Compared with the waitlist control group, although participants in Tai Chi group experienced significantly improvements in the PSS-10 mean scores at week 12 (P=0.006, partial η^2=0.073), there was no significant between-group difference in the PSS-10 mean scores at week 24 (P=0.077, partial η^2=0.031). The mean difference at week 24 was 1.27 points. The Cohen's d at week 24 was 0.21.

Subgroup analyses for participants with hypertension demonstrated that using a linear mixed model, the Tai Chi intervention significantly decreased the PSS-10 mean scores over 24 weeks,

compared with waitlist group (*P*=0.029). Significant differences between the two groups were both detected at week 12 (*P*=0.014) and week 24 (*P*=0.044).

In the ITT analysis which included all participants originally randomised, assuming no improvements for missing data, and using a linear mixed model, the Tai Chi intervention significantly decreased the PSS-10 mean scores over 24 weeks, compared with waitlist group (*P*=0.024). However, similarly, significant differences between the two groups were detected at week 12 (*P*=0.018), but not at week 24 (*P*=0.168).

In summary, the above analyses suggested that the 24-week standardised Tai Chi intervention was superior to waitlist group in reducing stress as measured by PSS-10 over 24 weeks. It is noteworthy that the between-group differences reached statistically significance at week 12 when there were two Tai Chi classes per week, while no further between-group differences were detected at week 24 when there was once per week (between week 12 to 24).

5.1.5 Secondary Outcome Measure

5.1.5.1 Psychological status

Anxiety

Baseline assessment

SAS is a self-report instrument that measures levels of anxiety in patients who have anxiety-related symptoms. Score ranges from 25 to 100, with higher scores indicating worse symptoms of anxiety. At baseline, the mean SAS scores were very similar between the two groups (*P*=0.976), 45.25±8.83 scores in the Tai Chi group and 45.20±9.61 scores in the waitlist control group. The comparisons of anxiety as measured by SAS between the two groups at baseline are presented in Table 5.6.

Table 5.6 Baseline comparisons of SAS scores between the two groups.

Variable	Tai Chi Group (n=60)	Waitlist Group (n=60)	*P* value
SAS, mean ± SD, score	45.25±8.83	45.20±9.61	0.976

Abbreviation: SAS, the Zung Self-Rating Anxiety Scale; SD, standard deviation.

Week 12

Anxiety as measured by SAS scale in the Tai Chi and waitlist groups at baseline, week 12 and 24 is presented in Table 5.7.

Table 5.7 SAS scores at baseline, week 12 and 24 in the Tai Chi and waitlist groups

	Tai Chi Group		Waitlist Group	
	No.	Mean (95% CI)	No.	Mean (95% CI)
Baseline	60	45.25 (43.17, 47.33)	60	45.20 (43.12, 47.28)
Week 12	54	39.95 (37.79, 42.10)	51	42.20 (40.00, 44.40)
Week 24	53	39.38 (37.21, 41.55)	49	41.90 (39.67, 44.12)

Note: SAS, the Zung Self-Rating Anxiety Scale; SAS score ranges from 25 to 100, with higher score indicating worse symptoms of anxiety.

As shown in Table 4.8, the mean SAS score of the waitlist control group decreased from 45.20 (95% CI: 43.12 to 47.28) scores at baseline to 42.20 (95% CI: 40.00 to 44.40) scores at week 12. The Tai Chi group had a greater decrease in SAS scores, with 45.25 (95% CI: 43.17 to 47.33) scores at baseline to 39.95 (95% CI: 37.79 to 42.10) scores at week 12, when compared to that of the waitlist control.

Week 24

At week 24, the mean SAS scores in both the Tai Chi and waitlist groups continued to decrease from week 12, and the Tai Chi group had a lower mean SAS score than the waitlist control group (39.38 vs 41.90, respectively). However, there was no significant between-group difference in anxiety as measured by SAS scale over 24 weeks (P=0.155). The residuals of SAS scores were normally distributed after checking the histogram of residuals.

In the ITT analysis, there were no significant between-group differences detected at 24 weeks (P=0.431).

In summary, although the Tai Chi group had a greater decrease in anxiety at week 12 and 24 than that of the waitlist group, statistical analyses demonstrated no between-group differences in SAS scores.

Depression

Baseline assessment

BDI-II is a 21-item self-report rating inventory that measures the existence and severity of symptoms of depression. Score ranges from 0 to 63, with higher scores indicating worse symptoms of depression. The comparisons of level of depression as measured by BDI-II between the two groups at baseline were presented in Table 5.8.

Table 5.8 Baseline comparisons of BDI-II scores between the two groups.

Variable	**Tai Chi Group (n=60)**	**Wait-list Group (n=60)**	***P* value**
BDI-II, mean ± SD, score	11.10±9.05	9.98±8.66	0.491

Abbreviation: BDI-II, the Beck Depression Inventory-II; SD, standard deviation.

The mean BDI-II scores were 11.10 ± 9.05 scores in the Tai Chi group and 9.98 ± 8.66 scores in the waitlist group. Although the BDI-II score of the Tai Chi group appeared higher than that of the waitlist group indicating worse symptoms of depression, there were no statistical differences in level of depression between the two groups at baseline (*P*=0.491).

Week 12

In this study, the level of depression was measured by BDI-II in the Tai Chi and waitlist groups at baseline, week 12 and 24 respectively and the results are summarised in Table 5.9.

Table 5.9 BDI-II scores at baseline, week 12 and 24 in the Tai Chi and waitlist groups

	Tai Chi Group		Waitlist Group	
	No.	Mean (95% CI)	No.	Mean (95% CI)

Baseline	60	11.20 (8.94, 13.26)	60	9.98 (7.82, 12.14)
Week 12	54	6.34 (4.12, 8.57)	51	9.88 (7.62, 12.14)
Week 24*	53	7.28 (5.05, 9.52)	49	10.22 (7.94, 12.51)

Note: BDI-II, the Beck Depression Inventory-II; BDI-II score ranges from 0 to 63, with higher score indicating worse depression. Using a mixed linear model, significant differences were detected between the Tai Chi group and waitlist group in decreasing BDI-II score at week 24 (*P*=0.001), favouring the Tai Chi group.

As shown in Table 5.9, the mean BDI-II scores of the Tai Chi group was markedly decreased, from 11.20 (95% CI: 8.94 to 13.26) at baseline to 6.34 (95% CI: 4.12 to 8.57) at week 12, while the mean BDI-II scores of the waitlist control group maintained at the similar level as the baseline scores (mean: 9.98; 95% CI: 7.82 to 12.14 at baseline vs 9.88 (7.62, 12.14) at week 12). There was a significant difference between the two groups in decreasing BDI-II mean scores between the two groups at week 12 (*P*<0.001), favouring the Tai Chi group.

Using ITT sample, a similar difference between the two groups was identified at week 12 (*P*=0.001) in decreasing BDI-II mean scores.

Week 24

At week 24, as shown in Table 5.9 and Figure 5.3, the mean BDI-II score in both the Tai Chi and waitlist control group had a slight increase from week 12. Compared with the waitlist group, the Tai Chi group had a lower mean BDI-II score (7.28 vs 10.22). Significant differences were detected between the Tai Chi group and waitlist group in BDI-II score at week 24 (*P*=0.001). The residuals of BDI-II scores were normally distributed after checking the histogram of residuals.

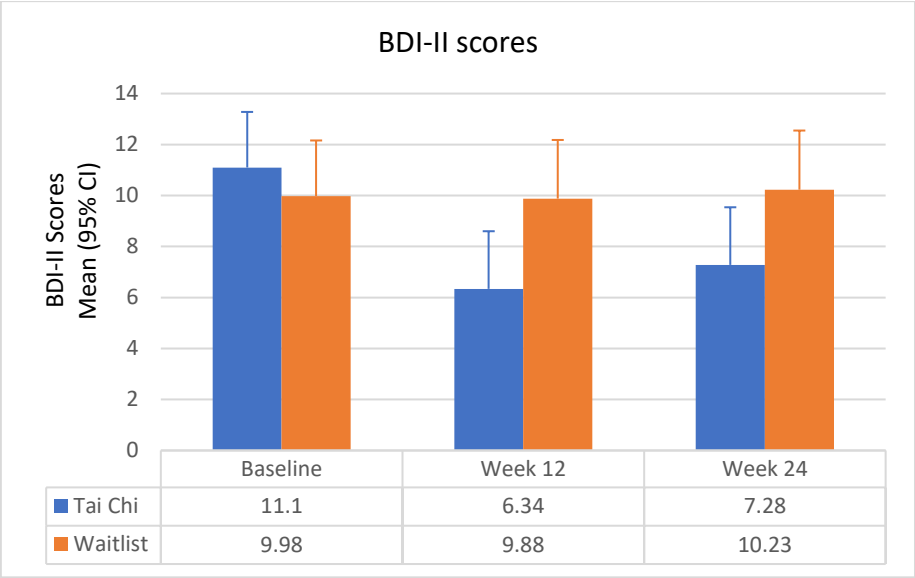


Figure 5.3 BDI-II score at baseline, week 12 and 24 of the Tai Chi and Waitlist group. Error bar indicate 95% confidence intervals (CI).

There were significant difference between the two groups in BDI-II mean scores between the two groups at week 12 (P<0.001) and week 24 (P=0.011), both favouring the Tai Chi group.

In the ITT analysis, we found that Tai Chi intervention significantly decreased the BDI-II mean scores over 24 weeks, compared with the waitlist control group (P=0.002). Significant differences were identified between the two groups both at week 12 (P=0.001) and week 24 (P=0.018), favouring the Tai Chi group.

Although there were significant differences between the Tai Chi group and waitlist control group in depression as measured by BDI-II, the interpretation of the findings should be with caution. One limitation of our data of BDI-II scores is that the data was not normally distributed and had significant skewness. However, because the sample size was relatively large, and the sample was similar between the two groups in this study, the findings appear to be reliable. After dealing with outliers using the winsorising method, there was still significant skewness and no change in direction of the results.

In summary, the analyses demonstrated that participants in the Tai Chi group experienced significantly greater decrease of BDI-II scores over the 24 weeks, and at week 12 and 24, respectively, indicating the beneficial effects of Tai Chi in reducing depression. In spite of that,

our data of BDI-II scores did not satisfy normal distribution and the substantial skewness did not disappear after dealing with outliers.

5.1.5.2 Cardiovascular function

Blood Lipid Profile

Baseline assessment

The comparisons of blood lipid profile, including total cholesterol, triglyceride, HDL-C and LDL-C, between the two groups are presented in Table 5.10.

Table 5.10 Baseline comparisons of blood lipid profile between the two groups.

Variable	Tai Chi Group (n=60)	Waitlist Group (n=60)	*P* value
Blood lipid profile, mean ± SD, mmol/L			
Total cholesterol	5.19±1.17	4.74±0.93	0.021
Triglyceride	1.54±0.85	1.39±0.58	0.248
HDL-C	1.38±0.30	1.31±0.26	0.184
LDL-C	2.99±0.85	2.77±0.93	0.187

Abbreviation: HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SD: standard deviation.

The mean triglyceride, HDL-C and LDL-C values in Tai Chi and waitlist groups were similar at baseline. There was no significant difference between the two groups. However, the mean total cholesterol in the Tai Chi group was significantly higher than that in the waitlist group (5.19 mmol/L in Tai Chi group vs 4.74 mmol/L in waitlist group), and the difference has reached a statistical significance (*P*=0.021).

Week 12

From baseline to week 12, the mean value of total cholesterol, triglyceride and LDL-C in Tai Chi group decreased slightly, while the mean value of those parameters maintained at the same level or slightly increased in waitlist group. The mean HDL-C in Tai Chi group slightly

increased from 1.38 (95% CI: 1.12 to 1.65) mmol/L at baseline to 1.41 (95% CI: 1.12 to 1.70) mmol/L at week 12, while in the waitlist group it remained at the similar level at 1.31 mmol/L. The comparisons of blood lipid profile at baseline, week 12 and 24 between the two groups are summarised in Table 5.11.

Table 5.11 Blood lipid profile at baseline, week 12 and 24 in the Tai Chi and waitlist groups

	Tai Chi Group		Waitlist Group	
	No.	Mean (95% CI)	No.	Mean (95% CI)
TC				
Baseline	60	5.19 (4.93, 5.45)	60	4.71 (4.45, 4.97)
Week 12	54	4.98 (4.71, 5.25)	51	4.71 (4.44, 4.99)
Week 24	53	4.95 (4.68, 5.22)	49	4.93 (4.66, 5.21)
TG				
Baseline	60	1.54 (1.38, 1.71)	60	1.39 (1.22, 1.55)
Week 12	54	1.49 (1.32, 1.66)	51	1.40 (1.22, 1.58)
Week 24	53	1.47 (1.29, 1.65)	49	1.39 (1.21, 1.57)
HDL-C				
Baseline	60	1.38 (1.12, 1.65)	60	1.31 (1.04, 1.58)
Week 12	54	1.41 (1.12, 1.70)	51	1.31 (1.00, 1.61)
Week 24	53	1.43 (1.12, 1.73)	49	1.67 (1.36, 1.98)
LDL-C				
Baseline	60	2.99 (2.75, 3.23)	60	2.75 (2.51, 2.99)
Week 12	54	2.89 (2.64, 3.13)	51	2.86 (2.60, 3.11)
Week 24	53	2.95 (2.69, 3.20)	49	3.01 (2.76, 3.27)

Notes: TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Week 24

There was no significant difference between the two groups in triglyceride (*P*=0.752), HDL-C (*P*=0.418) and LDL-C (*P*=0.073) over 24 weeks, except total cholesterol (*P*=0.007), estimated by a mixed linear model. The residuals of blood lipid profile including TC, TG, HDL-C and LDL-C were normally distributed after checking the histogram of residuals.

In the ITT analysis, we found that there was no significant difference between the two groups in total cholesterol (*P*=0.162), triglyceride (*P*=0.125), HDL-C (*P*=0.485) and LDL-C (*P*=0.495) over 24 weeks.

In summary, our results demonstrated that compared with waitlist group, Tai Chi intervention had no significant impact on blood lipid profile over 24 weeks.

Fasting Blood Glucose

Baseline assessment

The comparisons of fasting blood glucose at baseline between the two groups are presented in Table 5.12.

Table 5.12 Baseline comparisons of fasting blood glucose between the two groups.

Variable	Tai Chi Group (n=60)	Waitlist Group (n=60)	*P* value
FBG, mean ± SD, mmol/L	5.85±1.19	5.93±0.94	0.689

Abbreviation: FBG, fasting blood glucose; SD: standard deviation.

The fasting blood glucose was comparable between the Tai Chi and waitlist control groups at baseline (5.85 ± 1.19 mmol/L in the Tai Chi group compared with 5.93 ± 0.94 mmol/L in the waitlist group). There was no significant difference between the two groups in fasting blood glucose at baseline (*P*=0.689).

Week 12

In this study, fasting blood glucose of participants in the Tai Chi and waitlist control group at baseline, week 12 and 24 were summarised in Table 5.13.

Table 5.13 Fasting blood glucose over 24 weeks in the Tai Chi and waitlist groups

	Tai Chi Group		Waitlist Group	
	No.	Mean (95% CI)	No.	Mean (95% CI)
Baseline	60	5.86 (5.54, 6.17)	60	5.92 (5.60, 6.24)
Week 12	54	6.32 (6.00, 6.65)	51	6.16 (5.83, 6.50)
Week 24	53	6.37 (6.03, 6.70)	49	6.10 (5.76, 6.44)

As shown in Table 5.13, from the baseline to week 12, the mean value of fasting blood glucose increased slightly in both the Tai Chi and waitlist groups. The mean fasting blood glucose in Tai Chi group increased from 5.86 (95% CI: 5.54 to 6.17) mmol/L at baseline to 6.32 (95% CI: 6.00 to 6.65) mmol/L at week 12, and in waitlist group increased from 5.92 (95% CI: 5.60 to 6.24) mmol/L at baseline to 6.16 (95% CI: 5.83 to 6.50) mmol/L at week 12.

Week 24

There was no significant difference between the Tai Chi and waitlist control group in fasting blood glucose over 24 weeks (P=0.182). The residuals of FBG data were normally distributed after checking the histogram of residuals.

In the ITT analysis, we found that there was no significant between-group difference in fasting blood glucose over 24 weeks (P=0.572).

By checking for normality of both visually through plots and Shapiro-Wilk test, we found that the baseline data of fasting blood glucose did not match normal distribution. After log transformation of the data and estimated by the mixed linear model, there was no change of the distribution.

In summary, our above analyses consistently demonstrated that Tai Chi intervention was not superior to waitlist group in changing fasting blood glucose over 24 weeks.

C-Reactive Protein (CRP)

Baseline assessment

Fifty-six (56/60, 93.3%) participants had a CRP < 4 g/L in Tai Chi group, and 54 (54/60, 90.0%) in waitlist group. There was no significant difference in CRP between the Tai Chi and waitlist groups at baseline (*P*=0.509). The comparisons of CRP at baseline between the two groups are presented in Table 5.14.

Table 5.14 Baseline comparisons of C-reactive protein between the two groups.

Variable	Tai Chi Group (n=60)	Waitlist Group (n=60)	*P* value
C-reactive protein (<4.0)-No. (%)	56(93.3%)	54(90.0%)	0.509

Abbreviation: SD: standard deviation.

Week 12

The comparisons of CRP at baseline, 12 and 24 weeks between the two groups were presented in Table 5.15.

Table 5.15 C-reactive protein at baseline, 12 and 24 weeks of Tai Chi and waitlist groups

CRP	Tai Chi No./Total (%)	Wait-list No./Total (%)	Unadjusted odds ratio (95% CI)	Fixed Effect (time*group) *P* value
Baseline				
<4	56/60 (93.3)	54/60 (90.0)	0.64 (0.17, 2.40)	
≥4	4/60 (6.7)	6/60 (10.0)		
Week 12				0.144
<4	46/52 (88.5)	45/46 (97.8)	5.87 (0.68, 50.72)	
≥4	6/52 (11.5)	1/46 (2.2)		
Week 24				

<4	41/47 (87.2)	43/45 (95.6)	3.15 (0.60, 16.49)
≥4	6/47 (12.8)	2/45 (4.4)	

Note: CRP, C-reactive protein. Using generalized linear model with binary logistic model, there was no significant difference between the two groups in CRP over 24 weeks (*P*=0.144).

At week 12, the number of participants in the two groups who had a CRP < 4 mg/L was similar, with 46 (46/52, 88.5%) participants in Tai Chi group, and 45 (45/46, 97.8%) in waitlist group.

Week 24

At week 24, the number of participants who had a CRP < 4 mg/L in the two groups was similar, with 41 (41/47, 87.2%) participants in Tai Chi group, and 43 (43/45, 95.6%) in waitlist group. There was no significant difference between the Tai Chi and waitlist groups in CRP over 24 weeks (*P*=0.144).

Similarly, in the ITT analysis, we found that there was no significant between-group difference in CRP over 24 weeks.

In summary, there was no statistically significant difference in CRP between the Tai Chi and waitlist groups over 24 weeks.

Blood Pressure

Baseline assessment

The comparisons of blood pressure at baseline between the two groups are presented in Table 5.16.

Table 5.16 Comparisons of blood pressure at baseline between the two groups.

Variable	**Tai Chi Group (n=60)**	**Waitlist Group (n=60)**	***P* value**
Blood pressure, mean ± SD, mmHg			
Systolic	126.03±15.31	124.58±17.16	0.626
Diastolic	79.55±10.12	76.43±9.98	0.092

Abbreviation: SD: standard deviation.

The mean systolic and diastolic blood pressures in Tai Chi group were both slightly higher than that of the waitlist control group at baseline (systolic: 126.03 mmHg vs 124.58 mmHg, respectively; diastolic: 79.55 mmHg vs 76.43 mmHg, respectively). However, there were no significant differences between the two groups in both systolic and diastolic pressures at baseline (P>0.05).

Week 12

The comparison of systolic and diastolic blood pressures at baseline, week 12 and 24 between the two groups are presented in Table 5.17.

Table 5.17 Blood pressure at baseline, week 12 and 24 in the Tai Chi and waitlist groups

Blood Pressure	Tai Chi Group		Waitlist Group	
	No.	Mean (95% CI)	No.	Mean (95% CI)
Systolic				
Baseline	60	126.03 (122.28, 129.78)	60	124.58 (120.83, 128.33)
Week 12	54	126.41 (122.49, 130.32)	51	123.74 (119.66, 127.81)
Week 24	53	124.79 (120.84, 128.73)	49	124.07 (119.99, 128.14)
Diastolic				
Baseline	60	79.55 (77.10, 82.00)	60	76.43 (73.98, 78.89)
Week 12	54	79.84 (77.30, 82.38)	51	73.87 (71.24, 76.49)
Week 24*	53	76.74 (74.18, 79.29)	49	75.44 (72.81, 78.06)

Note: *Using a linear mixed model, there were significant differences between the two groups in diastolic blood pressure over 24 weeks (P=0.031).

As shown in Table 5.17, from the baseline to week 12, the mean systolic blood pressure in both the Tai Chi and waitlist groups maintained at the similar level, 126.03 (95% CI: 122.28 to 129.78) mmHg at baseline and 126.41 (95% CI: 122.49 to 130.32) mmHg at week 12 in Tai Chi group, and 124.58 (95% CI: 120.83 to 128.33) mmHg at baseline and 123.74 (95% CI: 119.66 to 127.81) mmHg at week 12 in waitlist group.

The mean diastolic blood pressure in Tai Chi group maintained at the similar level over the first 12 weeks, 79.55 (95% CI: 77.10 to 82.00) mmHg at baseline and 79.84 (95% CI: 77.30 to 82.38) mmHg at week 12 in Tai Chi group. In contrast, the mean diastolic blood pressure in the waitlist group slightly decreased from 76.43 (95% CI: 73.98 to 78.89) mmHg at baseline to 73.87 (95% CI: 71.24 to 76.49) mmHg at week 12.

There were significant differences between the two groups in diastolic blood pressure over 24 weeks. At week 12, there were significant difference between the two groups in the mean diastolic blood pressure between the two groups (P=0.010), indicating participants in the Tai Chi group controlled their diastolic blood pressure in a more stable status.

In the ITT analysis, similarly, there were no significant differences between the two groups in systolic blood pressure, but significant between-group differences were detected in diastolic blood pressure (P=0.017).

Week 24

There were significant differences between the two groups in diastolic blood pressure over 24 weeks (P=0.031), while no significant between-group differences were found in systolic blood pressure. The residuals of systolic and diastolic blood pressure data were normally distributed after checking the histogram of residuals.

As shown in Figure 5.4, the mean diastolic blood pressure in the Tai Chi group at baseline, week 12 and week 24 were all higher than that of the waitlist control group. However, over the 24 weeks, the mean diastolic blood pressure in the Tai Chi group exhibited a downward trend, while in the waitlist control group the trend was unstable with a decrease and an increase.

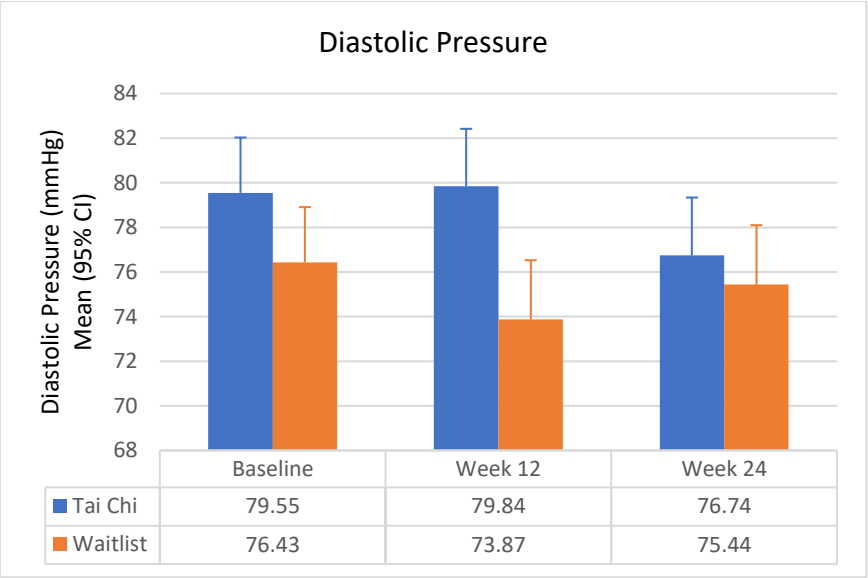


Figure 5.4 Diastolic pressure at baseline, week 12 and 24 of the Tai Chi and waitlist group. Error bar indicate 95% confidence intervals (CI).

We found significant between-group differences at 12 weeks (*P*=0.010), but no significant difference between the two groups at week 24 (*P*=0.910).

In the ITT analysis, there were significant differences in mean diastolic blood pressure between the two groups over 24 weeks (*P*=0.035). Similarly, using ITT sample, significant differences between the two groups in mean diastolic blood pressure were identified at week 12 (*P*=0.017) but not week 24 (*P*=0.837).

In summary, our above analyses demonstrated that there was no significant difference between the two groups in systolic blood pressure but in diastolic blood pressure at 12 weeks and over 24 weeks, indicating that Tai Chi intervention results in a more stable control of blood pressure over 24 weeks compared with the waitlist group.

Heart Rate

Baseline assessment

The comparisons of heart rate at baseline between the two groups are presented in Table 5.18. The mean heart rate in Tai Chi group was slightly higher than that in waitlist group (70.30 vs 68.97 BPM). However, this difference did not reach statistical significance (*P*>0.05).

Table 5.18 Baseline comparisons of heart rate between the two groups.

Variable	Tai Chi Group (n=60)	Waitlist Group (n=60)	*P* value
Heart rate, mean ± SD, BPM	70.30±10.26	68.97±10.49	0.483

Abbreviation: SD: BPM, beats per minute.

Week 12

From the baseline to week 12, the mean beats of heart rate in Tai Chi group slightly decreased from 70.30 (95% CI: 67.84 to 72.76) BPM at baseline to 69.39 (95% CI: 66.85 to 71.94) BPM at week 12. In contrast, in the waitlist group it maintained at the similar level, from 68.97 (95% CI: 66.50 to 71.43) BPM at baseline to 68.52 (95% CI: 65.90 to 71.13) BPM at week 12. The comparisons of heart rate at baseline, 12 and 24 weeks between the two groups are shown in Table 5.19.

Table 5.19 Heart rate at baseline, week 12 and 24 weeks in the Tai Chi and waitlist groups

	Tai Chi Group		Waitlist Group	
	No.	Mean (95% CI)	No.	Mean (95% CI)
Baseline	60	70.30 (67.84, 72.76)	60	68.97 (66.50, 71.43)
Week 12	54	69.39 (66.85, 71.94)	51	68.52 (65.90, 71.13)
Week 24	53	69.18 (66.63, 71.74)	49	67.95 (65.33, 70.56)

Week 24

There were no significant differences in heart rate between the two groups over week 24 (*P*=0.957). As shown in Table 4.20, although there were slight decreases in both groups at 24 weeks, the mean beats of heart rate per minute in both groups maintained around the similar level. The residuals of heart rate data were normally distributed after checking the histogram of residuals.

In the ITT analysis, there were also no significant between-group differences in heart rate over 24 weeks (*P*=0.256).

In summary, the analyses demonstrated that there was no significant difference in changing heart rate between the Tai Chi and waitlist groups over 24 weeks. Participants in both groups experienced a slight decrease in the beats of heart rate per minute.

Heart Rate Variability (HRV)

Baseline assessment

There were substantial missing data for the baseline HRV parameters due to recording issues. LF norm, HF norm, and LF/HF ratio were recorded in 88 participants (38 in Tai Chi group and 50 in waitlist group); total power was recorded in 57 participants (27 in Tai Chi group and 30 in waitlist group); and RMS SD, HRV index, and PNN50 were measured in 87 participants (48 in Tai Chi group and 39 in the waitlist group).

The baseline HRV parameters were all comparable between the two groups (P>0.05). Table 5.20 presents the baseline comparisons of HRV parameters between the two groups.

Table 5.20 Baseline comparisons of HRV parameters between the two groups.

Variable	Tai Chi Group (n=60)	Waitlist Group (n=60)	*P* value
HRV*			
LF norm, mean ± SD, n.u.	55.56±21.47	51.43±20.99	0.367
HF norm, mean ± SD, n.u.	44.47±21.48	48.58±20.98	0.371
LF/HF ratio, mean ± SD	2.03±2.04	1.69±1.84	0.427
TP, mean ± SD, ms^2	2202.26±6553.81	1713.23±3760.71	0.728
RMS SD, mean ± SD, ms	35.22±44.15	34.89±41.48	0.972
HRV index, mean ± SD	6.85±4.22	7.89±4.18	0.253
PNN50, mean ± SD, %	7.59±14.76	8.59±18.38	0.777

Abbreviation: HRV, heart rate variability; SD: standard deviation; n.u.: normalized unit; ms: millisecond.

*HRV reflects the modulation of cardiac function by autonomic and other physiological systems. Key parameters of HRV include time domain and frequency domain parameters:

a) LF norm, normalised low frequency-the ratio between absolute value of the low frequency and difference between total power and very low frequency;
b) HF norm, normalised high frequency-the ratio between absolute value of the high frequency and difference between total power and very low frequency;

c) LF/HF ratio-the ratio of low frequency and high frequency bands, indicating overall balance between sympathetic and parasympathetic systems;
d) TP, total power-a short-term estimate of the total power of power spectral density in the range of frequencies between 0 and 0.4 Hz, reflecting overall autonomic activity where sympathetic activity is a primary contributor;
e) RMS SD-the square root of the mean square of successive R-R interval differences;
f) HRV index, integral of the density of the R-R interval histogram divided by its height;
g) PNN50, percentage of successive R-R intervals that differ by more than 50 milliseconds

HRV data at baseline had many missing data for each of the key parameter because of recording issues (LF norm [n=88], HF norm [n=88], LF/HF ratio [n=88], TP [n=57], RMS SD [n=87], HRV index [n=87], HRV index [n=87], and PNN50 [n=87]).

