UNIVERSITY OF DERBY

DO HAEMODYNAMIC RESPONSES TO MENTAL STRESS TESTS PREDICT FUTURE BLOOD PRESSURE ONE YEAR LATER? PROSPECTIVE STUDIES IN THE UNITED KINGDOM AND THAILAND

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LIST OF ACRONYMS AND ABBREVATIONS

The following abbreviations and acronyms have been used in this thesis:

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BcLR	the Bartlett corrected log likelihood ration statistics
β	Beta coefficients
BHF	British Heart Foundation
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CHD	Coronary heart disease
CI	confidence interval
CO	Cardiac output = the blood volume that pumped from the cardiac muscle
CRD	Centre for Reviews and Dissemination
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
df	Degree of freedom
DSM	Diagnostic and Statistical Manual of Mental Disorders
dyne-sec.cm-^{5}	Unit for measuring vascular resistance; Pascal seconds per cubic meter
FMS	Finapres Medical System
HADS	Hospital Anxiety and Depression scale
HR	Heart rate
kg/m^2	kilogram per square metre
l/min	Unit for measuring volume of blood in the time of one minute; litres per minute
MANOVA	Multivariate analysis of variance
Mg/dl	milligram per decilitre
mmHg	millimetres of mercury
NHLBI	National Heart Lung and Blood Institute
ns	not significant

LIST OF ACRONYMS AND ABBREVATIONS (Continued)

r	Pearson's correlation coefficient
R^2	the coefficient of determination of a hierarchical regression
SBP	Systolic blood pressure
SD	standard deviation
SE	standard error
SPSS	Statistical Package for the Social Sciences
TPR	Total peripheral resistance = the resistance by pushing blood through the circulatory system (systemic vascular resistance)
UK	United Kingdom
WHO	World Health Organization

ABSTRACT

This thesis explored whether haemodynamic responses to psychological stress test predict future blood pressure (BP) levels: the Reactivity Hypothesis. The research included a systematic review and two prospective cohort studies in the UK and Thai samples. In addition, the Blunted Reactivity Hypothesis, which posits that cardiovascular reactivity is inversely related to symptoms of anxiety and depression, was examined in cross-sectional analyses. A systematic review with meta-analysis and meta-regression with 41 prospective cohort studies (from 1950 to 2012) examined whether cardiovascular responses to psychological stress tests predict future BP levels, hypertension status, preclinical coronary heart disease (CHD) and cardiac events. Three possible moderators were included in analyses: type of task (active versus passive coping), age group (children versus adults), and duration of follow-up (short versus long-term follow-up). The review found that systolic BP reactions to psychological stress tests predict future systolic BP levels and that there was better prediction in child samples with shorter follow-up periods. Similarly, diastolic BP reactions to psychological stress predicted future diastolic BP levels. Cardiovascular reactions to psychological stress tests did not predict hypertension, preclinical CHD, or cardiac events. Cross-sectional analysis of two studies conducted in the UK and Thailand provided some evidence that anxiety and depressive symptoms were negatively associated with cardiovascular reactivity: these findings supported the Blunted Cardiovascular Hypothesis. However, these relationships were observed in the UK sample, but not in the Thai sample. Further, Thai participants responded to psychological stress task with large cardiovascular reactions, of a similar magnitude to the UK participants and observed in previous studies of Europeans and North Americans. Finally, prospective analyses revealed that systolic BP responses to mental arithmetic predict future systolic BP levels after one year of follow-up in both UK and Thai individuals, after controlling for baseline cardiovascular activity and traditional risk factors. In contrast, haemodynamic responses did not predict future BP. These results provide support for the "Reactivity Hypothesis" although the effect sizes were relatively small. However, responses to only one of the three stressors, mental arithmetic, predicted future BP implicating beta-adrenergically mediated cardiovascular responses. However, there was no physiologic evidence (i.e., cardiac output responses) that suggested beta-adrenergic mechanisms. Accordingly, future studies should examine alternate mechanisms (e.g., platelet aggregation and endothelial function) and cardiovascular responses

in larger samples with a longer follow-up to further clarify the predictive value of reactivity in the development of hypertension, along with potential mechanisms.

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CHAPTER 1

Introduction: Prediction of hypertension and Future Blood Pressure Based on Haemodynamic Responses to Psychological Stress

Introduction

This chapter introduces psychological stress testing and discusses its importance in relation to hypertension. In the first section, hypertension will be defined, and its prevalence and importance described. Cardiovascular reactivity and the development of hypertension will be described in the second section; variation of the reactivity hypothesis will also be discussed here. In the third section, the relationship between psychological factors and cardiovascular reactivity will be examined; a new version of the reactivity hypothesis, the blunted reactivity hypothesis, will be considered here. Finally, the aims of this thesis will be outlined in the context of the literature reviewed.

1.1 Definition and Prevalence of Hypertension

1.1.1 Definition of Hypertension

High blood pressure (BP), or hypertension, is traditionally defined as a systolic blood pressure (SBP) greater than or equal to 140 mmHg or a diastolic blood pressure (DBP) greater than or equal to 90 mmHg. In a minority of cases (approximately 5 to 10 %), hypertension is secondary to a known cause, for example renal and adrenal disease (Viera & Neutze, 2010); these cases are known as secondary hypertension. However in most instances, the cause of the hypertension is unknown and it is classified as 'essential' hypertension, 'primary' hypertension, or 'idiopathic' hypertension (National Heart Lung and Blood Institute [NHLBI], 2010). Blood pressure level has been used to categorise BP and hypertension status in adults; these levels are presented in the summary table 1.1.

[#]a list of all acronyms and abbreviations used in the thesis can be found in page x-xi

Table 1.1 Classification of BP Levels in Adults

Classification	SBP (mmHg)		DBP (mmHg)
Normal	< 120	And	< 80
Prehypertension	120-139	Or	80-89
High BP - stage 1 - stage 2	 140-159 ≥ 160	 Or Or	 90-99 ≥ 100

(Chobanian et al., 2003; NHLBI, 2010)

1.1.2 The Burden of Hypertension

Hypertension is a major global health problem. Hypertension is the most significant risk factor associated with the prevalence of cardiovascular disease (CVD) (Ireland, 2009). In addition, the INTERHEART study (a large epidemiologic study designed to assess the importance of risk factors for coronary heart disease (CHD)) reported that hypertension was the most important factor for myocardial infarction across 52 countries in both the developed and developing world (Yusuf et al., 2004). Globally, an estimated 600 million people suffer from high BP and about 15% - 37% of adults have experienced hypertension (World Health Organization [WHO], 2002). This is projected to increase to 1.56 billion people (29% of the world's adults) by 2025 (Kearney, Whelton, Reynolds, Whelton, & He, 2005). Moreover, in 2012 a WHO report suggested that one in three adults already have raised BP (WHO, 2012). Furthermore, a meta-analysis of 61 prospective studies reported that hypertension was strongly correlated with CHD mortality at all ages; for each increase of 10 mmHg in resting DBP or 20 mmHg in resting SBP, a twofold increase in CHD mortality was observed (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002). Annually, 7.6 million premature deaths (13.5% of the total global death rate) were attributed to high BP (Lawes, Hoorn, & Rodgers, 2008). In addition, 47% of ischaemic heart disease worldwide was attributed to high BP (Lawes et al., 2008). Thus, the severity and global scope of high BP as a risk factor for mortality and disease is widely recognised.

In the United Kingdom, the Health Survey of England reported that there was a small decrease in the prevalence rates of hypertension for men and women between 2003 and 2006 (32% to 31% in males and 30% to 28% in females, respectively) (Allender et al., 2008). However, the annual cost of prescriptions for antihypertensive medicine has been increasing;

for example, it increased by £10 million between 2006 and 2007 (British Heart Foundation [BHF], 2012). Furthermore, it is estimated that controlling hypertension would prevent 41,400 deaths of the 124,000 CHD deaths each year (He & MacGregor, 2003). Also, it has been estimated that up to 14,000 UK citizens per year would survive if their mean SBP was decreased by 2 mmHg (Craig & Mindell, 2008).

In Thailand, the prevalence of hypertension is rising. Data from Thai National Health Examination Survey III in 2004 reported that the prevalence of hypertension (defined as SBP or/and DBP > at 140/90 mmHg) was 21.0% of the Thai populations (Aekplakorn et al., 2008). Further, the prevalence of hypertension slightly increased from 2004 to 2009 to 21.4% (Srithamrongwawat et al., 2010). Compared with data from hypertension surveys conducted between 1990 and 2011 among 38 developing countries, the ranking of the prevalence of hypertension in Thailand was at an intermediate level (Ibrahim & Damasceno, 2012). However, the proportions of diagnosed, treated, and controlled BP patients remained low (Aekplakorn et al., 2011). In addition, the rate of diagnosis, treatment, and control of high BP was lower in Thailand than in Colombia, England, the Islamic Republic of Iran, Mexico, Scotland and the United States of America (Gakidou et al., 2011). So, the numbers of Thai people at risk of developing CHD or dying from a myocardial infarction is high.

1.1.3 Pathophysiology of Hypertension

It has been known that hypertension is an elevation of BP that, in the long-term, can cause end-organ damage particularly at the heart and the brain. It is likely that a great many pathophysiologic factors contribute to the elevated BP in hypertensive patients; these include: raised sympathetic nervous system activity; overproduction of sodium-retaining hormones and vasoconstrictors; long-term high sodium intake; inadequate dietary intake of potassium and calcium; increased or inappropriate renin secretion; deficiencies of vasodilators, such as prostacyclin, nitric oxide; increased activity of vascular growth factors; endothelial dysfunction; and genetic factors (Beevers, Lip, & O'Brien, 2001; Oparil, Zaman, & Calhoun, 2003).

One of the factors that can lead to hypertension is sympatho-adreno-medullary dysfunction (see figure 1.1). Blood pressure is reliant on the balance between cardiac output (CO; the volume of blood the left ventricle ejects from the heart to systemic circulation in one minute) and systematic vascular resistance (TPR; the total of systemic resistance to blood flow by the

vasculature; Beevers et al., 2001). The adreno-medullary control system regulates systematic arterial pressure, heart rate (HR) and cardiac contractility. This system comprises of: a) the central pathways (from the brain) via pre-ganglionic and post-ganglionic sympathetic neurons and the adrenal medulla; b) the adrenergic neurons which release catecholamines; c) norepinephrine (noradrenalin) and epinephrine (adrenalin); d) post-synaptic and non-synaptic alpha- and beta-adrenergic receptors of cardiac and vascular tissues; and e) reflex and afferent pathways from peripheral tissue that alter the central mechanisms controlling the sympathetic and adreno-medullary tone (Krakoff & Garbowit, 1991).

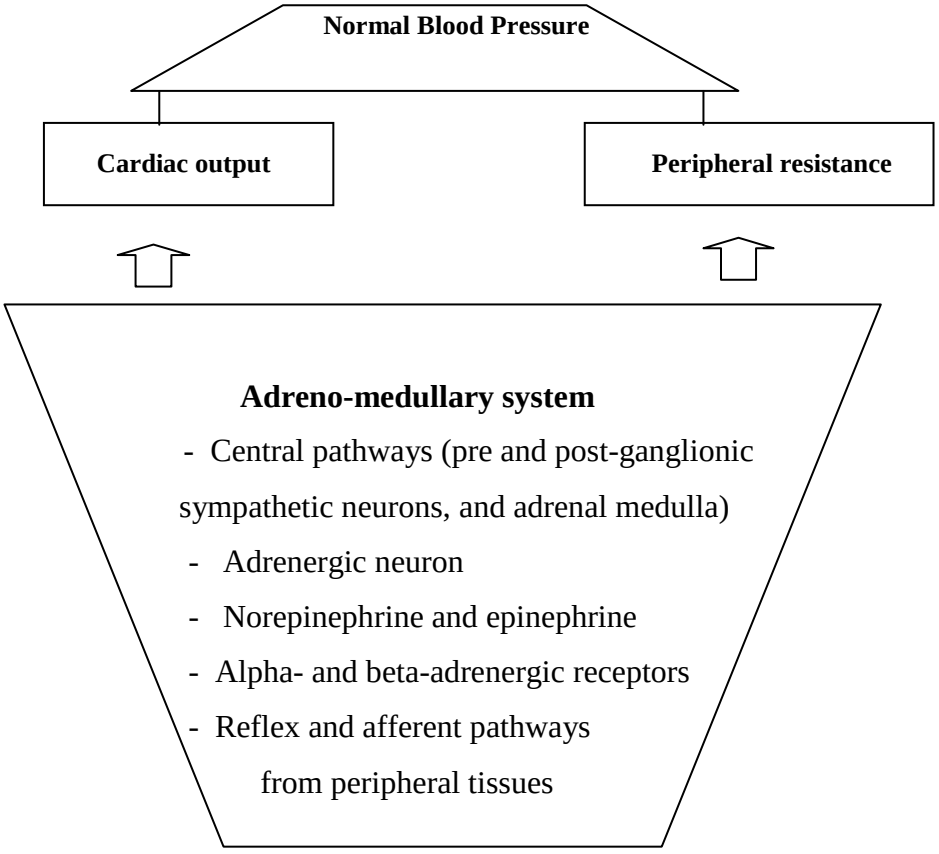


Figure 1.1 Mechanisms of Adreno-Medullary Hypertension

Generally, the sympatho-adrenal system regulates arterial pressure and HR during normal behavior. However, disturbance of sympatho-adrenal function may lead to high BP from disorders of the central nervous system (e.g., cerebrovascular disease), and an over production of catecholamines (Krakoff & Garbowit, 1991; Marvogiannis, Trambakoulos, Boomsma, & Osmond, 2002; Oparil et al., 2003). An excess of the production and release of can act on the two types of adrenergic receptor (namely alpha-adrenergic and beta-adrenergic receptors) which induce sympathetic nervous system hyperactivation and may increase BP

(Krakoff & Garbowit, 1991; Tsioufis et al., 2011). Excessive alpha-adrenergic activity causes vasoconstriction and increases peripheral vascular resistance. In contrast, activation of beta-adrenergic receptors results in vasodilator activation, increasing HR at the sinoatrial node in the cardiac muscle and leading to an increase in CO and cardiac contractility (Cryer, Rizza, Haymond, & Gerich, 1989). Further, in clinical pharmacological studies, alpha-adrenoceptor blockade results in a reduction of total peripheral resistance (TPR; the total of systemic resistance to blood flow by the vasculature) that leads to increased vasodilatation, whereas beta-receptor blockade results in decreased BP or CO (van Zwieten, 1986).

Therefore, patients with hypertension may have an increase in CO, and an increase in systematic vascular resistance, or both (Foëx & Sear, 2004; Mayet & Hughes, 2003). In younger age groups, increasing BP has been postulated to be caused by an elevation in CO and not raised peripheral resistance, whereas in older age groups increased systematic vascular resistance and increased stiffness of the vasculature is often dominant and thought to be responsible for increases in BP (Foëx & Sear, 2004). Further, both an increase in systematic vascular resistance and an increase in vascular constriction can lead to induced left ventricular hypertrophy and left ventricular diastolic dysfunction: this results in an increase in left ventricular afterload and contributes to left ventricular hypertrophy. Left ventricular hypertrophy impairs ventricular relaxation and delays filling of the ventricles that leads to diastolic dysfunction (Foëx & Sear, 2004; Edvardsen et al., 2006). In addition, vascular changes in hypertension are associated with mechanical and humoral factors resulting in inflammation processes, such as elevated plasma levels of C-reactive protein. C-reactive protein is a marker of increased cardiovascular events, sudden cardiac death and myocardial infarction (Sesso et al., 2003; Smith et al., 2005).

As discussed above, one mechanism linking pathophysiological interrelated factors to high BP is the sympathetic nervous system. There is much evidence to show that an over-active sympathetic nervous system elevates BP and contributes to the development of hypertension status via stimulation of the heart, peripheral vasculature, and kidneys. This, in turn, causes increases in CO and vascular resistance, and fluid retention (Opril et al., 2003). Further, decreased parasympathetic activation (which is coupled with increased sympathetic activation) leads to sustained increases in HR and also plays an important role in the pathogenesis of hypertension (Opril et al., 2003). In conclusion, high BP is a result of

increases in sympathetic nervous system activity (and decreases in parasympathetic nervous system activity) via increasing HR and cardiac contractility, or increasing systematic vascular resistance.

One factor that has been found to increase sympathetic nervous system activity is elevated responsiveness to stressful stimuli. Several studies have shown that exaggerated stress reactivity, whether in a laboratory setting or during stressful daily life events, may also contribute to an increased BP, sustained high BP and the development of hypertension (Fauvel et al., 2003; Kulkami, O'Farrell, Erasi, & Kochar, 1998; Trieber et al., 2003). Accordingly, the main focus of this thesis is on the relationships between cardiovascular responses to psychological stress in the laboratory and the development of increased BP.

1.1.4 Risk Factors for Hypertension

Currently, approximately 50% of the variance in hypertension can be predicted by traditional risk factors, including family history of CVD status, obesity, current smoking, diabetes mellitus, and hypercholesterolemia (Treiber et al., 2003). For example, many individuals with high BP are obese and have a positive family history of hypertension or CVD, or a family history of obesity. Approximately 30% of people with a high body mass index (BMI) have hypertension (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Further, high dietary intakes of sodium and lack of physical activity or a sedentary lifestyle increases the risk of hypertension development by 20% to 50% (Alton, 2005). However, despite this, approximately 50% of the variance in hypertension is still unexplained. Therefore, attention has focused on other potential risk factors.

It has, for instance, been shown that psychological stress can lead to repeated elevations of BP levels as well as stimulation of the sympathetic nervous system, which results in vasoconstriction (Lambert & Lambert, 2011; Kulkarni et al., 1998; Malpas, 2010). Therefore, stress-induced sympathetic activation may contribute to hypertension development. Indeed, psychological risk factors for essential hypertension have been reported in several studies. One of the earliest reports, by Hines and Brown in the 1930s, claimed that psychological stress could identify individuals at risk for developing hypertension in the future (Hine & Brown, 1936). In addition, Wood, Sheps, Elveback, and Schirger (1984) examined the role of psychological stress in the development of hypertension during a 45 year follow-up of Hines

and Brown's participants. They found that individuals with high cardiovascular reactions to the cold pressor stress test were at a greater risk of developing hypertension than individuals with low cardiovascular reactions. In recent years, many research studies have examined the role of cardiovascular responses to stress in the development and progression of hypertension using a prospective cohort design (Gordis, 2009). A prospective cohort design is a study that involves follow-up sampling for several years in a specific group of participants to assess the impact of exposure variables (e.g., risk factors) before the occurrence of an outcome (e.g., development of a disease, or mortality; Ho, Peterson, & Masoudi, 2008) This is the main focus of this thesis: does cardiovascular reactivity predict high BP levels in the future?

1.2 Cardiovascular Reactivity

1.2.1 Definition of Reactivity

Cardiovascular reactivity is defined as the pattern of an individual's haemodynamic responses (e.g., BP, HR) to a stressor or stressors (Trieber et al., 2003). A range of different stressors have been used, including cold pressor, mental arithmetic, and video game tasks. It has been proposed that increased physiological responses (i.e., cardiovascular reactivity) to these stressors may increase the risk of developing CVD including hypertension. Many research studies have found a positive association between cardiovascular responses to psychological street tests and later hypertension or high BP levels. For example, one study followed 910 white male medical students for 20 to 36 years (Menkes et al., 1989). In accord with earlier studies (e.g., Hines, 1937; Hines & Brown, 1936), they found that heightened BP responses during the cold pressor task were associated with later hypertension, even after controlling for baseline BP and traditional risk factors. This has been coined the "Reactivity Hypothesis". The Reactivity Hypothesis was originally conceptualized as an approach to identify individuals who exhibited cardiovascular "hyper-reactivity" to psychological stress tests. The Reactivity Hypothesis may relate to the risk of developing hypertension (Obrist, 1981), but the role that cardiovascular reactivity has been thought to play in the development of hypertension has altered over time (Treiber et al., 2001). Gerin et al. (2000) propose that there have been four reactivity models that that have been used to explain how reactivity might contribute to development of future increased BP; they are: marker; causal trait; situation-cause and; person by situation interaction. These are discussed in detail below.

1.2.2 Early Studies of Reactivity: Reactivity as "a Marker" for Hypertension Risk

The earliest studies suggested reactivity was "a marker" for hypertension risk. In the first study widely acknowledged to investigate reactivity, Hines and Brown attempted to devise a simple test to predict future hypertension (Hines & Brown, 1932). This study used a marker hypothesis that suggested that cardiovascular reactivity would predict hypertension but was not (necessarily) causally involved. Much of the early cardiovascular reactivity research used a cross-sectional design to examine cardiovascular reactivity in groups of individuals with high BP or individuals at risk of developing high BP (e.g., individuals with hypertension compared with normotensive individuals). For example, Thacker (1940) found that college students with baseline BPs in the hypertensive range had larger BP reactions to the cold pressor test than normotensive students.

The marker model is still being used today, although the measures and approaches are more sophisticated. For example, to test reactivity as a marker, Bhandari, Subramanian, Jain, and Ahuja (2006) investigated BP, HR, and mean BP responses to hand-grip exercise in individuals with and without a family history of hypertension. They found that participants with a parental history of hypertension status showed greater BP and HR reactivity than individuals with no family history of hypertension status. In these studies people with normotensive BP levels but with traditional risk factors, such as a positive family of hypertension status, displayed increased cardiovascular reactivity compared to those without risk factors (Fredrickson & Matthews, 1990). Thus, in this case cardiovascular reactivity is a marker of increased risk for hypertension, at least in part, due to its association with a family history of hypertension.

Adopting a cardiovascular reactivity marker model has important implications for how the stress task or stressor, and the person (participant of the study) is considered. With respect to the stress task, the model assumes that any task that provokes cardiovascular reactions can be used: the nature of the eliciting stimulus is arbitrary. Thus, the cold pressor task was used for many years in the earliest reactivity studies because it was easy to set up, administer and replicate. However, cold pressor tasks do not commonly occur in everyday life. Therefore, researchers have constructed laboratory situations that might accurately generalize to the real world and have included situations to which a person may be exposed to in everyday life, such as mental arithmetic and speaking in public speaking.

Mental arithmetic tasks have been one of the most commonly used psychological stressors because mental arithmetic occurs frequently in daily life and the protocols are relatively easy to administer. With respect to the response, cardiovascular reactivity was assumed to be a trait of the person; it was assumed that if an individual showed high cardiovascular reactions to a cold pressor task, they would show comparably high responses to other psychological stressors (e.g., mental arithmetic) as well. These exaggerated cardiovascular responses were associated with future hypertension because they were related to risk factors involved in the pathogenesis of hypertension. Reactivity was not considered as a causal factor in the etiologic of hypertension and its independence from other risk factors was not assumed. Indeed, most early prospective tests of the reactivity hypothesis did not include risk factors as covariates or control variables (Harland, Osborne, & Graybiel, 1964; Thomas & Duszynski, 1982; Wood et al., 1984). For example, Wood et al. (1984) compared BP recordings from normotensive participants who were hyperreactors (defined as participants who responded to the cold pressor test with an increase in SBP of at least 25 mmHg or an increase in DBP of at least 20 mmHg) with individuals who were normoreactors (participants who showed an increase less than 25 mmHg for SBP and 20 mmHg for DBP to cold pressor). At a 45 year follow-up, they found that individuals who developed hypertension were more likely to be hyperreactors than normoreactors. However, this study did not control for initial baseline BP, thus it may have been the case that the hyperreactors had higher initial resting BP than normoreactors. Further, other aspects of the situation (e.g., task and laboratory environment) were not considered in this study. Indeed, these situational factors were not considered in the Reactivity as "a Marker" version of the Reactivity Hypothesis; in more recent studies situational factors have been found to be important.

1.2.3 Reactivity as "a Causal Trait" to the Development of Hypertension

The use of many different stress tasks, including interviews and mental arithmetic, with similar findings lead some researchers to posit that cardiovascular reactivity may play a causal role in the development of hypertension. In this model, exposures to multiple stressors in everyday life are proposed to provoke cardiovascular reactions that are involved in the etiology of hypertension. As Manuck, Kamarck, Kasprowicz, and Waldstein (1993, p. 113-134) note:

" …. If a heightened cardiovascular responsivity to stress were to contribute directly to the development of hypertension, it must be assumed that the reactivity of the hyper-responsive

person is “expressed” frequently and over protracted intervals. To the extent that the intensity of real-life stimuli (stressors) needed to evoked expressions of reactivity is common in daily life, this assumption may be valid for persons living in all but the most benign environment.”

In this model reactivity is assumed to be “a causal trait”. Evidence supporting this causal role is provided by both human and non-human studies. Animal studies allow cardiovascular reactivity to be examined in isolation by completing studies in equivalent environments with genetically identical participants. Hallback and Folkow (1975) demonstrated that spontaneously hypertensive rats responded to stimuli more easily than normotensive rats. Further, the spontaneously hypertensive rats were associated with higher BP responses to changes in their environment (i.e., light, noise, and vibrations) than normative rats. Moreover, the spontaneously hypertensive rats developed hypertension after a period of six months whereas the normotensive rats did not. Also of relevance, Wendel and Bennett (1981) found a relationship between BP and pain sensitivity in spontaneously hypertensive rats and that this was related to endogenous opioid pathways and the development of hypertension. In addition, many animal studies have examined dietary, cardiovascular reactivity and cardiovascular disease (Kaplan, Manuck, Adams, Weingand, & Clarkson, 1987; Kaplan et al., 1983; Manuck, Kaplan, Adams, & Clarkson, 1988). For example, Manuck et al. (1988) found that in cynomolgus monkeys fed a cholesterol-containing diet, HR responses to a stressor were associated with the extent of atherosclerosis progression. Therefore, several animal studies support the hypothesis that exaggerated cardiovascular reactivity to stress contributes to the development and progression of CVD including increases in BP, hypertension, and preclinical CHD (i.e., carotid atherosclerosis).

With respect to cardiovascular reactions to stress and the development of hypertension in humans, many researchers have suggested that BP reactivity can predict future resting BP after statistically controlling for baseline BP and known risk factors. For example, in early predictive studies, Borghi, Costa, Boschi, Mussi, and Ambrosioni (1986) examined 54 young participants with borderline hypertension. They found that participants who developed hypertension in the subsequent five years had high BP responses to mental arithmetic, even after statistically controlling for baseline resting BP. There have been a number of more recent prospective cohort studies with larger sample sizes and longer follow-ups. For example, Carroll, Phillips, Der, Hunt, and Benzeval (2011) examined 1196 participants’ cardiovascular responses to the Paced Auditory Serial Addition Test (PASAT). They found

that SBP reactivity significantly predicted a 12-year increase in resting SBP levels after controlling for age group, sex, performance, socioeconomic status at baseline, resting BP at baseline, and BMI at baseline. Therefore, it was inferred that reactivity may be an independent, casual trait in a model of the development of hypertension (Gerin et al., 2000).

Thus, prospective animal and human studies have suggested that cardiovascular reactivity may be an independent predictor of hypertension, with a possible causal role. However, questions have been raised about whether reactivity is situated within the person: is reactivity trait-like?

1.2.3.1 Limitations of Reactivity as Trait and the Importance of Situation

Three questions have been asked about the trait-like nature of reactivity; these concern: i) the stability of reactivity over time; ii) the stability of reactivity across stressors; and iii) its generalizability to everyday situations.

- *Stability of cardiovascular reactivity over time and a range of tasks*

A number of studies have found that individuals differ in terms of their patterns of physiological responses to stressors. One example that evaluated patterns in different individuals with behaviourally enhanced cardiovascular reactivity is provided by Kasprowicz, Manuck, Malkoff, and Malkoff (1990). They examined 39 young male participants' haemodynamic reactivity on two occasions, four weeks apart. They found that test–retest (inter-session) correlations in cardiovascular activity were significant both at baseline and task periods. The test-retest correlation coefficents for SBP reactions to mental arithmetic and mirror tracing tasks were $r = 0.51$ and $r = 0.35$, respectively. Additionally, the consistency of individuals' cardiovascular reactions across the mental arithmetic and mirror tracing tasks were significant; for SBP reactivity, $r = 0.56$; for DBP reactivity, $r = 0.35$ and for HR reactivity, $r = 0.56$. These results suggested that the effect sizes of test-retest and inter-task correlations were medium to large (according to Cohen, 1992). Kamarck (1992) examined the haemodynamic reactions to a memory task, a psychomotor task, and a reaction time task in three groups of participant (college males, community males, and community females). They reported that task aggregation across the three tasks increased the internal consistency of SBP, DBP and HR measures and also improved the test-retest reliability of those responses, e.g., the test-retest coefficients for aggregated SBP responsiveness scores was $r = 0.79$, for aggregated HR responsiveness scores it was $r = 0.76$, and for aggregated DBP

responsiveness scores it was $r = 0.76$. In contrast test-retest correlations for single tasks on SBP measures ranged from 0.52 to 0.71, for DBP measures they ranged from 0.48 to 0.71, and for HR measures they ranged from 0.50 to 0.66. Thus, aggregation of scores across multiple tasks and sessions allow greater generalisability and improves the reliability of reactivity assessment compared to single task measures.

Kamarck et al. (1992) also assessed individual differences in cardiovascular reactions to psychological stressors and the effect on reliability of aggregating across sessions and across stressors. Reliability coefficients of SBP and HR reactivity were above 0.80 in the different samples (student and community participants). Further, they suggested that multiple occasions of assessment may be useful in cardiovascular reactivity measurement and that aggregating reactivity across tasks is more reliable than assessing cardiovascular reactions to a single task. Moreover, a meta-analysis of the test-retest reliability of reactivity found that HR responses provided the best test-retest reliability ($r = 0.56$), followed by SBP ($r = 0.41$) and DBP ($r = 0.35$) (Swain & Suls, 1996). In general, these studies suggest that cardiovascular reactivity has reasonable stability both over time and across stressors.

- *Generalisations to social situations and the real world*

In addition to temporal and situational (task) stability, for reactivity to play a causal role in the development of hypertension, laboratory studies need to provide a good model of everyday life; it is the cardiovascular reactions to *real-life stressors* that are thought to be predictive of hypertension (Manuck et al., 1993). Therefore it is important to demonstrate associations between cardiovascular reactivity in a laboratory setting and in a natural environment. Many researchers have used stressful situations in everyday life, such as mental arithmetic and public speaking, to construct valid laboratory stressors. Further, cardiovascular reactions to those laboratory stressors have been found to generalize to everyday life (Matthews, Owens, Allen, & Stoney, 1992; Turner et al., 1994; Turner & Sherwood, 1991). For example, Fredrikson, Blumenthal, Evans, Sherwood, and Light (1989) reported that individuals with relatively high levels of BP and HR measured in the laboratory during mental arithmetic were related to BP and HR levels recorded in the natural environmental setting, in particular in the work setting.

Karmarck, Schwartz, Janicki, Shiffman, and Raynor (2003) have also supported the hypothesis that individual differences in cardiovascular reactions in the laboratory setting are

associated with cardiovascular reactions during daily life: high SBP levels in daily life stress events were associated with greater SBP responses to laboratory stressors (a marksmanship task, a visual short-term memory task, a psychomotor task, and a version of the Stroop Colour-Word Conflict Test) after controlling for the effects of posture, activity, and substance use. Cornish, Blanchard, and Jaccard (1994) examined the relationship between 24-hour ambulatory BP (measuring BP over a 24 hour period) and BP obtained during laboratory stressors (i.e., mental arithmetic, cold pressor, orthostatic response, and treadmill exercise) with 30 normotensive healthy male and female participants. They found that laboratory BP was correlated with ambulatory BP; additionally laboratory baseline BP was more strongly associated with the ambulatory BP than was BP obtained during laboratory stressors. Further, Kamarck, Debski, and Manuck (2000) examined cardiovascular responses in a real-life session (classroom speech anticipation and speech delivery tasks) and speech in a laboratory session (computer tasks (i.e., target, tracking, scanning, Stroop), and speech tasks). They found that SBP, DBP, and HR responses to the classroom speeches were associated with responses in the laboratory setting. In addition, aggregating responses across the multiple laboratory tasks increased their association with SBP, DBP, and HR responses in the classroom (r = 0.30 for HR, r = 0.26 for SBP, and r = 0.40 for DBP). Thus, it appears that cardiovascular responses to stressors in the laboratory are related to responses in everyday life, particularly when aggregated responses can be calculated.