Week 12

The comparisons of HRV parameters between the two groups at baseline, week 12 and 24 are summarised in Table 5.21.

Table 5.21 Heart rate variability (HRV) over 24 weeks in the Tai Chi and waitlist groups.

HRV parameters	Group	Baseline Mean (95% CI)	Week 12 Mean (95% CI)	Week 24 Mean (95% CI)	Fixed Effect (time*group) *P* value
LF norm	Tai Chi	55.09 (48.62, 61.57)	49.72 (43.99, 55.45)	47.63 (41.62, 53.63)	0.557
	Waitlist	51.46 (45.74, 57.18)	49.86 (43.91, 55.81)	49.86 (43.53, 56.19)	
HF norm	Tai Chi	44.90 (38.42, 51.39)	50.15 (44.42, 55.89)	52.34 (46.33, 58.35)	0.554
	Waitlist	48.52 (42.80, 54.25)	50.14 (44.19, 56.09)	50.02 (43.69, 56.36)	
LF/HF ratio	Tai Chi	1.91 (1.37, 2.44)	1.52 (1.06, 1.99)	1.60 (1.13, 2.08)	0.881
	Waitlist	1.672 (1.20, 2.15)	1.49 (1.00, 1.97)	1.45 (0.96, 1.94)	
Total Power	Tai Chi	1684.29 (365.12, 3003.45)	1433.02 (354.03, 2512.01)	1148.53 (53.40, 2243.67)	0.709
	Waitlist	1566.73 (282.57, 2850.89)	1998.89 (881.22, 3116.56)	1373.97 (251.39, 2496.54)	
RMS SD	Tai Chi	34.88 (24.51, 45.24)	32.07 (21.96, 42.18)	32.35 (22.11, 42.60)	0.465
	Waitlist	34.73 (23.71, 45.74)	38.76 (28.34, 49.19)	32.48 (22.02, 42.95)	
HRV index	Tai Chi	6.70 (5.72, 7.68)	7.27 (6.31, 8.22)	7.09 (6.12, 8.06)	0.343
	Waitlist	7.78 (6.74, 8.81)	7.70 (6.72, 8.69)	7.29 (6.30, 8.27)	
PNN50	Tai Chi	7.412	5.10	6.96	0.244

	(3.44, 11.38)	(1.26, 8.94)	(3.05, 10.87)
Waitlist	8.64	8.97	6.32
	(4.36, 12.92)	(4.98, 12.95)	(2.32, 10.33)

Notes: LF norm, low frequency normalized; HF norm, high frequency normalized; LF/HF ratio, the ratio of low frequency and high frequency; RMS SD, root mean square of successive R-R interval differences; HRV index, integral of the density of the R-R interval histogram divided by its height; PNN50, percentage of successive R-R intervals that differ by more than 50 ms.

From the baseline to week 12, the mean LF norm in Tai Chi group decreased from 55.09 to 49.72, and in waitlist group decreased from 51.46 to 49.86. However, the mean HF norm increased in both groups over the first 12 weeks, from 44.90 to 50.15 in Tai Chi group, and 48.52 to 50.14 in waitlist group. Correspondingly, the LF/HF ratio decreased from baseline to week 12 slightly.

For the time domain, the mean RMS SD in Tai Chi group slightly decreased, while in the waitlist group slightly increased. The mean HRV index in Tai Chi group had a slight increase, whilst in the waitlist group maintained almost in the same level. The mean PNN50 in the Tai Chi group decreased from 7.41% at baseline to 5.10% at week 12, while increased from 8.64% at baseline to 8.97% at week 12.

Week 24

As estimated by a mixed linear model, there was no significant difference between the Tai Chi group and waitlist group in all HRV parameters at week 24 (P>0.05), including LF norm, HF norm, LF/HF ratio, total power, RMS SD, HV index and PNN50 (Table 5.21). The residuals of all HRV parameters were normally distributed after checking the histogram of residuals.

Similarly, in the ITT analysis, consistent findings were identified that no significant between-group differences in all the HRV parameters over 24 weeks (P>0.05).

In summary, our analyses demonstrated that Tai Chi group had no more significant changes in HRV parameters over 24 weeks compared with waitlist group.

5.1.5.3 Quality of life

Baseline assessment

The comparisons of SF-36 scores between the two groups were presented in Table 5.22. SF-36 was used to measure the quality of life of participants in this study. SF-36 is a generic outcome

measure designed to examine self-reported functional health and well-being, including concepts of physical functioning, role limitations due to physical problems, social function, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions. Score ranges from 0 to 100 in each of the eight domains, with higher scores indicating better health status.

Table 5.22 Baseline comparison of SF-36 between the Tai Chi and waitlist groups.

Variable	Tai Chi Group (n=60)	Waitlist Group (n=60)	*P* value
SF-36, mean ± SD, score			
Physical function	76.22±18.10	84.02±13.25	0.008
Role limitation (physical problems)	59.58±43.69	77.92±35.08	0.013
Bodily pain	73.73±20.06	79.43±20.01	0.112
General health	52.17±20.93	55.11±21.48	0.448
Vitality	68.33±18.33	72.08±18.90	0.272
Social functioning	78.67±22.83	81.25±21.48	0.524
Role limitation (emotional problems)	70.30±33.73	76.52±34.42	0.320
Mental health	69.33±20.70	72.00±18.86	0.462

Abbreviation: SF-36, the 36-item Short Form Health Survey Questionnaire; SD: standard deviation.

At baseline, there was no significant difference between the two groups in six domains of SF-36 (Score ranges from 0 to 100 in each of the eight domains, with higher scores indicating better health status) (P>0.05), except two domains (i.e. physical function and role limitation due to physical problems). The mean scores of the physical function and role limitation (physical problems) domains in the Tai Chi group was significantly lower than that of the waitlist control group (P=0.008 and P=0.013, respectively).

Week 12

From the baseline to week 12, the mean scores of all domains of SF-36 in Tai Chi groups had an obvious increase, while the mean scores of most domains of SF-36 in the waitlist group had

a decrease except general health, vitality, social functioning and mental health domains, which had a slight increase over the first 12 weeks.

Table 5.23 shows the quality of life as measured by SF-36 at baseline, 12 and 24 weeks in the two groups.

Table 5.23 Quality of life as measured with SF-36 from baseline to 12 and 24 weeks in the Tai Chi and waitlist groups.

Domain of SF-36	Group	No.	Baseline Mean (95% CI)	Week 12 Mean (95% CI)	Week 24 Mean (95% CI)	Fixed Effect (time*group) *P* value
Physical Function#	Tai Chi	54	76.22 (72.17, 80.27)	79.98 (75.78, 84.19)	78.66 (74.44, 82.89)	0.016
	Waitlist	51	84.02 (79.97, 88.07)	80.77 (76.48, 85.06)	78.91 (74.57, 83.26)	
Role Limitation (Physical)#	Tai Chi	54	59.58 (49.58, 69.59)	75.51 (65.08, 85.94)	67.76 (57.26, 78.26)	0.000
	Waitlist	51	77.92 (67.91, 87.92)	62.71 (52.04, 73.37)	60.79 (49.97, 71.62)	
Bodily Pain#	Tai Chi	54	73.73 (68.92, 78.55)	79.66 (74.63, 84.68)	79.50 (74.44, 84.56)	0.015
	Waitlist	51	79.43 (74.62, 84.25)	76.68 (71.53, 81.82)	74.50 (69.27, 79.72)	
General Health	Tai Chi	54	52.17 (46.99, 57.34)	60.25 (54.90, 65.59)	58.41 (53.04, 63.78)	0.314
	Waitlist	51	55.12 (49.94, 60.29)	58.02 (52.58, 63.46)	58.81 (53.32, 64.31)	
Vitality#	Tai Chi	54	68.33 (63.71, 72.95)	79.31 (74.53, 84.09)	80.26 (75.45, 85.06)	0.003
	Waitlist	51	72.08 (67.46, 76.70)	72.90 (68.03, 77.77)	75.57 (70.64, 80.49)	
Social Functioning	Tai Chi	54	78.67 (73.12, 84.21)	84.83 (79.10, 90.57)	80.15 (74.39, 85.92)	0.307
	Waitlist	41	81.25 (75.71, 86.79)	82.18 (76.33, 88.02)	82.41 (76.49, 88.32)	
Role Limitation (Emotional)	Tai Chi	54	70.30 (61.23, 79.37)	80.27 (70.81, 89.73)	75.18 (65.66, 84.70)	0.055
	Waitlist	51	76.52 (67.45, 85.59)	73.13 (63.45, 82.81)	65.22 (55.40, 75.04)	
Mental Health	Tai Chi	54	69.33 (64.56, 74.11)	74.33 (69.39, 79.27)	76.01 (71.04, 80.98)	0.167
	Waitlist	51	72.00 (67.22, 76.78)	72.47 (67.44, 77.51)	72.76 (67.66, 77.86)	

Notes: SF-36, the 36-item Short Form Health Survey. #As estimated by a mixed linear model, there were significant differences at 24 weeks between the two groups in following four domains of SF-36 scores: physical function (P=0.016), role limitation (physical problems) (P<0.001), bodily pain (P=0.015) and vitality (P=0.003), favouring the Tai Chi group.

Significant between-group differences were detected in the following four domains of SF-36 scores: physical function, role limitation (physical problems), bodily pain and vitality. For these four domains, there was no significant between-group difference in mean scores of the physical function and bodily pain domains at week 12 (P=0.305, P=0.093, respectively), while significant between-group differences were detected in the mean scores of the role limitation due to physical problems and vitality domains (P=0.004 and P=0.004, respectively), favouring the Tai Chi group.

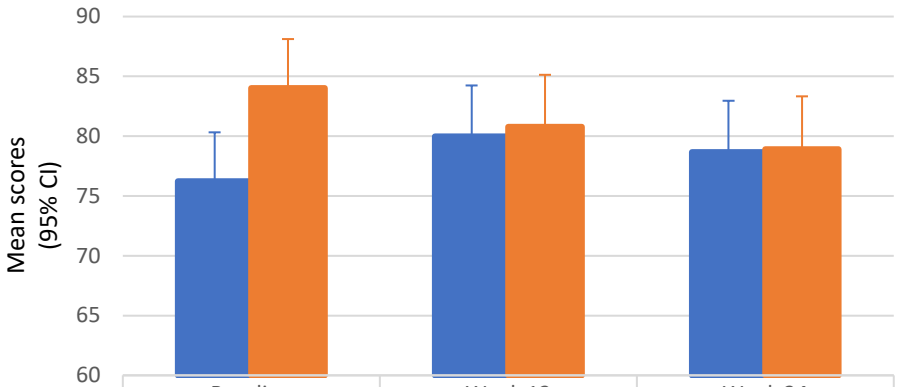
In the ITT analysis, similar findings were identified. There was no significant difference between the two groups in mean scores of the physical function and bodily pain domains at week 12 (P=0.341, P=0.206, respectively); however, the mean scores of the role limitation (physical problems) and vitality domains in the Tai Chi group were significant higher than that in the waitlist control group (P=0.018 and P=0.005, respectively).

Week 24

There were significant differences at 24 weeks between the two groups in following four domains of SF-36 scores: physical function (P=0.016), role limitation (physical problems) (P<0.001), bodily pain (P=0.015) and vitality (P=0.003), favouring the Tai Chi group. No significant difference was observed in other domains of SF-36 scores (P>0.05). The four domains of SF-36 were all related to physical health. The residuals of all the domains of SF-36 scores were normally distributed after checking the histogram of residuals.

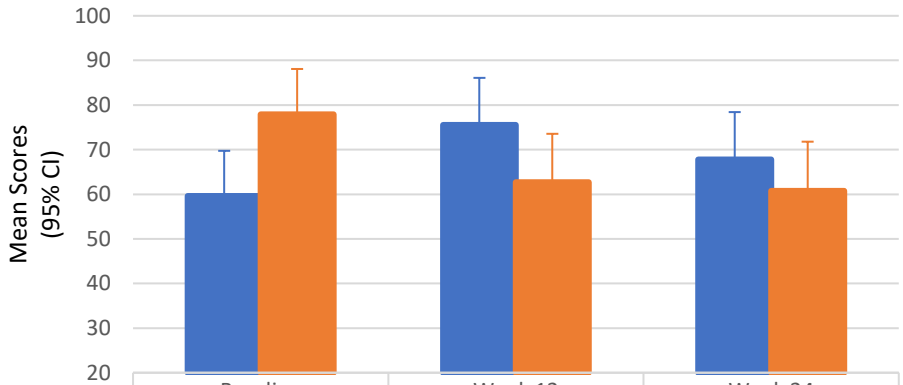
The changes of mean scores (95% CI) of the four mentioned domains of SF-36 are presented in Figure 5.5.

A. Physical function domain of SF-36



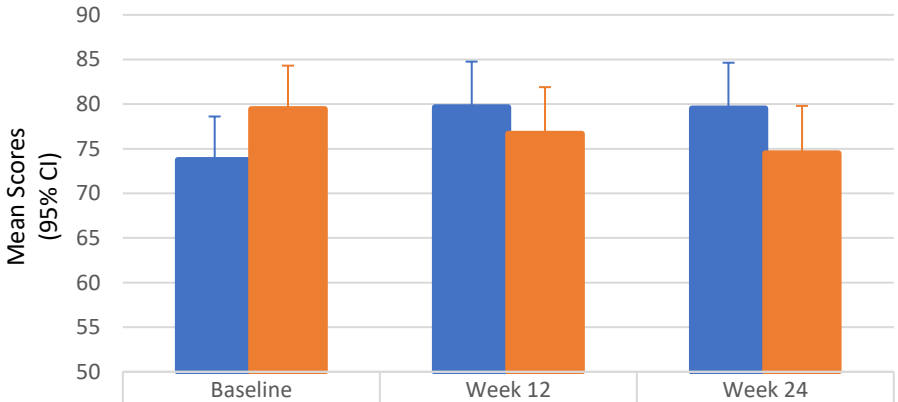
	Baseline	Week 12	Week 24
Tai Chi	76.22	79.98	78.66
Waitlist	84.02	80.77	78.91

B. Role limitation (physical problems) domain of SF-36



	Baseline	Week 12	Week 24
Tai Chi	59.58	75.51	67.76
Waitlist	77.92	62.71	60.79

C. Bodily pain domain of SF-36



	Baseline	Week 12	Week 24
Tai Chi	73.73	79.66	79.5
Waitlist	79.43	76.68	74.5

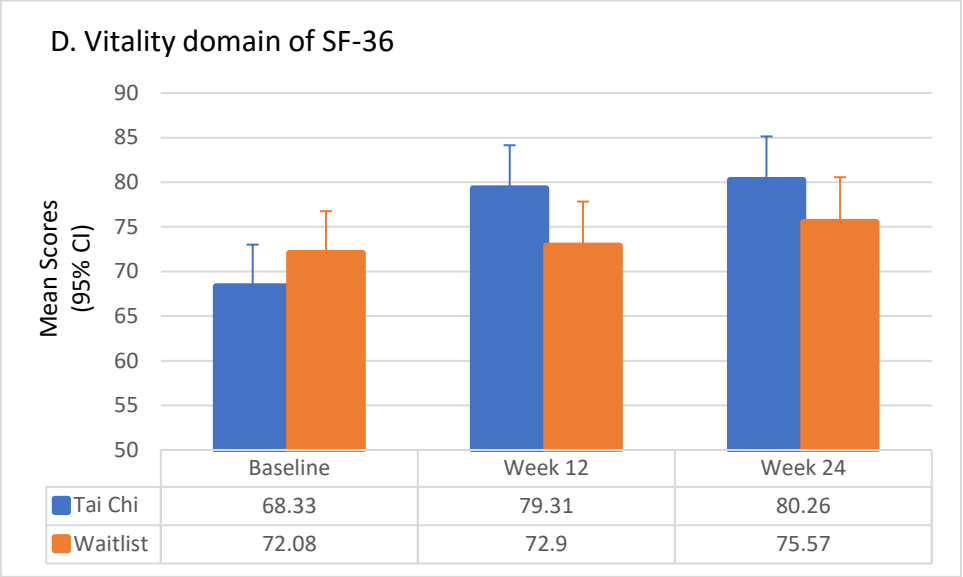


Figure 5.5 Four domains of SF-36 scores at baseline, week 12 and 24 in the Tai Chi and Waitlist group. Error bars indicate 95% confidence intervals (CI). Using a mixed linear model, there were significant differences at 24 weeks between the two groups in following four domains of SF-36 scores: physical function (*P*=0.016), role limitation (physical problems) (*P*<0.001), bodily pain (*P*=0.015) and vitality (*P*=0.003).

There is a markedly increase in physical function (Figure 5.5A), role limitation (physical problems) (Figure 5.5B), and bodily pain domains (Figure 5.5C) in the Tai Chi group over the first 12 weeks, and then a slight decrease from during week 12 and 24; while the mean scores of the three domains in the waitlist group experienced continuous decreases over 24 weeks.

While the mean scores of the vitality domain of SF-36 increased continuously in both groups over 24 weeks, the change was sharper in Tai Chi group. As shown in Figure 5.5D, compared with the waitlist group, the mean vitality scores in the Tai Chi group markedly increased from 68.33 at baseline to 79.31 at week 12, and continued the increase to 80.26 scores at week 24. In the waitlist group, the mean scores slightly increased from 72.08 at baseline to 72.90 at week 12, and 75.57 scores at week 24.

For the four domains which showed significant between-group differences over 24 weeks, only the mean scores of vitality in the Tai Chi group was superior to the waitlist group at week 24 (*P*=0.018). There was no significant difference between the two groups was identified at week 24 in other three domains: the physical function domain (*P*=0.255), role limitation (physical problems) (*P*=0.074) and bodily pain (*P*=0.050).

In the ITT analysis, our findings were similar. We found that the mean scores of the above four domains of SF-36 in the Tai Chi group were superior to that of the waitlist group over 24 weeks, as estimated with a linear mixed model. There were significant between-group differences over 24 weeks in physical function (*P*=0.028), role limitation (physical problems) (*P*=0.001), and vitality (*P*=0.003), except the bodily pain domain (*P*=0.054). For the four domains, there was no significant difference between two groups both at week 12 and 24 in physical function (*P*=0.341 and *P*=0.309, respectively) and bodily pain domains (*P*=0.206 and *P*=0.167, respectively); significant differences in role limitation (physical problems) were identified at week 12 (*P*=0.018) but not week 24 (*P*=0.188); while significant between-group differences were identified in vitality at week 12 (*P*=0.005) and 24 (*P*=0.022), favouring Tai Chi group.

In summary, our findings demonstrated that there were significant differences between the Tai Chi and waitlist groups in the physical function, role limitation (physical problems), bodily pain and vitality domains of SF-36 over 24 weeks, indicating the beneficial effects of Tai Chi intervention in improving quality of life in people with CHD and/or hypertension.

5.1.5.4 Physical fitness

Baseline assessment

6MWT measures the distance (in meter) covered during the 6-minute walk as an objective assessment of physical fitness, with higher scores indicating better fitness. The comparisons of 6MWT at baseline between the two groups were presented in Table 5.24.

Table 5.24 Baseline comparison of 6MWT between the Tai Chi and waitlist groups.

Variable	Tai Chi Group (n=60)	Wait-list Group (n=60)	*P* value
6MWT, mean ± SD, meter	494.77±79.61	518.83±94.01	0.133

Abbreviation: 6MWT: the 6-Minute Walk Test; SD: standard deviation.

The mean distance during the 6-minute walk in the Tai Chi group was lower than that of the waitlist control group, 494.77±79.61 meters in the Tai Chi group and 518.83±94.01 meters in the waitlist group. However, the difference did not reach statistical significance (*P*=0.133).

Week 12

The physical fitness as measured by 6MWT at baseline, 12 weeks and 24 weeks in the two groups was shown in Table 5.25.

Table 5.25 Physical fitness measured by 6MWT from baseline to 12 weeks and 24 weeks in the Tai Chi and waitlist groups.

	Tai Chi Group		Waitlist Group	
	No.	Mean (95% CI)	No.	Mean (95% CI)
Baseline	60	494.77 (470.82, 518.71)	60	518.83 (494.88, 542.77)
Week 12	54	558.41 (533.48, 583.34)	51	513.59 (488.59, 538.58)
Week 24*	53	552.81 (528.17, 577.44)	49	519.63 (494.42, 544.84)

Notes: 6MWT, 6 Minute Walk Test. The 6-minute walking test measures the distance (in meter) covered during the 6-minute walk as an objective assessment of physical fitness, with higher scores indicating better fitness. *Using a linear mixed model, there was a significant difference between the Tai Chi and waitlist groups in the mean walking distance during the 6-minute walk over week 24 (P<0.001), favouring the Tai Chi group.

Participants in the Tai Chi group had obvious improvements in their physical fitness from baseline to 12 weeks. The mean value of the walking distance changed from 494.77 (95% CI: 470.82 to 518.71) meters at baseline to 558.41 (95% CI: 533.48 to 583.34) meters at 12 weeks. In contrast, the mean distance during the 6-minute walking in the waitlist group slightly decreased from 518.83 (95% CI: 494.88 to 542.77) meters at baseline to 513.59 (95% CI: 488.59 to 538.58) meters at 12 weeks. Significant differences were detected between the two groups in 6MWT distance at week 12 (P<0.001), favouring the Tai Chi group.

In the ITT analysis with all participants originally randomised and assuming no improvements for missing data, similarly, the mean walking distance during the 6-minute walk in Tai Chi group was significantly higher than that of the waitlist control group at week 12 (P<0.001).

Week 24

As shown in Table 5.25, there was a significant difference between the Tai Chi and waitlist groups in the mean walking distance during the 6-minute walk over week 24 (P<0.001),

favouring the Tai Chi group. The residuals of 6MWT data were normally distributed after checking the histogram of residuals. Figure 5.6 presents the 6MWT at baseline, 12 weeks and 24 weeks of the Tai Chi and waitlist groups.

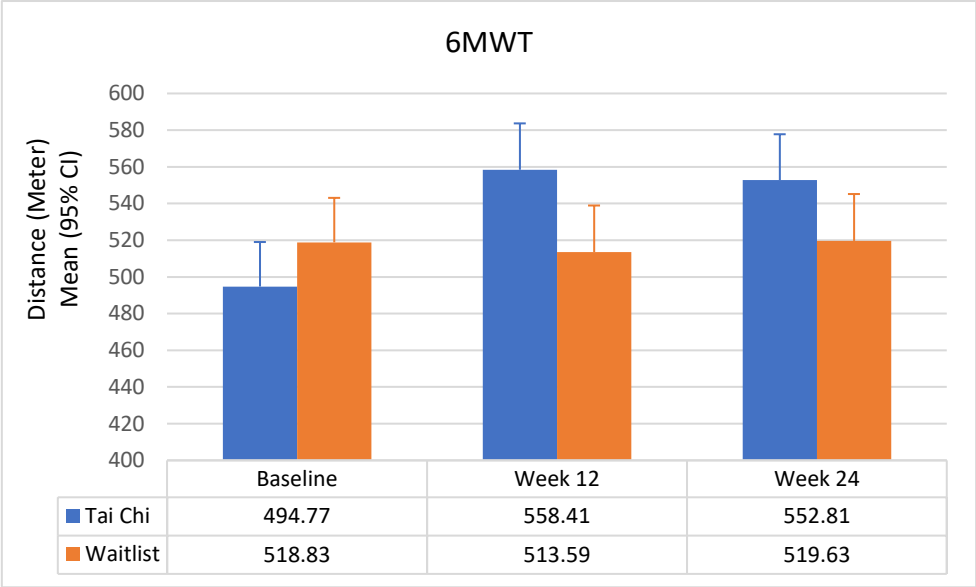


Figure 5.6 Walking distance during 6-minute walk at baseline, week 12 and 24 of the Tai Chi and waitlist group. Error bar indicate 95% confidence intervals (CI).

As shown in Figure 5.6, the mean distance during the 6-minute walk in the Tai Chi group experienced a dramatically increase over the first 12 weeks and then a slight decrease in the rest of the program. The mean distance of 6MWT increased from 494.77 (95% CI: 470.82 to 518.71) meters at baseline to 558.41 (95% CI: 533.48 to 583.34) meters at 12 weeks in Tai Chi group, and slightly decreased from 12 weeks to 552.81 (95% CI: 528.17 to 577.44) meters at 24 weeks. In contrast, the mean distance of 6MWT of participants in the waitlist group almost maintained at the similar level over 24 weeks. The mean distance slightly decreased from 518.83 (95% CI: 494.88 to 542.77) meters at baseline to 513.59 (95% CI: 488.59 to 538.58) meters at 12 weeks, and then increased from 12 weeks to 519.63 (95% CI: 494.42 to 544.84) meters at 24 weeks.

We found that there were significant differences between the two groups in the mean walking distance of 6MWT at week 12 (P<0.001, partial η^2=0.214) and week 24 (P=0.002, partial η^2=0.096), favouring the Tai Chi group. The Cohen's d at week 24 was 0.38.

Subgroup analyses for participants with hypertension demonstrated that using a linear mixed model, the Tai Chi intervention significantly increased the mean walking distance within the 6-minute walk over 24 weeks, compared with waitlist group (P<0.001). Significant differences between the two groups were both detected at week 12 (P<0.001) and week 24 (P=0.002), favouring the Tai Chi group.

In the ITT analysis including all participants originally randomised and assuming no improvements for missing data, similarly, there were significant differences between the two groups in the mean walking distance within the 6-minute walk over 24 weeks (P<0.001). Significant between-group differences were also identified at week 12 (P<0.001) and week 24 (P=0.001), favouring the Tai Chi group.

In summary, our above analyses consistently demonstrated that participants in the Tai Chi group experienced much more significant improvements of 6MWT distance than that of the waitlist group, indicating the beneficial effects of Tai Chi intervention in improving physical fitness.

5.1.6 Safety Outcomes

In this study, participants reported ten adverse events: eight in the Tai Chi group and two in the waitlist control group (see Table 5.26).

Table 5.26 Adverse events summary

Adverse Events	Tai Chi Group		Waitlist Group	
	Week 0-12	Week 13-24	Week 0-12	Week 13-24
Minor muscle soreness	3	0	0	0
Knee pains	2	0	0	0
Cancer	0	0	2*	0
Tiny fracture of rib bone	1	0	0	0
Ankle sprain	0	1	0	0
Bradycardia	0	1*	0	0
Subtotal	**6**	**2**	**2**	**0**
Total	**8**		**2**	

*Severe adverse events.

Five adverse events were related to the Tai Chi intervention. These include three minor muscle soreness and two knee pains which were reported in the Tai Chi group during the first 4 weeks of intervention. The symptoms of all participants affected disappeared after the correction of the wrong postures by the Tai Chi instructor.

Two adverse events were not related to the Tai Chi intervention. One participant (No. 204) aged 67 years old in the Tai Chi group experienced ankle sprain after one Tai Chi class on his way home. The participant returned to the Tai Chi class after one week of rest, and completed the study. Another participant (No. 229) with CHD aged 76 years old whose medical investigation revealed a tiny fracture of a rib bone at week 12. The reason of the fracture is unclear, and the participant reported that it might be related to his regular self-massage with a tapping tool at home.

Three serious adverse events were reported, but none of these were related to the Tai Chi intervention. These included two cases of cancer in the waitlist control group, one case of bradycardia (HR <40 BPM) in the Tai Chi group, and one case of a tiny fracture of a rib bone in the Tai Chi group. A participant in the Tai Chi group (No. 239), aged 77 years, experienced bradycardia after one of his regular swims in winter. This led to a pace-maker installation surgery at week 14, and a second surgery at week 20 to control the infection caused by the first surgery. The reason for the bradycardia remains unclear and the participant reported that it might be associated with his winter swimming. These three participants withdrew from the study as a result of adverse events.

5.1.7 Compliance

5.1.7.1 Class Attendance

Participants in the Tai Chi group were provided with 36 group classes with 72 hours in total over 24 weeks, consisting of 24 classes in the first 12 weeks (2 hours per session, two times per week) and 12 classes in the rest of the program (2 hours per session, one time per week).

The attendance rate of the 53 participants in the Tai Chi group who completed the study was 82.5% (1575/1908 sessions, n=53) over the 24-week Tai Chi program, with 83.5% (1113/1332 sessions, n=37) in Beijing recruitment centre and 80.2% (462/576 sessions, n=16) in Sydney recruitment centre. Missed sessions were typically attributable to time conflict, such as doctor's visit and family responsibility, based on the records of class attendance and patient diaries. Figure 5.7 shows the overall attendance rate.

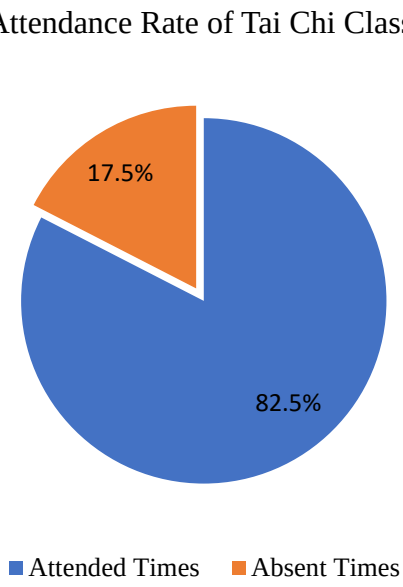


Figure 5.7 Class attendance rate of participants in the Tai Chi group who completed the 24-week Tai Chi program. A total of 53 participants completed the 24-week Tai Chi program (36 sessions with 72 hours in total).

5.1.7.2 Home Practice

Participants in the Tai Chi group were required to practice at least three other days outside of Tai Chi group classes at home each week. According to the weekly diaries of by the 53 participants in the Tai Chi group who completed the study, the average frequency of home practice was 3.98 days per week, varying from 0 to 7 days per week. Six (6/53, 11.3%) participants in Tai Chi group who completed the study reported that they did not practice at home at all or practiced less than three days per week over 24 weeks.

The Tai Chi program in our study consisted of warm-up exercises including walking lunges, 13-form thumping techniques, meditation, standing posture, and the 13-form modified Chen-style Tai Chi. Of the 53 participants in Tai Chi group who completed the 24-week program, 90.6% (48/53) of participants in Tai Chi group practiced the 13-form modified Chen-style Tai Chi in their home practice, while walking lunges, 13-form tapping exercise, meditation, and standing postures were practiced by 66.7% (36/53), 60.4% (32/53), 62.3% (33/53) and 41.5% (22/53) participants, respectively. The home practice rate for each component of the Tai Chi program of the 53 participants in Tai Chi group who completed the program over 24 weeks is presented in Figure 5.8.

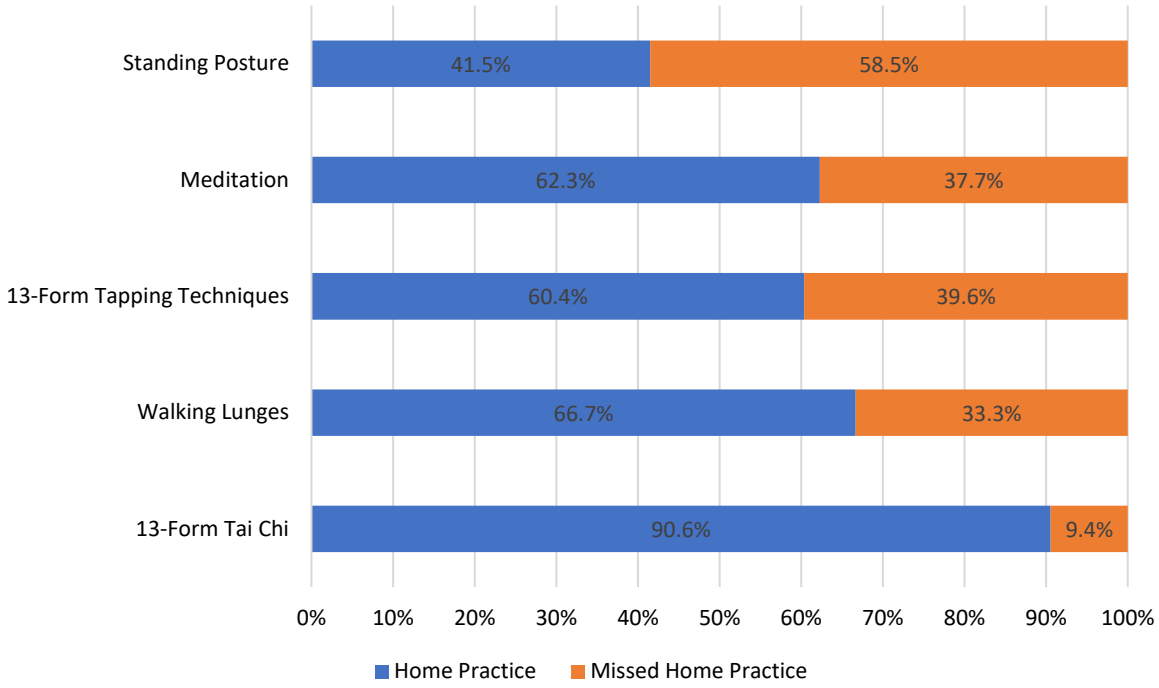


Figure 5.8 Home practice rate of each component of the Tai Chi program over 24 weeks. Of 53 participants in the Tai Chi group completed the 24-week randomised controlled trial, 90.6% practiced the 13-form modified Chen-style Tai Chi, 66.7% walking lunges, 60.4% 13-form thumping techniques, 62.3% meditation, and 41.5% standing posture in home practice.

5.2 Discussion

In this section, the main results are summarised, followed by an interpretation of these findings and comparisons with similar studies. The trial limitations and generalisability of the trial findings are presented in Chapter 7 General Discussion and Conclusion.

In this study, both English and Chinese versions of questionnaires were used for measuring stress, anxiety, depression and quality of life. We considered the cross-cultural equivalence was ensured because the high internal consistence, reliability and validity of both English and Chinese versions of questionnaires in the target population were both reported. In addition, the participants were all Chinese or Chinese-Australian and the majority of them completed the Chinese version of questionnaires.

5.2.1 Primary outcome measure: PSS-10

In the present study, we detected a statistically significant difference between the Tai Chi and waitlist groups in PSS-10 using a linear mixed model. Currently, there is no consensus on the clinically important change of PSS-10. Eskildsen et al. (2015) suggested that the estimates of

minimal clinically important change of the Danish version of PSS-10 were 11 points among participants with work-related stress complaints (Eskildsen et al., 2015). In the current study, the mean difference of PSS-10 at week 24 was only 1.27 points. Similarly, the Cohen's d at week 24 was 0.21, which was considered as a 'small' effect size (Cohen, 1988). All these appear to suggest that the change of PSS-10 in the present study is of little clinical significance.

The PSS-10 score ranges from 0 to 40, with higher scores indicating more perceived stress. Since the PSS-10 is not a diagnostic tool, cut-off ranges for high and low levels of stress do not apply. Previous literature suggests that an individual who experiences a marked level of stress is identified as PSS-10 score $\geq$20 (D. Y. Leung et al., 2010). However, in the current study, the baseline PSS-10 scores in the Tai Chi and waitlist groups were 12.73±6.08 scores and 11.55±6.18 scores, respectively. Accordingly, this lower PSS-10 score at baseline suggested that our participants did not experience a marked level of stress at baseline, which may limit the space for improvement in the current study.

The findings are similar to results of a previous RCT (Robins et al., 2016). Robins et al. (2016) found "marginally significant" (P=0.061) differences in decreasing the perceived stress as measured by PSS-10 at two months following the 8-week Tai Chi intervention between the Tai Chi and waitlist control groups, favouring the Tai Chi group. The baseline level of PSS-10 score in the latter study was also lower than 20.

Of interest in our study, improvements in PSS-10 were more marked during the first 12 weeks compared to the subsequent 12 weeks where classes were reduced to once per week. The possible explanation is 'dose-response relationship' of Tai Chi and its effectiveness. The reduced intensity of Tai Chi intervention during the second 12 weeks may have reduced benefits for stress release. In contrast, Wang et al. (2018) found no significant increase in benefits for groups who received Tai Chi twice weekly compared with once weekly at 24 weeks in their recent RCT involving 226 adults with fibromyalgia (C. Wang et al., 2018). This study was designed to test whether the effectiveness of Tai Chi depends on its dosage or duration (C. Wang et al., 2018). Participants were randomly assigned to either supervised aerobic exercise (24 weeks, twice weekly) or one of four classic Yang style supervised Tai Chi interventions (12 or 24 weeks, once or twice weekly). Salmoirago-Blotcher et al. (2017) also reported that increasing class frequency (twice versus three sessions/week) did not affect aerobic fitness after 12 weeks of Tai Chi training in people with CHD (Salmoirago-Blotcher et al., 2017). More

rigorously designed research is needed to explore the 'dose-response relationship' of Tai Chi interventions.

In addition, the effects of Tai Chi may have plateaued by the end of the first 12 weeks. 'Plateau effect' is a force of nature that lessens the effectiveness of once effective measures over time. In the current study, we found that there were statistically significant differences between the Tai Chi and waitlist groups at week 12, but no further between-group differences were detected at week 24. In contrast to our findings, Wang et al. (2018) found that participants with fibromyalgia who practised Tai Chi for a longer duration (24 weeks) experienced better improvements in the primary outcome, as measured with the revised fibromyalgia impact questionnaire (FIQR) scores, than those who practised for a shorter duration (12 weeks) (C. Wang et al., 2018). More rigorously designed research is needed to explore the plateau effects of Tai Chi and its effectiveness.

The underlying mechanism on how Tai Chi works for stress remains largely unclear. Previous literature suggested that Tai Chi-induced stress reduction may be associated with a lower level of cortisol (Lai, Liu, Lin, Tsai, & Chien, 2017). In addition, it has been reported that Tai Chi could enhance parasympathetic/vagal modulation (Lu & Kuo, 2014; Vaananen et al., 2002; Yeh, Wayne, & Phillips, 2008) and decrease the sympathetic modulation (Kalsaria et al., 2012; Lu & Kuo, 2003, 2006; Motivala et al., 2006), although this does not receive support from the results of heart rate variability in the current study (see Sections 5.1.5.2).

5.2.2 Secondary outcome measures

5.2.2.1 Psychological status

Anxiety

In the current study, the Tai Chi and waitlist control groups were balanced in anxiety levels as measured by SAS scores at baseline. Participants in the Tai Chi group demonstrated a greater decrease in anxiety as measured by SAS at 12 and 24 weeks.

Our findings are consistent with that of previous studies. One study conducted in Taiwan involving 76 people with high-normal or stage I hypertension demonstrated that the Tai Chi group had significantly lower levels of state and trait anxiety at week 12 as measured with the State and Trait Anxiety Inventory (STAI), compared with the baseline (Tsai et al., 2003). However, Tsai et al. (2003) did not report the comparison between Tai Chi group and the

sedentary life control group after intervention. More recently, a 3-arm RCT involving 50 healthy but stressed participant was conducted to determine the effects of 12-weeks of Tai Chi practice on anxiety as measured by STAI (S. Zheng et al., 2018). Similarly, this study demonstrated significant improvements in state and trait anxiety from baseline for both Tai Chi and exercise groups ($P<0.01$) at week 6 and 12, while the waitlist group had no significant changes; the Tai Chi group was superior to the waitlist group in improving state and trait anxiety ($P<0.01$).

Two other studies conducted in mainland China also used SAS to measure anxiety outcome (H. Song, 2013; F. Sun & Sun, 2014). Song (2013) investigated the effects of a 12-week Tai Chi program on anxiety, depression, QoL, and glucose metabolism outcomes in 40 Chinese participants with impaired glucose metabolism (H. Song, 2013). Song (2013) found that Tai Chi program plus health education group was superior to the health education alone group in decreasing SAS scores at week 12 (H. Song, 2013). The mean SAS scores of the intervention and the control groups decreased 14.58 and 8.9 scores from baseline to week 12, respectively (H. Song, 2013). Similarly, Sun and Sun (2014) involving 90 participants with primary hypertension found that compared with the health education group, the Tai Chi group had better SAS reduction scores at week 8 ($P<0.01$) (F. Sun & Sun, 2014). Sun and Sun (2014) found the mean SAS scores of the Tai Chi group and the health education group decreased 4.79 and 0.67 from baseline to week 8, respectively (F. Sun & Sun, 2014).

The lack of replication of these findings in the current study could be due to two reasons. First, the characteristics of participants were different. Song (2013) investigated a clinical population with impaired glucose metabolism and a higher baseline SAS scores (55.09 ± 11.25 and 54.13 ± 11.69 in the intervention and the control group) (H. Song, 2013), while Sun and Sun (2014) investigated participants with primary hypertension and a lower baseline SAS scores (33.58 ± 6.37 and 35.67 ± 5.43, in Tai Chi and health education groups, respectively), compared with participants with CHD and/or hypertension in our study (45.25 ± 8.83 and 45.20 ± 9.61, in the Tai Chi and waitlist groups, respectively) (F. Sun & Sun, 2014). Second, the samples of the previous studies were smaller than that of our study, in which the estimate of the magnitude of the 'positive' effect could be exaggerated (Button et al., 2013).

Depression

In the present study, participants in the Tai Chi group experienced a slightly higher depression level than that of the waitlist control group at baseline, but this was not statistically significant. At week 12, the Tai Chi group showed a marked decrease in depression as measured by the BDI-II score while the waitlist group maintained at the original level. At week 24, there was a slight increase of BDI-II scores in both groups, but the BDI-II scores of the Tai Chi group continued to be lower. There were significant differences between the two groups at 12 and 24 weeks, in the favour of the Tai Chi group.

The current findings support the finding in Robins et al.'s study (Robins et al., 2016). Robins et al. (2016) used the Center for Epidemiological Studies-Depression (CES-D) (scale from 0-60, with high scores indicating greater depressive symptoms) to measure the effects of Tai Chi on depression in 96 women with increased cardiovascular risks (Robins et al., 2016). Participants who randomly received an 8-week Tai Chi program had a significantly lower level of depression at 16 weeks compared to participants in the waitlist group (P=0.001). As identified earlier, the two studies shared some similarities, including study design (i.e. prospective RCT), comparison (i.e. Tai Chi group versus waitlist control), major statistical analysis method (i.e. a mixed linear model), Tai Chi intervention (i.e. instructor-led group classes plus encouraged home practice) and subject population (i.e. participants with CVD risks).

Our findings are also consistent with results of two other studies (H. Song, 2013; E. Zhang, 2014) conducted in China using the Zung Self-Rating Depression Sale (SDS) (scale from 20-80) to assess depression. These studies found significant between-group differences. However, Sun and Sun (2014) found no significant differences between the Tai Chi and health education groups in reducing depression measured by SDS at week 8 in participants with hypertension (F. Sun & Sun, 2014). The inconsistency could be due to the differences in measurements and time-points for measuring depression. In addition, this study was underpowered due to the small sample size.

The underlying mechanism of Tai Chi for depression remains unclear. Previous literature suggested that it may be related to the link between inflammation and depression. Inflammation could produce depression in vulnerable individuals by lowering plasma tryptophan and diminishing brain serotonin activity, and low serotonin function may compromise mechanisms

involved in maintaining recovery from depression (Cowen & Browning, 2015). A Korean RCT suggested that alteration of blood serotonin level might be involved in the mechanism behind Tai Chi-induced depression management (Oh & Kim, 2016). Another study also reported Tai Chi could reduce inflammatory markers and CRP in older adults with major depression (Lavretsky et al., 2011).

5.2.2.2 Cardiovascular function

Blood Lipid Profile

We tested the total cholesterol, triglyceride, HDL-C, LDL-C of all participants at baseline, 12 and 24 weeks. At baseline, the two groups were balanced regarding the mean triglyceride, HDL-C and LDL-C values, but the mean total cholesterol was higher in the Tai Chi group than that of the waitlist group; the difference was statistically significant. At week 12, the Tai Chi group had a slight decrease in the level of total cholesterol, triglyceride and LDL-C, while the waitlist group maintained the same level or had a slight increase in these blood lipid parameters. The level of HDL-C showed a slight increase in the Tai Chi group, while it remained at a similar level in the waitlist group. No significant between-group differences in the blood lipid profile were found at week 24.

Previous literature has assessed the potential benefits of Tai Chi for blood lipid profile in people with CHD, diabetes, overweight and obesity. Our findings are consistent with the results published in majority of previous studies. One RCT involving 53 patients with type 2 diabetes found that although there was a significant within-group difference for total cholesterol in the Tai Chi group, there was no significant between-group difference at week 24 (Lam et al., 2008). Similarly, a 3-arm RCT involving 374 middle-aged adults (<40% with overweight or obesity) found the Tai Chi group had no statistical improvement in blood lipid profile, compared with no treatment (Hui, Xie, Woo, & Kwok, 2015).

In contrast, one previous study involving 60 patients with CHD found that Tai Chi combined with standard care was superior to standard care alone in improving total cholesterol, triglyceride, LDL-C and HDL-C at 12 weeks (F. Chen & Lv, 2013). Considering these inconsistent findings, more studies are needed to confirm the effects of Tai Chi on blood lipid profiles.

Fasting Blood Glucose (FBG)

In the present study, participants in the Tai Chi and waitlist groups at baseline had similar FBG levels and were in the normal range. At week 12, the level of fasting blood glucose in both groups increased slightly but still in the normal range. At week 24, there was no significant between-group difference in fasting blood glucose. The lower FBG at baseline may have limited the space for improvement in the study.

Similar findings have been reported in previous literature. Robins et al. (2016) also found no significant difference in changing FBG between the Tai Chi and waitlist groups at 8 and 16 weeks in their RCT involving 96 women with cardiovascular risks aged 35 to 50 years (Robins et al., 2016). Similarly, the FBG of Tai Chi and waitlist groups at baseline was also in the normal range. Another RCT involving 300 Chinese adults aged 45-80 years with diagnosed hypertension also showed no significant difference in lowering FBG between the Tai Chi and the control groups (participants who attended non-exercise-related activities such as reading and learning computer software applications) at 12 months (J. Sun & Buys, 2015). The FBG of both groups at baseline was also in the normal range.

In contrast, potential benefits of Tai Chi on FBG have been reported in a non-randomised controlled trials with a small sample (n=39) of people with diagnosed type 2 diabetes (Ahn & Song, 2012). This study found that a standardized 12-week Tai Chi significantly improved FBG and HbA1c. Considering the inconsistent findings in literature, more rigorously-designed research is needed to explore the benefits of Tai Chi on FBG.

C-Reactive Protein (CRP)

In the present study, there was no significant difference in CRP levels between the Tai Chi and waitlist groups at baseline assessments. At 24 weeks, there was no significant difference in CRP levels between the two groups. CRP data in this present study were categorized into less than 4.0 and equal to or more than 4.0 mg/L, because the pathology results from Beijing and Sydney Pathology Laboratories were reported based on different value ranges. According to the Australian Bureau of Statistics, the test reference range for normal CRP levels is <5.0 mg/L, while CRP levels >10.0 mg/L are indicative of an acute infection or inflammation (Australian Bureau of Statistics, 2014). However, the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) recommend: low risk, <1.0 mg/L; average risk,

1.0-3.0 mg/L; and high risk, >3.0 mg/L; if the CRP level is >10 mg/L, then the test should be repeated and the patient examined for sources of infection or inflammation (G. L. Myers et al., 2004). Accordingly, CRP levels in the present study were categorized into binary data based on the original laboratory reports of CRP levels <4.0 mg/L or ≥4.0 mg/L.

Our findings are consistent with the results of Robins et al.'s RCT with a similar population (Robins et al., 2016). This study involving 96 women with cardiovascular risks demonstrated no statistical difference in hsCRP (high-sensitivity assay) level between the Tai Chi group and the waitlist group at weeks 8 and 16.

Blood Pressure

In the current study, the mean systolic and diastolic blood pressures in the Tai Chi group were slightly higher than that of the waitlist control group at baseline. However, the differences did not reach statistical significance. At week 12, the average systolic and diastolic blood pressures in both groups maintained at a similar level. At week 24, there were significant differences in diastolic blood pressure but not in systolic blood pressure between the two groups. The average systolic and diastolic blood pressure of both groups were in the normal range at baseline, which may have limited the space for improvement in the study.

Similar to our findings, Nery et al. (2015) found that a 12-week Tai Chi program did not change systolic and diastolic blood pressure (Nery et al., 2015). One recent 3-arm trial involving 50 healthy but stressed participants also found no significant between-group differences in blood pressure (S. Zheng et al., 2018). Similarly, this cohort had normal blood pressure so a significant finding was unlikely.

Potential benefits of Tai Chi in the management of blood pressure have been previously reported. One recent RCT involving 158 older Chinese adults with essential hypertension demonstrated a significant decline in blood pressure and body mass index were found in the Tai Chi group when compared with the usual care group (C. Ma, Zhou, Tang, & Huang, 2018). In comparison with our cohort, although taking antihypertensive agents, the baseline SBP and DBP of participants in this study was higher than that of our participants and in Grade I (mild) hypertension (systolic: 140-159mmHg and/or diastolic: 90-99 mmHg). This lower blood pressure at baseline may impact on the space for improvement in the current study.

Another recent RCT involving a sample of 300 Chinese adults aged ≥45 years and diagnosed with hypertension also found significant between-group differences in lowering SBP and DBP using the general linear model analysis (J. Sun & Buys, 2015). Compared to baseline, the Tai Chi group had a 10-point difference for SBP (from 130.71±16.65 to 120.28±14.63 mmHg) and 7 points for DBP (82.21+7.94 mmHg to 75.31±14.53 mmHg) at 12 months. In this study the Tai Chi group attended group training for a relatively long duration, namely 12 months, 3 hours per week, and 2-hour home practice, while the control group attended non-exercise-related activities such as reading and learning computer software applications for the same period. In contrast, the shorter duration of Tai Chi intervention may be a reason why no change of blood pressure was found in the current study.

The mechanism of Tai Chi for blood pressure remains unclear. Endothelin-1 (ET-1) is a powerful vasoconstrictor peptide and regulator of blood flow that plays an important role in blood pressure (BP) elevation (Schiffrin, 2001). Previous studies reported that the change in ET-1 was significant after 3-month of Tai Chi training in the Tai Chi group (Lu & Kuo, 2013; Mao & Sha, 2006). Another study demonstrated that Tai Chi practice significantly increased the plasma nitric oxide (NO), carbon monoxide (CO) and hydrogen sulphide (H_2S) levels (X. Pan et al., 2015) and lowered blood pressure. Correlations were observed in this study between he changes of blood pressure and changes in these gaseous signalling molecules. Tai Chi could also decrease sympathetic activity (Motivala et al., 2006) and in particular stress-induces sympathetic nervous activity (Flaa et al., 2008), indicating another possible mechanism of Tai Chi for reducing blood pressure.

Heart Rate

In the current study, participants in both groups had similar baseline heart rate, which was in normal range. At 24 weeks, the mean beats of heart rate in the Tai Chi and waitlist groups experienced a slight decrease. There was no significant difference at week 24 in heart rate between the Tai Chi and waitlist control group.

Our findings are consistent with the results of some previous studies. One recent quasi-experimental study involving a sample of 110 older sedentary adults with a clinical diagnosis of metabolic syndrome showed no significant changes in resting heart rate in the Tai Chi group compared with the non-exercise control group at 24 weeks (Mendoza-Núñez, Arista-Ugalde, Rosado-Pérez, Ruiz-Ramos, & Santiago-Osorio, 2018). Another study involving 60 patients

aged 73.8±6 years with chronic heart failure demonstrated that resting heart rate decreased by 11.2% in the Tai Chi combined with endurance training group and by 6.8% in the endurance training alone group, with no significant between-group difference at 12 weeks (Caminiti et al., 2011). One 25-week randomised trial involving 32 older adults (Motivala et al., 2006) and another 12-week quasi-experimental trial involving 39 Chinese adults aged >45 years with cardiovascular risks (Taylor-Piliae, Haskell, & Sivarajan Froelicher, 2006) demonstrated similar results. Additionally, one systematic review and meta-analysis found the pooled results of six studies (including one randomised controlled, one non-randomised controlled trial, and four case series) with 986 healthy participants showed a significant decline in resting heart rate (SMD=-0.72, 95% CI -1.27, -0.18, P=0.01, I^2=89%) (G. Zheng, Li, et al., 2015). It is noteworthy that the population in this systematic review was healthy adults, the heterogeneity among the pooled studies was relatively high, and the methodological quality of the included studies was limited. Hence, more future research is needed to confirm the effects of Tai Chi for resting heart rate.

The potential reason why no significant changes were found in the current study may be related to the lower baseline level. In Wolf et al.'s study, the baseline resting heart rate was 74 (SE: 1.2) and 73 (SE: 1.2) in the Tai Chi and control groups, respectively (Wolf et al., 2006). In contrast, the average resting heart rate at baseline in the present study was around or less than 70. This may impact the space for improvement in this current study.

Heart Rate Variability

In the present study, the HRV parameters were similar at baseline between the Tai Chi and waitlist groups. At 12 and 24 weeks, no significant differences in all HRV parameters were found between the Tai Chi and waitlist control groups.

Similar results were observed in three previous longitudinal studies on Tai Chi. No statistically significant differences were found in the resting HRV parameters in patients with chronic heart failure (Yeh, Wayne, et al., 2008), coronary artery disease (Chang et al., 2008), or CHD (Sato, Makita, Uchida, Ishihara, & Masuda, 2010). However, these three studies found the positive acute effects on HRV immediately after practice (Chang et al., 2008), possible enhancements in parasympathetic modulation (Yeh, Wayne, et al., 2008), and a significant increase in baroreflex sensitivity which is an alternative marker of autonomic activity (Sato et al., 2010).

Deep breathing has been reported to increase the parasympathetic modulation and enhance the vagal modulation (Modesti, Ferrari, Bazzini, & Boddi, 2015). It is well known that deep breathing is a component of Tai Chi practice. This may be an underlying mechanism of the beneficial effects of Tai Chi on HRV.

5.2.2.3 Quality of life

At baseline, the two groups in the present study were balanced in quality of life as measured with SF-36, except in two domains (i.e. physical function and role limitation due to physical problems). The mean scores of the physical function and role limitation due to physical problems domains in the Tai Chi group were significantly lower than that of the waitlist control group. At week 12, the mean scores of all domains of SF-36 in the Tai Chi group significantly increased, while that of the waitlist group slightly decreased except general health, vitality, social functioning and mental health domains. At week 24, significant between-group differences were detected in the physical function, role limitation due to physical problems, bodily pain and vitality domains of SF-36, favouring the Tai Chi group. The increase of mean scores was more dramatic at week 12 in which there were two Tai Chi classes per week as opposed to only one Tai Chi class per week for the second 12 weeks.

Our findings support previous literature on Tai Chi for quality of life. The meta-analyses of four RCTs (Han et al., 2010; Meng, 2014; X. Pan, 2016; F. Wu et al., 2010) involving 359 participants with CVD and/or cardiovascular risks demonstrated that compared with usual care alone, a Tai Chi program in combination with usual care significantly improved quality of life in all domains of the SF-36, including physical functioning (mean difference [MD]: 5.47, 95% CI: 0.66, 10.28, I^2=84%), role limitation due to physical health (MD: 11.82, 95% CI: 8.26, 15.38, I^2=32%), role limitation due to emotional health (MD: 8.27, 95% CI: 5.56, 10.98, I^2=0%), energy/vitality (MD: 7.03, 95% CI: 1.92, 12.14, I^2=81%), mental health (MD: 7.86, 95% CI: 4.29, 11.44, I^2=48%), social functioning (MD: 9.81, 95% CI: 5.19, 14.42, I^2=68%), bodily pain (MD: 6.34, 95% CI: 2.45, 10.23, I^2=53%), and general health (MD: 10.04, 95% CI: 7.15, 12.93, I^2=27%) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (scale from 0 to 105) (MD: -11.10, 95%CI: -15.52, -6.68, I^2=73%).

Similar findings were also observed in a healthy but stressed population. In this 3-arm (Tai Chi, exercise and waitlist groups) RCT of 50 healthy but stressed adults (mean age 33.9 years), the

Tai Chi group had significant improvements in both the mental health domain (P<0.01) and the vitality domain (P<0.01) of SF-36 at weeks 6 and 12; when compared with the waitlist groups, Tai Chi was superior in improving mental health domain (P<0.05) (S. Zheng et al., 2018).

These positive findings are supported by our meta-analyses of five studies (Sang et al., 2015; Yao et al., 2010; Yeh et al., 2004; Yeh et al., 2013; S. Zhang & Chen, 2011), which showed a significant difference in the MLHFQ total scores in favour of Tai Chi in combination with usual care group (MD: -11.10, 95%CI: -15.52, -6.68, I^2=73%). Similarly, in the population with heart failure, one recent systematic review and meta-analysis involving seven trials found that the Tai Chi group had significantly lower scores of the MLHFQ than that of the control group, indicating the Tai Chi group had a better quality of life (Ren et al., 2017). Although the QoL was measured by a different instrument; it might enhance the strength of evidence that Tai Chi is beneficial for improving QoL.

The mechanism as to how Tai Chi impacts QoL has not yet been well understood. According to WHO, QoL is defined as individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (World Health Organization, 2018h). QoL is affected by complex factors including physical health, psychological state, independence level, social relationships, personal beliefs and their relationship to salient features of the environment (World Health Organization, 2018h). In this current study, the physical function, role limitation due to physical problems, bodily pain and vitality domains of SF-36 improved significantly in the Tai Chi group when compared with the control group. In addition, the perceived stress decreased significantly in the Tai Chi group. The decreased stress may be associated with the increased QoL (Achat et al., 1998; Colovic, Lecic-Tosevski, Mandic, & Toskovic, 2009). These findings indicate that improvements in physical function and vitality (energy), decreases in bodily pain and stress, and increases in activity levels and social support may play a role in Tai Chi-related improvements in quality of life.

5.2.2.4 Physical fitness

In the present study, participants in both groups had similar baseline levels of physical fitness. The mean distance of the 6-minute walk in the Tai Chi group was lower than that of the waitlist group. At week 12, the Tai Chi group experienced significant improvements in the 6MWT

compared with that of the waitlist group at week 12. At week 24, the Tai Chi group had maintained a similarly high level of physical fitness.

In the present study, the mean 6MWT distance of participants in the Tai Chi group increased 63.64 meters from baseline to week 12 and increased 58.04 meters from baseline to week 24; while the distance of the waitlist group stayed at a similar level over 24 weeks. The Cohen's d at week 24 was 0.38, which indicating a 'small' effect size. However, a change of 14.0 to 30.5 meters in the 6MWT is suggested as being a clinically important difference across multiple patient groups (Bohannon & Crouch, 2017). Accordingly, our findings in 6MWT are clinically meaningful.

This result is consistent with those of previous studies. Caminiti et al. (2011) found that Tai Chi plus endurance training was superior to endurance training alone in improving the 6MWT at 12 weeks in people with chronic heart failure (Caminiti et al., 2011). One recent meta-analysis involving seven trials demonstrated that Tai Chi is associated with a significantly improved 6MWT in people with heart failure (Ren et al., 2017). These findings indicate that Tai Chi may be an alternative option for improving physical fitness.