1.2.4 Reactivity as "a Situation Cause" in the Development of Hypertension

The Situation Cause model also hypothesizes that reactivity plays a causal role in the development of hypertension. In contrast to the Causal Trait model, studies have focused on social dimensions of the situation such as social isolation and social interaction that tend to exaggerate or minimize cardiovascular reactivity. To date, animal models have been developed to investigate relationships between stress-induced BP responses, hypertension, and CVD (Lawler, Zheng, Li, Wang, & Edgemon, 1996; Manuck, Adams, McCaffery, & Kaplan, 1997; Malpas, 2010; Sanders & Lawler, 1992; Watson, Shively, Kaplan, & Line, 1998). Animal studies have demonstrated the importance of the social situation in the development of hypertension. For example, Henry, Stephens, and Santisteban (1975) examined social interaction and BP reactivity in mice. They found that BP increased in male mice kept in an over-crowded population cage compared to a control group who were kept in a normal box with sibling males. The total period of exposure to the stimulation was also associated with high BP, and resulted in the development of aortic arteriosclerosis and

myocardial fibrosis. Vender, Henry, Stephens, Kay, and Mouw (1978) also found that plasma renin activity and BP were higher in mice kept in an interconnected box system (population cage) which increased social interaction and competition compared to those who were isolated. They suggested that enhanced psychosocial interactions induced hypertension and resulted from hyperactivity of the sympathetic nervous system that produced pituitary-adrenocortical hormones. In addition, animal studies have reported that stress exposure to particular social environments and those where the animal may learn to avoid shock may play a causal role in the development of hypertension (Ely, Caplea, Dunphy, & Smith, 1997; Galeno, Van Hoesen, & Brody, 1984; Sanders, Wirtz-Nole, DeFord, & Erling, 1994). In sum, the results suggest an animal model whereby large cardiovascular responses to specific social environments are related to increases in BP over time.

In human studies the focus has been on dimensions of the situation that tend to exaggerate or minimize cardiovascular reactivity including social evaluation and social support. For example, Kamarck, Manuck, and Jennings (1990) investigated the effect of two social conditions; completing a mental arithmetic alone or with a friend. Participants in the alone condition showed a higher magnitude of cardiovascular reactivity compared with the participants in the friend condition. Further, a high subjective perception of job strain (high job demand) has been related to greater BP reactions to a Stroop stress test in healthy individuals, than in participants with low job strain (Fauvel, Quelin, Ducher, Rakotomalala, & Laville, 2001). This model emphasizes aspects of the task or situation that provoke cardiovascular responses rather than individual differences. Thus the cardiovascular reactivity as a situation cause model posits the type of stress task, along with aspects of the wider environment, may influence cardiovascular reactivity and the subsequent development of hypertension.

1.2.4.1 Nature of Psychological Stressors; Active and Passive Coping Tasks

A variety of standardised acute psychological stressors have been used to model stress in the laboratory; these include mental arithmetic, simulated public speaking tasks, problem solving tasks, Stroop colour/word interference tasks, mirror tracing, recall of negative emotions, anger interviews, car-driving simulations, star tracing, video gaming, and cold pressor tests (Brydon & Steptoe, 2005; Jennings et al., 2004; Matthews, Zhu, Tucker, & Whooley, 2006; Stewart, 2006; Tuomisto, Majahalme, Kahonen, Fredrikson, & Turjanmaa, 2005). One way of dividing responses to psychological tasks is based on the type of coping associated with

the task (active or passive) and the consequent sympathetic nervous system responses (Andreassi, 2006; Sherwood & Turner, 1992). As described by Obrist et al. (1976), active coping tasks are psychological stressors that demand attention and vigilance or mental effort but require little physical effort or physical activity. Active coping tasks generally appear to elicit sympathetic nervous system responses that stimulate cardiac and vascular beta-adrenergic receptors. Usually changes in BP in response to active coping tasks are underpinned by increases in HR and CO. Examples of active coping tasks include reaction time, mental arithmetic, video games, Stroop colour word test, Raven's Matrices (Sherwood & Turner, 1992), social stressors, problem-solving (Lehrer et al., 1996), and time-paced memory test (Bosch et al., 2001). Passive coping tasks, on the other hand, are defined as those where an individual has little or no control over the situation or outcome; they involve passive sensory intake or vigilance that are correlated to sympathetic activation eliciting vasoconstriction (and increases in TPR) through alpha-adrenergic receptor stimulation. Passive coping tasks include the cold pressor test (Ring et al., 1999), habituation tests, watching humorous films (Sherwood & Turner, 1992; Tuomisto et al., 2005) or videos showing surgical operations (Bosch et al., 2001). Therefore, type of coping task has been categorised into two types, active and passive; these coping tasks are presented in the summary table 1.2

Table 1.2 Classification of active and passive coping tasks

Type of task	**Definition**	**Patterns of haemodynamic reactivity**	**Patterns of adrenergic receptor**
Active coping	demand attention and vigilance or mental effort	Increased CO, decreased TPR	Beta-adrenergic cardiovascular responses
Passive coping	no control over the outcome of a situation	Increased TPR, decreased CO	Alpha-adrenergic cardiovascular responses

However, a number of studies have found that BP responses to active coping tasks may be elicited via increases in systematic vascular resistance, accompanied by increases in alpha-adrenergic activity, rather than by cardiac performance (Waldstein, Bachen, & Manuck,

1997). Waldstein et al. (1997) assessed haemodynamic responses to active coping tasks (Stroop and mirror tracing tasks) and found that TPR responses to active coping tasks increased more than indices of cardiac performances (e.g., pre-ejection period, stroke index, cardiac index). In addition, Sherwood, Dolan, and Light (1990) have suggested that individual differences in haemodynamic responses to psychological stress tests interact with the type of task, to provoke alpha- and/or beta- adrenergic responses. Therefore, it would be useful to have a more comprehensive assessment of haemodynamic reactions. In other words, assessment of haemodynamic patterns may be useful to understand psychophysiological mechanisms and aid in the prediction of future BP.

There have been few prospective studies that have examined the predictive utility of cardiovascular reactions to different active and passive coping tasks within the same study (Flaa, Eide, Kjeldsen, & Rostrup, 2008; Girdler et al., 1996; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Sterwart & France, 2001; Trieber et al., 1994; Tuomisto et al., 2005). Moreover, results of these studies are quite inconsistent. Tuomisto et al. (2005) examined cardiovascular reactions to several different types of psychological stress tasks (e.g., active coping, passive coping)) using a variety of outcome measures (i.e., causal future BP, and use of antihypertensive medication) at 9-12 year follow-up in 82 adult participants. They found that SBP responses to psychological stress tasks improved the prediction of future BP 9-12 years later. Further, they reported that cardiovascular reactions to active coping tasks afforded better prediction of future increased BP or hypertensive medication use than cardiovascular reactions to passive coping tasks, thus implicating the importance of active coping and beta-adrenergic responses. Flaa et al. (2008) investigated SBP, DBP, and HR reactions to mental arithmetic tasks (active coping) and cold pressor tasks (passive coping) in 80 healthy men with a re-examination after 18 years. They reported that SBP and DBP reactions to both tasks were significant predictors of future BP, after adjusting for traditional risk factors (resting SBP, family history of hypertension status, and BMI at entry); although reactions to the mental arithmetic task (active coping) appeared to be better predictors than the cold pressor task (passive coping).

Markovitz et al. (1998) examined cardiovascular reactions to video games, star tracing, and cold pressor tasks with 3320 healthy adults. After five years follow-up, only BP reactions to the video game (an active coping task) predicted BP increases over the five years follow-up; cardiovascular reactions to the cold pressor tasks (a passive coping task) did not. However,

BP responses to the star tracing task, widely regarded as an active coping task did not predict BP increases. They concluded that BP responses to stressors provoking primarily a beta-adrenergic cardiovascular reactivity may be predictive of significant BP change and hypertension status, but the failure of BP responses to star tracing cautions against a simplistic interpretation. Markovitz argued that the star tracing task may have provoked a mixed alpha- and beta-adrenergic response although no data from their study was available to confirm this. In contrast, Girdler et al. (1996) found that SBP reactions to passive coping tasks (a passive speech task, a cold pressor task), and not active coping tasks (reaction time, active speech) were predictive of BP at two year follow-up; passive coping tasks were mediated by alpha-adrenoceptor stimulation as indexed by TPR increases. Thus, Girdler et al. (1996) concluded that passive coping tasks may be better predictors of future BP than active coping tasks, although their study had the smallest sample size (n = 40) and shortest follow-up period (two years).

Therefore, to date, results of studies comparing active and passive coping tasks are mixed and/or inconsistent. Differences in sample size, tasks, and follow-up duration may account for such differences. In particular it is notable that only one of the studies recruited and followed more than 100 participants (Markovitz et al., who follow more than 3000 participants). In addition, types of coping tasks should be a consideration regarding the prediction of future BP levels or hypertension status.

1.2.4.2 Importance of Task and Impedance Cardiograph (Underlying Haemodynamics)

Cardiovascular reactivity is commonly described as a change in BP or HR activity from a resting baseline state to a stressed state (Obrist, 1981). While BP and HR are the most common measures of cardiovascular reactivity, other cardiovascular parameters have been used such as CO and TPR. CO reflects myocardial performance and TPR indexes vascular performance (Blascovich, Vanman, Mendes, & Dicerson, 2011; Brownely, Hurwitz, & Schneiderman, 2000; Sodolski & Kutarski, 2007; Turner, 2000).

Impedance cardiography is a non-invasive method of monitoring cardiac function (Woltjer, Bogaard, & de Vries, 1997) that has afforded researchers the opportunity to assess patterns of haemodynamic responses. In particular, researchers have focused on two dimensions of haemodynamic responses to psychological stressors that underpin BP regulation: cardiac responses and vascular responses. Cardiac responses are defined as central mechanisms (e.g.,

CO) and vascular responses defined as peripheral mechanisms (e.g., TPR) that are involved in the control of BP. It has been shown that different types of tasks can evoke different patterns of cardiovascular changes. For example, the cold pressor, a passive coping task, has been shown to provoke a vascular pattern of response in which alpha-adrenergic and vascular sympathetic activation was heightened (Kasprowicz et al., 1990; Willemsen et al., 1998). Similar results were reported by Gregg, James, Matyas, and Thorsteinsson (1999), who examined mental arithmetic (an active coping task) and a cold pressor task. They found that mental arithmetic elicited myocardial responses (increases in CO reactivity) and the cold pressor test elicited vascular patterns of reactivity (increases in TPR reactivity). A further study found that a reaction time task (an active coping task) was associated with relatively greater changes in CO, and passive viewing of two film segments (a passive coping task) tended to increase vascular resistance (Sherwood et al., 1990). Thus, impedance cardiography measures can provide useful information for a comprehensive assessment of haemodynamic patterns beyond that of BP monitoring. It allows the determinants of BP changes to be assessed.

1.2.4 Interaction of Situation and Person in Reactivity Models

More recent models of cardiovascular reactivity have focused on the interaction between person and situation. The interaction of situation and person model suggests that the involvement of reactivity in the development of hypertension is complex and involves trait-like aspects of reactivity situated within the person as well as situational factors such as task type and social environment. It proposes that, over time, people develop hypertension if the environments that they inhabit provoke exaggerated responses; high stress environments or stress reactive people alone do not elevate a person's risk of developing hypertension. Research that focused on the trait dimension of hostility provides early examples of the person-interaction situation (Christensen & Smith, 1993; Smith & Allred, 1989; Suarez & Williams, 1990). For example, Suarez and William (1989) reported that men with high hostility scores (measured using the Cook and Medley Hostility scale; Cook & Medley, 1954) showed exaggerated cardiovascular reactions in a harassment condition, but that these exaggerated reactions were not observed in men with low hostility scores. Further, Lepore (1995) found that low hostile participants who received social support from a confederate had smaller increases in BP to a speech task than low hostile participants without support, and high hostile participants with or without support. Thus, the relationship between situation

characteristics and the person's characteristics (e.g., personality) mediate the prediction of cardiovascular reactivity.

Turning to haemodynamic responses, Sherwood et al. (1990) have suggested that individual differences in haemodynamic responses to psychological stress tests interact with the type of task, to provoke different patterns of alpha- and/or beta-adrenergic responses. For example, Waldstein et al. (1997) assessed haemodynamic responses to active coping tasks (Stroop and mirror tracing tasks) and found that BP responses to active coping tasks elicited increases in BP via increases in systematic vascular resistance, presumably eliciting alpha-adrenergic activity, rather by than increases in cardiac performance (e.g., pre-ejection period, stroke index, cardiac index). Willemsen et al. (1998) found that a mental arithmetic task produced a mixed pattern of alpha- and beta-adrenergic cardiovascular reactions, whereas the pattern of responses to cold pressor was predominantly alpha-adrenergic. Thus, these studies suggest that cardiovascular reactions to different type of task (active and passive coping tasks) may differ with respect to the underlying haemodynamic changes even though the size of BP responses may be similar.

Few prospective studies have utilised a person-by-situation cause model. One prospective cohort study examined the combination of genetic susceptibility and environmental stress exposure with cardiovascular reactions to psychological stress tests (reaction time and cold pressor tasks) to predict BP over ten years later (Light et al., 1999). They found that participants with a combination of high daily stress (measured using the Daily Stress Inventory), as well as a positive family history of hypertension status and high stress responsiveness demonstrated the highest increases in SBP and DBP levels at 10-year follow-up. However, while enticing, these findings are limited due to the restrictive sample (65 men). Another prospective cohort study investigated the effects of sex, age, and socioeconomic status on cardiovascular reactivity to a psychological laboratory stressor (PASAT) in healthy participants over a 12-year follow-up period (Carroll et al., 2011). They found that BP reactivity to psychological stressors predicted future BP status after controlling for age cohort, sex, performance scores on the stress test, socioeconomic status at baseline, resting BP at baseline, taking BP medication at baseline, and the BMI at baseline. Importantly, they further found that reactivity was a particularly strong predictor of BP levels in low socio-economic status individuals (manual group) and men rather than women.

Therefore, future studies should attempt to clarify which factors (i.e., person by situation interactions) could lead to future high BP or hypertension.

To summarise, in this sub-section four reactivity models have been described and discussed here: marker, causal trait, situation cause and person by situation interaction. These have been used to explain how cardiovascular reactivity might contribute to development of hypertension. While early models focused on personal or situational factors, the most recent models have recognised the importance of both and have focused on the interaction of person and situation in predicting future BP. The person by situation model can be argued to be a true biopsychosocial model, as it assumes that biological (genetic and trait-like) characteristics interact with the psychosocial environment to result in the development of hypertension.

1.3 Cardiovascular Reactivity and Hypertension Status

Based on the wealth of literature in this area (such as that cited above) many reports have evidenced that haemodynamic responses to psychological stress may play a key role in the progression of CVD including hypertension stutus (Barnett, Spence, Manuck, & Jennings, 1997; Kop, 1999; Schwartz et al., 2003). The proposed models of causal pathways between stress and hypertension recognise the biological, personal and social characteristics that may be important. These proposed models showing causal pathways between cardiovascular reactivity to stress and hypertension are displayed in figure 1.2. The relationship between stress exposure and maintain BP elevation is moderated by genetic factor or predisposition factors (e.g., BMI, smoking). These stressors have been categorised into three groups: a) acute stress such as laboratory stressors, mental activity, emotional status; b) episodic stress occurring for several months to two years such as depression, exhaustion; c) chronic stress which continue for more than ten years such as low socioeconomic status. The individual's responses to the stressor(s) affect one of several pathophysiological pathways, such as increases in sympathetic nervous system (i.e., increased BP, increased HR), decreases in parasympathetic nervous system, and imbalance between vasoconstrictors and vasodilators that can lead to BP elevation and hypertension. Consequently, it is this model that will be investigated and used as a conceptual framework in this thesis.

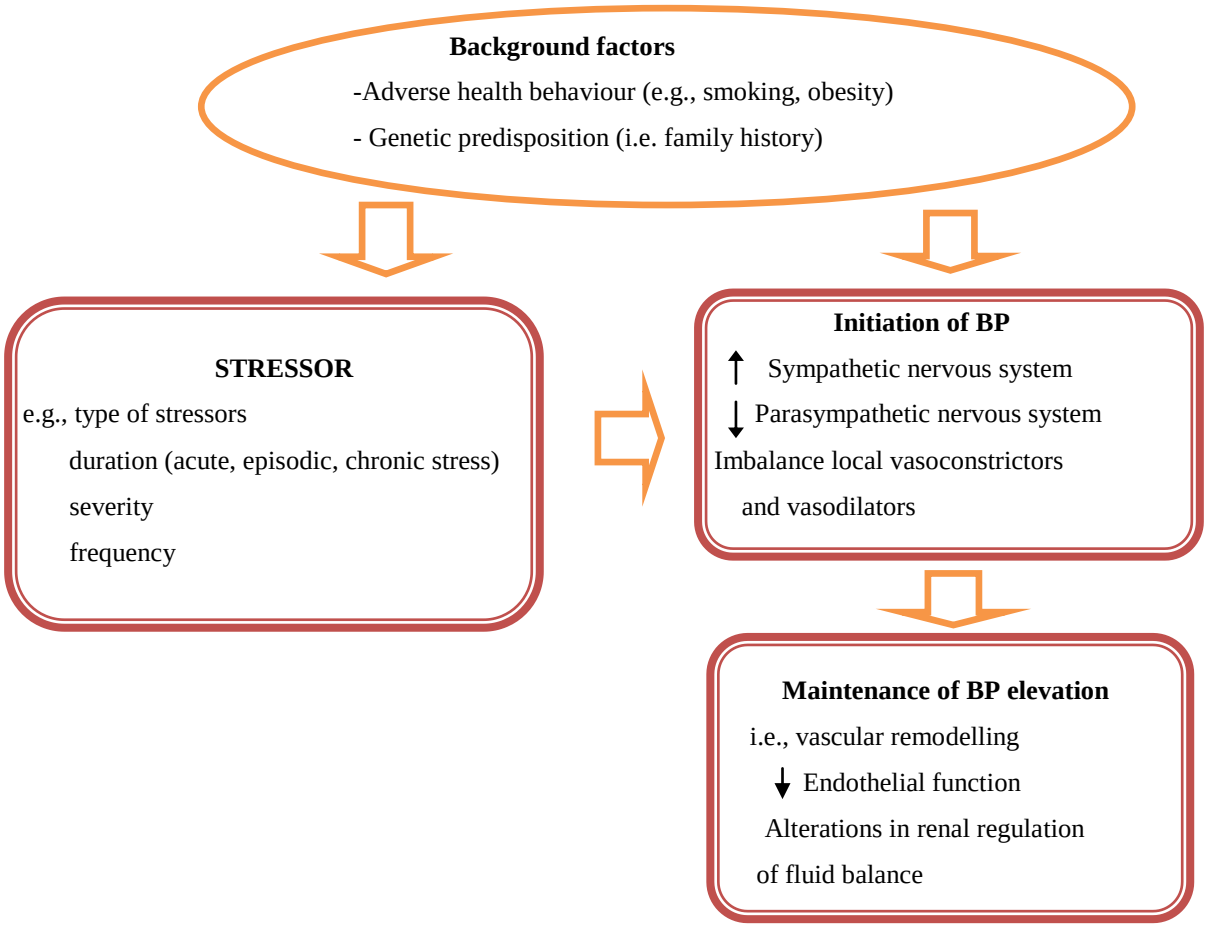


Figure1.2 Pathophysiological pathways between cardiovascular reactivity to stress and hypertension

1.4 Cross-Cultural Differences, Cardiovascular Reactivity and Hypertension Status

Exaggerated cardiovascular responses to psychological laboratory stressors have been associated with increased risk for developing hypertension and CVD. However little is known about the role of cardiovascular reactivity across different countries, although many studies have focused on ethnic differences in haemodynamic reactions to laboratory stress tests and CVD. Ethnicity is an important demographic factor in predicting CVD prevalence and mortality. It encompasses both genetic and cultural differences including language, religion and diet (Kreatsoulas & Anand, 2010). Individual differences in ethnic backgrounds are associated with variations in lifestyles, geography, and socio-economic status. Therefore, differences in ethnic background may provide some explanation for increased CVD and hypertension prevalence and mortality (Chaturvedi, 2003; Chaturvedi, McKeigue, & Marmot, 1993; Wild & Mckeigue, 1997). However, the mechanisms linking differences in ethnic background with hypertension are unclear.

Differences in lifestyle factors may, in part, account for ethnic differences in hypertension rates. There is a lower prevalence of raised BP (hypertension) rates in the South-East Asia Region (37.3% for males and 34.9% for females) compared to Europe (44.5% for males and 37.1% for females; WHO, 2011). Racial/ethnic disparities in CVD risk factors, for example, diet, obesity, smoking, and physical activity, have been suggested as factors accounting for these differences (Finkelstein, Khavjou, Mobley, Haney, & Will, 2004; Kurian & Cardarelli, 2007). For example, particular dietary patterns have been associated with an increased risk of developing CVD (Odegaard, Koh, Yuan, Gross, & Pereira, 2012); Western-style diets, reflecting a high intake of red and processed meat, refined grains, french fries, and sweets and desserts, are linked to a higher risk of CVD and total mortality, whereas eating diets with high vegetable, fruit, legumes, fish, poultry, and whole grains contents, more typical of Asian populations, are related to a lower risk of CVD and total mortality (Heidemann et al., 2008). Further, the greatest contributing risk factor for hypertension and CVD in many populations is obesity (Hirani, Zaninotto, & Primatesta, 2007; Pischon et al., 2008; Taylor et al., 2010). In the UK, the average BMI for both males and females is high (27.1 kg/m^2 and 26.8 kg/m^2, respectively; with 23% of men defined as obese (BMI > 25 kg/m^2); Scarborough, et al., 2010). In Thailand, data collected by the Ministry of Public Health found that the average BMI was 23.6 kg/m^2 (Narksawat, Podang, Punyarathabundu, & Podhipak, 2007); considerably lower than the UK population figures. Direct comparison using WHO data (WHO Expert Consultation, 2004) also reveals that Thais have a lower BMIs than those in Western countries. Therefore, different rates of hypertension and CVD by ethnicity maybe explained by behavioural factors.

Another mechanism that has been used to explain different rates of hypertension by ethnic background is cardiovascular reactivity (see figure 1.2). Research on ethnic differences in CVD have primarily focused on African American participants since they have a higher incidence of high BP or hypertension than Caucasians (Anderson, 1989; Murphy, Alpert, Moes, & Somes, 1986; Murphy, Alpert, Willey, & Somes, 1988). Concomitantly, it has been found that there are differences in cardiovascular responses to psychological stress tests by ethnicity (Dysart, Treiber, Pflieger, Davis, & Strong, 1994, Sherwood, May, Siegel, & Blumenthal, 1995); many researchers have been reported that African Americans demonstrate greater cardiovascular reactivity and more prolonged cardiovascular responses to psychological stress tests than European Americans (Barnes et al., 2000; Blascovich, Spencer, Quinn, & Steele, 2001; Lepore et al., 2006; Saab et al., 1997).

To date only three published studies have directly compared cardiovascular responses to laboratory stressors in Asian and Caucasian participants. In the first, Stoney, Hughes, Kuntz, West, and Thornton (2002) examined differences in cardiovascular responses to speech and mental arithmetic tasks in 37 Asian Indian and 43 Caucasian college students. Asian Indian men and women had significantly lower SBP reactions to both stressors, relative to European American men and women; there were no differences in haemodynamic responses. A second study examined cardiovascular reactions to two counter-balanced anger provocation role-play situations in 40 White men and 20 Indian male students who immigrated to the United States. Participants were instructed to suppress or express their anger in counterbalanced order. White men showed a heightened cardiac response to anger expression, something not seen among Indian men. In contrast, Indian men exhibited delayed DBP recovery from anger expression when asked to engage in anger exhibition, a behavior not congruent with their culture of origin (Suchday & Larkin, 2004). Finally, Shen, Stroud, and Niaura (2004) assessed BP and HR responses to stress in 77 Caucasian Americans and 43 Asian Americans; most were identified as of East Asian origin. Asian Americans demonstrated lower SBP and HR responses to all four laboratory stress tests (speech, serial subtraction, mirror tracing, and handgrip tasks) than did Caucasian students with the largest differences being evident during the serial subtraction task. Taken together, these studies suggest that Asians may show reduced cardiovascular reactions to psychological stressors compared to Caucasians. However, it is worth noting that these studies have been of residents in the United States and acculturation may be important (Berry, 1992). In spite of this limitation, these findings are consistent with epidemiological studies that report that Asians have lower CVD mortality and hypertension prevalence compared to Caucasian individuals. Therefore, these findings support the hypothesis that the smaller cardiovascular responses to stress seen in Asians may account for their decreased risk of developing hypertension or CVD. However, to date, only one Japanese study has examined whether cardiovascular reactivity is prospectively related to high BP in Asians (Kasagi, Akahoshi, & Shimaoka, 1995).

In addition to examining differences between American and Asian participants, there is some limited evidence of cross-cultural differences in cardiovascular reactivity within Asian participants. Kaur and Bishop (2003) examined ethnic differences in cardiovascular responses to a neutral reading task, an anger recall interview, a cold pressor task, and a mental arithmetic task with harassment. They found that Chinese and Malays residing in Singapore exhibited increased SBP and cardiac reactions compared to Indians residing in

Singapore. In a second study of Indians living in India and Singapore, they found that participants living in India showed higher SBP, HR and cardiac responses, while Indians residing in Singapore showed higher TPR index reactivity. Despite these interesting interactions between residency and ethnicity, still relatively little is known about cardiovascular reactivity in Asian populations, and no data exists about Thai participants in Thailand. Thus, haemodynamic responses to psychological stressors will be explored in different countries (i.e., Thailand and the UK).

1.5 Symptoms of Depression and Anxiety, and Cardiovascular Reactivity

The versions of the Reactivity Hypothesis described up to this point have focused on hypertension, in particular, and CVDs, more generally. However, some researchers have proposed that exaggerated cardiovascular reactions may predict other conditions. For example, Boyce et al. (1995) reported that children with high cardiovascular reactivity were more likely to develop respiratory illnesses in high stress environments than children with low cardiovascular reactivity or those in low stress environments. Furthermore, in some early studies, high BP reactivity was related to higher depression scores and greater rates of depression (Kibler & Ma, 2004); similar relationships have been reported with anxiety scores and clinical diagnoses of anxiety. These relationships are significant because depression and, to a lesser extent, anxiety have been associated with greater rates of CVD and poorer prognosis after myocardial infarction and other cardiovascular events; indeed, cardiovascular reactivity has been proposed as one mechanism linking depression and anxiety to poor cardiovascular prognosis (Carney, Freedland, & Veith, 2005). These studies are reviewed below, followed by an examination of studies relating cardiovascular reactivity with anxiety and depression.

1.5.1 Anxiety and Depression, and CVD

For over 30 years studies have examined the prospective relationship between depression and anxiety, on the one hand and hypertension status, CHD, and CVD, on the other (e.g., Davidson, Jonas, Dixon, & Markovitz 2000; Jonas, Franks, & Ingram, 1997; Kahn, Medaie, Neufeld, Riss, & Goldbourt, 1972). For example, Davidson et al. (2000) examined the relationship between depression and hypertension in over 3300 young healthy men and women and followed them up for five years. They reported that participants with depression (measured by the Center for Epidemiological Studies Depression Scale) had a higher incidence of hypertension (defined as BP of 160/95 mmHg or more) than those without

depression after five years follow-up. So, depression is an important and widely recognised factor related to CVD (see Grippo and Johnson (2002) for a review). An association between anxiety symptoms and hypertension has also been reported, although in fewer studies. For example, an epidemiological study of 2992 normotensive American participants followed for 7 to 16 years demonstrated that that the risks for incident hypertension (defined as BP of 160/95 mmHg or more) and treated hypertension (defined as prescription of antihypertensive medications) in both white and black participants (Jonas et al., 1997) were associated with anxiety symptoms. Further, Rutledge and Hogan (2002) quantitatively reviewed 15 prospective cohort studies that tested the hypotheses that depression and anxiety predict the development of hypertension. They found that both depression and anxiety increased the risk of developing hypertension over a one year or greater follow-up. Further, high psychosocial distress increased the risk of hypertension by approximately 8%, compared to low psychological distress. Thus, most studies support the hypothesis that anxiety and depressive symptoms are associated with the development of future hypertension status.

Symptoms of anxiety and depression have also been related to the development of CHD and CVD in a number of large prospective studies (Ariyo et al., 2000; Everson-Rose & Lewis, 2005; Player, King, Mainous, & Geesey, 2007; Shen et al., 2008). For example, Ariyo et al. (2000) investigated 4493 participants who were free of CVD, and assessed depressive symptoms using the Depression Scale of the Center for Epidemiological Studies. Six years later they found that depressive symptoms were an independent risk factor for the development of CHD and angina without concurrent myocardial infarction. In addition, meta-analysis of eight cohort studies reported that depression was associated with an increased incidence of mortality and associated cardiac events (e.g., heart transplantation, new cardiac events; Relative Risk = 2.1) (Rutledge, Reis, Linke, Greenberg, & Mills, 2006). For anxiety, a meta-analysis of 12 prospective cohort studies with at least six months follow-up found that anxiety was associated with adverse outcomes after myocardial infarction; specifically anxiety was associated with all-cause mortality (odds ratio = 1.47), cardiac mortality (odds ratio = 1.23), and new cardiac events (odds ratio = 1.71) (Roest, Martens, Denollet, & de Jonge, 2010a). A further meta-analytic review (Roest, Martens, Jonge, & Denollet, 2010b) assessed the association between anxiety (including anxiety, panic, phobia, post-traumatic stress, and worry) and the risk of CHD (the end points were cardiac death, myocardial infarction, and cardiac events, e.g. angina pectoris) in 20 prospective studies (follow-up periods ranging from 2.0 to 20.9 years). Anxious participants had a 26% increased risk of

incident CHD and a 48% increased risk of cardiac events (Roest et al., 2010b). With respect to depression and the risk for CVD, a recent systematic review and meta-analysis of prospective cohort studies indicated that depressive symptoms were associated with myocardial infarction (odds ratio = 1.60). These relationships were maintained and still significant after adjusting for traditional risk factors (e.g., age, BMI, current cigarette smoking history, history of hypertension). In short, there is substantial evidence that anxiety and depression play an independent role in the development of CVD (including hypertension status, CHD status, and CVD events).

The association between depression, anxiety and CVD is complex and the mechanisms linking them have not been fully elucidated (Goldston & Baillie, 2008; Grippo & Johnson, 2002; Halaris 2009; Joynt, Whellan, & O'Connor, 2003; Krantz & McCeney, 2002; Rozanski, Blumenthal, & Kaplan, 1999). For example, Halaris (2009) suggested that the relationship between depression and CVDs involves multiple factors and multiple pathways including sympathoadrenal activation and homeostatic imbalance between the sympathetic and the parasympathetic systems (with diminished vagal tone and loss of HR variability in depression).

Joynt et al. (2003) suggested seven potential mechanisms for the relationship between depression and CVD. Depression has been associated with changes in an individual's health status that may influence the development and course of CVD, including noncompliance with medical treatment (Gallagher, Viscoli, & Horwitz, 1993; Horwitz et al., 1990). In addition, individuals with depression are more likely to have other cardiovascular risk factors including smoking (Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Quattrocki, Baird, & Yurgelun-Todd, 2000) and hypertension (Shinn, Poston, Kimball, St Jeor, & Foreyt, 2001; Wilson et al., 1998) that impact on prognosis. Depression is also associated with physiological changes that negatively influence the cardiovascular system, for example, nervous system activation (Gold, Gabry, Yasuda, & Chrousos, 2000; Matthews et al., 1998), cardiac rhythm disturbances, systematic and localized inflamation (Carney, Freedlan, Rich, Smith, & Jaffe, 1993; Pires, Lehmann, Steinman, Baga, & Schuger, 1999), localized inflammation (Appels, Bar, Bar, Bruggeman, & de Baets, 2000; Kop et al., 2002) and hypercoagulability (Mendelson, 2000; Shimbo et al., 2002). Further, stress may be an underlying trigger that leads to depression and the development of CVD (Jiang et al., 1996; Rosengren, Tiblin, & Wilhelmsen, 1991). Joynt et al. (2003) also suggested that genetic

predisposition for any of those mechanisms might be responsible for the development of both depression and CVD in an individual.