Three other RCTs of Tai Chi for physical fitness in people with chronic heart failure, conducted by the same research group, reported contradictory results (Yeh et al., 2011; Yeh et al., 2004; Yeh et al., 2013). Two RCTs were favourable, but the third failed to detect a significant difference between groups. One trial involving 30 patients with chronic heart failure demonstrated that patients in Tai Chi in combination with usual care group showed a significant increase in the distance walked in 6 minutes (P=0.001) at 12 weeks, compared with the usual care, including pharmacologic therapy and dietary and exercise counselling (Yeh et al., 2004). Similarly, one trial involving 16 participants with heart failure with preserved ejection fraction demonstrated that the 6-minute walk distance in the Tai Chi group significantly increased more at 12 weeks (P=0.02), compared with aerobic exercise (Yeh et al., 2013). However, in the third study with 100 participants with CHF, no significant between-group difference in 6MWT distance was detected at 12 weeks, when compared Tai Chi with a time-matched education group (Yeh et al., 2011).

The underlying mechanism on Tai Chi for physical fitness remains unclear. A meta-analysis demonstrated that Tai Chi could significantly impact aerobic capacity expressed as peak oxygen uptake (VO_2peak) (Taylor-Piliae, 2008; Taylor-Piliae & Froelicher, 2004). Additionally, one

recent three-arm RCT involving 374 middle-aged participants found that Tai Chi practice consumed a smaller amount of energy metabolism but produced similar health benefits as self-paced brisk walking, by having higher effects on resting energy expenditure (REE) and improving maximal oxygen intake (VO_2max) and REE-kilocalorie expenditure (Hui et al., 2016).

Another mechanism may be related to the impact on musculoskeletal system. A 16-week Tai Chi practice resulted in a 19.9% increase in muscle strength of the knee flexors in old people (J. X. Li et al., 2009), indicating the beneficial effects of Tai Chi in improving postural stability and proprioception of knee and ankle (J. X. Li et al., 2008). Similar findings have been reported in a 48-week, single-blind RCT, which demonstrated that Tai Chi significantly improved the physical dimension and ambulation categories (Greenspan et al., 2007). Another study found that Tai Chi was superior to resistance training in increasing serum parathyroid hormone and reducing the urinary calcium level, indicating that Tai Chi is beneficial for bone metabolism (C. L. Shen et al., 2007).

5.2.3 Safety Outcomes

In the present study, no severe adverse events associated with Tai Chi intervention were reported, indicating that Tai Chi appears to be safe in a population with CHD and/or hypertension.

One important and effective strategy used to promote the safe practice of Tai Chi among participants in our study was close supervision to avoid incorrect practices in each class throughout the study period. In the Tai Chi group, three participants reported minor muscle soreness and two reported knee pains within the first four weeks; after correcting the incorrect postures/practice by the instructions and under the close supervisions of the Tai Chi instructor, these instances of pain disappeared.

The findings are consistent with that of previous studies. Wayne et al. (2014) systematically assessed the frequency and quality of adverse events reported in RCTs on Tai Chi, and only 33% of the 153 included RCTs reported adverse events information (Wayne et al., 2014). Tai Chi was unlikely to result in serious adverse events, but might be associated with minor musculoskeletal aches and pains (Wayne et al., 2014). Similarly, our previous bibliometric review involving 507 clinical studies on Tai Chi identified that only 20.7% of the studies

reported safety information and of those, 65 (12.8%) studies identified no adverse events during the study period, 40 (7.9%) studies reported adverse events not related to the Tai Chi intervention, and no serious adverse events were reported (G. Yang et al., 2015).

5.2.4 Compliance

5.2.4.1 Class Attendance

In our study, the overall class attendance rate of the Tai Chi group was 82.5% and the attendance was good in both Australia and China. This high attendance rate demonstrates the feasibility of the 24-week Tai Chi program for patients with CHD and/or hypertension.

A high adherence to Tai Chi classes was also reported in previous studies conducted outside of China. Taylor-Piliae et al. (2006) found a high adherence (87%$\pm$0.18) to a 12-week community-based Tai Chi class among ethnic Chinese adults aged >45 years old with cardiovascular risk factors, living in the San Francisco Bay Area of the USA (Taylor-Piliae, Haskell, & Sivarajan Froelicher, 2006). Yeh et al. (2011; 2013) reported a good adherence among patients with chronic heart failure in their studies conducted in the USA, with a mean attendance of 75% and 66.7% in the 12-week Tai Chi and education groups, respectively (Yeh et al., 2011), and with a mean attendance of 89% and 88% in the Tai Chi and aerobic exercise groups, respectively (Yeh et al., 2013). Our previous comprehensive review involving 507 clinical studies on Tai Chi intervention identified that Tai Chi clinical studies have been conducted in 20 countries worldwide and have involved a variety of population, indicating the potential wide acceptance of Tai Chi (G. Yang et al., 2015).

The high adherence rate may be an advantage of Tai Chi when compared with CR programs. As mentioned before, utilization of CR by people with CHD historically has been poor (Grace et al., 2016; Ruano-Ravina et al., 2016). In addition, effective implementation of CR after acute coronary syndrome, coronary revascularisation, and heart failure has remained suboptimal, with overall participation rates <50% over recent decades despite international recommendations (Dalal et al., 2015). This indicates a need for other effective therapeutic options. Tai Chi may be better accepted by this cohort. Even for people with CHD declining CR, the retention rate of Tai Chi program was 90.0% in a 9-month study (Salmoirago-Blotcher et al., 2017).

Influential factors to trial participation and adherence to the Tai Chi program from the perspectives of our participants were explored by a qualitative sub-study and are reported in detail in Chapter 5. We assumed that one possible reason for a relatively high compliance to

the Tai Chi program in our study may be related to availability. The majority of participants in our study were older adults, with an average age of 65.08±6.38 years in the Tai Chi group and 63.55±9.01 years in the waitlist control group. In addition, retirees were predominant in both groups (i.e. 93.3% and 80.0%, respectively). Secondly, it was convenient for participants to come to the group-based Tai Chi classes in the present study. The Tai Chi classes were held in a community hospital in Beijing and in a charity foundation located in a Chinese community in Sydney. As such, most participants had a low burden of travel time and expense.

Another possible reason for the relatively high attendance may be associated with the characteristics of Tai Chi interventions. Wang et al. (2018) found that participants with fibromyalgia assigned to the Tai Chi training maintained higher and more consistent attendance than those assigned to supervised aerobic exercise which is used as a current standard treatment (C. Wang et al., 2018). Wang et al. (2018) thus suggested that "Tai Chi, which consists of the gentler, low impact meditative sequence of movements with minimal side effects, may be better embraced by patients with fibromyalgia in the long term" (C. Wang et al., 2018). Similarly, people with CHD and/or hypertension often have limited exercise capacity and few exercise options, but proper exercise is important for the management of CVD and cardiovascular risks in this population. In addition, it is reported that Tai Chi can improve exercise self-efficacy in people with heart failure (Yeh, Chan, Wayne, & Conboy, 2016). Hence, Tai Chi, a low-to-moderate intensity exercise program, with multiple therapeutic components, may a safe and effective choice to this cohort (Wayne et al., 2013).

5.2.4.2 Home Practice

In the present study, we assessed the compliance of home practice using the weekly diaries of participants. Participants in the Tai Chi group were required to practice at least three other days when there were no classes. The overall compliance of home practice was high with the average frequency (i.e. 3.98 days per week). However, 11.3% participants in the Tai Chi group did not practice at home at all during the study. In addition, the rates of walking, 13-form thumping techniques, meditation, and standing postures at home practice were relatively low (66.7%, 60.4%, 62.3%, and 41.5%, respectively), which may potentially affect the outcomes of this study.

Unfortunately, in most studies where participants were encouraged or required to do home practice (Barrow et al., 2007; Han et al., 2010; X. Liu et al., 2013; X. Pan, 2016; Robins et al., 2016; J. Sun & Buys, 2015; Yeh et al., 2011; Yeh et al., 2004; Yeh et al., 2013), the frequency

and length of home practice was not monitored or reported. Corresponding strategies to support and monitor the home practice are needed, since home practice is important to promote independent practice for long-term benefits and to achieve sufficient “dosage/intensity”.

Several strategies have been proposed to enhance the adherence to home practice. Telecommunication-based exercise and community centre-based exercise groups have demonstrated higher rates of compliance, fall reduction and balance, and health improvements among community-dwelling elders, compared with home video-based exercise (G. Wu, Keyes, Callas, Ren, & Bookchin, 2010). The differences might be attributed to the lack of real-time supervision and social interaction in the home-based exercise group (G. Wu et al., 2010). In the present study, the communication/interaction through WeChat (a multi-purpose social media and mobile application) was regarded as a facilitator to home practice by most participants, as presented in Chapter 6. Future studies are recommended to consider some supporting strategies for home-based practice.

5.2.5 Implication for Clinical Practice

Tai Chi appears effective in reducing stress as measured by PSS-10 and improving physical fitness as measured by 6MWT, compared with waitlist control. As discussed in previous section, the findings in 6MWT are clinically meaningful, however, the change of PSS-10 in the present study is of little clinical significance.

Tai Chi appears safe for people with CHD and hypertension to practice in a group class and at home. No adverse events related to Tai Chi practice were observed during the study. Close supervision and the specially designed Tai Chi program are helpful strategies for safety of participants in the current study. Previous studies involving participants with CVD and/or cardiovascular risk factors reported that a physician (Yeh et al., 2004), a trained cardiac rehabilitation nurse (Barrow et al., 2007) or a healthcare provider (Sang et al., 2015) were also in attendance in addition to the Tai Chi instructors to monitor the safety during the class sessions. Several studies monitored the heart rate, blood pressure or ECG of participants to control exercise intensity (Han et al., 2010; X. Pan, 2016; Tsai et al., 2003; P. Wang et al., 2009; X. Wang et al., 2013; F. Wu et al., 2010; Yao et al., 2010; E. Zhang, 2014; S. Zhang & Chen, 2011). These strategies could be considered in a clinical setting if necessary.

Tai Chi practice seems enjoyable and well accepted by people with CHD and/or hypertension. The high adherence and retention rate in the current study indicates the acceptance of Tai Chi by this population. In contrast, the utilisation of cardiac rehabilitation is relatively low. Participation rates in cardiac rehabilitation programs following ST-elevation myocardial infarction (STEMI) is about 25-35% in western countries (Urbinati & Tonet, 2018). A large prospective audit in Australia and New Zealand found only 46% of eligible patients were documented as referred to CR and even fewer were discharged with sufficient secondary prevention (Redfern et al., 2014). In addition, since Tai Chi requires no dedicated equipment, time or environment, it is an accessible, convenient, long-term choice for people with CVD and/or cardiovascular risk factors and a wider population.

Nevertheless, this study has some limitations and the results should be interpreted with caution. Due to the characteristics of Tai Chi, a double-blind study design was not applied in this study. The lack of blinding might lead to biases in the results, since participants in the Tai Chi may have positive beliefs and high expectations with respect to the benefits of Tai Chi, while the effect size across outcomes of the waitlist control group may deteriorate due to nocebo effect. The placebo and nocebo effects are seen as psychobiological phenomena that arise from the therapeutic context in its entirety, including sham treatments, the treatment expectations and previous experience of patients, and physician-patient verbal and non-verbal communications (Colloca, Sigaudo, & Benedetti, 2008). Although participants in the waitlist control group were offered an equivalent were offered and equivalent Tai Chi program at the termination of the study, the nocebo effects may still exist in this study.

5.2.6 Summary and Conclusions

CVD is the leading cause of morbidity and mortality worldwide. Although the mortality rates of CVDs have fallen in many high-income countries over the last three decades, they remain a considerable disease burden on both individuals and society as a whole. CHD represents the most common type of CVD. Hypertension is the number one contributor of CVD.

Psychological risk factors such as stress, anxiety, and depression have been known to play a significant and independent role in the development and pathogenesis of CVD and its complications. However, current management strategies for people with CVD and its complications often focus on physical outcomes and lack components to manage the psychological factors, such as stress, anxiety and depression.

Tai Chi may be a beneficial option for this population. The main components of Tai Chi include movements, meditation and imagination, and deep/abdominal breathing, so practitioners may gain both physical and psychological benefits from Tai Chi. In recent years, an increasing number of studies have demonstrated potential benefits of Tai Chi interventions on stress, anxiety, depression, quality of life and cardiovascular function.

This international multi-centre RCT involving 120 participants with CHD and/or hypertension conducted in Beijing and Sydney was designed to assess the impacts of a 24-week standardised Tai Chi intervention on psychological stress as measured by PSS-10, anxiety as measured by SAS, depression as measured by BDI-II, cardiovascular function (including blood pressure, heart rate, HRV, blood lipid profile, fasting blood glucose, and CRP), quality of life as measured by SF-36 and physical fitness as measured by 6MWT, compared with the waitlist group. All outcomes were measured at baseline, 12 and 24 weeks. The cross-cultural equivalence was achieved considering both English and Chinese versions of measurements used in this study have high internal consistency, reliability, validity and reliability. In addition, all participants enrolled in this study are Chinese and Chinese-Australian.

Using a mixed linear model, our findings demonstrate that a 24-week standardised Tai Chi intervention resulted in statistically significant improvements in PSS-10 scores and the 6MWT distance in patients with CHD and/or hypertension compared with the waitlist group at week 24. Significant differences were also observed in depression, diastolic blood pressure and quality of life between the Tai Chi and waitlist groups. The compliance to the Tai Chi class and home practice in the Tai Chi group was relatively high. No severe adverse events related to Tai Chi were reported during the study.

Furthermore, compliance to Tai Chi intervention was relatively high. In older adults, especially those with CHD and/or hypertension who often have limited exercise capacity and few exercise options, Tai Chi could provide an accessible and enjoyable option for this population.

In conclusion, a 24-week standardised Tai Chi intervention appears to be beneficial and safe in reducing stress and improving physical fitness in patients with CHD and/or hypertension.

Chapter 6: Perceptions of Participants on Trial Participation and Adherence to Tai Chi Intervention: A Qualitative Study

This chapter presents a qualitative study embedded into our randomised controlled trial (RCT of Tai Chi in people with CHD and/or hypertension). After a brief introduction, this chapter describes the methods of the qualitative study in detail. Section 6.3 presents the results, including characteristics of participants who completed the exit interview, and facilitators and barriers to trial participation and compliance. Section 6.4 discusses the findings within the context of previous literature. The reporting of this study is in accordance to the Standards for Reporting Qualitative Research (SRQR) (Appendix 16).

6.1 Introduction

6.1.1 Problem Formulation

Successful trial recruitment of participants and adherence to interventions is critical to evaluate outcomes and to practice an effective intervention among the target population in real world. Unfortunately, in people with CVD, little is known about the factors influencing trial participation and adherence to Tai Chi intervention. Factors that influence trial participation and adherence to Tai Chi intervention have been explored in previous qualitative studies with diverse populations.

One qualitative study conducted semi-structured focus group interviews with 87 older, low-income, and ethnically diverse individuals to identify barriers and promoters for enrolment to a community-based Tai Chi program before the initiation of a 16-week Tai Chi program (Manson, Tamim, & Baker, 2017). Manson et al (2017) identified six categories, including physical and mental health, time of day, socialization, program pairing, accessibility, and appropriate leadership/teacher (Manson et al., 2017). The participants in focus groups of this

study were not from a Tai Chi clinical trial. Therefore, the findings may have the potential to elucidate the facilitators and challenges this vulnerable population has with respect to enrolling in community-based Tai Chi program, but not for clinical trial participation and adherence.

One recent qualitative study examined the appropriateness and acceptability of 14-week modified Tai Chi and yoga programmes in an Australian residential aged care setting by exploring experiences and perspectives of 16 frail older residents and three staff participants (Saravanakumar, Higgins, Van Der Riet, & Sibbritt, 2018). Saravanakumar et al. (2018) identified nine themes that reflected the uniqueness of the programs including (1) novel, new and exciting; (2) smoothness, rhythm and flow; (3) slow and mindful; (4) gentle but rewarding; (5) moving whole body; (6) perceived benefits; (7) worthwhile; (8) feeling alive; (9) calming and relaxing, which indicated that modified Tai Chi and yoga was acceptable, appropriate, enjoyable and helpful (Saravanakumar et al., 2018). The focus groups were undertaken with residents and staff who participated in the yoga and Tai Chi arms of a three-arm RCT. However, the findings inform whether Tai Chi and yoga programs are appropriate in a residential aged care setting from the experience and perspectives of participants, but not for clinical trial participation and adherence involving people with CVDs.

A four-session "introduction to Tai Chi" for veterans with post-traumatic stress symptoms examined feasibility, qualitative feedback and satisfaction associated (Niles et al., 2016). Niles et al (2016) found that almost 90% (17/19) of those eligible following the telephone screen enrolled in the program, three-quarters (76.4%) of the participants attended at least three of the four Tai Chi sessions, and 93.8% endorsed being very or mostly satisfied with the program (Niles et al., 2016). Themes emerged in their qualitative data analysis indicate favourable impressions of the Tai Chi program, and the perceived benefits are associated with high rates of satisfaction. The focus groups and individual interviews were undertaken with 17 veterans with post-traumatic stress symptoms. The findings of this qualitative study indicate that Tai Chi appears to be feasible and safe for this population and is perceived to be beneficial and is associated with high rates of satisfaction. However, little is known about the influential factors for clinical trial participation and adherence involving people with CVDs.

An investigation of the motivations for practising Tai Chi among 34 survivors of severe acute respiratory syndromes (SARS) in post-SARS Hong Kong (Siu, 2016) revealed that health concerns and social experiences motivated the participants to practice Tai Chi. These included experiencing health deterioration in relation to SARS-associated sequelae, coping with

unpleasant experiences during follow-up biomedical treatments, a desire to regain an active role in recovery and rehabilitation, overcoming SARS-associated stigmas by establishing a new social network and preparing for potential future stigmatization and discrimination. The findings of this qualitative study provide insights of the motivations of SARS survivors for practicing Tai Chi, but more investigation is needed to inform the influential factors for clinical trial participation and adherence involving people with CVDs.

A qualitative study evaluated the feasibility of using a pragmatic network of community-based Tai Chi schools to deliver a 9-month Tai Chi intervention to women with osteopenia and explored the impact of this design feature on facilitators and barriers to trial recruitment and participant adherence during and after the trial (Fischer et al., 2014). Exit interviews were conducted with 43 participants randomised to the Tai Chi group. Fischer et al. (2014) found that direct facilitators included convenience of class locations and times, alternative learning modalities, quality of teaching, community and social support, and perceived health benefits, while barriers consisted primarily of time-related issues (Fischer et al., 2014). This qualitative study suggests factors related to the use of pragmatically delivered interventions for fostering both study participation and posttrial adherence to the Tai Chi program among participants with osteopenia, but little is known about the perception of people with CVDs.

The existing qualitative studies provide valuable insights of some influential factors of enrolling in Tai Chi practice from the perspectives of diverse populations, including older, low-income, and ethnically diverse individuals, frail older residents, veterans with post-traumatic stress symptoms, survivors of severe acute respiratory syndromes (SARS), and women with osteopenia. These factors can not only inform researchers how to improve trial recruitment and implementation of intervention for a target population, but also be useful to enhance the adherence and promote effective treatments. However, less is known about the factors that influence trial participation and adherence to Tai Chi during and after a randomised controlled trial in people with CVD.

6.1.2 Purpose

The integration of qualitative research into clinical research introduced distinct formats of interviews, which greatly expanded the process of data collection and enhanced the depth of information being gathered (DiCicco-Bloom & Crabtree, 2006). Hence, through incorporating a qualitative sub-study in the main randomised controlled trial and using semi-structured interviews we aimed to explore the participants' perceptions of their trial participation and

adherence to Tai Chi. The research question of this qualitative study is "What are the perceptions of the trial participants on the facilitators and barriers to trial participation and adherence to Tai Chi intervention?"

6.2 Methods

6.2.1 Qualitative Approach

We conducted exit interviews to explore participants' perceptions of what influenced their trial participation and adherence to the Tai Chi intervention during and after the randomised controlled trial.

6.2.2 Sampling Strategy

A purposive sampling was applied to maximise the depth and richness of the data. Participants of the Tai Chi group from the main randomised controlled trial who completed the 24-week Tai Chi program in Beijing and Sydney were invited to voluntarily participate in the interviews. No incentives were offered for participation.

6.2.3 Ethical Considerations

Ethical approval for this qualitative sub-study was covered in the approval for the randomised controlled trial (Ethics approval number: H11189; 2015BZHYLL0233). Written informed consent was obtained from each interviewee before the interview. In addition, verbal confirmation to record the interview was obtained at the beginning of each session.

6.2.4 Data Collection

The data source in this qualitative study was semi-structured interviews that are the most widely used interviewing format for qualitative research (DiCicco-Bloom & Crabtree, 2006).

Semi-structured interviews were chosen to allow in-depth interviews that encourage interviewees to answer pre-set open-ended questions or topics to be explored by the interviewer (Mason, 1994). Open-ended questions are used for seven main primarily purposes: understanding reasons for reluctance or refusal; determining the range of options to be used in closed-ended questions; evaluating how well questions work; testing methodological theories and hypothesis; checking for errors; encouraging more truthful answers; and providing an opportunity for feedback (Singer & Couper, 2017). Most commonly, semi-structured interviews

are conducted once with an individual or a group to uncover rich descriptive data on the personal experiences of participants (Corbin & Strauss, 2008).

Establishing rapport with participants is important for the interviewer to collect meaningful data (Merriam, 1998). In qualitative research, rapport is described as 'a feeling of connection, mutual comfort, and conversational ease' (Cappella, 1990), or 'a distance reducing, anxiety-quieting, trust-building mechanism' (Glesne, 1999), which facilitates the data collection process. When a researcher and interviewee have established rapport, the relationship is marked by confidence and trust (Glesne, 1999). Rapport is important because in a qualitative study, 'the researcher is the primary instrument for gathering and analysing data and as such, can respond by maximizing opportunities for collecting and producing meaningful information' (Merriam, 1998). In the present study, the semi-structured interviews took place in the same location as where the participants had Tai Chi classes had been held to create a sense of familiarity and security. The principal investigator (GYY) conducted all the face-to-face individual interviews. Interviewees were familiar with the interviewer, in her role as the researcher of the study and one of the Tai Chi instructors of the 24-week Tai Chi classes. The established relationship and the familiar environment enhanced rapport and trust, creating a relaxed, comfortable atmosphere during interviews.

The semi-structured interview schedule was applied flexibly to gather focused, qualitative data. Each interview began with warm-up or demographic questions to help the participants feel comfortable; then moving on to focused questions using the interview guide. Further prompts were rarely required as most participants freely shared and described their experiences and perspectives on the Tai Chi program. The interviews allowed flexibility for dialogue and toward the end each interviewee was asked - "*Is there anything else you would like to tell me?*". Hence, the interviews varied in length from 10 minutes to 30 minutes, with the average lasting 28 minutes.

Each semi-structured interview was guided by ten open-ended questions in English or Chinese (Mandarin). The questions were developed following two underlying principles: (1) avoid leading the interview or imposing meanings, and (2) create a relaxed, comfortable conversation (Zorn, 2010). Table 6.1 presents the core questions used as the interview guide for the semi-structured exit interview.

Table 6.1 Core questions as the interview guide for the semi-structured exit interview

Question 1:	How did you know about Tai Chi before your participation in this program?
Question 2:	How did you find out about this Tai Chi program?
Question 3:	What was your expectation for participating in this program?
Question 4:	Did participating in the Tai Chi program have any impacts on your daily life?
Question 5:	What physical benefits did you find from participating in the Tai Chi program?
Question 6:	Were there any benefits from participating in the Tai Chi program on coping with stress or any other emotions?
Question 7:	Did participating in the Tai Chi program have any influence on your social life?
Question 8:	Would you recommend the Tai Chi program to other cardiovascular patients?
Question 9:	Would you like to continue the Tai Chi practice after the completion of the study?
Question 10:	What do you think would be the main barriers to hindering your future Tai Chi practice?

To capture the interview data more effectively and accurately, the interviews were audio-recorded. The researcher checked that the recording device was functioning properly throughout the interview by checking the recording time during each interview. The recording of the interview made it easier for the researcher to focus on the interview process and enabled the researcher to generate 'verbatim transcripts' of the interviews.

6.2.5 Data Processing

The interviews were audio-recorded, transcribed verbatim and imported into the NVivo (Version 11, QSR International Pty Ltd.) software. NVivo is a popular computer-assisted qualitative data analysis software program. It enables researchers to:

- Store and organize: Store, sort and retrieve all data in one platform, from quantifiable demographic information to qualitative open-ended questions and interviews.
- Categorize and analyse: With powerful data management tools to categorize and classify data, NVivo automatically sorts sentiment, themes and attributes in seconds.
- Visualize and discover: Easily cross tabulate mixed methods data and visualize the results to brainstorm and map ideas, explore connections between project items and discover new paths of investigation with query and visualization tools (NVivo, 2018).

As a result, NVivo helps researcher back up findings with evidence and work more efficiently (Bergin, 2011). The use of NVivo software and manual procedures facilitated the thematic coding and analysis process throughout the research.

6.2.6 Data Analysis

Thematic analysis was chosen for analysing qualitative data in this study because it followed a standard procedure for conducting qualitative analysis to ensure clarity and rigour in process (Coffey & Atkinson, 1996). This consists of six steps, including familiarising with the data, generating initial codes, searching for themes, reviewing potential themes, defining and naming themes, and producing the report (Braun & Clarke, 2006).

Step 1. Familiarising with the data

'Verbatim transcripts' of the interviews were generated by the researcher (GYY) in English or Chinese depending on the language spoken by the participants. Two researchers (GYY and XL), both fluent in Chinese and English, independently read each transcript carefully several times, and took notes on initial ideas on the text.

Step 2. Generating initial codes

Code is defined as "shorthand labels – usually a word, short phrase, or metaphor – often derived from the words of participants, which are assigned to data fragments defined as having some common meaning or relationship" (Carpenter & Suto, 2008). This initial coding process involved reading the transcripts and allocating codes to segments of the data that conveyed what was happening in concise terms. Two researchers (GYY and XL) independently coded four transcripts (two from Beijing participants and two from Sydney participants) manually as a pilot, and generated as many codes as possible for the data. Coded text was highlighted, and the corresponding codes were listed in the margins of the transcripts. The percentage of agreement between the two researchers in the initial analysis was low, ranging from 20% to 40%.

The two researchers had a meeting to discuss the codes each week to collaboratively develop a code list. Interrelated codes were integrated to form a category to delimit the number of codes and categories. Constant comparing and contrasting techniques were facilitated across codes by recording memos and queries to establish category boundaries, systematically assign data segments to categories, and summarise the content of each category (Tesch, 1990). Since categories identified could be influenced by the literature and background reading, and the experience and value of researchers (Ryan & Bernard, 2000), caution was taken by the two

researchers to ensure the categories reflected the data instead of forcing the data to fit in with the categories. In this way, the code list was refined and reinforced within the first month of the data analysis.

The principal investigator (GYY) then coded all transcripts using NVivo software according to the code list. Appendix 17 demonstrates examples of the coding process.

Step 3. Searching for themes

The two researchers sorted the different codes into potential themes using NVivo software and focused on the broader level of themes. This step was a continuation of the bottom-up process in which the broader themes fit the categories. This resulted in a collection of themes and sub-themes.

Step 4. Reviewing potential themes

The two researchers refined the themes by reviewing at the level of the coded data and the level of the themes. All codes and data extracts were reviewed to ensure that all data formed a coherent pattern. Each theme in relation to the data and the relationship between themes was reviewed to ensure the themes reflect the meaning of the data as a whole.

Step 5. Defining and naming themes

After continuous revision of the themes, the two researchers focused on capturing the essence of what each theme was about and what aspect of the data each theme captured. Sub-themes were identified where appropriate. Interrelated themes were integrated into domains. Themes and sub-themes were named in a concise way, to immediately give the reader a sense of what the theme is about. Themes and sub-themes are described below.

- *Internal/external motivation* captures the internal or external driving force of participants that triggers them to participate in the trial and adhere to the Tai Chi protocol.
- *Positive feeling* relates to the positive emotions of participants. This theme has three sub-themes, including positive feelings toward Tai Chi, positive feelings toward this project, and positive feelings about the learning experience.
- *Benefits of Tai Chi* identifies the health benefits of Tai Chi perceived and reported by the participants.

- *Future practice* refers to the willingness of participants to continue the Tai Chi practice after the study.
- *Subjective concerns* are the internal factors that participants worried about, which may influence their action of trial participation and adherence.
- *Objective concerns* relate to the external factors that participants worried about, which may influence their action of trial participation and adherence.

Step 6. Producing the report

The final analysis of the data and the results were reported in the below section. Evidence was provided to support each theme using quotations from the data.

6.3 Results

This section presents the findings, with selected illustrative quotations from the interviews. The principle investigator (GYY) selected illustrative quotations, and discussed and confirmed their appropriateness with the second researcher (XL). All Chinese quotations were translated into English by the principle investigator (GYY) and verified by the other researcher (XL).

6.3.1 Participant Characteristics

Thirty-four participants in the Tai Chi group who completed the study agreed to participate in an interview. Of the 34, 19 (55.9%) were from the Beijing recruitment centre and 15 (44.9%) from the Sydney recruitment centre.

The mean age of participants was 66.35±4.87 years, and 55.9% were women. Of the 34 participants, 31 (91.2%) had hypertension, 8 (23.5%) had CHD, and 5 (14.7%) had both hypertension and CHD. Participant characteristics of the qualitative sub-study are presented in Table 6.2.