One pathway linking psychological factors to cardiovascular mortality that has received attention is that of cardiovascular reactivity. Many versions of the reactivity hypothesis propose that exaggerated BP and HR reactivity is associated with preclinical manifestations of increased CVD risk, and that psychological factors (e.g., anxiety and depression) may contribute to those exaggerated cardiovascular responses (Everson-Rose & Lewis, 2005; Strike & Steptoe, 2004) - although most studies proposing reactivity as a pathway linking psychological factors to CVD risk have adopted a trait model. The present thesis is also concerned with such relationships, i.e., those between depression and anxiety, and cardiovascular reactivity.

1.5.2 Anxiety, Depression and Cardiovascular Reactivity

Many research studies have identified that anxiety and depression may contribute prospectively to enhanced physiological responses; exaggerated physiological reactivity has been posited as one mechanism linking psychological factors to mortality from CVD and hypertension status (Everson-Rose & Lewis, 2005). Several prospective studies have evidenced the mechanisms linking psychological stress with physiological correlates. These have consistently demonstrated that high cardiovascular reactivity confers a risk for elevated BP and other cardiovascular outcomes (Rozanski et al., 1999; Rozanski & Kubzansky, 2005; Strike & Steptoe, 2004). Further, chronic stress exposures and background stress may increase cardiovascular reactivity over time. For example, Matthews, Gump, Block, and Allen (1997) examined 150 children and adolescents and found that children with high background stress had greater DBP and TPR reactions to four laboratory stressors (reaction time, mirror tracing, cold pressor and social competency interview tasks) than their low background stress counterparts. In addition, a number of studies have recognised that anxiety and depression might be related to cardiovascular reactivity and may consequently predict future CVD including hypertension status (Rosengren, Orth-Gomer, Wedel, & Wilhelmsen, 1993). Further, a considerable number of studies have identified that symptoms of anxiety and depression are associated with cardiovascular responses to laboratory psychological stressors (Carroll, Phillips, Hunt, & Der, 2007; Matthews, Nelesen, & Dimsdale, 2005; Phillips, Hunt, Der, & Carroll, 2011; Schwerdtfeger & Rosenkaimer, 2011;Young, Nesse, Weder, & Julius, 1998). Thus, anxiety and depressive symptoms have been related to larger

cardiovascular responses to psychological stressors and these may contribute to hypertension development.

1.5.3 Blunted Cardiovascular Reactivity

However, more recent evidence has suggested that anxiety and depression and other negative health outcomes (e.g., obesity) are related to blunted cardiovascular responses. A new hypothesis has been proposed by Carroll, Phillips, and Lovallo (2012) called the "Blunted cardiovascular reactivity" hypothesis. In contrast to the "Reactivity hypothesis", the Blunted cardiovascular reactivity hypothesis notes that low cardiovascular reactivity is associated with some poor health outcomes, such as high symptoms of anxiety and depression (Carroll et al., 2007; Phillip 2011; Phillips & Hughes, 2011; Phillips et al., 2011). For example, Carroll et al. (2007) assessed symptoms of anxiety and depression (measured with the the Hospital Anxiety and Depression Scale (HADS)) and cardiovascular reactions to the PASAT with a large community study in Scotland. They revealed that SBP and HR reactions to the PASAT were negatively associated with depression and anxiety scores. Other studies of blunted cardiovascular reactivity have found that obese individuals (defined as a BMI $\geq$ 30 kg/m^2) have smaller HR reactions to the PASAT than their non-obese counterparts (Phillips, 2011). Further, Phillips, Carroll, Ring, Sweeting, and West (2005) examined the relationship between life events exposure within the previous 12 months and BP and HR response to the PASAT in 585 healthy young adults. They reported that the number of life events was negatively correlated with cardiovascular reactivity. Chida and Hamer (2008) reviewed 161 studies of chronic psychological factors and acute psychological responses to laboratory stress in healthy participants from 1950 to 2008. Using meta-analytic techniques, they found that negative psychological or behavioural traits, including anxiety, neuroticism, and negative affect, and depressive mood, were associated with decreased cardiovascular reactivity. Therefore, this new hypothesis, the "Blunted cardiovascular reactivity" will be explored within this thesis. Accordingly, the relationships between cardiovascular reactivity and anxiety and depression will be examined in both normotensive healthy UK and Thai adult participants in this thesis to test the Blunted Reactivity Hypothesis and versions of the Reactivity Hypothesis.

1.6 Aims of the Thesis

In this chapter, the importance of hypertension and high BP has been considered; in particular, the prevalence, epidemiology, and pathophysiology of hypertension status have

been considered. The models used to explore the relationships between cardiovascular reactivity and hypertension have been described, and their limitations discussed.

Early researchers did not consider reactivity to be a causal factor in the development of hypertension and so assessed BP and HR responses to a non-specific stressor (usually cold pressor), and did not assess whether reactivity was an independent predictor of hypertension in prospective studies (Falkner, Kushner, Onesti, & Angelakos, 1981; Thomas & Duszynski, 1982; Thomas et al., 1988). In contrast, later researchers have recognized the importance of person-environment interactions and so have assessed background stress in addition to more complex measures of reactivity (e.g., TPR and CO) to a number of tasks (Chen, Matthews, Salomon, & Ewart, 2002; Musante et al., 2000). Most recently, researchers have tested "blunted cardiovascular reactivity" and demonstrated that cardiovascular reactivity may not be positively associated with certain specific health measures (e.g., depressive symptoms) as previously thought. Hence, in this thesis the predictive value of a range of cardiovascular responses (e.g., SBP, DBP, HR, CO, and TPR) to psychological stress tests will be explored. To consider the possibility of cardiovascular responses as predictors of subsequent CVD, the importance of cardiovascular responses in predicting hypertension and BP using systematic review, meta-analysis and meta-regression was first explored (chapter 2). This information helped determine how useful cardiovascular responses to psychological stress tests might be in the prediction of future hypertension status (e.g., increased BP levels). From this, two empirical, cross-sectional studies explored how anxiety and depression are related to cardiovascular reactivity (chapter 4). Finally, cardiovascular reactivity in Thailand and the UK and its utility in predicting increases in BP over a one-year period was also explored (chapters 5 and 6).

1.6.1 The Aims of the Investigation:

Within these studies the aims were as follows:

1. To assess the patterning of cardiovascular responses to psychological stress tests in healthy participants;
2. to assess the relationship between psychosocial factors and cardiovascular responses;
3. to assess the relationship between cardiovascular responses to three psychological stress tests and resting BP levels at one year follow-up.

1.6.2 Research Questions:

Specific to the studies, the research questions were:

1. How large are changes in cardiovascular parameters to psychological stress tests in UK and Thai participants?
2. What relationships are there between cardiovascular reactivity and psychological factors?
3. Can cardiovascular responses to single or multiple, active or passive psychological stress tasks predict hypertension and raised BP over a one year follow-up?

These were investigated according to the conceptual framework set out in figure 1.2 (page 21).

1.6.4 Expected outcomes:

Based upon this thesis of research and investigations herein, this thesis will therefore provide:

1. Knowledge of the magnitude of cardiovascular responses to psychological stress in healthy adults in Thailand and the UK**.**
2. A review of literature describing predictive outcomes of psychological stress tests.
3. Information on the most appropriate test to predict hypertension in healthy people.
4. Information about the contribution of other risk factors (psychophysiological factors) that might correlate with cardiovascular response to determine hypertension or increases in BP.

Taken together, this thesis will provide unique information about the importance of cardiovascular reactivity in predicting hypertension, anxiety and depression in Thai and UK samples.

CHAPTER 2

Cardiovascular Responses to Psychological Stress Tests and Future Blood Pressure: A Systematic Review, with Meta-analysis and Meta-regression

2.1 Introduction

Many studies have suggested that physiological responses to psychological stress can influence the course of hypertension and CHD. Specifically, research has suggested that cardiovascular responses to psychological stress contribute to the development of CHD, increase the risk of developing high BP levels (Carroll et al., 2001; Flaa, Eide, Kjeldsen, & Rostrup, 2008) and increase the risk of death in people with CVD (Goldberg et al., 1996; Kamarck et al., 2000; Laukkanen et al., 2004; Sheps et al., 2002; Weidner et al., 2001). As discussed in chapter 1, much of this research has been based on the reactivity hypothesis which states that cardiovascular responses to stress are implicated either as a marker for hypertension and CHD, or may play a causal role in the disease process (Krantz & Manuck, 1984).

The first tests of cardiovascular reactivity were introduced in the 1930s by Hines and Brown (Hines, 1937, 1940) and used a cross-sectional design to examine if people with elevated resting BP, although not in the hypertensive range, had larger cardiovascular responses to psychological stress than normotensive individuals. These studies found that individuals at risk of developing hypertension showed higher cardiovascular reactivity than individuals not at risk; in consequence it was inferred that cardiovascular reactivity might be a marker or a risk factor for hypertension (Gerin et al., 2000). However, cross-sectional studies are primarily used to determine prevalence at one point in time rather than the development of a condition (Mann, 2003). In contrast, a prospective study design can involve follow-up sampling for several years and can determine the relationships between (a) the development of a disease and, (b) patient outcome measures and/or, (c) risk factors (Gordis, 2009). Since 1980, several longitudinal research studies have reported significant relationships between cardiovascular responses to mental or emotional stressors and subsequent hypertension status or changes in resting BP levels. In addition, the data from some of these studies demonstrated that BP responses to psychological stress tests successfully predicted future BP levels and CVD events (Allen, Matthews, & Sherman, 1997; Kop, Gottdiener, Patterson, & Krantz, 2000; Menkes et al., 1989).

Psychological stress testing has been linked to a broad range of CVD outcomes such as hypertension and CHD (Gerin et al., 2000). The psychological stress tests have been categorised into two groups based on coping: active coping tasks involve effort to achieve actual or perceived control over the consequences of a stressful event, whereas passive coping tasks refer to tasks where an individual did not exert effort or control over situational outcomes (Waldstein, Bachen, & Manuck, 1997). Further, cardiovascular responses to active coping tasks are primarily beta-adrenergically mediated, whereas cardiovascular responses to passive coping tasks are primarily alpha-adrenergically mediated. However, there are few studies that have compared the ability of responses to active and passive coping tasks to predict future BP (Girdler et al., 1996; Trieber et al., 1994).

The first reactivity studies used a cold pressor test (a tank of ice-cold water), a passive coping task (Gerin et al., 2000) that has been widely used to identify people with a risk of CVD who might develop hypertension status or CHD (Barnett, Hines, Schirger, & Gage, 1963; Flaa et al., 2008; Kasagi, Akahoshi, & Shimaoka, 1995; Menkes et al., 1989; Wood, Sheps, Elveback, & Schirger, 1984). However, some studies have reported that cardiovascular responses to the cold pressor test were poor predictors of increased BP (e.g., Carroll, Davey Smith, Sheffield, Willemsen, & Sweetnam, 1996), hypertension status (Thomas et al., 1988) and ischaemic heart disease (Carroll, Davey Smith, Willemsen, & Sheffield, 1998). In other words, findings from studies using the cold pressor task have been inconsistent, probably because the stressor primarily elicits an alpha-adrenergic response (Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998). More recent studies have used active coping tests to investigate their predictive utility of cardiovascular stress testing, in part, because of the inconsistent findings from cold pressor studies, but also due to a recognition that the naturalistic nature of tasks may be important in causally predicting future hypertension (as discussed in chapter 1). These studies have demonstrated that BP responses to mental arithmetic or other active coping tasks predict the development of hypertension status (Falkner, Kushner, Onesti, & Angelakos, 1981). Further, several longitudinal studies have reported that cardiovascular responses to stressors which primarily produce a beta-adrenergic response (active coping tasks such as mental arithmetic tasks, video game tasks) are predictive of future BP or the development of hypertension (Matthews, Woodall, & Allen, 1993; Murphy, Alpert, & Walker, 1992). In addition, some studies that used both active and passive stressors suggest that responses to active coping tests may be better predictors of

future BP than responses to passive coping tasks, in particular the cold pressor test (Brody, Veit, & Rau, 1996; Flaa et al., 2008).

Responses to active coping tests have been shown to involve beta-adrenoceptor activity that may be predictive of enhanced cardiovascular activity, whereas passive coping tasks primarily elicit alpha-adrenergic nervous system activity. There is substantial evidence that active coping might result in greater alpha-adrenoceptor activation or reduced beta-adrenergic mediated activation (Sherwood, Allen, & Obrist, 1986). One method of examining alpha- and beta-adrenergic (see chapter 1, section 1.2.4.1) activities is to measure underlining haemodynamic reactivity by using an impedance cardiogram: systematic vascular resistance and CO can be derived from the impedance measures (Obrist et al., 1978; Sherwood et al., 1986). These studies have suggested that BP responses during active coping tasks are elicited by increases in CO and decreases in vascular resistance. For example, Sherwood, Dolan, and Light (1990) describe research using a reaction-time task as an active and passive task in a repeated measures design; in the active coping condition, participants were asked to depress a button as quickly as possible, whereas in the passive condition they had to observe a team-mate performing the same task. They found that increases in BP during the active task were accompanied by an elevation in CO; in contrast, increases in BP during the passive task were associated with pronounced increases in vascular resistance and relatively modest increases in CO (Sherwood et al., 1990). Further, Montoya, Brody, Beck, Veit, and Rau (1997) found that mental arithmetic (an active coping task) provoked a pattern of responses consistent with beta-adrenergic activation (namely, large CO and HR responses), whereas cold pressor (a passive coping task) provoked a pattern of responses consistent with alpha-adrenergic activation (namely large TPR responses).

There have been a number of reviews that focus on the Reactivity Hypothesis but most of these are somewhat dated (e.g., Krantz & Manuck, 1984). A more recent and large review of 39 prospective studies evaluated the hypothesis that cardiovascular responses can contribute to the prediction of the development of CVD (high BP, preclinical CHD, and cardiac events) (Treiber et al., 2003). This review examined the relationship between responses and follow-up BP levels; specifically SBP exceeding 140 mmHg and/or DBP exceeding 90 mmHg. They suggested that cardiovascular reactivity may predict the development of hypertension. In addition, much research has suggested that heightened BP and hypertension have been associated with increased preclinical CHD, and with an increased risk of developing CVD

(Chobanian & Alexander, 1996; Kannel, 1996; Lakka, Salonen, Kaplan, & Salonen, 1999; Verdecchia et al., 2001). Therefore, preclinical measures (i.e., increased left ventricular mass or wall thickness in the carotid arteries) have been used as an assessment of hypertension risk. Treiber et al. (2003) found limited support for the role of reactivity in predicting hypertension in adults. Interestingly, studies of children (ten studies) revealed a more consistent positive correlation between cardiovascular responses and future BP, particularly in small studies with short follow-up, compared to studies of adults (Treiber et al., 2003). However, Treiber's review only focused on HR and BP response to psychological stressors; few prospective studies had reported haemodynamic data at this time. Further, this review was not systematic nor provided meta-analysis (i.e., using statistical methods to combine results from several studies into a single quantitative estimate; Petticrew & Roberts, 2006) and, thus the studies described may be potentially biased, and the conclusions drawn may be open to interpretation.

Two more recent reviews have employed meta-analysis to assess whether cardiovascular reactivity predicts CVD states (e.g., future high BP, cardiovascular risk status). First, Gasperin, Netuveli, Dias-da-Costa, and Pattussi (2009) reviewed six cohort studies and found a small effect for the prediction of future high BP levels (odds ratio = 1.21) from BP responses to laboratory stressors. However, this review only included adults who demonstrated an increase in BP, defined as a BP (SBP or DBP) increase of ≥ 3.5 mmHg. As such, the majority of published studies were omitted from the analyses and no studies of children were included.

The most recent review (Chida & Steptoe, 2010) used meta-analytics techniques to integrate finding from 36 published cohort studies. Their meta-analyses found that cardiovascular reactivity was significantly associated with poor cardiovascular risk status longitudinally (≥ 3 years) ($r = 0.091$). In addition, this review reported that high cardiovascular reactivity was associated with cardiovascular outcomes including a higher incidence of hypertension and greater SBP and DBP levels (rs = 0.101, 0.117 and 0.077, respectively). In contrast, high cardiovascular reactivity was not associated with coronary calcification, carotid intima-media thickness, or CVD events. Analysis of stressor type demonstrated that only cardiovascular responses to cognitive tasks (which are active coping tasks) were predictive ($r = 0.094$) of later cardiovascular risk status; however as there was high heterogeneity for each of the

outcomes measures, simple interpretation of these effects was rendered impossible. Additional sub-analyses found stronger associations between cardiovascular reactivity and preclinical disease states in men compared to women (r = 0.117), younger aged individuals (defined as ≤ 18 years) compared to older aged individuals (r = 0.097) and healthy individuals compared to individuals at high risk of CVD (r = 0.110). Only SBP and DBP reactivity were associated poor cardiovascular outcomes (r = 0.096 and 0.122, respectively), but in this case heterogeneity was not reported. While the review provides a useful summary of much of the research to date it is limited in a number of ways. First, the definition of psychological stressor in this review focused on non-metabolically demanding tasks; therefore, the cold pressor task, a passive coping task used in many prospective studies, was excluded from the review. However, the cold pressor test has been frequently used as a stressor and its inclusion within reviews of the Reactivity Hypothesis is warranted. Wolf and Hardy (1941) reported that the differences in cardiovascular reactivity were due to differences in reactions to the pain from one participant to another and the pressor effect was related to the pain itself or to the participant's reaction to pain, i.e., the reactivity was psychological. Further studies support the notion that there are individual differences in pain responsivity and that these are associated with psychological measures (Chen, Dworkin, Haug, & Gehrig 1989; Grosse, Prchal, Diaz Puertas, & Coviello, 1993). Peckerman et al. (1994) suggested that cardiovascular responses to cold pressor are an aggregate of several phasic activities, including arterial vasoconstriction provoked by cold and pain. Further, increases in HR and venous blood return were associated with pain. Accordingly, the cold pressor test is frequently defined as a psychological stressor and so studies using the cold pressor are included in this review.

Moreover, both meta-analytic reviews used meta-analysis rather than multivariate meta-regression to synthesize the prediction of future high BP or CVD states by cardiovascular reactivity. Meta-analysis provides a technique for combining results from separate studies to arrive at pooled effect sizes estimates, whereas meta-regression principles are the combination of meta-analytic methods with regression analysis. Multivariate meta-regression therefore provides a means of assessing both single and multiple predictors of effect sizes from variables derived from individual studies (Sutton & Higgins, 2008).

2.2 Questions Addressed by the Review

As mentioned above, none of the reviews have addressed the predictive value of the type of psychological stress tests (active versus passive coping tasks), age group of the participants (adults versus children) and duration of studies (in terms of shorter and longer term follow-up). To clarify these issues, meta-regression techniques were employed to explore cardiovascular responses to psychological stress tests in prospective cohort studies for prediction of future SBP, DBP, hypertension status, preclinical CHD and cardiac events. These compare the effects of different types of coping tasks (active and passive coping tasks), group of participants (adults and children) and length of follow-up data by haemodynamic reactivity (SBP, DBP, HR, CO, and TPR responses to stress) within one analysis. The present systematic review applied meta-regression and meta-analysis to address a number of questions:

1. Do cardiovascular responses to psychological stress tests predict future BP levels (SBP and DBP), hypertension status, preclinical CHD, and cardiac events?
2. Does the predictive value of cardiovascular responses differ between active and passive coping tasks?
3. Does the predictive value of cardiovascular responses to psychological stress tests differ between child and adult samples?
4. Does the predictive value of cardiovascular responses to psychological stress tests differ in short and long term follow-ups?

2.3 Method

2.3.1 Search Strategy

A scoping search was carried out based upon the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care (CRD, 2008), the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011) and Systematic Reviews in the Social Sciences: A practical guide (Petticrew & Roberts, 2006). The following electronic databases were searched: Cochrane library, Medline, Web of Knowledge, PubMed and PsycINFO (including SPORTDIscus and CINAHL) from 1950 to July 2012 (see appendix table 2.1). In addition, the articles from Treiber's review (2003) and Chida and Steptoe's meta-analysis (2010) were included and examined.

2.3.2 Inclusion and Exclusion Criteria

The inclusion criteria were prospective cohort studies that examined the relationship between psychophysiological responses and future cardiovascular pathophysiology published between 1950 and July 2012. Participants had to be healthy (i.e., no reported CVD) and included studies of children and adults. Studies using psychological or psychological stress tests were included. The studies reported at least one of the following outcome measures: CVD, BP or hypertension in a prospective longitudinal study. Further, all journal articles were in English.

The exclusion criteria were as follows: the studies were cross-sectional or retrospective cohort study design; they were reviews, editorial articles or dissertations; they did not measure physiological responses to psychological stress tests; or they did not include measure of BP or CVD at baseline and follow-up.

2.3.3 Definition

The current review focused on active and passive coping tasks (Koolhass et al., 1999; Obrist, 1976; Wingfield, 2003). This review assesses the coping mechanisms developed in response to psychological stressors in terms of active coping tasks (proactive or fight-flight) and passive coping tasks (reactive or conservation-withdrawal) response as defined by Koolhass et al. (1999). Thus, active coping is characterized by a high level of active avoidance, aggression, and other actions indicating active attempts to counteract the stressful stimulus. Further, those tasks requiring "effortful striving"; that is, tasks where participants were forced to complete a challenge that they felt could be accomplished if sufficient effort was expended, are described as active coping tasks. A passive coping task, on the other hand, involves immobility and low levels of aggression, and includes tasks where the individual had to passively accept the administration of the task with no ability to control it (e.g., cold pressor tasks, anticipation tasks).

Hypertension status was defined as high BP (SBP/DBP > 140/90 mmHg) and/or taking anti-hypertensive medication. Cardiac events were defined and determined using the International Classification of Disease (ICD-10; World Health Organization, 2010).

Cardiac events are defined as cardiac mortality or cardiac morbidity, for example, an incidence of ischaemic heart disease, CHD or coronary artery disease (e.g., myocardial infarction) as determined by International Classification of Disease (ICD-10).

Cardiovascular reactivity is defined as haemodynamic reactions to a psychological stress test; this review focused on the most commonly used measures: SBP, DBP, HR, CO, and TPR. Therefore, these measures are included in the meta-regression and/or meta-analysis models.

2.3.4 Quality Appraisal

Two independent evaluators conducted quality assessment based upon the CRD's recommendations for prognostic tests (CRD, 2008). Checklists were created and focused mainly on defining the review question including the population, inclusion criteria, measurement of reactivity, diagnosis criteria, blinding of outcome assessments, sample sizes, percentage of drop outs, number of years of follow-up, methods, statistics, and availability of follow-up data for all participants (see appendix table 2.2).

2.3.5 Data Extraction

The following information was extracted from each of the studies included in the review: whether there were clear inclusion and exclusion criteria, age at entry to study, number of years of follow up, number of drop outs, type of stressor used to elicit cardiovascular reactions, outcome measurement (BP, hypertension, preclinical CHD, and cardiac events) and results of analysis with and without the covariant in the multivariable analysis. The review also calculated effect sizes between cardiovascular reactions (SBP, DBP, HR, CO, and TPR) to psychological stress tests (either active coping or passive coping tasks) and cardiovascular outcomes (BP, hypertension, preclinical CHD, and cardiac events). Prior to calculating the effect sizes in terms of Pearson product-moment correlation coefficient (*r*), appropriate equations were applied to convert common statistics. The effect sizes were then transformed into *r* by difference statistics, for example, chi-square (χ^2), *t*-test, *F*-tests, mean and standard deviation, odds ratio and R^2. The reviewers also contacted study authors if there were insufficient data reported to calculate an *r*-value (n = 3; Jokiniitty, Tuomisto, Majahalme, Kahonen, & Turjanmaa, 2003; Malpass et al., 1997; Matthews et al., 2004). However, if a study reported only *p*-value and sample sizes, *r* was computed from the *p*-value and an $r_{equivalent}$ as recommended by Rosenthal and Rubin (2003).

2.3.6 Meta-Regression

The R program and package (Huizenga, Visser, & Dolan, 2011) was used to conduct random-effect meta-regression analyses. The advantages of the Bartlett-corrected log-likelihood Ratio

statistics (BcLR) are that it has lower type I error rates than other approaches to moderation and is also more powerful when there are a small number of studies (Huizenga et al., 2011). Therefore, it was used to examine whether there were differences in the prediction of future BP and CVD by cardiovascular reactivity moderated by: types of task (active/passive coping tasks); types of participant (adult/child); and length of follow-up study (see Figure 2.1). Where there was an inadequate number of studies to conduct meta-regression, a meta-analysis was conducted.

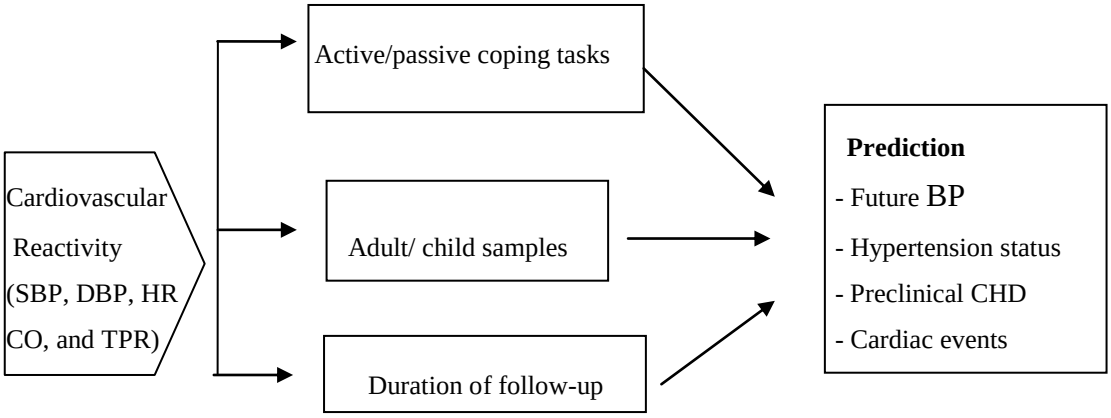


Figure 2.1 Regression model of cardiovascular reactivity and the prediction of cardiovascular risk status (i.e., future BP, hypertension status, preclinical CHD, and cardiac events)

2.4 Results

2.4.1 Sample Characteristics

Forty-two studies were found to be eligible for inclusion in the analyses; however, one study (Light et al., 1999) was excluded from meta-analyses and meta-regression models because the effect sizes combined responses to both active and passive psychological stress tasks (see figure 2.2 and appendix tables 2.3 and 2.4).

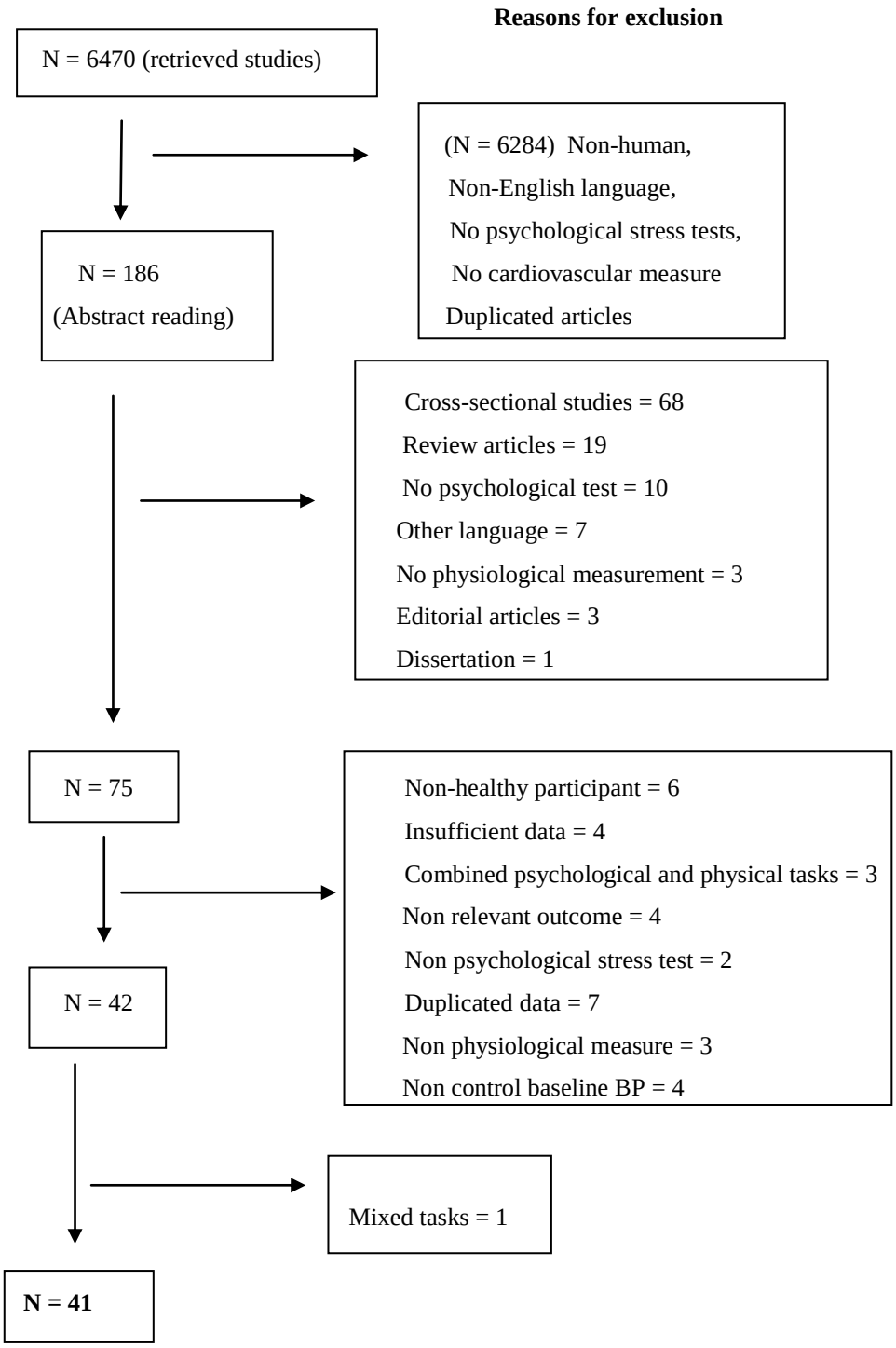


Figure 2.2 Numbers of selected studies and reasons for exclusion

Consequently, *41* studies were included in the meta-analyses and meta-regressions (see table 2.1). Thirty-one studies investigated adult participants, nine studies investigated children and one study reported results from adult and child groups. The duration of follow-up ranged from 0.77 to 36 years. The average length of follow-up in the prediction of future BP was

6.27 years; hypertension status, it was 12.67 years; preclinical CHD, it was 4.39 years, and cardiac events, it was 16.5 years.

The majority of studies had a relatively short follow-up, with 28 reporting a follow-up of less than 10 years; this period of follow-up also included all of the child studies (n = 10). Thirteen studies had a follow-up of 10 or more years (one study had a long and short term follow-up). Most of the studies (n = 21) investigated future BP as the main outcome measures; 11 studies focused on hypertension status (defined by diagnosis or medical treatment); four studies focused on cardiac events (e.g., myocardial infarction); and nine studies used preclinical CHD as the outcome measures. A number of techniques were used to assess preclinical CHD: five studies used ultrasound to assess carotid intima-media thickness (thickness of the innermost two layers of the arterial wall) or carotid plaque (size of the plaque on the inner arterial wall); two studies used echocardiography to assess left ventricular mass (thickening of the ventricular walls); and two studies used electron beam tomography to assess coronary calcification (calcium deposit at a coronary artery).