Table 6.2 Characteristics of the study population involved in the exit interview (n=34)

Characteristic	Value
Age-yr (mean ± SD)	66.35±4.87
Female sex-No. (%)	19 (55.9)
Body-mass index (BMI) (mean ± SD)	25.35±2.49

Higher education-No. (%)	17 (50.0)
Retired- No. (%)	32 (94.1)
Smoker-No. (%)	0
Family history of CVD- No. (%)	27 (79.4)
Disease-No. (%)*	
Hypertension	31 (91.2)
CHD	8 (23.5)
Both	5 (14.7)
Baseline PSS-10 score (mean ± SD)	12.38±5.43
Baseline SAS score (mean ± SD)	42.71±8.76
Baseline BDI-II score (mean ± SD)	10.32±2.10.03
Baseline SF-36 total score (mean ± SD)	565.74±134.62
Baseline 6MWT-meter (mean ± SD)	490.78±71.93

Notes: BMI, the body-mass index; CHD, coronary heart disease; PSS-10, the Perceived Stress Scale 10-item; SAS, the Zung Self-Rating Anxiety Scale; BDI-II, the Beck Depression Inventory-II; SF-36, the 36-item Short Form Health Survey Questionnaire; 6MWT, the 6-minute walking test measures the distance (in meter).
* Some participants had both hypertension and CHD.

6.3.2 Synthesis and Interpretation

The analysis identified two major domains - facilitators and barriers with six key themes and 31 codes.

The four themes under the domain of facilitators were:

- Theme 1: internal/external motivation
- Theme 2: positive feeling. Positive feeling has three sub-themes: feelings toward Tai Chi, feelings toward the project and feelings about the learning experience.
- Theme 3: benefits of Tai Chi
- Theme 4: future practice

Under the domain of barriers, two themes were dominant:

- Theme 5: subjective concerns, and
- Theme 6: objective concerns

The sub-themes, themes and domains were presented in Table 6.3.

Table 6.3 Sub-themes, themes and domains identified in the qualitative study

References within transcript	Sources/ Number of Participants	Code	Sub-theme	Theme	Domain
10	8	Wish to improve health	-	Theme 1: Internal/external motivation	**Facilitators**
2	2	Interested in exercise for heath			
8	8	Long-cherished wish to learn Tai Chi			
7	7	Curiosity toward Tai Chi			
3	3	Family support			
3	3	Chinese culture	Feelings toward Tai Chi	Theme 2: Positive feeling	
2	1	Easy to learn			
4	3	Extensive and profound			
2	2	Long history			
8	6	Suitable for the elderly			
12	11	Good for health			
3	3	Convenient to practice			
6	6	Formal organization	Feelings toward the project		
3	3	Target population			
21	17	Tai Chi instructors	Feelings about the learning experience		
12	9	Environment			
13	9	Communication platform			
9	7	Tai Chi protocol			
16	14	Daily activity	-	Theme 3: Benefits of Tai Chi	
37	25	Physical health			
46	27	Psychological wellbeing			
17	16	Social life			
29	25	Wish to continue practice	-	Theme 4: Future practice	
22	21	Wish to promote Tai Chi			
1	1	Difficult to learn Tai Chi	-	Theme 5: Subjective/internal concerns	**Barriers**
2	2	Harm to knees if not practiced properly			
2	2	No group atmosphere			
4	4	Time conflict	-	Theme 6: Objective/external concerns	
1	1	Health problem			
2	2	Air pollution			
2	2	Travel difficulty			

6.3.2.1 Facilitators to Participation and Adherence

Theme 1: Internal/external Motivation

The majority of participants expressed that improving health was a major motivator for them to participate in the project and to adhere to the Tai Chi program. Some participants reported that although they would have liked to improve their health through exercise in the past, they felt they now had more limited choices because of their age and health conditions. Some participants expressed that they were interested in any activity that was good for their health, and later they realised that Tai Chi was a good choice for them.

> *I hope I can pick up some exercise, relaxation techniques, and meditation, which will improve my mental and psychosocial aspects. (Male, 75 years, Sydney)*

> *Only in recent years I feel my body, physical movement does not coordinate with my mind, I start to explore some means…It stays in my mind to learn Tai Chi, to improve my physical health, to coordinate my mind and my arms and legs, to prevent falling, when I was invited to this class. (Male, 66 years, Sydney)*

Learning Tai Chi was a long-cherished wish of some participants. They have heard of Tai Chi and its potential benefits for health or watched Tai Chi practice, but had not had any opportunity to learn it previously.

> *I once watched Tai Chi practice many years ago, Yang style, so I always want to learn Tai Chi. However, not until this time, the opportunity never comes. (Female, 63 years, Beijing)*

Since some participants were interested in Tai Chi and had been looking for an opportunity to learn it for a long time, they cherished the learning opportunity offered to them in this project. This, in return, enhanced their participation and adherence to the Tai Chi program.

Some participants were curious about Tai Chi and its potential benefits for health; for these participants, one motivation for them to participate was to see what would happen in relation to their health.

> *Try and see. I never learned Tai Chi before. I had no idea of Tai Chi in the past. Because I have hypertension, I think Tai Chi might be helpful…So I participated to try and see what would happen to me. (Male, 71 years, Sydney)*

> *I wanted to try and see what on earth is Tai Chi? I heard that Tai Chi could be beneficial for this or that, for health, for peaceful mind and calm, so I participated in this program. (Male, 64 years, Sydney)*

Curiosity motivated participants to engage in the Tai Chi program. Moreover, their curiosity about the potential impacts on their health during the learning process enhanced their adherence to the Tai Chi intervention both during and after the completion of the research.

Family support, either emotional or practical, was also a facilitator for some participants to participate and adhere to the Tai Chi program, particularly for those who were usually preoccupied with family and domestic responsibilities.

> *My husband helped with housework or other matters, as a support. He supports me to learn Tai Chi, so I am very happy. (Female, 64 years, Beijing)*

Theme 2: Positive Feeling

Feelings toward Tai Chi. Most participants explained their perception of Tai Chi had changed over the 24-week intervention duration. Prior to participation, most had little understanding of Tai Chi.

Participants in Sydney with Chinese heritage mentioned their passion for Chinese culture. They regarded Tai Chi, with its long history, as "an essential treasure of Chinese culture"; this was a big motivator for them to participate in the Tai Chi program.

> *Before I leant Tai Chi, I had already known that Tai Chi is a treasure of our Chinese culture, with a long history. Without this belief I don't think I would join the class. (Male, 64, Sydney)*

During and after their participation, some participants established new views on Tai Chi. The terms "profound", "unlimited", and "regularly" were frequently used to describe the Tai Chi intervention by some participants.

> *After I learnt Tai Chi, I started to realize that Tai Chi is so profound, not just movements. I only know a little about it, so I very much want to know more, all of them. This is the beginning. Later, I found I can't bite off more than I can chew. So I just want to master the Tai Chi program I learned from the class, and have a deeper understanding. (Female, 67 years, Beijing)*

> *It's hard at the beginning. It's hard and easy. It takes time, step by step, to fully digest…After I know the basics of Tai Chi, Wow, I see, Tai Chi is such an unlimited world. It can bring so many beautiful benefits to people and their life. (Male, 64 years, Sydney)*

> *Because you know it is good for you. Tai Chi, you have to do it regularly, in every day, definitely. Then I think you will get the full benefits from it, otherwise it's useless to do it for 24 weeks, you will forget it. (Female, 66 years, Sydney)*

In addition, participants reported the specially designed 13-form Tai Chi was easy to learn and convenient to practice due to no strict requirements of time, location and equipment. Specifically, some participants reported that they felt the Tai Chi protocol used in the trial was well suited to their health condition and exercise capacity.

> *Tai Chi is particularly suitable for the elderly to practice. No very vigorous movement such as kicking legs. I dare not to bend my knees too much, because I heard it will do harm to the knees. There is no such problem in our 13-form Tai Chi program. (Male, 67 years, Sydney)*

Feelings toward the project. Many participants felt the target disease/condition (i.e., hypertension or coronary heart disease) of the Tai Chi randomised trial matched their health situation. Some participants felt positively to the program, because it was held by health researchers from the university and doctors from hospitals, and considered it would be well designed. One participant felt the project involved a very qualified Tai Chi instructor, which motivated her to participate in the program.

> *It was organized by the university and hospitals, so it should be very formal or authentic. (Female, 67 years, Beijing)*

> *I thought this was such a good opportunity, because the teacher was from Western Sydney University, a PhD candidate, and had a background of Chinese medicine. I thought the teacher should be very qualified. Where can you find such a good teacher? (Female, 63 years, Sydney)*

Some participants expressed a wish for more sessions per week and for a longer duration.

> *I am strongly satisfied with the project. I never met such terrific teacher, such fabulous environment, and such excellent teaching before. However, the duration is too short. Is it? There should be some following series. (Female, 66 years, Beijing)*

Feelings about the learning experience. All participants reported satisfaction with their learning experience with most identifying the characteristics and teaching quality of the Tai Chi instructors as major factors in motivating them to complete the half-year program. Participants frequently used the terms “earnest”, “responsible”, “patient”, “selfless”, “knowledgeable”, “nice”, and “dedicated” to describe the characteristics of the Tai Chi instructors. Participants felt their Tai Chi instructor gave them “clear”, “precise”, “detailed” instructions, explanations and demonstrations, which were essential in developing and maintaining their learning interest and adherence to the Tai Chi program.

> *I was completely a layman, ho ho. I know nothing about Tai Chi. Two main reasons can explain why I can complete the half-year program. Two factors, I think, are very important. Firstly, I met a very good teacher. She gave us Tai Chi instruction very*

patiently and earnestly…so that I gradually become interested in Tai Chi and had a deeper understanding of it. (Male, 64 years, Sydney)

The teaching was very precise and very earnest. I find I can understand [the instruction]. In addition, what's the purpose of the movements and how to experience the peace and stillness, [the instructors] gave very detailed explanation… To my surprise, really, I could meet such terrific teachers, so qualified and so excellent. (Female, 67 years, Beijing)

I was so touched, because the instructor was earnest, selflessly dedicated, and hard-working. I thought the classes were well organized. In addition, [the instructor was] wholehearted and very responsible. I was so touched, so I would like to study hard. If not study well, I would feel guilty for my instructor, and feel sorry for Tzu Chi's support. (Female, 72 years, Sydney)

The learning environment of the Tai Chi class was another important facilitator identified in our study. The venue of the Tai Chi class was described by some participants as "good", "quite", and "clean", which all contributed as facilitators for participants to attend the class. Moreover, participants reported that they benefited from the group-learning "atmosphere" in the Tai Chi program. Participants found it was "encouraging" when classmates around were learning and practicing earnestly, and they could learn from each other. Timely responses from the instructors through face-to-face or online communications were also important.

I feel it's different from practicing at home. There is an atmosphere when we practice together, and we can help each other. More importantly, the face-to-face instruction. I am interested in the timely correction and instruction…We have a WeChat group, it's good that the Tai Chi instructor shares some knowledge there. We can ask questions, share our experience and have discussions. (Male, 71 years, Sydney)

I think everyone learn earnestly in the class. So, when we organize to practice together after class, we are very united. We are all glad to learn, and happy to practice. In the park of our community, very good, we practice together every day. (Female, 63 years, Beijing)

The use of a social media communication tool on smart phones among the participants further facilitated adherence to the Tai Chi program indirectly. In the Tai Chi group of the randomised controlled trial, a WeChat group (a Chinese multi-purpose social media mobile application developed by Tencent Holdings Ltd) was set up to promote timely feedbacks between participants and Tai Chi instructors to support the home practice. Even though some participants had never used it before, the application was widely accepted and used once the researchers introduced WeChat in the study.

Theme 3: Benefits of Tai Chi

All participants reported they benefited to some extent from participating in the Tai Chi program, including psychological well-being, physical health, social life and daily life activity.

Participants frequently used the terms "calm", "peaceful", "happy", "relaxed", "bright", "pleasure", and "joyful" to describe in the interviews to talk about their mood or state of mind because of their Tai Chi practice. In addition, some participants reported they found it "easier to control the temper", "not take things too hard" or were "less stressed and depressed".

> *I was very emotional and easy to be anxious in the past. Now, I cannot say nope. There are always some different things in life and work stress. But, I feel better…Tai Chi broadens my mind. Human should be harmonious with the environment… I would not take things too hard. (Female, 63 years, Sydney)*

> *My body becomes relaxed, so mentally I feel better and be more confident in whatever I do than before. In the past, I always regarded myself as a severely sick person, and I was different from others…especially after the stent-installation. I was a bit depressed in the past two years, very stressed and didn't want to communicate with others. After Tai Chi practice, daily practice, I feel my body gets better and my well-being has improved. (Male, 64 years, Beijing)*

Notably, two participants expressed their perceived benefits in other psychosocial aspects.

> *I find I'm more alert, mentally. May be because of the music and the slow movement, I found I had calm effects. Particularly, strange, I found my short-memory is not quite good because when doing Tai Chi, I can't remember the sequences. And since then, I found there is improvement. It definitely improves my short-term memory. (Male, 75 years, Sydney)*

> *Tai Chi helps me to concentrate. When practice Tai Chi, I concentrate on the movements and details, such as the principles of moving hands and arms, so it stops my mind from wandering. (Male, 67 years, Sydney)*

Participants frequently reported perceived physical benefits such as improvements in balance, flexibility, strength, sleep quality and duration, or better control of blood pressure, blood sugar or the blood lipid profile. Only one participant perceived his physical health unchanged.

Social aspects of the Tai Chi program were also praised. Participants enjoyed the social interaction in the physical Tai Chi group class, during their group practice outside of class, and through WeChat.

> *We get together to practice Tai Chi on Monday, Wednesday and Friday in the playground. After practice, we often have a discussion on how to improve. We also share our own experience and always feel very happy…We miss each other if two days no see, so we contact online through WeChat. (Female, 67 years, Beijing)*

Furthermore, they identified their participation in the Tai Chi program had some positive impacts on their daily activity because they felt happier and more energetic after Tai Chi practice.

> *In the past, I could only do small amounts of activity. My body was not able to do more, or my whole body felt uncomfortable at night. In the evening I always wanted to have a walk, but I couldn't…Now, I can, and after walking I feel very relaxed and comfortable. (Female, 61 years, Beijing)*

> *After practice, I am often in very good mood. I feel it's easier to do some housework. (Female, 67 years, Beijing)*

Some participants who found that nothing obvious had changed, did note that when they added Tai Chi practice into their daily life, there was a structure of a daily "routine activity" or a hobby, this made their "boring" retired life more "regular" and "interesting".

> *In the past, I had nothing to do, just stay at home and had no activity. Now, I practice Tai Chi, meditation, standing posture etc. every day. It takes around one and a half hour. After the practice, my mood becomes bright and I want to go out and walk around. (Male, 69 years, Sydney)*

Theme 4: Future Practice

All participants expressed a desire to continue the Tai Chi practice. Three participants reported that they would immediately start their advanced Tai Chi classes after the trial.

> *I will continue to practice Tai Chi. For me, Tai Chi and the 13-form Thumping Techniques, I would practice them for the rest of my life. I would say, they will be a part for the rest of my life, an important part. Particularly, for the elderly, it's much necessary for us to learn Tai Chi and the 13-form Thumping Techniques, so that we can be peace and calm. (Male, 64 years, Sydney)*

> *I used half a year to learn it. If I forgot it, it's a waste of my time. In addition, Tai Chi practice has many benefits to me. Why not continue to practice it? I learned it for free and I can continue to practice it for free. (Male, 67 years, Sydney)*

> *I notice that I improve a lot. I feel I still have many space to improve at the end of the program. I will sort them out by watching the DVD. (Male, 75 years, Sydney)*

> *We have a group with around 10 people to practice together in the park…We practice together every day and even not have a break during weekends. (Female, 65 years, Beijing)*

Throughout the intervention period, the Tai Chi instructors repeatedly stressed that Tai Chi learning is an endless process, which had impacts on the decision of some participants with respect to future long-term practice.

> *'My movements are very stiff, so it might take me a long time to become soft and graceful. Therefore, it's inevitable for me to practice 'for three years to lay a solid foundation and ten years to achieve greater success, or even for a longer time' (Male, 64 years, Sydney).*

All participants reported that they were extremely satisfied with their participation in the Tai Chi program and would recommend the program to others if there were more classes in the future.

> *I am sure I would like to recommend the Tai Chi class to others, no matter they have cardiovascular diseases or not. For example, I would suggest my wife to come. (Male, 67 years, Sydney)*
>
> *If there is such Tai Chi class again in the future, I will recommend it to others. … It is better to learn Tai Chi in a class. You can't learn it by yourself. (Male, 64, Beijing)*

6.3.2.2 Barriers to Participation and Adherence

Theme 5: Subjective Concerns

Subjective concerns included possible adverse effects, difficulty of learning the Tai Chi sequence due to perceived complexity and maintaining self-discipline for home practice.

A few participants thought the Tai Chi practice may harm their knees because they heard it from television news, so they preferred not to start learning until they found a good teacher.

> *I heard from television news, several times that some people visited the orthopaedic department because their knees were painful. Why? They all practiced Tai Chi. These people didn't know how to practice appropriately, and they didn't master the right postures and skills. So I dare not to start learning it. (Male, 66 years, Beijing)*

A few participants thought Tai Chi was a complex exercise and would be too difficult for them to learn at first. One described her past failed learning experience of Tai Chi. Another participant recalled his experience of watching his sister practicing the 108-form Yang-style Tai Chi when he was young, which impressed him but intimidated him with its complexity. However, their worries alleviated by learning that this intervention was a specially designed Tai Chi program with only 13 movements.

> *Tai Chi is too difficult to learn. In the past, I tried three times to learn Tai Chi in my community, but finally I gave up. I thought, alas, why was it so hard to learn? I learned*

the movements in class but I forgot all of them when I went home. So I gave up three times. (Female, 66 years, Beijing)

The participants who had often practiced outdoors with group members were very keen to continue practicing Tai Chi. However, when probed about the different parts of the Tai Chi program (i.e. 13-form Tai Chi, walking, meditation, standing posture and the 13-form Thumping Techniques), some participants explained it was very challenging for them to practice meditation and the 13-form Thumping Techniques by themselves at home, due to laziness or their lack of motivation without the group atmosphere.

The 13-form Thumping Techniques, for me, it's hard to do the whole set of it. Actually, I have plenty of time, but I think I lack willpower. It's hard to practice at home. For example, when I just sit there for meditation, my minds were wandering, such as boiling a kettle of water. So I stand up to boil the water and then do other housework. (Male, 62 years, Beijing)

Theme 6: Objective Concern

Objective barriers which were expressed as potentially inhibiting Tai Chi practice included concerns about the possible poor quality of the outdoor air due to high levels of fine particulate matter ($PM_{2.5}$) (Beijing participant), being sick or occupied by work or other activities, family responsibilities (such as looking after their grandchildren).

I have a grandson to look after. If he is sick, I would be worried about him and not go out. (Female, 60 years, Beijing)

Other possible barriers to participating and recommending Tai Chi to others included travel distance and time conflicts.

6.4 Discussion

6.4.1 Summary of Main Findings

Our study identified six facilitators and barriers influencing participants' trial participation and adherence to the Tai Chi intervention both during and after the study. Facilitators included internal/external motivation, positive feelings, benefits of Tai Chi, and future practices. Barriers related to subjective and objective concerns. A clear understanding of these factors, of what has worked and what hasn't, can aid in the development of robust strategies to proactively address these factors to promote trial recruitment, retention and adherence to Tai Chi intervention and similar mind-body therapies, in order to support the robust evaluation of outcomes.

6.4.2 Facilitators to Trial Participation and Adherence

Important themes emerged under the domain of facilitators for trial participation and adherence, including internal/external motivation, positive feelings towards Tai Chi, the project, the learning experience, benefits of Tai Chi, and future practice. Some factors support previous qualitative studies (Fischer et al., 2014; Yeh et al., 2016), while others may provide additional insight into the beneficial factors influencing the trial participation and adherence of participants. The details are discussed below.

6.4.1.1 Internal/external motivation

Improving health was the major motivator for the majority of our participants with CHD and/or hypertension to participate and complete the Tai Chi program. Health improvement was also identified as a significant facilitator in a community-based Tai Chi program provided to 87 older adults from lower socioeconomic backgrounds in Canada (Manson, Tamim, & Baker, 2017).

In contrast, Fischer, Fugate-Woods and Wayne (2014) found that accessibility and convenience (such as situating the classes in community-based schools) were the primary motivators to participate and adhere to a Tai Chi program for women with osteopenia (Fischer et al., 2014). Our participants with CHD and/or hypertension who attended Tai Chi classes held at a fixed location and time, did not name accessibility and convenience as their priority. Perhaps as the majority of our participants came from the same community and classes were held in facilities close by this was less of an issue. In our CVD cohort, although accessibility and convenience may have been a concern, the desire to participate in a health promoting activity was the powerful driving force sustaining their trial participation and adherence. Demonstrating scientific evidence about the potential benefits of the intervention for health improvement may be considered as a key factor in the success of future trials and enrolment in Tai Chi programs.

Learning Tai Chi was a long-cherished wish for some study participants. The interactive learning process involved in Tai Chi may be considered as a motivating component for some participants, which may enhance and sustain trial participation and adherence (Cook & Artino, 2016). Helping potential participants identify any internal motivations for learning may help assist and sustain their enrolment and performance during future trials or programs.

6.4.1.2 Positive feelings

Our participants frequently expressed that their perception of Tai Chi had changed gradually over the study period. Most participants had minimal knowledge of Tai Chi before participating

in the trial, although most had perceived Tai Chi as "good for health". When their knowledge deepened they developed more skills of Tai Chi through the learning experience and came to regard Tai Chi as "profound" and "unlimited" mind-body exercise. Learning as a motivator can be seen as two-fold. Initially, the 'idea' or 'concept' of learning is a motivator, and secondly, the 'actual' learning during the intervention can be seen to sustain engagement in the Tai Chi program over the longer term.

Several participants mentioned Chinese culture, regarding Tai Chi as "an essential treasure of Chinese culture". Tai Chi, with its long history, has multiple attractive components, integrating the essence of Chinese culture including Chinese folk and military martial arts, breathing and meditative techniques, philosophy of *yin* and *yang*, and theory of traditional Chinese medicine (Tang & Gu, 2012). For some, Tai Chi may be seen as a way in which to open a door of learning, to understand and experience Chinese culture.

The Tai Chi program used in our study was perceived as particularly suitable for participants' health conditions and exercise capacity. The 13-movement Tai Chi program was designed to be easy to learn and convenient to practice, with no strict requirements of time, location and equipment for home practice. The program design enhanced confidence to continue to participate, particularly for older adults with limited physical capacity. Other advantages of Tai Chi, such as low-to-moderate intensity, should be articulated to potential participants during the recruitment period. Designing or selecting a Tai Chi program suitable for the target population, according to their health, mental and cognitive conditions, and exercise capacity is considered likely to improve engagement and compliance.

In our study the Tai Chi instructor(s) were crucial in motivating participants' adherence to the Tai Chi intervention; this finding is consistent with that of previous literature. Fischer et al. (2014) identified characteristics of Tai Chi instructors, such as their expertise, knowledge and authenticity, patience and providing support, inspired the attendance and performance of participants with osteopenia (Fischer et al., 2014). Similarly, in a qualitative study in veterans with post-traumatic stress symptoms, Niles et al. (2016) found the positive energy and supportive comments from the Tai Chi instructor contributed to ongoing participation and adherence to the Tai Chi program (Niles et al., 2016). Individual attention and modification of movements based on individual needs from Tai Chi instructors were also considered important in sustaining engagement.

Our findings support previous literature that has reported the importance of a helpful learning environment. Fischer et al. (2014) identified that community and social support from Tai Chi instructors, teaching assistants and classmates was an incentive for class attendance and regular practice (Fischer et al., 2014). Yeh et al. (2016) also suggested that social support in the Tai Chi classes, including motivation from others, shared understandings and difficulty contributed to self-efficacy and empowerment with additional gains being internal focus of control, self-awareness and stress management for participants with heart failure (Yeh et al., 2016). A longitudinal epidemiological study followed up 1,636 people with CHD over 13 years and found that social support may function as a resilience factor against the long-term cardiovascular risk associated with depression (Lie et al., 2017). Community, practical and emotional supports may thus explain to some extent why Tai Chi is beneficial for cardiovascular health and psychosocial wellbeing in participants with CHD and/or hypertension.

6.4.1.3 Benefits of Tai Chi

The benefits of committing to a regular and sustained Tai Chi practice for participants include psychological wellbeing, physical health, social life and daily life activities. These finding are similar to other studies in other population groups. Women with osteopenia experienced improvements in balance and flexibility, a reduction in pain related to less joint stiffness or postural imbalances, an increase in energy and endurance for daily activities and strength, fewer headaches and improved sleep, an increase in mental alertness, and being calmer and more relaxed mentally (Fischer et al., 2014). In people with heart failure, perceived benefits included improvements in strength, energy, flexibility, balance, and endurance; a decrease in pain and stiffness; awareness/mindfulness; and relaxation and calmness (Yeh et al., 2016).

Tai Chi addresses all biopsychosocial aspects of health. The WHO defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (World Health Organization, 2018b). Results from our study and other studies, indicate that Tai Chi covers all three of these dimensions of health from the perspective of participants.

Self-reported benefits of Tai Chi may help the generation of hypotheses for future research on the effects of Tai Chi interventions. For example, a possible future hypothesis may explore the impact of a Tai Chi intervention on sleep, loneliness and social isolation for people at risk of CHD. The association of sleep duration and quality with CHD has been widely reported in previous epidemiological studies (Strand et al., 2016). A recent large-scale cohort study

following a total of 60,5686 participants aged 40 years or older for an average of 5.6 years also demonstrated that short sleep duration and poor sleep quality are associated with the risk of CHD (Lao et al., 2018). One systematic review and meta-analysis (Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016) of longitudinal observational studies demonstrated that poor social relationships are associated with a 29% increase in risk of incident CHD (pooled RR: 1.29, 95%CI: 1.04 to 1.59).

Physical activity plays an important role in the prevention and control of CVD and in addressing overweight and obesity (Koolhaas et al., 2017; J. Myers et al., 2015). However, the increasingly busy environment is reducing opportunities for physical activity, particularly in urban settings (J. Myers et al., 2015). Our findings indicate that Tai Chi practice is one enjoyable option for people to improve their regular physical activity, which in the long term may be likely improve their cardiovascular and general health.

6.4.1.4 Future practice

In the present study, all interviewees expressed a strong desire to continue with their Tai Chi practice after the 24-week study. One underlying reason for this may be because we continually stressed the importance of the long-term learning and regular practice of Tai Chi throughout the intervention. Most importantly, in comparison with other physical activities, Tai Chi has a special advantage in that it is a life-long enjoyable learning process with multiple levels to achieve rather than the simple repetition of movements. Furthermore, the intensity and structure of a Tai Chi program can be easily tailored to health conditions and the personalised requirements of practitioners. Enhancing perceptions and understandings of the necessity and feasibility of maintaining a Tai Chi program may therefore improve long-term adherence after study completion.

Regular physical activity is a key to preventing and treating non-communicable diseases (NCDs) and some mental disorders. WHO recommended adults aged 18 years and above should do at least 150 minutes of moderate-intensity physical activity throughout the week, or do at least 75 minutes of vigorous-intensity physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity (World Health Organization, 2018e). WHO has launched several plans addressing this issue since 2004. The recent "*WHO Global action plan on physical activity and health 2018-2030: More active people for a healthier world*" (World Health Organization, 2018g) provides an opportunity to refocus and renew efforts at promoting physical activity. Considering the potential benefits to individuals and wider society

of long-term commitment to Tai Chi programs and their sustainable development, Tai Chi is a sound and appropriate option for long-term health and economic benefits in this population in particular, and in the wider population more generally.

6.4.3 Barriers to Trial Participation and Adherence

Our study also identified some subjective and objective concerns as barriers to trial participation and adherence, including concerns related to the Tai Chi intervention, personal reasons, environmental factors, travel distance and time conflicts. Fischer et al. (2014) also identified travel considerations and time-related factors (time required for Tai Chi practice and the 9-month duration of the study) as barriers to participation and adherence in some participants (Fischer et al., 2014).

In the present study, some participants expressed concerns about the potential harm of inappropriately practicing Tai Chi. The safety of Tai Chi has been examined and although Tai Chi was unlikely to result in serious adverse events, it might be associated with minor musculoskeletal aches and pains (Wayne et al., 2014). Accordingly, future researchers would need to ensure appropriate communication and discussion on the potential risks and benefits of Tai Chi interventions with potential participants. A proactive approach to developing strategies to deal with the potential risks should be considered. These strategies could include selecting an experienced Tai Chi instructor and developing a suitable Tai Chi program for a special cohort.

Other barriers such as 'laziness', the lack of group atmosphere in home practice, may be addressed through the development of more robust and remote support strategies to more effectively support and facilitate independent practice at home.

Some participants identified air pollution as a potential barrier to have outdoor Tai Chi practice. The "*WHO Global action plan on physical activity and health 2018-2030: More active people for a healthier world*" (World Health Organization, 2018g) highlights the contributions of all relevant sectors, including environment, education, health, sport and technology to accelerate progress to control non-communicable diseases. Notably, Tai Chi is convenient to practice and has no limitations of time, location and equipment. When the outdoor environment is not optimal, indoor practice can be an alternative.