Table 2.1 Details of Studies (N = 41)

Type	Number of studies (%)
Age of participants	
Adult	31 (75.61)
Child	9 (21.95)
Adult & Child	1 (2.44)
Length of follow-up	
Short time duration (<10 years follow-up)	28 (68.29)
Long time duration (≥ 10 years follow-up) *	13 (29.27)
Outcome measures	
BP *	21 (51.22)
Hypertension status/ hypertensive medication **	11 (26.83)
Preclinical investigation of CHD	9 (21.95)
CVD events	4 (9.76)
Types of task	
Active psychological coping	18 (43.90)
Passive psychological coping	8 (19.51)
Both active and passive psychological coping task	6 (14.63)
Both psychological and physical stress tests	9 (21.95)

* one study examined both short and long term follow-ups in the same sample, but the meta-regression was conducted using the long term follow-up data only (more than 10 years)

** investigated both increased future BP and future hypertension status

2.4.2 Methodological Characteristics

2.4.2.1 Task

Eighteen studies used at least one active coping task and eight studies used at least one passive coping task; six studies included both active and passive coping tasks. The most frequently used psychological stressors were cold pressor tasks; mental arithmetic tasks and video game tasks were also commonly employed. Table 2.2 displays the types and frequency of stressor used (i.e., active coping, passive coping and/or physical).

Table 2.2 Type of stressors used to elicit cardiovascular reactivity (N = 41)

Stressor	Number of studies (%)
Active coping tasks	
Mental arithmetic	10 (24.39)
Video game	9 (21.95)
Mirror tracing	8 (19.51)
Speech test	6 (14.63)
Stroop colour word test	5 (12.20)
Reaction time	3 (7.32)
Memory test	2 (4.88)
Manometer	1 (2.44)
Social problem competence	1 (2. 44)
Stress interview	1 (2.44)
Psychomotor task (Tracking)	1 (2.44)
Marksmanship task (Target)	1 (2.44)
Visual short term (Scanning)	1 (2.44)
Anger-recall discussion	1 (2.44)
Car driving stimulation	1 (2.44)
Anger Provocation interview	1 (2.44)
Passive coping tasks	
Cold pressor	19 (46.34)
Anticipatory exercise	2 (4.88)
Emotional imagery	1 (2.44)
Humorous film	1 (2.44)
Habituation test	1 (2.44)
Tourniquet ischemia	1 (2.44)
Physical tasks	
Postural change /orthostasis	6 (14.63)
Hand grip	3 (7.32)
Bicycle tasks	3 (7.32)
Treadmill	2 (4.88)
Step test	1 (2.44)

2.4.2.1 Cardiovascular Reactivity Measures

The evaluation of cardiovascular responses to psychological stress was performed using a range of measures. Most studies included SBP and DBP responses, many included HR responses, but only a limited number included impedance-based measures (e.g., TPR, CO, pre-ejection period, stroke volume, and mean successive difference); high-frequency HR variability and pulse pressure were also examined in some studies (see table 2.3).

Table 2.3 Type of cardiovascular measures in psychological stress tests (N= 41)

Cardiovascular measure	Number of studies (%)
Systolic blood pressure (SBP)	40 (97.56)
Diastolic blood pressure (DBP)	40 (97.56)
Heart rate (HR)	28 (68.29)
Total peripheral resistance (TPR)	10 (24.39)
Cardiac output (CO)	10 (24.39)
Heart rate variability (HRV)	4 (9.76)
Pre ejection period (PEP)	3 (7.32)
Stroke volume (SV)	1 (2.44)
Pulse pressure (PP)	1 (2.44)

A series of random effects meta-regressions using BcLR (Huizenga et al., 2011) were conducted using the R statistical program with the meta-test package. The prediction of cardiovascular outcomes by cardiovascular reactivity with active/passive coping task, adult/child sample, and duration of follow-up serving as moderating variables was examined. Individual/multiple task was not included as a categorical moderator due to a small numbers of studies employing multiple tasks (n = 7). Where the number of samples was insufficient and/or multicollinearity was an issue, a BcLR meta-analysis was conducted instead without moderating variables.

Here, the review will present analyses testing whether haemodynamic reactions to psychological stress tests predict future BP levels (see table 2.4) and then will focus on the prediction of preclinical CHD, hypertension status and cardiac events (see table 2.5).

2.4.3 Prediction of Future Blood Pressure Levels

2.4.3.1 Predictors of Future SBP Levels

Results from the SBP reactivity meta-regression model indicated a significant prediction of future SBP (see table 2.4). Length of follow-up and age grouping were significant moderators: child populations provided better prediction than adult populations, and shorter follow-up times afforded better prediction of future SBP than longer follow-up times. However, there was no moderator effect by type of task (active versus passive coping tasks).

Results from the DBP reactivity and HR reactivity meta-regression models revealed variance estimates close to zero. Therefore, these reactivity models was analysed by meta-analyses. DBP reactivity was a borderline significant predictor of future SBP levels, but did not reach the a priori alpha levels for statistical significance (p = .067). HR reactivity did not predict future SBP levels. Finally, the results from CO and TPR reactivity models were examined by meta-analysis due to the limited number of datasets and were found not to be significant predictors of future SBP levels (see table 2.4).

2.4.3.2 Predictors of Future DBP Levels

Meta-analysis was used to examine SBP, DBP and HR reactivity models predicting future DBP levels due to the variance estimates of zero in the meta-regression models. DBP reactivity was a significant predictor of future DBP levels, whereas SBP and HR reactivity were not. Again, prediction of future DBP levels by CO or TPR reactivity was examined by meta-analysis due to the limited number of datasets but neither was a significant predictor of future DBP levels (see table 2.4).

Table 2.4 Results of the random effects meta-regression analyses showing number of studies (N), number of data points (k), Bartlett-corrected Log-Likelihood Ratio (BcLR), coefficient (B), and standard error (SE) for prediction of future BP

Predictors	Outcomes					
	SBP			DBP		
	(N;k)	BcLR	B ± SE	(N;k)	BcLR	B ± SE
SBP reactivity						
Intercept	**(20; 36)**	**8.70****	**0.16 ± 0.04**	(10; 19)	0.16[a]	0.01 ± 0.01
Active-Passive	(14; 24 - 9; 12)	0.43	0.05 ± 0.04	(10; 14 - 3; 5)		
Adults-Children	**(14; 26 - 7; 10)**	**18.46*****	**-0.23 ± 0.04**	(8; 15- 3; 4)		
Length of follow-up	**(20; 36)**	**11.26*****	**0.02 ± 0.01**	(10; 19)		
DBP reactivity						
Intercept	(11; 21)	3.04[a, +]	0.05 ± 0.03	**(19; 34)**	**7.05**[a,**]	**0.04 ± 0.01**
Active-Passive	(10; 15 - 4; 6)			(16; 22 - 9;12)		
Adults-Children	(7; 15 – 4; 6)			(14; 26- 6;8)		
Length of follow-up	(11; 21)			(19; 34)		
HR reactivity						
Intercept	(6; 10)	0.29 [a]	0.12 ± 0.03	(6; 10)	1.71[a]	0.05 ± 0.03
Active-Passive	(6; 6 – 2; 4)			(6; 6 – 2; 4)		
Adults-Children	(5; 9 – 1; 1)			(5; 9 – 1; 1)		
Length of follow-up	(6; 10)			(6; 10)		
CO reactivity						
Intercept	(2; 4)	0.77 [b]	-0.07 ± 0.06	(2; 4)	0.36 [b]	-0.05 ± 0.06
Active-passive	(2; 2 – 1; 2)			(2; 2 – 1; 2)		
Adults-children	(2; 4 – 0; 0)			(2; 4 – 0; 0)		
Length of follow-up	(2; 4)			(2; 4)		
TPR reactivity						
Intercept	(2; 4)	0.00 [b]	0 ± 0.06	(2; 4)	0 [b]	0 ± 0.06
Active-Passive	(2; 2 – 1; 2)			(2; 2 – 1; 2)		
Adults-Children	(2; 4 – 0; 0)			(2; 4 – 0; 0)		
Length of follow-up	(2; 4)			(2; 4)		

[a] variance estimate was zero; therefore meta-analysis was conducted and is reported here

[b] Multicollinearity in the moderators was found; therefore predictors were collapsed into one and meta-analysis was conducted instead

Intercept = active-passive coping tasks (0 = passive coping task, 1 = active coping task) × adults/children (0 = children, 1 = adults) × length of follow-up (years)

$^{+}$ $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$

2.4.4 Predictors of Future Diagnostic Status

Table 2.5 presents the results of the meta-analyses and meta-regression that focus on the prediction of future diagnostic status (i.e., preclinical CHD, hypertension incidence, and cardiac states). Findings from preclinical CHD, hypertension status and cardiac events are discussed in turn.

First, predictors of future preclinical CHD were examined using meta-regression or meta-analytic models where appropriate. Meta-regression models revealed that neither SBP reactivity nor HR reactivity were significant predictors of future preclinical CHD. Meta-analytical models for DBP, CO, and TPR reactivity were performed due to variance estimates of zero; reactivity measures were not significant predictors of future preclinical CHD in these models.

Second, a meta-regression model of future hypertension status revealed that SBP reactivity was a borderline significant predictor of hypertension status, but did not reach the a priori alpha levels for statistical significance (p = .092). Further, SBP reactions to the *passive* coping tasks provided better prediction of hypertension status than SBP reactions to *active* coping tasks (p = .045). In addition, length of follow-up was a borderline moderator, but did not reach the a priori alpha levels for statistical significance; shorter follow-up was associated with better prediction (p = .087). By contrast, DBP reactivity was not a significant predictor of hypertension status; there were no significant moderators.

Finally, two separate meta-analytic models predicting cardiac events revealed that neither SBP nor DBP reactivity were significant predictors. The model of HR reactivity had an insufficient number of datasets (k = 1) to permit predictive modelling.

Table 2.5 Results of the random effects meta-regression analyses showing number of studies (N), number of data points (k), Bartlett-corrected Log-Likelihood Ratio (BcLR), coefficient (B), and standard error (SE) for prediction of preclinical CHD, hypertension status, and cardiac events

Predictors	**Outcomes**								
	Preclinical CHD			**Hypertension status**			**cardiac events**		
	(N;k)	BcLR	B ± SE	(N;k)	BcLR	B ± SE	(N;k)	BcLR	B ± SE
SBP reactivity									
Intercept	(8; 15)	0.03	-0.01 ± 0.06	(10;17)	2.85^{+}	0.19 ± 0.10	(3; 3)	1.44^{b}	0.03 ± 0.02
Active-Passive	(6; 12 - 3; 3)	0.21	0.03 ± 0.05	**(7;11 – 6;6)**	**4.02***	**-0.14 ± 0.06**	(1; 1 – 2;2)		
Adults-Children	(6; 11 – 2; 4)	1.16	0.07 ± 0.06	(10; 17 - 0; 0)	0.04	0.02 ± 0.08	(3; 3 – 0; 0)		
Length of follow-up	(8; 15)	0.00	-0.00 ± 0.01	(10;17)	2.93^{+}	-0.01 ± 0.00	(3; 3)		
DBP reactivity									
Intercept	(7; 14)	0.03 ^{a}	0.00 ± 0.01	(9; 17)	0.26	0.07 ± 0.14	(4; 4)	2.07^{b}	0.04 ± 0.02
Active-Passive	(6; 12 – 2; 2)			(6; 12 – 5;5)	0.09	0.03 ± 0.09	(1;1 – 3; 3)		
Adults-Children	(5; 10 – 2; 4)			(9; 17 - 0; 0)	0.00	0.01 ± 0.11	(3; 3 – 0; 0)		
Length of follow-up	(7; 14)			(10; 17)	0.68	-0.01 ± 0.01	(4;4)		
HR reactivity									
Intercept	(8; 15)	0.05	0.03 ± 0.12	(0; 0)			(1;1)		
Active-Passive	(7; 13 – 2; 2)	0.00	-0.01 ± 0.16				(0; 0 – 1; 1)		
Adults-Children	(6; 11 – 2; 4)	0.21	-0.06 ± 0.12				(1; 1 – 0; 0)		
Length of follow-up	(8; 15)	0.84	-0.01 ± 0.01				(1;1)		

CO reactivity Intercept Active-passive Adults-children Length of follow-up	 (3; 5) (2; 3 – 2; 2) (3; 5 – 0; 0) (3; 5)	0.01[a]	-0.00 ± 0.04	(0; 0)			0; 0		
TPR reactivity Intercept Active-Passive Adults-Children Length of follow-up	 (3; 5) (2; 3 – 2; 2) (3; 5 – 0; 0) (3; 5)	0 [a]	0 ± 0.04	(0; 0)			0; 0		

[a] variance estimate was zero; therefore meta-analysis was conducted and is reported here

[b] Multicollinearity in the moderators was found; therefore predictors were collapsed into one and meta-analysis was conducted instead

Intercept = active-passive coping tasks (0 = passive coping task, 1 = active coping task) × adults/children

(0 = children, 1 = adults) × length of follow-up (years)

$^{+}$ $p < .1$, * $p < .05$

2.5 Discussion

The present review is the first meta-analysis and meta-regression to evaluate the predictive value of cardiovascular responses to both active and passive stressors with respect to future BP, hypertension status, preclinical CHD, and cardiac events. This review also explores how the predictive value is different between active and passive coping tasks, between adults and children, and short and long-term follow-up. The analyses revealed that SBP reactivity predicted future SBP levels; in addition, SBP reactivity was a better predictor of future SBP in children than adults and in studies with a shorter follow-up period. Similarly, DBP reactivity predicted the future DBP; there were no moderators. With respect to the development of hypertension status, SBP reactivity was a borderline significant predictor of hypertension status and a short follow-up was also a better predictor of hypertension development than a longer follow-up, although this did not reach the criteria for statistical significance. Further, SBP reactions to *passive* coping tasks provided better prediction of hypertension status than SBP reactions to *active* coping tasks. Cardiovascular reactivity did not predict preclinical CHD or CVD events.

2.5.1 Cardiovascular Responses to Psychological Stress Tests: Prediction of Future BP Levels, Hypertension Status, Preclinical CHD and Cardiac Events

2.5.1.1 Prediction of Future BP Levels

Several questions have been addressed regarding cardiovascular reactions to psychological stress and the prediction of cardiovascular risk status (including future SBP, DBP, hypertension status, preclinical CHD, and cardiac events). These hypotheses were tested using meta-regression for the first time in this thesis (where statistically permitted).

The review found that cardiovascular responses to psychological stress tests predicted future BP levels although the effect sizes were small. In the meta-regression analyses with a total of 36 reports, the review found that individuals with high SBP reactions to psychological stress tests had an elevated risk for high SBP levels prospectively. In addition, DBP reactivity predicted future DBP levels. These findings corroborated the results of previous meta-analyses (Chida & Steptoe, 2010; Gasperine et al., 2009). However, the magnitude of coefficients is relatively small for the prediction of future SBP or DBP levels. None of the other measures of reactivity (HR, CO, and TPR) predicted future BP. In addition, most of these predictive relationships showed a zero estimated variance, and the effect sizes were close to zero after controlling for initial baseline BP or traditional risk factors. Further, in the

CO and TPR reactivity meta-regression models, multicollinearity was an issue so meta-regression could not be used.

One possible explanation for these findings is that the use of impedance cardiograms is a relatively recent addition to testing; most of the prospective research studies before 2000 were performed with simple parameters (namely, SBP, DBP, and HR). Hence, only two studies (with four data sets) that used CO and TPR reactivity as predictors were included in the meta-regression models (Girdler et al. 1996; Steptoe & Marmot, 2005). Whilst at least two other published prospectives studies used CO or TPR reactivity to predict future BP they could not be used in the present analyses. This is because responses to a combined physical (treadmill test) and psychological stress task (mental arithmetic) were used in one study (Del Rosario, Treiber, Harshfield, Davis, & Strong, 1998). In the other study, cardiovascular responses were averaged from multiple psychological stressors (Mathews, Salomon, Brady, & Allen, 2003). Matthews et al. (2003) found that SBP, DBP and CO reactions averaged across four tasks (mirror tracing, reaction time, cold forehead and stress interview) predicted future SBP levels over a three year follow-up, after adjusting for baseline cardiovascular activations, age group, gender, race, duration between visits and change in BMI. Accordingly, haemodynamic responses to psychological stress testes may predict future BP. Thus, future prospective studies should include haemodynamic reactions to multiple psychological laboratory stressors.