6.4.4 Limitations

This qualitative study has some limitations. Firstly, the relationship between the interviewer and participants may influence the results, because the interviewer is also one of the Tai Chi

instructors. As a result, a reporting bias from participants may exist because the participants ("students") might report what they thought the interviewer ("instructor") expected. Therefore, the positive results generated from this qualitative study should be interpreted with caution. However, the exit interviews were conducted in the end of the study, which may reduce this reporting bias because of the completion of Tai Chi class. In addition, interview responses were consistent with those self-reported in the weekly patient diaries.

Secondly, the interview participants did not include those who refused to participate in this trial. They would potentially provide valuable information for developing strategies to improve enrolment. Consequently, some factors associated with the trial participation and adherence to the Tai Chi intervention from the participants' point of view may not have been identified.

Thirdly, there may be a potential interviewer bias. Although the interview was designed to be semi-structured and the questions were open-ended, around half the questions were about the 'benefits' of Tai Chi, which may lead participants to report more positive results.

Finally, the generalizability of the results may be limited considering the participants were all Chinese or Chinese-Australian. More research involving other background or ethnic origin are needed to confirm our findings.

6.4.5 Implications for Future Research

Recruitment is a key challenge in all clinical trials. Effective strategies to improve recruitment of Tai Chi studies or other exercise studies may be address the concerns of potential participants. The current qualitative study identified certain concerns of participants about Tai Chi, such as harming knees if not practiced properly. Therefore, during recruitment, future researchers are suggested to have appropriate communication with potential participants on the potential risks and benefits of Tai Chi and the strategies to ensure safety in the study. The other concern of participants identified in this qualitative study was that Tai Chi was too complex to learn. Accordingly, it is strongly recommended to develop or select a Tai Chi protocol tailored to the target participants. In addition, it is important to explain the requirements of physical capacity to potential participants and allow participants to ask questions to solve their concerns in recruitment.

Our findings suggested some strategies of promoting adherence in clinical trials of Tai Chi, including identifying motivations of participants and improving the learning experience. The

current qualitative study found that a strong internal motivation of participants was to improve their health. In addition, reducing concerns of participants by guiding them to practise Tai Chi appropriately to ensure their safety, such as protecting their knees, during the study period. The characteristics and teaching of the Tai Chi instructors were also an important stimulus to the adherence. It is strongly suggested that an experienced Tai Chi instructor should be involved in the protocol development and intervention instructions.

Tai Chi practice seems enjoyable and well accepted by people with CVD and/or cardiovascular risk factors. The high adherence and retention rate in the current study indicates the acceptance of Tai Chi by this population. All participants in the qualitative study reported that they enjoyed the learning experience and would like to continue with Tai Chi after the completion of the 24-week study. CVD and other non-communicable chronic diseases require long term prevention and management which may be addressed by adoption of Tai Chi for the longer term. In addition, since Tai Chi requires no dedicated equipment, time or environment, it is an accessible, convenient, long-term choice for people with CVD and/or cardiovascular risk factors and a wider population.

6.4.6 Influences on Cultural Context

Although from different geographic locations, namely Beijing and Sydney, our participants are all Chinese or Chinese-Australian. They shared great similarities in perception of participation and adherence to Tai Chi, including internal/external motivations, positive feelings towards Tai Chi, the project and the learning experience, benefits of Tai Chi, future practice and concerns. The major differences due to the influences on cultural context among our participants are as follows:

(1) Beijing participants mentioned their motivations included family support or their concerns included time conflict because of ‘looking after the grandchildren’. The possible reason is because it is a tradition in China that ‘the grandparents are expected to help look after their grandchildren’ and there is a high expectation of their family responsibilities.
(2) Sydney participants mentioned their positive feelings toward Tai Chi, regarding Tai Chi as “an essential treasure of Chinese culture”. For some participants outside of China, Tai Chi may be seen as a way in which to open a door of learning, to understand and experience Chinese culture.

(3) Participants in two sites expressed their positive feelings toward the venue and group-learning ‘atmosphere’, but the majority of Beijing participants also mentioned the benefits of WeChat. The possible reason is that WeChat is a popular Chinese social media communication tool in China but not in Australia. However, even though some Sydney participants had never used it before, the application was widely accepted and used once introduced in the study.

(4) Beijing participants expressed one of their facilitators of Tai Chi practice is ‘group atmosphere’ and ‘no group atmosphere’ outside of class or after the study is a concern of barrier for home practice and future practice. The underlying reason is that the population in Beijing is much larger and denser than that of Sydney. It is easier for participants in Beijing to form a group after class to practice together compared to participants in Sydney. They were accustomed to practice in a group and it would be a challenge for them to continue the practice by themselves at home.

(5) Beijing participants expressed a subjective concern about the possible adverse events of Tai Chi practice due to improper practice as indicated by media coverage. The possible reason is that it is common in China to see people practice Tai Chi, but not all people learn Tai Chi from a good teacher who would address important skills such as how to protect their knees during practice. Therefore, some improper practice did harm to their knees and these cases caught media’s attention.

Chapter 7: General Discussion and Conclusion

This chapter consists of a general discussion of the thesis. It synthesises and summarises the main findings of the systematic review, the RCT and the qualitative study. The strengths and weaknesses of the studies are discussed, and further research directions are suggested. Based on the general discussion, a conclusion is drawn.

7.1 Summary of Findings

This doctoral research was designed to explore the impact of a Tai Chi intervention on psychological well-being and cardiovascular function in people with CHD and/or hypertension. There are three main components including a systematic review, a multicentre RCT, and a qualitative sub-study. The results support the beneficial effects of Tai Chi for this population.

The systematic review of 25 RCTs demonstrated that Tai Chi may be effective and safe in improving quality of life in people with CVD and/or cardiovascular risk factors. However, there was a lack of strong, well-designed studies that demonstrate unequivocally the beneficial effects of Tai Chi in decreasing stress, depression, anxiety and mood disturbances in this population. The methodological quality of studies included in this systematic review was generally poor to moderate.

In our RCT, psychological stress and physical fitness in people with CHD and/or hypertension were all significantly improved by the 24-week Tai Chi program compared to the waitlist group ($P<0.01$). No adverse events related to the Tai Chi intervention were observed.

The qualitative study involving 34 interviewees from the Tai Chi group of the RCT identified the factors influencing participants' trial participation and adherence to Tai Chi during and after the study. The facilitators of undertaking and continuing Tai Chi fall under four themes: internal/external motivation, positive feelings (toward Tai Chi, the project, and the learning

experience), benefits of Tai Chi, and future practices. The barriers of practice related to several subjective and objective concerns.

The main findings of this doctoral research are summarised below.

7.1.1 Main Findings of the Systematic Review

To the best of our knowledge, this is the first systematic review comprehensively evaluating the effects of Tai Chi on psychological well-being and quality of life in people with CVD and/or cardiovascular risk factors. Twenty-five RCTs involving 2,084 participants published between 2003 and 2016 were included in this systematic review. The methodological quality of the studies included was generally low to moderate as assessed by Cochrane risk of bias tool and GRADE.

Tai Chi appears to be potentially effective in improving QoL in people with CVD and/or cardiovascular risk factors. The meta-analyses demonstrated that Tai Chi significantly improved all domains of the SF-36 (scale of each domain from 0 to 100) including physical functioning (MD: 5.47, 95%CI: 0.66, 10.28, I^2=84%), role limitation due to physical health (MD: 11.82, 95%CI: 8.26, 15.38, I^2=32%), role limitation due to emotional health (MD: 8.27, 95%CI: 5.56, 10.98, I^2=0%), energy/vitality (MD: 7.03, 95%CI: 1.92, 12.14, I^2=81%), mental health (MD: 7.86, 95%CI: 4.29, 11.44, I^2=48%), social functioning (MD: 9.81, 95%CI: 5.19, 14.42, I^2=68%), bodily pain (MD: 6.34, 95%CI: 2.45, 10.23, I^2=53%), and general health (MD: 10.04, 95%CI: 7.15, 12.93, I^2=27%) and the MLHFQ (scale from 0 to 105) (MD: -11.10, 95%CI: -15.52, -6.68, I^2=73%).

The evidence to support beneficial effects of Tai Chi for stress, depression, anxiety and mood disturbances in this population is inconsistent. One study on stress showed that a specially designed 8-week short-form Tai Chi program significantly decreased stress in people with cardiovascular risks, as assessed by the PSS 10-item (scale from: 0 to 40) (MD -2.45, 95% CI: -3.06, -1.84) (Robins et al., 2016). Other studies demonstrated that Tai Chi reduced psychological measures including depression, anxiety and improved mood compared to the control group (Robins et al., 2016; H. Song, 2013; F. Sun & Sun, 2014; Tsai et al., 2003). In contrast, a meta-analysis of two studies demonstrated no significant difference in decreasing depression between the Tai Chi plus usual care and usual care alone groups (H. Song, 2013; E. Zhang, 2014).

Tai Chi appears safe to practice in this population. No adverse events related to Tai Chi were reported. However, only 32.0% studies included in this systematic review reported safety information.

The majority of studies included in this systematic review had high or unclear risk of bias. Stronger, better-designed studies exploring the effects of Tai Chi for psychological well-being and quality of life in people with CVD and/or cardiovascular risk factors are warranted.

7.1.2 Main Findings of the RCT

In this international, multicentre, randomised, controlled trial of participants with CHD and/or hypertension, 85% of 120 randomised participants completed the trial, 53 in the Tai Chi group and 49 in the waitlist group. The Tai Chi group demonstrated a significant reduction in PSS-10 scores at week 24 (Mean, 10.44; 95% CI, 8.86 to 12.03) compared with the waitlist group (Mean, 11.71; 95% CI, 10.01 to 13.34) (P=0.009). The findings suggest that a 24-week standardised Tai Chi intervention results in a significant reduction in psychological stress over 24 weeks in people with CHD and/or hypertension.

The mean 6MWT distance increased 58.04 meters over the 24 weeks in the Tai Chi group, while the waitlist group maintained at the similar level. The difference in 6MWT distance between groups is statistically significant (P<0.01).

We also detected significant differences in depression, diastolic blood pressure, and quality of life between the Tai Chi and waitlist control groups. The between-group differences in other secondary outcomes did not reach significance. No severe adverse events related to Tai Chi were observed during the study.

Compliance and attendance to the Tai Chi was high at 82.5% of all classes being attended by the 53 participants during the 24-week program. Compliance with home practice was also high, with 90.6% of participants practicing the 13-form Tai Chi. The proportion of practicing the walking, 13-form thumping techniques, meditation, and standing postures at home was 66.7%, 60.4%, 62.3% and 41.5%, respectively.

7.1.3 Main Findings of the Qualitative Sub-study

In the qualitative study, 34 participants in the Tai Chi group who completed the 24-week study agreed to be interviewed. Facilitators and barriers were identified as the two major domains, and six key themes with 31 codes emerged under the two domains.

Four themes that facilitated trial participation and adherence were identified. They were internal/external motivation, positive feelings, benefits of Tai Chi, and future practice. A major internal motivation was to improve health. Positive feelings had three sub-themes: positive feelings toward Tai Chi, the project, and the learning experience. Tai Chi instructor(s) were crucial in motivating participants' adherence to Tai Chi. The participants identified the benefits of committing to a regular and sustained Tai Chi practice included improvements in psychological well-being, physical health, social life and daily life activities.

Under the domain of barriers to participation and adherence, subjective and objective concerns were the two predominating themes. Subjective concerns were fears relating to the practice such as learning Tai Chi was difficult for them and that Tai Chi might harm their knees if not practiced properly. Objective concerns included time conflict, air pollution, laziness and a lack of group atmosphere.

7.2 Strengths and Weaknesses

One unique feature of this doctoral project was using a combination of qualitative and quantitative methods. This enabled the analyses of the existing RCTs and the rigorously designed RCT, to be further understood through the insights provided by participants through interviews. Specific strengths and limitations in each of the three qualitative and quantitative studies are discussed below.

7.2.1 Strengths and Weaknesses of the Systematic Review

A strength of the current systematic review is the comprehensive, bilingual literature search. We searched the major English and Chinese databases and trial registers, and screened reference lists of relevant studies to identify eligible studies.

A further strength is that we followed rigorous methodology in interpreting findings from our systematic review and meta-analyses. The methodological quality of the included studies was assessed by the risk of bias tool provided by the Cochrane Handbook for Systematic Reviews of Intervention. This tool considers selection bias, detection bias, attrition bias, reporting bias and other bias. The overall quality of the body of evidence for each outcome was assessed using GRADE criteria, considering study limitations, consistency of effect, imprecision, indirectness, and publication bias.

There are several limitations of this systematic review. Firstly, we did not conduct meta-analysis for some psychological outcomes due to significant heterogeneity among the included

studies. For those outcomes, results from individual studies were summarised and analysed. Secondly, most studies included did not apply blinding of outcome assessors. It is difficult to blind the participants and personnel in Tai Chi study, however, blinding the outcome assessors can minimise the performance bias. Thirdly, although the 25 studies reported outcomes of psychological well-being and quality of life, most of them focused more on physical outcomes as their primary outcomes. Consequently, there might be a risk of underpowered evaluation in some of the psychological outcomes, and we can only summarise related outcomes based on the limited evidence.

7.2.2 Strengths and Weaknesses of the RCT

This trial followed a rigorous methodology and has a set of well-defined research questions. We minimised the selection bias in this RCT and balanced known and unknown confounding factors through randomisation and allocation concealment. Eligible participants were randomly assigned to either the Tai Chi or waitlist group at a ratio of 1:1. An independent statistician generated the random allocation sequence, using a computer program that generated random number. Allocation concealment was achieved by using sequentially numbered, sealed, and opaque envelopes.

Another advantage of this trial is that the Tai Chi intervention used was specifically designed by a Tai Chi master with more than 30 years of Tai Chi experience – Master Zhang Peijun. The protocol took into consideration the physical capacity and psychological requirements of the target population. The relatively high adherence to the Tai Chi protocol in attendance to the group classes and home practice indicates the feasibility and acceptance of the Tai Chi intervention.

This RCT has several limitations. Firstly, the inability to provide a double-blind study design which might lead to biases in the results, since participants may have positive beliefs and high expectations with respect to the benefits of Tai Chi. In addition, the effect size across outcomes of the control group may deteriorate due to nocebo effect. It is a challenge to design a ‘sham Tai Chi’, considering the multiple components within a Tai Chi intervention. Tsang et al. (2007) used sham exercise (calisthenics and gentle stretching) as control in a single-blinded, RCT to control factors such as attention/social interaction (with classmates and Tai Chi instructor) and participation in movement activities/classes (Tsang, Orr, Lam, Comino, & Singh, 2008; Tsang et al., 2007). However, it remains uncertain whether a ‘sham exercise’ is appropriate as a

placebo control for Tai Chi, as the sham intervention failed to mimic the multiple components of Tai Chi such as intention, expectation, social support, interaction and community.

Secondly, the fact that the Tai Chi intervention was delivered by two different Tai Chi instructors in the two recruitment centres may influence the results. In the Beijing recruitment centre, Master Zhang Peijun was the primary instructor, while in the Sydney recruitment centre, the principle investigator, who has learned Tai Chi from Master Zhang Peijun for 10 years, was the primary instructor. Since the implementation of a Tai Chi intervention is an interactive teaching and learning process, efforts from both the Tai Chi instructors and the participants can influence the outcomes. To minimise these influences, we performed the following strategies in this study:

(1) A well-designed standardised protocol of a Tai Chi intervention was applied in Beijing and Sydney recruitment centres.
(2) The recruitment started in the Beijing centre first. Master Zhang Peijun worked as the primary instructor in the Beijing centre. These training sessions were mirrored by the principal investigator who worked as the primary instructor at the Sydney recruitment centre. By doing so, consistency was maximised between the two centres.
(3) In the Sydney recruitment centre, two training sessions were delivered by Master Zhang Peijun *via* videoconferencing to the participants in the Tai Chi group. In addition, Master Zhang frequently provided teaching support to the primary instructor in Sydney recruitment centre.

The attendance rate of Tai Chi classes was high and similar in the two centres, indicating that the Tai Chi intervention may have been successfully delivered by the two instructors.

Thirdly, home practice, contributing to part of the 'dosage/intensity' of the Tai Chi intervention, measured by frequency and practice time, may have varied among participants in the Tai Chi group. Although the adherence to Tai Chi at home practice was relatively high, the home practice was not done under supervision. Furthermore, since efforts from participants can influence their proficiency, the extent of mastering the important principles of Tai Chi intervention such as relaxation, concentration and meditative skills into their practice may have varied among participants. To minimise the influence of the variation of home practice, we utilised the following strategies:

(1) Participants in the Tai Chi group were encouraged to have at least three days of home practice and record it in their weekly diary.
(2) DVDs and instructional handbooks were provided to support home practice.
(3) A smartphone multi-purpose social media application called WeChat was used to give timely feedback from the instructors to participants to support their home practice.
(4) A question-and-answer session was integrated into the 20-minute break in each class to help participants enhance their understanding of the intervention.

Finally, the duration of this study, although longer than most previous trials (G. Yang et al., 2015), may have not been sufficiently long to maximise the benefits. It is widely believed by many life-long Tai Chi practitioners that the health benefits of Tai Chi improve with time as the practitioners master more skills and principles of Tai Chi. This is supported by recent clinical studies (Han et al., 2010; Y. Li et al., 2014; Wayne et al., 2015). Consequently, the long-term beneficial effects of Tai Chi in people with CHD and/or hypertension are still unknown.

7.2.3 Strengths and Weaknesses of the Qualitative Sub-Study

The semi-structured interview encouraged participants to discuss their perceptions of their trial participation and their adherence to the Tai Chi intervention. These inputs helped inform more in-depth understanding of the intervention.

There are several limitations of the qualitative sub-study. First, the interviewer who is the principal investigator was also one of the Tai Chi instructors. This may lead to a reporting bias from participants. Participants may say what they think the interviewer wishes to hear. This bias may have been reduced by conducting the interviews at the end of the study. Interview responses were similar to those self-reported in the weekly patient diaries.

Second, we did not interview people who refused to participate in this trial. They probably provide valuable information source for developing strategies for improving enrolment. This means that some factors influencing trial participation and adherence to the Tai Chi intervention may not have been identified in this study.

The third limitation of the qualitative sub-study is that, although the interview was semi-structured and the questions were open-ended, around half the questions were related to the ‘benefits’ which may lead participants to report more positive results, leading to a potential interviewer bias.

Finally, our interviewees were all Chinese or Chinese-Australian, which may limit the generalizability of our results. However, facilitators to trial participation and adherence to Tai Chi intervention were similar among the population as those previously reported among Western population (Fischer et al., 2014; Yeh et al., 2016).

7.3 Implications

7.3.1 Implications for Clinical Care

The findings of this doctoral project support the use of a Tai Chi intervention as an option for the prevention and management of people with established CVD and/or cardiovascular risk factors. Tai Chi improved quality of life and physical fitness, and reduced psychological stress and depression in our RCT (Chapter 4 and 5) and these findings were supported by our systematic review (see Chapter 3).

Tai Chi appears safe for people with CVD and/or risk factors to practice in a group class and at home. No adverse events related to Tai Chi practice were observed in our trial or found in the systematic review. Most previous studies applied a modified or simplified Tai Chi program for the participants with CVD and/or risk factors. In three previous studies, a physician (Yeh et al., 2004), a trained cardiac rehabilitation nurse (Barrow et al., 2007) or a healthcare provider (Sang et al., 2015) were also in attendance in addition to the Tai Chi instructors to monitor the safety during the class sessions. Several studies monitored the heart rate, blood pressure or ECG of participants to control exercise intensity (Han et al., 2010; X. Pan, 2016; Tsai et al., 2003; P. Wang et al., 2009; X. Wang et al., 2013; F. Wu et al., 2010; Yao et al., 2010; E. Zhang, 2014; S. Zhang & Chen, 2011). These strategies could be considered in a clinical setting if necessary.

Tai Chi practice seems enjoyable and well accepted by people with CVD and/or cardiovascular risk factors. The high adherence and retention rate in the current study indicates the acceptance of Tai Chi by this population. All participants in the qualitative study reported that they enjoyed the learning experience and would like to continue with Tai Chi after the completion of the 24-week study. CVD and other non-communicable chronic diseases require long term prevention and management which may be addressed by adoption of Tai Chi for the longer term. In addition, since Tai Chi requires no dedicated equipment, time or environment, it is an accessible, convenient, long-term choice for people with CVD and/or cardiovascular risk factors and a wider population.

Nevertheless, the findings of the current systematic review and the RCT should be interpreted with caution. Although several individual studies in the systematic review showed statistical differences between Tai Chi and control groups in reducing stress and depression, the results might not achieve clinical significance.

7.3.2 Implications for Future Work

More studies are needed to assess the effects of Tai Chi in improving psychological well-being and quality of life as their primary outcomes in people with CVD and/or cardiovascular risk factors. Most studies included in the systematic review assessed the psychological outcomes and quality of life as secondary outcomes. It is not clear whether a Tai Chi intervention specifically designed to target psychological benefits would be of more effective in reducing stress and depression. In addition, the sample size calculations for these studies were based on physical biomarkers such as blood pressure not psychological measures. Consequently, there may be a risk of underpowered evaluation in these trials on the effects of psychological well-being and quality of life in this cohort.

The combination of quantitative and qualitative methods balance weaknesses of each methodology. Mixed methods may enhance the evaluation of potential benefits of Tai Chi, since the multiple mind-body components of Tai Chi may work independently and synergistically (Wayne et al., 2013). Alternatively, psychosocial outcomes which can address patient-centred experiences may be applied in future clinical studies, as well as using physical biomarkers.

The design of a double-blind, placebo-controlled, randomised trial for a Tai Chi intervention for CVD is a methodological challenge. To date, most clinical studies on Tai Chi utilised no treatment, waitlist control or conventional exercises (such as endurance, resistance/strength, flexibility exercises or brisk walking) as control groups. ‘Sham-exercise control’ has yet been widely accepted. Considering the multiple components of Tai Chi such as social interaction and community, the necessity for sham-exercise controls is debatable. However, more research is needed to explore the design of control groups in future Tai Chi trials.

Patients with chronic non-communicable disease like CVD often suffer from other concomitant conditions/diseases and needs long-term management tools. Tai Chi, with multiple mind-body components, may be a potential option for the long-term prevention and management. However, less is known about the long-term effects of Tai Chi in this population. A pragmatic RCT with

a long follow-up period might be one possible study design option to determine the overall effectiveness of Tai Chi and the long-term benefits of Tai Chi in this cohort.

"Dosage/intensity" of Tai Chi is another issue in clinical trials. Our previous bibliometric review of Tai Chi clinical studies found that Tai Chi practice varied from 10 minutes to 2 hours each session, three 60-minute sessions per week (61/464, 13.1%) and two 60-minute sessions per week (58/464, 12.5%) were most popular, and the most common duration was 12 weeks (122/464, 26.3%), followed by 24 weeks (83/464, 17.9%) (G. Yang et al., 2015). In most studies included in our systematic review, Tai Chi was mostly practiced in group classes, and only 36.0% of studies encouraged or required home practice. Safety considerations may have been the reason for not including home practice in some of these studies (i.e. people with or at risk of CVDs practicing Tai Chi with no appropriate supervision from instructors or healthcare providers). However, lack of home practice generates concerns regarding the intensity of Tai Chi in these studies. In addition, home practice is important to promote independent practice for long-term benefits and to achieve sufficient "dosage/intensity", and should thus be strongly encouraged in future research.

An additional variable is the extent to which participants are able to master the Tai Chi skills. Our program was closely supervised and introduced in a progressive manner to secure the learning, but we did not measure the extent participants master the skills. A cross-sectional study investigated physiological parameters in 10 high-level (about 10-year experience) male Tai Chi practitioners and 10 ordinary-level (about 2-year experience) male Tai Chi practitioners aged 20-24 years during Tai Chi practice (Xiong, He, & Ni, 2013). This study demonstrated that the high-level group had significantly higher energy expenditure, heart rate, oxygen uptake and tidal volume, and less inhalation time, when compared with the ordinary-level group. More research is needed to confirm the findings.

Standardisation of a Tai Chi intervention for a specific cohort and reporting in details is crucial for the interpretation and repetition of the results of clinical trials. Since a Tai Chi intervention is an interactive learning process, the contents of the program, the expertise of Tai Chi instructors, and the efforts of participants may all influence the outcomes of the intervention. We found most studies included in our systematic review did not report sufficient details of the Tai Chi intervention, such as the components of the Tai Chi program and the expertise of the Tai Chi instruction providers.

Many people with CVD and/or risk factors might have poorer physical capacity than that of healthy individuals. In our trial, we allowed participants to progress at their own comfortable pace and intensity if they could not achieve the standardised requirement. Participants were also provided with chairs for resting during the break, and if necessary, at any time during the group classes. Several studies included in our systematic review reported using similar strategies. We recommend to consider the degree of variability for a standardised Tai Chi program in clinical trials and report in details.

Recruitment is the key challenge in all clinical trials. The current qualitative study identified that some participants had certain concerns about Tai Chi, such as harming knees if not practiced properly. Future research needs to ensure appropriate communication and discussion on the potential risks and benefits of a Tai Chi intervention during recruitment. The other concern of participants was that Tai Chi was too complex to learn. To address this concern, we suggest tailoring the Tai Chi protocol to the target participants, and to explain the requirements of physical capacity to potential participants in recruitment.

Strategies should be developed to promote adherence in future research. These could include identifying motivations of participants and improving the learning experience. The current qualitative study identified that a strong internal motivation of participants was to improve their health. In addition, reducing concerns of participants by guiding them to practise Tai Chi appropriately to ensure their safety, such as protecting their knees, during the study period. The characteristics and teaching of the Tai Chi instructors was also an important stimulus to the adherence. It is suggested to invite an experienced Tai Chi instructor to be involved in the protocol development and intervention instructions.

Additionally, all participants reported in the current qualitative study that they benefited from committing to regular and sustained Tai Chi practice to some extent, covering psychological well-being, physical health, social life and daily life activity. These self-reported benefits of Tai Chi may help the generation of hypothesis for future research. A possible hypothesis may explore the beneficial effects of a Tai Chi intervention on improving sleep quality and duration or reducing loneliness and social isolation.

7.4 Conclusion

Cardiovascular disease (CVD) is the number one cause of morbidity and mortality worldwide. Coronary heart disease (CHD) is the most common type of CVD. Hypertension is the leading cause of heart disease and stroke. Stress, anxiety and depression are associated with the development and progression of CVD and its complications, reduces health-related quality of life, impedes physical functioning, and increases recurrent cardiac events and risk of mortality. People with established CVDs often suffer from stress, anxiety and depression, which are frequently undertreated with current management strategies.

In recent years, research on Tai Chi for health and well-being has increased. Numerous studies have demonstrated various physical and psychological benefits of Tai Chi, including improvements in psychological stress, anxiety, depression, quality of life and cardiovascular function. However, there is still a lack of studies primarily investigating the effectiveness of a Tai Chi intervention on psychological stress, anxiety and depression, particularly in patients with CHD and/or hypertension.

This doctoral project was conducted to explore the effects of a Tai Chi intervention on psychological well-being and cardiovascular function in people with CHD and/or hypertension. It included a systematic review, an international, multicentre RCT and a qualitative sub-study undertaken during 2015 to 2017.

The current systematic review demonstrated that Tai Chi is potentially effective and safe in improving quality of life in people with CVD or cardiovascular risk factors. Individual studies reported the benefits of Tai Chi in decreasing stress, depression, anxiety and mood disturbance. The methodological quality of included studies was generally poor to moderate. More high-quality RCTs exploring the beneficial effects of Tai Chi on psychological well-being and quality of life in this population are warranted.

The current RCT demonstrated that a 24-week standardised Tai Chi intervention is effective in improving psychological stress and physical fitness in patients with CHD and/or hypertension when compared with the waitlist control group. The Tai Chi intervention was safe to practice under the supervision of Tai Chi instructors during class and at home.

The current qualitative study identified several facilitators and barriers influencing trial participation and adherence from the perspectives of participants. Future research is needed to

further evaluate these facilitators and barriers to improve the study design, recruitment and implementation.

To sum up, Tai Chi may be effective to improve psychological stress, fitness and quality of life and appears safe to practice in people with CHD and/or hypertension.

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Appendix 1 – PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	45
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	xii-xv
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	45-46
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	46
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	46
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	47
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	47-48
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	48-49
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	49
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	50

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	47
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	50-51
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	53
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	53-54
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	50-53
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	54
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	54, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	54-68, Table 3.2, 3.3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	69-70, Figure 3.2, 3.3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	69-70, Table 3.4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	74-83, Table 3.4, 3.5, Figure 3.4, 3.5,

			3.6, Table 3.6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	69-70, Figure 3.2, 3.3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	78
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	83-84
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	84-85
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	85
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 2 – Data extraction form

Review title or ID	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
General Information	
Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Study Methods (extract information from descriptions as stated in report/paper)	
Design *(e.g. parallel, crossover)*	
Start date	
End date	
Duration of participation *(from recruitment to last follow-up)*	
Participants (extract the description as stated in report/paper. *Include comparative information for each intervention or comparison group if available)*	
Setting *(including location and social context)*	
Inclusion criteria	
Exclusion criteria	
Total no. randomised	
Baseline imbalances	
Withdrawals and exclusions *(if not provided below by outcome)*	

Age	
Sex	
Illness and Severity	
Co-morbidities	
Other relevant socio-demographics	
Subgroups measured	
Subgroups reported	
Intervention groups (extract the description as stated in report/paper. *Copy and paste table for each intervention and comparison group)*	
Group name	
No. randomised to group	
Description *(include sufficient details, e.g. style, form, components)*	
Duration of treatment	
Timing *(e.g. frequency, duration of each practice)*	
Learning method *(e.g. DVD, instructors, one-to-one, in group)*	
Providers *(e.g. a Tai Chi instructor with 10 years of experience etc. if relevant)*	
Co-interventions	
Compliance	
Outcomes (extract the description as stated in report/paper. *Copy and paste table for each outcome*	
Outcome name	

Time points measured *(specify whether from start or end of intervention)*							
Time points reported							
Outcome definition *(with diagnostic criteria if relevant)*							
Person measuring/ reporting							
Scales: upper and lower limits *(indicate whether high or low score is good)*							
Is outcome/tool validated?		☐Yes ☐No ☐Unclear					
Imputation of missing data *(e.g. assumptions made for ITT analysis)*							
Assumed risk estimate *(e.g. baseline or population risk noted in Background)*							
Results	*Dichotomous outcome*	**Intervention**		**Comparison**			
		No. with event	Total in group	No. with event	Total in group		
	Continuous outcome	**Intervention**			**Comparison**		
		Mean	SD	No. Participants	Mean	SD	No. Participants

Risk of Bias assessment		
Domain	Risk of bias	Support for judgement *(include direct quotes where available with explanatory comments)*
	Low High Unclear	

Random sequence generation *(selection bias)*	☐ ☐ ☐	
Allocation concealment *(selection bias)*	☐ ☐ ☐	
Blinding of outcome assessment *(detection bias)*	☐ ☐ ☐	
Incomplete outcome data *(attrition bias)*	☐ ☐ ☐	
Selective outcome reporting? *(reporting bias)*	☐ ☐ ☐	
Other bias	☐ ☐ ☐	
Other information (extract the description as stated in report/paper**)**		
Key conclusions of authors		
Notes:		

Appendix 3 – CONSORT Checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	86
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	xii-xv
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	85 & Chapter 2
	2b	Specific objectives or hypotheses	86
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	87
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Appendix 13
Participants	4a	Eligibility criteria for participants	87-88
	4b	Settings and locations where the data were collected	89

Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	91-93
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	93-99, Table 4.1
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Appendix 13
Sample size	7a	How sample size was determined	88
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	91
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	91
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	91
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	91
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	91
	11b	If relevant, description of the similarity of interventions	N/A
	12a	Statistical methods used to compare groups for primary and secondary outcomes	101-102

Statistical methods	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	101-102
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	104-107, Figure 5.1
	13b	For each group, losses and exclusions after randomisation, together with reasons	104-5, Table 5.1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	107
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	107-110, Table 5.2, 5.3
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	104, Figure 5.1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	110-143
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	122-123
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	114, 138
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	140-141
Discussion			

Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	162, 189-191
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	161-162
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	143-161
Other information			
Registration	23	Registration number and name of trial registry	86
Protocol	24	Where the full trial protocol can be accessed, if available	86
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	N/A

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Appendix 4 – Description of the Tai Chi intervention

English Version

Instruction: The standardized Tai Chi intervention is offered over a period of 24 weeks, consisting of a 12-week intensive Tai Chi intervention period (from week 1 to 12) and a 12-week sustained Tai Chi intervention period (from week 13 to 24). In the intensive period the Tai Chi class lasted 120 minutes per session, twice weekly; in the sustained period the Tai Chi class also lasted 120 minutes per session, once weekly. The classes were held both in a capacious room. The details are showed in the following table.

Week	**Activities**	**Duration, min**
1	*Introductory session: overview of program*	
	1st Class:	120
	a) Tai Chi history, theories and principles	30
	b) Demonstration of Tai Chi intervention	30
	c) Questions and answers	20
	d) Description of class format	10
	e) Learning walking lunges	15
	f) Learning standing posture	15
	2nd Class:	120
	a) Tai Chi theories and principles	20
	b) Learning meditation	20
	c) Learning standing posture	20
	d) Learning 13-form of Thumping Techniques	30
	e) Learning the 1st movement of the 13-form Chen-style Tai Chi	30
2-12	Walking lunges *(Repeated during all sessions)*	10
	Meditation *(Repeated during all sessions)*	10
	13-form of Thumping Techniques *(Repeated during all sessions)*	30
	Short break and Question-and-Answer	20
	Review and learning the 2nd-13th movement of the 13-form Chen-style Tai Chi consecutively (1-2 new movement(s) each week)	50
13-24	Walking lunges *(Repeated during all sessions)*	10
	Meditation *(Repeated during all sessions)*	10
	13-form of Thumping Techniques *(Repeated during all sessions)*	30
	Short break and Question-and-Answer	20
	Review the sequence of the 13-form Chen-style Tai Chi, focusing on the principle of each movement, *Qi* and mind	50

Chinese Version 中文版本

说明：太极拳干预持续时间为 24 周，包括 12 周的强化干预期（从第 1 到 12 周）和 12 周的持续干预期（从 13 到 24 周）。在强化干预期，每次太极拳课为 120 分钟，一周两次；在持续干预期，每次太极拳课为 120 分钟，一周一次。太极拳课均为室内教学。具体干预内容和安排如下表：

周	活动项目	时间（分钟）
1	介绍太极拳干预	
	第一节课:	120
	1. 介绍太极拳的历史、理论和原则	30
	2. 太极拳干预的示范	30
	3. 问答环节	20
	4. 介绍上课形式	10
	5. 学习打坐	15
	6. 学习站桩	15
	第二节课:	120
	1. 太极拳理论和原则	20
	2. 学习打坐	20
	3. 学习站桩	20
	4. 学习养生十三功	30
	5. 学习十三式太极拳的起式	30
2-12	大步走(每节课练习)	10
	打坐 (每节课练习)	10
	养生十三功(每节课练习)	30
	休息和问答环节	20
	复习和学习十三式陈式太极拳的第 2-13 个动作(每周学习 1-2 个新动作)	50
13-24	大步走 (每节课练习)	10
	打坐(每节课练习)	10
	养生十三功(每节课练习)	30
	休息和问答环节	20
	复习十三式陈式太极拳套路，注重动作的细节，并体悟太极内涵	50

Appendix 5 – Participant Diary

We collected the data using pre-designed participant diary. The participant diary sample is as follows:

Sample of Participant Diary

Date (DD/MM/YY)	**Meditation**	**Walking**	**13-form Chen-style Tai Chi**	**13-form Thumping Techniques**	**Standing Posture**
	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________
	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________
	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________
	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________
	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________	◯Yes, ___min; ◯No, Reason: ___________

Chinese Version 中文版本

患者日记

日期 (年 月 日)	养生静坐	健步走	养生太极十三式	养生十三功	养生静坐
	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________
	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________
	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________
	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________
	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________	◯练习，__分钟 ◯未练，原因： ________

Appendix 6 – Perceived Stress Scale (PSS-10)

English Version Sample of PSS-10

Name: _____ ID: _____ Date: ____/_____/_____

INSTRUCTION: The questions below ask you about your feelings and thoughts during **THE LAST MONTH**. In each case, please indicate your response by placing a check mark **"√"** over the circle representing **HOW OFTEN** you felt or thought a certain way.

	Never	**Almost Never**	**Some-times**	**Fairly Often**	**Very Often**
	0	**1**	**2**	**3**	**4**
1. In the last month, how often have you been upset because of something that happened unexpectedly?	□	□	□	□	□
2. In the last month, how often have you felt that you were unable to control the important things in your life?	□	□	□	□	□
3. In the last month, how often have you felt nervous and "stressed"?	□	□	□	□	□
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	□	□	□	□	□
5. In the last month, how often have you felt that things were going your way?	□	□	□	□	□
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	□	□	□	□	□
7. In the last month, how often have you been able to control irritations in your life?	□	□	□	□	□
8. In the last month, how often have you felt that you were on top of things?	□	□	□	□	□
9. In the last month, how often have you been angered because of things that were outside your control?	□	□	□	□	□
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	□	□	□	□	□

Chinese Version 中文版本-应激感受量表（PSS-10）

指导语：以下问题询问你在过去一个月的一些感受和想法，对于每一个问题，请选出符合你的情况。

	从未有	几乎没有	偶尔	经常	非常多
	0	1	2	3	4
1.在过去的一个月里，你有多少时间因为发生意外的事情而感到心烦意乱？	□	□	□	□	□
2.在过去的一个月里，有多少时间你感到无法掌控生活中重要的事情？	□	□	□	□	□
3.在过去的一个月里，有多少时间你感觉到神经紧张或“快被压垮了”？	□	□	□	□	□
4.在过去的一个月里，有多少时间你对自己处理个人问题的能力感到有信心？	□	□	□	□	□
5.在过去的一个月里，有多少时间你感到事情发展和你预料的一样？	□	□	□	□	□
6.在过去的一个月里，有多少时间你发现自己无法应付那些你必须去做的事情。	□	□	□	□	□
7.在过去的一个月里，日常生活中有多少时间你能够控制自己的愤怒情绪？	□	□	□	□	□
8.在过去的一个月里，有多少时间你感到处理事情得心应手（事情都在你的控制之中）？	□	□	□	□	□
9.在过去的一个月里，有多少时间你因为一些超出自己控制能力的事情而感到愤怒？	□	□	□	□	□
10.在过去的一个月里，有多少时间你感到问题堆积如山，已经无法逾越？	□	□	□	□	□

本量表译自 Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. Journal of Health and Social Behavior. 24, 385-396. 王振（2008）上海交通大学医学院附属精神卫生中心

Appendix 7 – Zung Self-Rating Anxiety Scale (SAS)

English Version Sample of SAS

For each item below, please place a check mark (√) in the column which best describes how often you felt or behaved this way during the past several days. Bring the completed form with you to the office for scoring and assessment during your office visit.

Place check mark (√) in correct column.	**A little of the time**	**Some of the time**	**Good part of the time**	**Most of the time**
1. I feel more nervous and anxious than usual.				
2. I feel afraid for no reason at all.				
3. I get upset easily or feel panicky.				
4. I feel like I'm falling apart and going to pieces.				
5. I feel that everything is all right and nothing bad will happen.				
6. My arms and legs shake and tremble.				
7. I am bothered by headaches neck and back pain.				
8. I feel weak and get tired easily.				
9. I feel calm and can sit still easily.				
10. I can feel my heart beating fast.				
11. I am bothered by dizzy spells.				
12. I have fainting spells or feel like it.				
13. I can breathe in and out easily.				
14. I get feelings of numbness and tingling in my fingers and toes.				
15. I am bothered by stomach aches or indigestion.				
16. I have to empty my bladder often.				
17. My hands are usually dry and warm.				
18. My face gets hot and blushes.				
19. I fall asleep easily and get a good night's rest.				
20. I have nightmares.				

Chinese Version 中文版本-焦虑自评量表（SAS）

姓名：_____ 编号：_____ 填表日期:_____年_____月____日

请针对以下描述，根据您的情况，在适当的地方打勾“√”	几乎没有	偶尔	经常	绝大部分或全部时间
1. 我觉得比平常更容易紧张和着急（焦虑）。				
2. 我无缘无故地感到害怕。				
3. 我容易心里烦乱或觉得惊恐。				
4. 我觉得我可能将要发疯。				
5. 我觉得一切都好，也不会发生什么不幸。				
6. 我手脚发抖打颤。				
7. 我因为头痛、劲痛和背痛而苦恼。				
8. 我感觉容易衰弱和疲乏。				
9. 我觉得心平气和，并且容易安静坐着。				
10. 我觉得心跳很快。				
11. 我因为一阵阵头晕而苦恼。				
12. 我有晕倒发作或觉得要晕倒似的。				
13. 我呼气吸气都感到不容易。				
14. 我手脚麻木和刺痛。				
15. 我因为胃痛和消化不良而苦恼。				
16. 我常常要小便（尿意频繁）。				
17. 我的手常常是干燥温暖的。				
18. 我脸红发热。				
19. 我容易入睡并且整夜睡的很好。				
20. 我做恶梦。				

Appendix 8 – Beck Depression Inventory-II (BDI-II)

English Version Example of BDI-II

Name: _____ ID: _____ Date: _____/_____/_____

Instruction: Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. **Circle** the number beside the statement you have picked.

1. Sadness 0 I do not feel sad. 1 I feel sad much of the time. 2 I am sad all the time. 3 I am so sad/unhappy that I can't stand it.	**12. Loss of Interest** 0 I have not lost interest in other people or activities. 1 I am less interested in other people or things than before. 2 I have lost most of my interest in other people or things. 3 It's hard to get interested in anything.
2. Pessimism 0 I am not discouraged about my future. 1 I feel more discouraged about my future than I used to be. 2 I do not expect things to work out for me. 3 I feel my future is hopeless and will only get worse.	**13. Indecisiveness** 0 I make decisions about as well as ever. 1 I find it more difficult to make decisions than usual 2 I have much greater difficulty in making decisions than I used to. 3 I have trouble making any decisions.
3. Past failure 0 I do not feel like a failure. 1 I have failed more than I should have. 2 As I look back, I see a lot of failures. 3 I feel I am a total failure as a person.	**14. Worthlessness** 0 I do not feel I am worthless. 1 I don't consider myself as worthwhile and useful as I used to. 2 I feel more worthless as compared to other people. 3 I feel utterly worthless.
4. Loss of Pleasure 0 I get as much pleasure as I ever did from the things I enjoy. 1 I don't enjoy things as much as I used to. 2 I get very little pleasure from the things I used to enjoy.	**15. Loss of Energy** 0 I have as much energy as ever. 1 I have less energy than I used to have. 2 I don't have enough energy to do very much. 3 I don't have enough energy to do anything.

3 I can't get any pleasure from the things I used to enjoy.	
5. Guilty Feelings 0 I don't feel particularly guilty. 1 I feel guilty over many things I have done or should have done. 2 I feel quite guilty most of the time. 3 I feel guilty all of the time.	**16. Changes in Sleeping Pattern** 0 I have not experienced any change in my sleeping pattern. 1 I sleep somewhat less than usual. 2 I wake up 1-2 hours early and can't get back to sleep. 3 I wake up a few hours early and can't get back to sleep.
6. Punishment Feelings 0 I don't feel I am being punished. 1 I feel I may be punished. 2 I expect to be punished. 3 I feel I am being punished.	**17. Irritability** 0 I am no more irritable than usual. 1 I am more irritable than usual. 2 I am much more irritable than usual. 3 I am irritable all the time.
7. Self-Dislike 0 I feel the same about myself as ever. 1 I have lost confidence in myself. 2 I am disappointed in myself. 3 I dislike myself.	**18. Changes in Appetite** 0 I have not experienced any change in my appetite. 1 My appetite is somewhat less than usual. 2 My appetite is much less than before. 3 I have no appetite at all.
8. Self-Criticalness 0 I don't feel I am any worse than anybody else. 1 I am critical of myself for my weakness or mistakes. 2 I blame myself all the time for my faults. 3 I blame myself for everything bad that happens.	**19. Weight Loss** 0 I haven't lost much weight, if any, lately. 1 I have lost more than five pounds. 2 I have lost more than ten pounds. 3 I have lost more than fifteen pounds.
9. Suicidal Thoughts or Wishes 0 I don't have any thoughts of killing myself. 1 I have thoughts of killing myself, but I would not carry them out. 2 I would like to kill myself. 3 I would kill myself if I had the chance.	**20. Tiredness or Fatigue** 0 I am no more tired or fatigued than usual. 1 I get more tired or fatigued more easily than usual. 2 I am too tired or fatigued to do a lot of the things I used to do. 3 I am too tired or fatigued to do most of the things I used to do.

10. Crying 0 I don't cry any more than I used to. 1 I cry more than I used to. 2 I cry over every little thing. 3 I feel like crying, but I can't.	**21. Loss of Interest in Sex** 0 I have not noticed any recent change in my interest in sex. 1 I am less interested in sex than I used to be. 2 I am much less interested in sex now. 3 I have lost interest in sex completely.
11. Agitation 0 I am no more restless or wound up than usual. 1 I feel more restless or wound up than usual. 2 I am so restless or agitated that it's hard to stay still. 3 I am so restless or agitated that I have to keep moving or doing something.	

Chinese version 中文版本

Beck 抑郁自评量表-II（BDI-II）

填表说明：

1.仔细阅读每项，结合您最近一周内的情绪（包括今天）作出符合自己情况的选择，再接着做下一题;

2. 选择 4 种情况中的一种（0、1、2、3）；

3. 建议时间约 5-10 分钟。

（一） 0. 我没有感到悲伤。 1. 我有时感到悲伤。 2. 我总是感到悲伤，而且不能摆脱它。 3. 我感到极度悲伤或不愉快，不堪忍受。	（十二） 0. 我对别人没有失去兴趣。 1. 与过去相比，我对别人的兴趣减退了。 2. 我对别人已没有多大兴趣了。 3. 我对别人已经毫无兴趣。
（二） 0. 我对未来有足够的信心。 1. 我对未来信心不足。 2. 我感到对未来没有什么可期望。 3. 我感到未来毫无希望，情况也不会改善。	（十三） 0. 我仍象往常一样自己可以决定事情。 1. 与过去相比，我常推迟作出决定。 2. 与过去相比，我常难以作出决定。 3. 我不能做成任何决定。
（三） 0. 我没有失败的感觉。 1. 我感到我比一般人失败的多些。 2. 当我回顾过去时，我看到的都是失败。 3. 我感到自己总是失败，毫无出息。	（十四） 0. 我感到自己各方面跟过去一样。 1. 我担心自己在变老或失去魅力。 2. 我感到青春已逝而失去魅力。 3. 我确信自己很丑。
（四） 0. 我对做过的事，没有什么不满意的。 1. 我对做过的事，不太满意。 2. 我对任何事情都感到不满意。 3. 我对一切都感到厌倦。	（十五） 0. 我能和往常一样地工作。 1. 开始去做某些事时要付出很大的努力。 2. 我不得不强迫自己去做事情。 3. 我什么事也干不成。
（五） 0. 我不感到有什么罪恶感。 1. 有时，我感到自己有罪。 2. 大部分时间内，我感到自己有罪。 3. 我总是感到自己有罪。	（十六） 0. 我象往常一样睡的香。 1. 我不如以前睡得香。 2. 我比过去早 1~2 小时醒来，而且再难入睡。 3. 我比过去早几小时醒来，而再也不能入睡。

（六） 0. 我不认为我会受罚。 1. 我感到我可能受罚。 2. 我预感到我会受罚。 3. 我感到我正受到惩罚。	（十七） 0. 我并不感到比往常更容易疲倦。 1. 我比过去容易疲倦。 2. 我做什么事情都容易疲倦。 3. 我疲乏得不愿意做什么事了。
（七） 0. 我从没有大失所望的感觉。 1. 我有时有对自己感到失望。 2. 我对自己感到厌恶。 3. 我十分怨恨自己。	（十八） 0. 我的食欲和以前一样好。 1. 我的食欲不如以前好。 2. 我的食欲很差。 3. 我没有一点食欲。
（八） 0. 我从不人为我比别人差。 1. 对自己的缺点和错误总是感到不满。 2. 对自己的失败总是在责备自己。 3. 对所有的过错总是在谴责自己。	（十九） 0. 近来我的体重没有减轻多少。 1. 我的体重减轻了 2 公斤多。 2. 我的体重减轻了 5 公斤多。 3. 我的体重减轻了 7 公斤多。
（九） 0. 我从没有想过要自杀。 1. 我想过自杀，但没有干过。 2. 我想要去自杀。 3. 如果有机会，我会自杀的。	（二十） 0. 我对自己的健康并不比往常更担心。 1. 我担心自己的健康，如胃不舒服、便秘。 2. 我很担心自己健康，很难去顾及其他。 3. 我非常担心自己的健康，根本不能想别的事情。
(十） 0. 我不象一般人那样爱哭。 1. 我比过去爱哭了。 2. 我近来爱哭了。 3. 我过去总爱哭，但现在想哭也哭不出来了。	（二十一） 0. 最近我对性的兴趣跟过去一样没有变化。 1. 我不象往常那样对性感兴趣。 2. 我现在对性没有多大兴趣。 3. 我对性完全失去了兴趣。
（十一） 0. 和过去相比，我现在生气并不更多。 1. 我现在比过去更容易生气发火。 2. 我觉得现在所有的时间都容易生气。 3. 过去使我生气的事，现在一点也不能使我生气了。	

Appendix 9 – Medical Outcomes Study 36-Item Short Form Healthy Survey (SF-36)

Name: _____ ID: _____ Date: _____/_____/_____

Instruction: Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

1. In general, would you say your health is:

◯ Excellent ◯ Very Good ◯ Good ◯ Fair ◯ Poor

2. Compared to one year ago, how would you rate your health in general now?

◯ Much better now than one year ago

◯ Somewhat better now than one year ago

◯ About the same

◯ Somewhat worse now than one year ago

◯ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(1) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

◯ Yes. Limited a lot ◯ Yes. Limited a Little ◯ No. Not limited at all

(2) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

◯ Yes. Limited a lot ◯ Yes. Limited a Little ◯ No. Not limited at all

(3) Lifting or carrying groceries

◯ Yes. Limited a lot ◯ Yes. Limited a Little ◯ No. Not limited at all

(4) Climbing several flights of stairs

◯ Yes. Limited a lot ◯ Yes. Limited a Little ◯ No. Not limited at all

(5) Climbing one flight of stairs

◯ Yes. Limited a lot ◯ Yes. Limited a Little ◯ No. Not limited at all

(6) Bending, kneeling, or stooping

◯ Yes. Limited a lot ◯ Yes. Limited a Little ◯ No. Not limited at all

(7) Walking more than a mile

◯ Yes. Limited a lot ◯ Yes. Limited a Little ◯ No. Not limited at all

(8) Walking several blocks

◯ Yes. Limited a lot ◯ Yes. Limited a Little ◯ No. Not limited at all

(9) Walking one block

◯ Yes. Limited a lot ◯ Yes. Limited a Little ◯ No. Not limited at all

(10) Bathing or dressing yourself

◯ Yes. Limited a lot ◯ Yes. Limited a Little ◯ No. Not limited at all

PHYSICAL HEALTH PROBLEMS:

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?

(1) Cut down the amount of time you spent on work or other activities

◯ Yes ◯ No

(2) Accomplished less than you would like

◯ Yes ◯ No

(3) Were limited in the kind of work or other activities

◯ Yes ◯ No

(4) Had difficulty performing the work or other activities (e.g., it took extra effort)

◯ Yes ◯ No

EMOTIONAL HEALTH PROBLEMS:

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)?

(1) Cut down the amount of time you spent on work or other activities

◯ Yes ◯ No

(2) Accomplished less than you would like

◯ Yes ◯ No

(3) Didn't do work or other activities as carefully as usual

◯ Yes ◯ No

SOCIAL ACTIVITIES:

6. Emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

◯ Not at all ◯ Slightly ◯ Moderately ◯ Severe ◯ Very Severe

PAIN:

7. How much bodily pain have you had during the past 4 weeks?

◯ Not at all ◯ Slightly ◯ Moderately ◯ Severe ◯ Very Severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

◯ Not at all ◯ Slightly ◯ Moderately ◯ Severe ◯ Very Severe

ENERGY AND EMOTIONS:

9. These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

(1) Did you feel full of pep?

◯ All of the time

◯ Most of the time

◯ A good Bit of the Time

◯ Some of the time

◯ A little bit of the time

◯ None of the Time

(2) Have you been a very nervous person?

◯ All of the time

◯ Most of the time

◯ A good Bit of the Time

◯ Some of the time

◯ A little bit of the time

◯ None of the Time

(3) Have you felt so down in the dumps that nothing could cheer you up?

◯ All of the time

◯ Most of the time

◯ A good Bit of the Time

◯ Some of the time

◯ A little bit of the time

◯ None of the Time

(4) Have you felt calm and peaceful?

◯ All of the time

◯ Most of the time

◯ A good Bit of the Time

◯ Some of the time

◯ A little bit of the time

◯ None of the Time

(5) Did you have a lot of energy?

◯ All of the time

◯ Most of the time

◯ A good Bit of the Time

◯ Some of the time

◯ A little bit of the time

◯ None of the Time

(6) Have you felt downhearted and blue?

◯ All of the time

◯ Most of the time

◯ A good Bit of the Time

◯ Some of the time

◯ A little bit of the time

◯ None of the Time

(7) Did you feel worn out?

◯ All of the time

◯ Most of the time

◯ A good Bit of the Time

◯ Some of the time

◯ A little bit of the time

◯ None of the Time

(8) Have you been a happy person?

◯ All of the time

◯ Most of the time

◯ A good Bit of the Time

◯ Some of the time

◯ A little bit of the time

◯ None of the Time

(9) Did you feel tired?

◯ All of the time

◯ Most of the time

◯ A good Bit of the Time

◯ Some of the time

◯ A little bit of the time

◯ None of the Time

SOCIAL ACTIVITIES:

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 with friends, relatives, etc.)?

◯ All of the time

◯ Most of the time

◯ A good Bit of the Time

◯ Some of the time

◯ A little bit of the time

◯ None of the Time

GENERAL HEALTH:

11. How true or false is each of the following statements for you?

(1) I seem to get sick a little easier than other people

◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

(2) I am as healthy as anybody I know

◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

(3) I expect my health to get worse

◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

(4) My health is excellent

◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

Chinese version 中文版本

SF-36生活质量调查表

姓名：_____受试者编号：_____ 填表日期：_____年____月___日

☐基线 ☐12周 ☐24周

1. 总的来说，您的健康状况是：

☐非常好 ☐很好 ☐好 ☐一般 ☐差

2. 跟1年前相比您觉得自己的健康状况是：

☐比1年前好多了 ☐比1年前好一些 ☐跟1年前差不多

☐比1年前差一些 ☐比1年前差多了

健康和日常活动

3. 以下这些问题都和日常活动有关。请您想一想，您的健康状况是否限制了这些活动？如果有限制，程度如何？

（1） 重体力活动。如跑步、参加剧烈运动等：

☐很大程度受限制 ☐有些限制 ☐毫无限制

（2） 适度的活动。如移动一张桌子、扫地、打太极拳、做简单体操等：

☐很大程度受限制 ☐有些限制 ☐毫无限制

（3） 手提日用品。如买菜、购物等：

☐很大程度受限制 ☐有些限制 ☐毫无限制

（4） 上几层楼：☐很大程度受限制 ☐有些限制 ☐毫无限制

（5） 上一层楼：☐很大程度受限制 ☐有些限制 ☐毫无限制

（6） 弯腰、屈膝、下蹲：☐很大程度受限制 ☐有些限制 ☐毫无限制

（7） 步行1500米以上的路程：

☐很大程度受限制 ☐有些限制 ☐毫无限制

（8） 步行1000米以上的路程：

☐很大程度受限制 ☐有些限制 ☐毫无限制

（9） 步行100米的路程：□很大程度受限制 □有些限制 □毫无限制

（10） 自己洗澡、穿衣：□很大程度受限制 □有些限制 □毫无限制

4. 在过去4个星期里，您的工作和日常活动有无因为身体健康的原因而出现以下这些问题？

（1）减少了工作或其他活动时间：□是 □不是

（2）本来想要做的事情只能完成一部分：□是 □不是

（3）想要干的工作或活动种类受到限制：□是 □不是

（4）完成工作或其他活动困难增多（比如需要额外努力）：□是 □不是

5. 在过去4个星期里，您的工作和日常活动有无因为情绪的原因（如压抑或忧虑）而出现以下这些问题？

（1）减少了工作或活动时间：□是 □不是

（2）本来想要做的事情只能完成一部分：□是 □不是

（3）干事情不如平时仔细：□是 □不是

6. 在过去4个星期里，您的健康或情绪不好在多大程度上影响了您与家人、朋友、邻居或集体的正常社会交往？

□没有影响 □有一点影响 □中等影响 □影响很大 □影响非常大

7. 在过去4个星期里，您有身体疼痛吗？

□没有疼痛 □有一点疼痛 □中等疼痛 □严重疼痛 □很严重疼痛

8. 在过去4个星期里，您的身体疼痛影响了您的工作和家务吗？

□没有影响 □有一点影响 □中等影响 □影响很大 □影响非常大

您的感觉

9. 以下这些问题是关于过去1个月里您自己的感觉，对每一条问题所说的事情，您的情况是什么样的？

（1） 您觉得生活充实：

□所有的时间 □大部分时间 □比较多时间

□一部分时间 □小部分时间 □没有这种感觉

（2） 您是一个敏感的人：

□所有的时间 □大部分时间 □比较多时间

□一部分时间　　□小部分时间　　□没有这种感觉

（3） 您的情绪非常不好，什么事都不能使您高兴起来：

□所有的时间　　□大部分时间　　□比较多时间

□一部分时间　　□小部分时间　　□没有这种感觉

（4） 您的心理很平静：

□所有的时间　　□大部分时间　　□比较多时间

□一部分时间　　□小部分时间　　□没有这种感觉

（5） 您做事精力充沛：

□所有的时间　　□大部分时间　　□比较多时间

□一部分时间　　□小部分时间　　□没有这种感觉

（6） 您的情绪低落：

□所有的时间　　□大部分时间　　□比较多时间

□一部分时间　　□小部分时间　　□没有这种感觉

（7） 您觉得筋疲力尽：

□所有的时间　　□大部分时间　　□比较多时间

□一部分时间　　□小部分时间　　□没有这种感觉

（8） 您是个快乐的人：

□所有的时间　　□大部分时间　　□比较多时间

□一部分时间　　□小部分时间　　□没有这种感觉

（9） 您感觉厌烦：

□所有的时间　　□大部分时间　　□比较多时间

□一部分时间　　□小部分时间　　□没有这种感觉

10. 不健康影响了您的社会活动（比如走亲访友）：

□所有的时间　　□大部分时间　　□比较多时间

□一部分时间　　□小部分时间　　□没有这种感觉

总体健康情况

11. 请看下列每一条说法，哪一种答案最符合您的情况？

（1） 我好像比别人容易生病：

□绝对正确　　□大部分正确　　□不能肯定

□大部分错误　　□绝对错误

（2） 我跟周围人一样健康：

□绝对正确　　□大部分正确　　□不能肯定

□大部分错误　　□绝对错误

（3） 我认为我的健康状况在变坏：

□绝对正确　　□大部分正确　　□不能肯定

□大部分错误　　□绝对错误

（4） 我的健康状况非常好：

□绝对正确　　□大部分正确　　□不能肯定

□大部分错误　　□绝对错误

Appendix 10 – Weekly Status Check

Instruction: This form should be completed in the last session each week by participants.

Name: _____ Study ID #: _____
Date: _____ Week #: _____
Telephone: _____ Email: _____

During the past week have you had any of the following?

	Yes	No
1. Acute illnesses	❒	❒
Please specify_____		
2. Change in medication (prescribed, over-the-Counter, herbal, nutritional supplement)	❒	❒
Please specify_____		
3. Visits to a health care professional	❒	❒
Kind_____		
Indication_____		
Treatment_____		
4. New physical, mental, or emotional symptoms of any kind	❒	❒
Please describe: _____		
5. Smoking or Alcohol use	❒	❒
Describe the frequency and amount: _____		
6. Have you attended all exercise sessions?	❒	❒
If not, number attended_____		
Reason for missed session(s): _____		

7. Other Questions or Comments of subject:

_____

Comments:

- ❑ protocol completed
- ❑ not completed due to death
- ❑ not completed due to refusal, drop-out or loss to follow-up
- ❑ not completed due to medical illness or incapacity
- ❑ not completed due to examiner failure or error
- ❑ not completed due to other: _____

Chinese version 中文版本-每周情况调查

说明：请在每周最后一次太极课填写此表格。

姓名：_____ 患者编号#：_____
日期：_____ 第几周#：_____
电话：_____ 电子邮箱：_____

在过去一周内您是否出现如下情况？

	是	否
1. 急性疾病	❒	❒
具体情况描述_____		
2. 变换用药（处方药，非处方药，草药，保健品）	❒	❒
具体情况描述_____		
3. 看医生	❒	❒
病名_____		
症状_____		
治疗方案_____		
4. 出现任何新的身体、心里或情绪上的症状	❒	❒
请描述:_____		
5. 吸烟或饮酒	❒	❒
请描述频次和用量：_____		
6. 您参加了本周所有的太极课程吗?	❒	❒
如果没有全参加，那么参加的次数_____		
没参加太极课的原因_____		
7. 其他问题、意见、感受:		

评语:

- ❑ 完成方案
- ❑ 由于死亡未能完成方案
- ❑ 由于拒绝参加、脱落或失访未能完成方案
- ❑ 由于疾病或体能状况未能完成方案
- ❑ 由于其他原因未能完成方案：_____

Appendix 11 – Checklist of Risk Contraindications

Contraindications to exercise testing

-Absolute Acute myocardial infarction (within two days)

-High-risk unstable angina

-Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise

-Symptomatic severe aortic stenosis

-Uncontrolled symptomatic heart failure

-Acute pulmonary embolus or pulmonary infarction

-Acute myocarditis or pericarditis

-Acute aortic dissection

Relative*

-Left main coronary stenosis

-Moderate stenotic valvular heart disease

-Electrolyte abnormalities

-Severe arterial hypertension†

-Tachyarrhythmias or bradyarrhythmias

-Hypertrophic cardiomyopathy and other forms of outflow tract obstruction

-Mental or physical impairment leading to inability to exercise adequately

-High-degree atrioventricular block

* Relative contraindications can be superseded if the benefits of exercise outweigh the risks.

† In the absence of definitive evidence, the committee suggests systolic blood pressure of >200mmHg and/or diastolic blood pressure of >10 mm Hg.

Appendix 12 – Adverse Event From

General	
Event	_____ _____ _____ _____ _____
Onset Date	☐☐ / ☐☐☐ / ☐☐☐☐
Resolve Date	☐☐ / ☐☐☐ / ☐☐☐☐
☐ Ongoing	

Severity	
Indicate the severity of the event	☐ Mild
	☐ Moderate
	☐ Severe

Frequency	
Indicate the frequency of the event	☐ Intermittent
	☐ Single Episode

Action Taken with Study Intervention	
Please indicate what action was taken regarding the Study Treatment	☐ None
	☐ Study Intervention Interrupted

	☐ Study Intervention Permanently Discontinued
	☐ Additional Treatment Given

Action Taken with Participant	
Indicate what action was taken regarding the participant (Check all relevant options)	☐ Withdrawn
	☐ Treatment Given, Specify _____
	☐ Other, Specify _____
	☐ No Action

Causality	
In the investigator's judgment, what was the most likely cause of the Adverse Event	☐ Study Intervention
	☐ Disease under study
	☐ Other Illness _____
	☐ Concomitant Treatment _____
	☐ Other _____

Serious Adverse Event	
Is this a serious adverse event?	☐ Yes (Please complete an SAE form)
	☐ No

Sign Off

This AE report has been carried out by:	_____ Signature

Date	__ __ / __ __ __ / __ __ __ __

Investigator Sign Off

Investigator Sign Off	_____ Signature
Date	__ __ / __ __ __ / __ __ __ __

Appendix 13 – Human Research Ethics Committee Approval Letters

Locked Bag 1797
Penrith NSW 2751 Australia
Office of Research Services

ORS Reference: H11189

University of Western Sydney

HUMAN RESEARCH ETHICS COMMITTEE

29 June 2015

Associate Professor Dennis Chang
School of Science and Health

Dear Dennis,

I wish to formally advise you that the Human Research Ethics Committee has approved your research proposal H11189 "Effects of Tai Chi on Stress and Cardiovascular Function in `Younger¿ Patients with Coronary Heart Disease", until 31 March 2018 with the provision of a progress report annually if over 12 months and a final report on completion.

Conditions of Approval

1. A progress report will be due annually on the anniversary of the approval date.

2. A final report will be due at the expiration of the approval period.

3. Any amendments to the project must be approved by the Human Research Ethics Committee prior to being implemented. Amendments must be requested using the HREC Amendment Request Form: http://www.uws.edu.au/__data/assets/pdf_file/0018/491130/HREC_Amendment_Request_Form.pdf

4. Any serious or unexpected adverse events on participants must be reported to the Human Ethics Committee via the Human Ethics Officer as a matter of priority.

5. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the Committee as a matter of priority

6. Consent forms are to be retained within the archives of the School or Research Institute and made available to the Committee upon request.

Please quote the registration number and title as indicated above in the subject line on all future correspondence related to this project. All correspondence should be sent to the email address humanethics@uws.edu.au.

This protocol covers the following researchers:
Dennis Chang, Alan Bensoussan, Nerida Klupp, Jianping Liu, Hosen Kiat, Guoyan Yang

Yours sincerely

[redacted]

Professor Elizabeth Deane
Presiding Member,
Human Researcher Ethics Committee

Locked Bag 1797
Penrith NSW 2751 Australia
Research Engagement, Development and Innovation (REDI)

WESTERN SYDNEY UNIVERSITY

REDI Reference: H11189

HUMAN RESEARCH ETHICS COMMITTEE

11 July 2016

Associate Professor Dennis Chang
School of Science and Health

Dear Dennis,

RE: Amendment Request to H11189

Research Engagement, Development and Innovation (REDI) has received a request to amend your approved research protocol H11189 "Effects of Tai Chi on Stress and Cardiovascular Function in Younger Patients with Coronary Heart Disease".

The amendment has been reviewed and I am pleased to advise that it has been approved, as follows:

- Addition of site - Buddhist Compassion Relief Tzu Chi Foundation, Eastwood NSW

- Documentation shared with participants updated to reflect the change in inclusion criteria

- Inclusion criteria revised to 40 years of age and regardless of gender

- Inclusion of participants with diagnosed hypertension

- Inclusion criteria no longer includes participants experiencing a marked level of stress

- Incorporation of exit interview for participants

- Seattle Angina Questionnaire to be replaced by 36-item Short as quality of life instrument

Please do not hesitate to contact the Human Ethics Officer at humanethics@westernsydney.edu.au, if you require any further information.

Regards

[redacted]

Professor Elizabeth Deane

Presiding Member,
Human Researcher Ethics Committee
Western Sydney University

北京中医药大学医学伦理审查表

<table>
<tr><td colspan="4">项目名称：太极拳对冠心病患者压力及心血管功能的临床效果研究</td></tr>
<tr><td colspan="4">项目负责人：杨国彦　　职称：博士研究生　　单位：西悉尼大学</td></tr>
<tr><td colspan="4">项目联系人：曹卉娟　　电话：13466615885　　邮箱：huijuancao327@hotmail.com</td></tr>
<tr><td colspan="4">合作研究单位：北京中医药大学</td></tr>
<tr><td colspan="4">请求审查类型：□申请项目■批准后项目□延续项目□委托项目</td></tr>
<tr><td colspan="4">研究项目主管部门（来源）：澳大利亚国家辅助医学研究所（National Institute of Complementary Medicine）</td></tr>
<tr><td colspan="4">研究对象：冠心病患者</td></tr>
<tr><td colspan="4">涉及临床医学研究内容及研究方案摘要
本研究设计为前瞻性随机对照试验，包含悉尼和北京两个临床中心。拟将 126 例冠心病患者随机分配进入太极拳组和等待队列组（各 63 例），其中北京常营社区分中心观察 80 例，悉尼分中心观察 46 例。太极拳干预组患者共计接受 24 周的太极拳干预，包括 12 周强化干预（每周 2 次课，每次 60-90 分钟）和 12 周持续干预（每周 1 次课，每次 60-90 分钟），课程内容包括打坐、大步走、13 式陈式太极拳和太极十三功。等待队列组试验期间保持日常活动，24 周后开展与干预组同样的太极拳干预。</td></tr>
<tr><td colspan="2">观察目的：探讨 24 周太极拳干预对冠心病患者（40-65 岁）心理压力的影响。</td><td colspan="2" rowspan="4">观察单位：
北京市常营社区</td></tr>
<tr><td colspan="2">观察例数：80 例（北京）</td></tr>
<tr><td colspan="2">观察方法：随机对照试验</td></tr>
<tr><td colspan="2">拟完成时间：2018 年 3 月</td></tr>
<tr><td>会议地点</td><td>北京中医药大学科技处会议室</td><td>会议时间</td><td>2015 年 7 月 17 日</td></tr>
<tr><td>伦理委员会综合结论：</td><td colspan="3">伦理委员会意见：
经审核，同意项目“太极拳对冠心病患者压力及心血管功能的临床效果研究”开展临床研究。
主任委员：[redacted]（盖章）
时间：</td></tr>
<tr><td>项目批号</td><td colspan="3">2015BZHYLL0233</td></tr>
</table>

Appendix 14 – Participant Information Sheet

Human Research Ethics Committee
Office of Research Services

University of Western Sydney

Participant Information Sheet (Medical)

Project Title: Effects of Tai Chi on Stress and Cardiovascular Function in Patients with Coronary Heart Disease and/or hypertension

Who is carrying out the study?

Chief Investigator: A/Prof Dennis Chang, National Institute of Complementary Medicine, School of Science and Health, Western Sydney University;
Principal Investigator: Ms Emily Yang, PhD Candidate, National Institute of Complementary Medicine, School of Science and Health, Western Sydney University;
Principal investigator: Prof Jianping Liu, Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China;
Principal investigator: Prof Hosen Kiat, Medicine and Cardiology, Macquarie University Hospital and Australian School of Advanced Medicine, Macquarie University;
Principal investigator: Prof Alan Bensoussan, National Institute of Complementary Medicine, School of Science and Health, Western Sydney University;
and Principal investigator: Dr Nerida Klupp, National Institute of Complementary Medicine, School of Science and Health, Western Sydney University.

You are invited to participate in a study conducted by the National Institute of Complementary Medicine (NICM), School of Health and Science, Western Sydney University.

What is the study about?

Coronary heart disease is a leading cause of morbidity and mortality in both developed and developing countries. Hypertension (high blood pressure) is the most important preventable cause of heart disease and stroke worldwide. Tai Chi (as known as Tai Chi Chuan/Quan or Taiji) is a form of Chinese martial art incorporating Chinese folk and military martial arts and ancient breathing and meditation techniques. In recent years, research on Tai Chi for health and well-being has flourished. An increasing level of evidence has demonstrated a variety of physical and psychosocial benefits of Tai Chi, such as including improving stress, anxiety, depression, quality of life and cardiovascular function.

The purpose of this study is to evaluate whether Tai Chi has an effect on stress, anxiety, depression and cardiovascular function in patients aged 40 years old or above, with coronary heart disease and/or hypertension. This study will help provide us with more information into the effects of Tai Chi and whether it can provide additional therapeutic benefits to patients with coronary heary disease and/or hypertension.

This is a higher degree research project and the results of this research will be included in a Doctor of Philosophy (PhD) thesis of Emily Yang who is a principal researcher of this project. This research is being conducted by the National Institute of Complementary Medicine, Western Sydney University.

What does the study involve?

If you agree to take part in this study you will be asked to sign the Consent Form prior to any study procedures being performed. The treatment being investigated in this study is a mild to moderate intensity of mind-body exercise in the form of Tai Chi.

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out which treatment is better, we need to put people into different groups to compare the effects of the different types of treatment to see if one is better over the other.

In this study, you will randomly be assigned to one of two groups:
1. Tai Chi group
2. Wait-list control group

You will have a 50% chance of being assigned into the Tai Chi group or the wait-list (control) group. If you are placed in the Tai Chi group, you will be asked to attend two classes of intensive Tai Chi per week for 12-weeks, followed by attendance at one class of moderate-intensity Tai Chi per week for the next 12-weeks.

If you are placed in the wait-list (control) group you will be asked to continue with your regular daily activity for 24-weeks, and refrain from starting any new exercise programs and activities during this time. You will then be invited to take part in the equivalent Tai Chi intervention after the study is complete.

You will also be asked to attend three study visits (regardless of which group you are allocated to) at the beginning (Week 0), middle (Week 12) and end (Week 24) of the study. At these visits you will be asked to complete four questionnaires about your psychological status of stress, anxiety, depression and quality of life. On these visits your fitness level, blood pressure and heart function will be monitored, and you will have a blood sample taken to measure the the level of inflammation, fats and sugar in your blood (C-reactive protein, lipids and glucose). At your last visit, if you were in the Tai Chi group, you will be asked to complete an exit interview.

How much time will the study take?

The study will go for a duration of 24-weeks. If you are placed into the Tai Chi group, each Tai Chi class will last for approximately 60-90 minutes. The study visits will take approximately one to two hours to complete all of the assessments, questionnaires and have your blood test performed.

Will the study benefit me?

The study aims to further medical knowledge and may improve future treatments for improving stress, anxiety, depression, cardiovascular function, quality of life and physical fitness in people with coronary heart disease and/or hypertension. You may or may not experience direct benefits from participating in this study, however you will have the benefit of knowing that you will be receiving Tai Chi from an experienced and trained Tai Chi practitioner. Your blood tests will also be free of charge.

Will the study have any risks?

You may feel some soreness and discomfort after Tai Chi program. However, this is to be expected at the start of any new form of physical activity. The Tai Chi intervention of this study is specifically designed for people with coronary heart disease. In addition, all Tai Chi classes will be full instructed and supervised by an experienced and qualified Tai Chi practitioner to ensure the safety of all participants.

Having a blood sample taken may cause minor discomfort, bruising, infection or bleeding.

How is this study being paid for?

This research project is being conducted and funded by the National Institute of Complementary Medicine (NICM), at the Western Sydney University.

Will anyone else know the results? How will the results be disseminated?

All aspects of the study, including results, will be confidential and only the researchers will have access to your results, except as required by law.

Can I withdraw from the study?

Your participation is entirely voluntary. If you do participate and decide to withdraw from the study, you can do so at any time without giving any reason. Whatever your decision, it will not affect your medical treatment or your relationship with the medical staff.

Can I tell other people about the study?

Yes, you can tell other people about the study by providing them with the chief investigator's contact details. They can contact the chief investigator to discuss their participation in the research project and obtain an information sheet.

What if I require further information?

When you have read this information, A/Prof Dennis Chang will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact A/ Prof Dennis Chang, at (02) 4620 3920.

What if I have a complaint?

If you suffer any injuries or complications as a result from this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment.

If you have any complaints or reservations about the ethical conduct of this research, you may contact the Ethics Committee through the Office of Research Services on Tel +61 2 4736 0229 Fax +61 2 4736 0013 or email humanethics@uws.edu.au.

Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome. If you agree to participate in this study, you may be asked to sign the Participant Consent Form.

The information sheet is for the participant to keep and the consent form is retained by the researcher.

Appendix 15 – Participant Consent Form

Human Research Ethics Committee
Office of Research Services

University of Western Sydney

Participant Consent Form

Project Title: Effects of Tai Chi on stress and cardiovascular function in patients with coronary heart disease and/or hypertension

I,……, consent to participate in the research project titled "Effects of Tai Chi on stress and cardiovascular function in patients with coronary heart disease and/or hypertension."

I acknowledge that

I have read the participant information sheet or have had it read to me and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s.

The procedures required for the project and the time involved have been explained to me, and any questions I have about the project have been answered to my satisfaction.

I consent to taking part in the study and parti cipating inthe Tai Chi or wait-list group, completing questionnaires for stress, anxiety and depression, having my fitness level, blood pressure and heart function monitored, having my blood samples collected, having an exit interview at the end of the trial (if in the Tai Chi group), and complying with the study procedures.

I understand that my involvement is completely volunatry confidential and that the information gained during the study may be published but no information about me will be used in any way that reveals my identity.

I understand that I can withdraw from the study at any time, without affecting my relationship with the researcher/s now or in the future.

Signed: _____

Name: _____

Date: _____

Return Address: NICM Bldg 22, University of Western Sydney, Campbelltown Campus, Locked Bag 1797, Penrith NSW 2751

This study has been approved by the University of Western Sydney Human Research Ethics Committee.

The Approval number is: H11189

If you have any complaints or reservations about the ethical conduct of this research, you may contact the Ethics Committee through the Office of Research Services on Tel +61 2 4736 0229 Fax +61 2 4736 0013 or email humanethics@uws.edu.au. Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.

Appendix 16 – Standards for Reporting Qualitative Research (SRQR)

http://www.equator-network.org/reporting-guidelines/srqr/

Page/line no(s).

Title and abstract

Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	164
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	xii-xv

Introduction

Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	164-166
Purpose or research question - Purpose of the study and specific objectives or questions	166

Methods

Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	167
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	N/A
Context - Setting/site and salient contextual factors; rationale**	
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	167
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	167
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	167-169

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	169
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	167
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	169
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	170-172
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	170-171

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	173-182
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	173-182

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	182-190
Limitations - Trustworthiness and limitations of findings	188

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	188
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	N/A

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388

Appendix 17 – Examples of the Coding Process

Transcript-Participant No. 235

Interviewer: I am very glad to see you complete the half year Tai Chi class. Many thanks for your cooperation. In the coming minutes, I will ask you several questions on your experience, feeling and feedback about the Tai Chi program. Could you please introduce your health status before you starting the Tai Chi class?

Participant No. 235: Sure. It's like this. I was diagnosed as atrial fibrillation by the doctor. The doctor introduced and I was invited to participate in this program, so I came. At the beginning, I was a layman for Tai Chi because I haven't learnt it before. So I was a zero beginner at first and it was a process that I came to Tai Chi. In the learning process, I gradually entered the door of Tai Chi because of the patience, earnest, serious and responsible instruction of the Tai Chi instructor. We practiced step by step, according to the requirements of the Tai Chi instructor. Firstly, we practiced the 13-Form Thumping Techniques. After practicing the 13-Form Thumping Techniques, I feel, most importantly, I need to calm down. Another thing is, when I practice Tai Chi I should get rid of my wandering ideas. The wandering mind is not good for my health. I think the major function of the 13-Form Thumping Techniques is helping me to calm down. After calming down, you need to realize the essence. I think these two points played the major function. In addition, when practice the 13-Form Thumping Techniques you will get the benefits, gradually, not immediately. I experienced it. At the beginning, although I sit there when I practiced the 13-Form Thumping Techniques, my mind was wandering. I didn't know what I was thinking, right? Hehehe, I couldn't calm down and be mindful. Since I have been busy in working at Australia for around thirty years, at the beginning it is difficult for me that I suddenly came to this quiet environment to practice the 13-Form Thumping Techniques. However, it is hard and it is easy. If you really want to enter the door and realize the essence of the 13-Form Thumping Techniques, I think it needs time. During the half year of learning, I gradually know myself better, which is beneficial to my health.

Interviewer: I am very glad that you share it with me. Hehehe. How did you know about Tai Chi before your participation in this program?

Participant No. 235: As I mentioned before, when I received the invitation I was a layman of Tai Chi. Hehehe, I actually know nothing about Tai Chi. Hehehe, the reason why I can continue to learn it for a half year, there are two factors, two premises, I think they play the most important roles. Firstly, I met a good teacher. She taught us Tai Chi patiently and seriously. In addition, after the instruction of each movement, she explained the potential effects of each movement for the body, which enhanced my understanding of Tai Chi. Secondly, although I haven't learnt Tai Chi before, I know Tai Chi is the essence of the thousands of years of Chinese culture legacy, and part of the treasure of Chinese culture. Promoting Tai Chi in Australia is a promotion of Chinese culture. Moreover, our Tai Chi instructor taught us diligently, earnestly, seriously, and patiently. So I had a deeper understanding of Tai Chi and became more interested in learning Tai Chi.

Interviewer: Thanks for sharing with me. What was your expectation for participating in this program?

Participant No. 235: As I always say,at the beginning I was a zero beginner. For my health, hehehehe, I wanted to try and see whether it can help me. Hehehe, I wanted to try and see what on earth is Tai Chi? I heard that Tai Chi could be beneficial for this or that, for health, for peaceful mind and calm, so I participated in this program. Through the half year of learning, I felt Tai Chi indeed could help calm down the mind. It was my main experience. Once calming down the mind, one's spiritual world would be unconventional.

Interviewer: Yeah. Many things come very naturally after that.

Participant No. 235: Yeah. Many things come naturally. Once calming down the mind, one will think and then a comprehension and understanding comes out. The environment of Tzu Chi Foundation is good. When we enter the front gate, we will see the couplet reads "The Jing Si Dharma-lineage is a path of diligent spiritual practice; the Tzu Chi School of Buddhism is a road through the world". It requires beyond the worldly fickleness,

completely calm down the mind and heart, return back to nature, and return back to human pure nature. “Man’s nature at birth is good”.

Interviewer: Practicing Tai Chi is doing subtraction.

Participant No. 235: This process is it doesn’t happen at once, and it needs slowly learn and experience it. In addition, I would like to repeat it again; it is such an honour for us to have such a serious and dedicated teacher.

Interviewer: Thanks. Did participating in the Tai Chi program have any impacts on your daily life?

Participant No. 235: Yes, there are some changes. When I, if, learn Tai Chi at the class, because some movements, there are two parts, I want to say. I learn Tai Chi for 2 hours each class, and because the movements are not easy to master, so when I come back home I continue to practice again and again. Gradually, I merged the things I learnt from the teacher to my own movements. There are always some parts I am not familiar with. It is not possible I stop learning at home after the 2-hour learning at class. It’s not possible. It’s one hand of the learning and practicing process. Another hand, I think it plays the major role. When I was in trouble, when I felt moody, or when I was angry, I would think what my Tai Chi teacher said. I mean Tai Chi can help one to calm down. Then I would do what my Tai Chi teacher told me. What is it? I would do standing postures. Standing posture, it is easy to say, and it seems easy to do. However, it you can truly carry out standing posture and calm down the mind, it needs perseverance. I would think what my teacher told me; sometimes I closed my eyes when doing standing posture, and try not to think anything. By doing so, I can gradually calm down my fickle mind and become not easy to lose my temper. I would do as much as I can. It reduced my unnecessary stress and helped me a lot. After this, I would practice Tai Chi. Actually, what I think the process of practicing Tai Chi? I think it is an activity which gradually improve one’s lifestyle. It can bring you into a quiet and peaceful world. It is beneficial for my mental and emotional health. Especially, for people like me who have some problem with heart and atrial fibrillation, When I feel unwell because of atrial fibrillation, I will practice Tai Chi immediately. I practice it slowly, feel it slowly, and gradually calm down myself.

Interviewer: I know you are handling some issues of your company and it is a stress for you. Were there any benefits from practicing in the Tai Chi program on coping with stress or any other emotional feelings?

Participant No. 235: I think Tai Chi is the main facilitator for me to deal with my stress. Tai Chi, as I mentioned before, the main effect of Tai Chi is helping people to calm down and become quiet. No matter how great the stress you bear, if you integrate the essence of Tai Chi into your blood and put it into your practice, you will gradually digest the stress. But how can you digest the stress? It depends on your daily practice, step by step, continuous practice. Tai Chi will help you to some extent.

Interviewer: Did participating in the Tai Chi program have any influence on your social life?

Participant No. 235: It’s related to the essence of Tai Chi. Tai Chi itself can help people to calm down. To some extent, Tai Chi helps to deal with the relationships between people and people, people and things, and people and family.

Interviewer: Would you recommend the Tai Chi program to other cardiovascular patients? I would like to see whether you are satisfied with the Tai Chi program.

Participant No. 235: Satisfied. The teacher taught us such seriously and dedicatedly, with compassion. We are very satisfied during the learning process. The only thing is, is it possible that we can learn more movements than just the 13 movements? It seems the time to practice the 13-form Tai Chi is a bit short. It takes around three minutes. Sometimes it takes only two minutes because the speed of different people is different. Is it possible we extend a bit longer and add more movements, according to the health status of older people?

Interviewer: Yes. We actually have more forms, such as 24-form and 83-form. The reason why we provide the 13-form Tai Chi here because it is not hard to practice for one time and you can practice anytime. So it takes not too much effort to remember the movements. It is easy to remember the movements and sequence. However, the practice needs to be correct and master the essence. The key is not about how many movements you practice. The key is how to practice the movement correctly, and feel how to use the mind to lead the qi and blood and the movement of whole body.

Participant No. 235: What you said reminder me about my experience and feeling at first. At the beginning, I thought, wow, so many things, so many movements, 13 movements, I can't learn it. When the teacher asked us 'Did you get it' , I always the first one to say 'No'. Ho ho ho, however, after a half year of learning, I mastered the 13 movements. Then I have higher requirements to myself. I have a higher goal to achieve, so I think the 13 movements are not enough for me. Hohoho, is it possible to add more movement? What does this mean? It's hard at the beginning. It means the process of learning Tai Chi for me is that I had no idea of Tai Chi at first and gradually entered the door of Tai Chi. After I know the basics of Tai Chi, Wow, I see, Tai Chi is such an unlimited world. So I gradually know Tai Chi, gradually entered the role, and have higher and higher goals. So I proposed my expectation to you about adding more movements. Of course, my idea may be wrong.

Interviewer: Sure. We have many forms. We hope our students not only learn the movements but also go deeper. Could each movement, especially the junctions between movements be practiced very smoothly? The first requirement is change the hardness into softness. The body becomes flexible and the heart tender.

Participant No. 235: Hehehe, I am not flexible. I am inflexible. As you can see, my Tai Chi performance is inflexible. As I told you just now, I have been in Australia for 30 years. I work every day, and I never go for Tai Chi. I am very happy to see Tai Chi gradually help me soften my inflexible body.

Interviewer: Hehehe. So it is better just practising this form again and again. You can practise it several times. When practise each movement, you can think the principle such as how to move as a whole and how to use the waist as the leader to move the whole body.

Participant No. 235: Yeah. I found my mistake and the teacher pointed it out to me too. It is that when I practice Tai Chi I move my hands first not my waist.

Interviewer: Hehehe. As we mentioned just now, practicing Tai Chi is doing subtraction. You need to know what dominate the movements. Life is the same. If you find it in Tai Chi, you can find your life is in the same way. What is the most important thing to you? If you master the main thing, other things often come naturally. This rule can be used in our daily life. If we continue to hold a similar Tai Chi class, would you like to recommend other people to practice Tai Chi?

Participant No. 235: Yes, definitely. I have a habit that when I want to practice Tai Chi, I don't mind where it is, even in public space. So when people ask me about Tai Chi, I will definitely recommend it to them. This is a promotion, especially at Australia, a promotion of Chinese traditional Tai Chi culture. I think it is a good deed.

Interviewer: Yeah. It is a treasure of Chinese culture. We share it with more people.

Participant No. 235: Treasure! Tai Chi is a treasure of our Chinese culture, with a history of thousands of years. Without this belief I don't think I would join the class. Hehehe.

Interviewer: Many thanks for sharing it with me. Would you like to continue the Tai Chi practice after the completion of the study?

Participant No. 235: I will definitely continue to practice Tai Chi. For me, Tai Chi and the 13-form Thumping Techniques, I would practice them for the rest of my life. I would say, they will be a part for the rest of my life, an important part. Particularly, for the elderly, it's much necessary for us to learn Tai Chi and the 13-form Thumping Techniques, so that we can be peace and calm.

Interviewer: Great. We also hope to bring Tai Chi to more people. Hope it can become a daily self-care method, and people can continue use it for their health.

Participant No. 235: Thanks, many thanks! Tai Chi is such a gift from our teacher. It is a precious wealth for us.

Interviewer: What do you think would be the main possible barriers to hindering your future Tai Chi practice?

Participant No. 235: So far, it seems no barriers. For now though, I think there is no factors inhibiting my practice. You can practice Tai Chi anytime anywhere. I often practice it no matter where it is. Particularly, the standing posture you taught us needs no special venue or site, and you can practice it anytime anywhere.

Interviewer: Thanks. That's it. Is there anything else you would like to tell me?

Participant No. 235: No. I think I want to say it again. I am so glad to meet such a good teacher. Many thanks!

Interviewer: Thanks. Thanks for your perseverance and cooperation.