2.5.1.2 Prediction of Preclinical CHD

The review found that none of the cardiovascular responses to psychological stress test measures predicted preclinical CHD. The results are consistent with Chida and Steptoe (2010), who reported that neither carotid intima-media thickness nor coronary calcification outcomes were related to cardiovascular reactivity. Given that most (six of eight) studies included in the current review used active coping tasks and so were included in Chida and Steptoe's review the similarity in these findings in unsurprising. In contrast, Trieber et al.'s (2003) review of eight studies concluded that cardiovascular reactivity was associated with increased left ventricular mass or carotid atherosclerosis. They found that six of the eight prospective cohort studies demonstrated associations between cardiovascular reactivity and these outcomes (i.e., left ventricular mass and carotid atherosclerosis). However, of those six prospective studies, two studies reported aggregated cardiovascular responsivity across physical and psychological stress tests (Georgiades, Lemne, Faire, Lindvall, & Fredrikson,

1997; Murdison et al., 1998) and two studies recruited participants at high risk for CVD such as participants with ischemic heart disease (Barnett, Spence, Manuck, & Jennings, 1997; Everson, Kaplan, Goldberg, & Salonon, 1996). Thus, the studies that were included in their review included different tests and different populations to those in the current meta-regression models.

2.5.1.3 Prediction of Future Hypertension Status

SBP reactions to psychological stressors were a borderline predictor for essential hypertension status based on analysis of 17 data sets from 10 studies; DBP reactivity was not a predictor. In contrast, Chida and Steptoe (2010) included only six associations in their meta-analysis and found significant associations between cardiovascular reactivity and hypertension status. In addition to including different studies in the two reviews, individual studies have used different definitions of hypertension status. For example, some studies defined it by the use of antihypertensive medication or measured SBP $\geq$ 140 or DBP $\geq$ 90 mmHg (Carroll, Phillips, Der, Hunt, & Benzeval, 2011; Markovitz et al., 1998; Matthews et al., 2004), whereas other studies used a definition of using antihypertensive medication or SBP $\geq$ 160 mmHg and/or DBP $\geq$ 90 mmHg (Carroll et al., 2001). While some studies simply asked participants to record their hypertension status by questionnaire at follow-up; BP was not monitored (Carroll et al., 2012; Menkes et al., 1989; Tuomisto, Maiahalme, Kahonen, Fredrikson, & Turjanmaa, 2005). Accordingly, differences in the included studies and the definition of hypertension might account for the different findings from the two reviews.

2.5.1.4 Prediction of Cardiac Events

With respect to cardiac events (defined as cardiac mortality or cardiac mobility), there was no prediction by cardiovascular responses to psychological stress. Meta-regression analyses were not conducted as multicollinearity was present; there were only four studies in total. Although meta-analyses were conducted to predict future cardiac events, associations with cardiovascular reactivity were not demonstrated. Chida and Steptoe (2010) also reported that cardiovascular reactivity was not related to CVD events (i.e., stroke events, myocardial infarction incidence), even though they included 15 associations and 13 of those were with patients who would be more likely to have events.

2.5.2 Cardiovascular Responses to Psychological Stress Test: Comparison between Active and Passive Coping Tasks

The second hypothesis was that cardiovascular responses to active and passive coping tasks would differentially predict future BP and CVD events. SBP reactions to *passive* coping tasks offered a better prediction of future hypertension status than SBP reactions to *active* coping tasks, although the effect size was relatively small. The type of task did not moderate any other predictive relationship. Chida and Steptoe (2010) focused primarily on active coping tasks; they reported that cardiovascular responses to cognitive tasks (e.g., mental arithmetic, mirror tracing) were associated with later cardiovascular risk status, whereas cardiovascular responses to other types of stressors (public speaking, stress interview, emotion induction or combined tasks) were not. One possible explanation for differences in the present findings and those of Chida and Steptoe is that different definitions of types of coping task were used. As noted in the inclusion and exclusion criteria, active coping tasks in this review are defined as situations where individuals cope by exerting mental effort or they attempt to counteract the stressful stimulus; so active coping tasks comprise cognitive tasks, stress interview tasks and public speaking tasks. In contrast, passive coping tasks involve immobility and low levels of aggression, and include tasks where the individual has to passively accept the administration of the task with no ability to control it. Consequently, some tasks that previous reviews and studies have described as active coping tasks were defined as passive coping tasks here, for example, anticipation of exercise (see table 2.2). Interestingly, in this review, most studies (seven of 11) that used passive coping tasks had a long-term follow-up effect (mean = 14.82 years of follow-up) compared to active coping tasks (mean = 8.60 years of follow-up). This may reflect differences in the duration of follow-up rather than task type. Meta-regression found that the duration of follow-up was a borderline moderator of the SBP reactivity -- hypertension status relationship. However, it was short-term follow-up that afforded better prediction, thus it is unlikely that duration explained why SBP reactions to *passive* coping tasks offered a better prediction of future hypertension status than SBP reactions to *active* coping tasks.

The cold pressor task (a passive coping task) has been used to predict future CVD states (including future SBP and DBP levels) since 1950 and so more passive coping studies have a long-term follow-up; thus, this meta-regression does not allow easy interpretation of these moderators. Moreover, several studies have found that BP responses to active coping tasks may be elicited via increases in systematic vascular resistance, presumably through increases

in alpha-adrenergic activity, rather than by cardiac performance (Waldstein et. al, 1997). Waldstein et al. (1997) assessed haemodynamic responses to active coping tasks (Stroop and mirror tracing tasks) and found that TPR responses to active coping tasks increased more than indices of cardiac performances (e.g., pre-ejection period, stroke index, cardiac index). In addition, Sherwood et al. (1990) have suggested that individual differences in haemodynamic responses to psychological stress tests interact with type of task, to provoke alpha- and/or beta-adrenergic responses. In summary, although cardiovascular responses to passive coping tasks were found to be better predictors of *hypertension status* than cardiovascular responses to active coping tasks, the year of testing, definitions of active and passive coping and the definition of hypertension status render interpretation difficult.

Moreover, the finding that cardiovascular responses to passive coping tasks were better predictors of *hypertension status* than cardiovascular responses to active coping tasks differs from the findings where *future BP* was used as the outcome measure*; there was* no evidence of moderation by task type for the relationships between cardiovascular reactivity and *future BP*. Factors that may account for differences found when hypertension rather than future BP was used as the outcome variable include: different ages at entry, the duration of follow-up, covariates included in analyses, and mechanisms of hypertension. The average age at entry in the prediction of future BP was 27.13 years (including child and adult groups; range 9.23-56.6 years), whereas mean age at entry in the prediction of hypertension development was 37.56 years (only adult participants; range 23.1-51.0 years). Additionally, the duration of follow-up in the prediction of future BP was shorter (6.2 years; range 2-18 years) than the prediction of hypertension development (11.7 years; range 4.1-28 years), respectively). According to pathophysiology of hypertension (detailed in chapter 1, Section 1.1.3), patients with hypertension (sustained elevated BP) of several years standing have increased peripheral vascular resistance, but their cardiac index and stroke volume are generally normal or reduced (Foëx & Sear, 2004; Mayet & Hughes, 2003). So, these patients have a reduction in arterial compliance and a central shift in blood volume that results in reduced venous compliance (Mayet & Hughes, 2003). In older patients, the systemic vascular resistance is elevated resulting to stiffness of the vasculature, and then increases in vascular tone because of increased alpha-adrenoceptor stimulation (Foëx & Sear, 2004). It has been found that passive coping tasks are correlated to sympathetic activation eliciting vasoconstriction (increases in TPR) through alpha-adrenergic receptor stimulation. Therefore, cardiovascular responses to passive coping tasks may be an effective predictor if performed on middle-aged

participants older than 35 years with a long follow-up, when they become more prone to develop hypertension. In younger individuals (e.g., less than 19 years old) participants with heightened BP have increased peripheral resistance, and small increases in cardiac index have been observed (Mayet & Hughes, 2003). In this review, studies focusing on future BP were more likely to recruit children and follow-up after a shorter period of time. For example, the youngest participants were recruited by Murphy et al. (1992), who examined cardiovascular responses to video game tasks in children with an average age of 9.23 years and who were followed up five year later. Parker et al. (1987) examined cardiovascular response to cold pressor in children aged 5-14 years (mean aged 11.6 years) over a two-year period. It is for these reasons (i.e., the wide range of ages utilised); therefore that differential cardiovascular response patterns observed between active and passive coping tasks may not predict future BP.

Another possible reason for the differences in analyses with hypertension or future BP is that, the number of control variables might be also important. In early prospective longitudinal hypertension studies, that used cold pressor (passive coping) tasks, few control variables (i.e., only initial baseline BP, age, BMI) were included in analyses. For example, Menkes et al. (1989) used initial baseline BP, family history of hypertension, and cigarette smoking as covariates. Similarly, Kasagi et al. (1995) used initial baseline BP, attained age, and BMI as control variables. Carroll et al. (1996) used age, initial BP and pre-cold pressor baseline BP as covariates. More recently, hypertension studies have used active coping tasks and multiple covariances. For example, Carroll et al. (2012) used Stroop, mirror image, and speech tasks as psychological stressors and ten control variables (i.e., age, sex, socio-economic status, BMI, antihypertensive medication, baseline BP, smoking status, and stress task commitment). Similarly, Carroll et al. (2011) used the PASAT as the psychological stressor and adjusted for seven variables: age, sex, PASAT performance, socio-economic status at baseline, resting BP at baseline, taking hypertensive medication at baseline, and BMI. Thus, the number and type of covariate has changed over time along with a change in focus from passive coping tasks to active coping tasks; this makes simple comparison of these types of stressor problematic.

So, the findings of the review where different outcome variables are the focus should be interpreted with caution; it may be the case that differences in the predictive utility of BP responses to passive coping tasks compared to active coping tasks are not due to

pathophysiological mechanisms but are artefacts of methodological differences in samples, follow-up duration and/or the covariates included in analyses.

2.5.3 Cardiovascular Responses to Psychological Stress Test: Comparison between Children and Adults

The third hypothesis was that the predictive value of cardiovascular responses to psychological stress tests would differ between children and adults. Age was a significant moderator of the SBP reactivity – future SBP relationship; in child samples (defined as aged less than 18 years old) SBP reactivity was a better predictor of future SBP levels than it was in adult samples. Similarly, Chida and Steptoe (2010) reported that the association between cardiovascular reactivity and future cardiovascular risk status was stronger in younger samples (defined as age ≤ 18 years old). To date, only one study (Matthews et al., 1993) examined cardiovascular reactivity as a predictor of future BP in both children (an average aged 13.4 years) and adults (an average aged 43 years) using the same stress tasks. They reported that high SBP reactions to mental arithmetic task were a better predictor of future SBP levels over 6.5 years in boys compared to adults (men and women). Similarly, DBP responses to mental arithmetic tasks or mirror tracing tasks were also better predictors of future DBP levels in boys compared to adults. Potentially, coping mechanisms or stressful life experiences might be a possible reason to explain the associations between SBP reactivity and the prediction of future SBP. Older adults may have smaller stress responses to stressors than younger adults as they have learnt to cope with them (Stawski et al., 2008). So, SBP reactivity within child groups may provide a better prediction of future SBP than within adult participants. In addition, Carsternsen, Isaacowitz, and Charles (1999) have demonstrated that age differences and emotional experience play a role in the regulation of emotion; older adults can deal with stressors and have a better emotional regulation than younger adults. Similarly, some studies have reported that the patterns of coping response might explain why older people experience less stress than younger people; adults use a great number of strategies including distancing, positive reappraisal or avoidance (Folkman, Lazarus, Pimley, & Novacek, 1987; Sorkin & Rook, 2006). Hence, child samples respond to laboratory stressors in a more exaggerated manner (Matthews et al., 1993) which may help to explain why there is a better prediction of future SBP by cardiovascular reactivity in children than in adults.

Importantly Matthews et al. (1993) also found that children had large changes in weight and height at follow-up. They suggested that changes in reproductive hormone levels may have played a role. Therefore, physiological changes in children may affect future BP levels substantially. In addition, predisposing factors such as high BMI and genetic risk may affect the relationship between cardiovascular reactivity and future BP levels (Clark, Greenberg, Harris, & Carson, 2012; Light et al., 1999; Wu, Snieder, & de Geus, 2010). The role of these factors should be examined in future studies (Brummett, Siegler, Ashley-Koch, & Williams, 2011).

2.5.4 Cardiovascular Responses to Psychological Stress Test: Comparison Between Short and Long Term Follow-Ups

Finally, the review examined whether the predictive value of cardiovascular responses to psychological stress tests differed between short (defined as less than ten years follow-up) and long duration of follow-ups (defined as greater than or equal to ten years follow-up). The review found that *shorter* follow-up times were associated with better prediction of future SBP levels by SBP reactivity than *longer* follow-up times. This contrasts with the findings of Chida and Steptoe's (2010) meta-analysis; they reported that longer-term follow-up was associated with better prediction of cardiovascular status by cardiovascular reactivity than shorter-term follow-up. However, their definition of long-term follow-up was different to the one used here: they used a three years cut-point compared to the ten years cut-point used here. Using a cut-point of ≥ 3 year of follow-up, the present review would have only included one study that predicted future SBP in adults from SBP reactivity (two years follow-up; Girdler et al., 1996), whereas 12 studies would have been defined as having a long term follow-up. Comparison between the two reviews is therefore difficult.

In the current meta-regression only the longest follow-up data was included for analysis to avoid double counting. However, a number of previous studies have examined the duration of follow-up (short and long-term) in the same sample. For example, Moseley and Linden (2006) used cardiovascular reactivity across three tasks (mental arithmetic, anger-recall and handgrip tasks) to predict future BP levels after three years and ten years follow-up among normotensive individuals. They found that cardiovascular responsivity predicted future BP more strongly at three year follow-up than at ten year follow-up. Similarly, follow-up data from the West of Scotland study revealed that SBP reactions to the PASAT predicted subsequent SBP levels more strongly at five years than at 12 years (Carroll et al., 2003,

2011). In the Whitehall II study, cardiovascular reactions to a Ravens matrices task predicted future SBP levels more strongly at five years than at ten years follow-up (Carroll et al., 1995, 2001). Thus, the findings of this review accord with empirical studies. It is not clear why the relationships were stronger in the studies with shorter follow-ups. It may be the case that in studies with follow-up periods of more than ten years, attrition was an important factor; for example, fewer unhealthy individuals may have taken part in the follow-up and so weakened associations between reactivity and future BP. Further, Moseley and Linden suggested that stimulant hormone levels (e.g., stress hormones, growth hormone, and sex hormone) decline with increasing older age, particularly after 40 years of age. Those studies that examined reactivity and BP at two different follow-ups recruited middle aged adult participants (an averaged aged at entry was 37.23 ± 9.11). So, these changes coupled with changes in behaviour (e.g., diet and exercise) are likely to contribute to changes in BP over time with longer follow-up periods, and so the contribution of cardiovascular reactivity may be reduced over time.

2.6 Strengths and Limitations of the Review

The strengths of the review are the inclusion of studies that assessed cardiovascular responses to psychological stress tests and predicted future BP (either SBP or DBP) or diagnostic status (i.e., preclinical CHD, hypertension status and cardiac events) in healthy samples. In addition to systematically reviewing appropriate databases, journal articles from previous reviews (Chida & Steptoe, 2010; Trieber et al., 2003) were included. Consequently, this review provides a large and up-to-date review of the literature. Further, meta-regression was used to compare the predictive utility of cardiovascular reactivity between different task groupings (active and passive coping tasks), age groupings (adults and children), and lengths of follow-up data. The review also analysed a variety of measures of cardiovascular reactivity (namely SBP, DBP, HR, CO, and TPR.

However, this review does have a number of limitations. Firstly, the data was only collected from English language publications. This said, few studies were excluded because they were in a language other than English. Indeed, less than 100 non-English language studies from the 6470 retrieved from the electronic database were excluded. Secondly, earlier prospective studies did not control for potential confounding factors, for example, baseline cardiovascular parameters (Armstrong & Rafferty, 1950; Harland, Osborne, & Graybiel, 1964) and so were excluded from the review. Thirdly, it should also be noted that some of the research studies

have only reported a positive association between cardiovascular reactivity and future incident BP or hypertension status, or clinical heart disease. Most studies reported at least one significant relationship between cardiovascular reactivity and cardiovascular status; other relevant studies that did *not* find relationships may have not been published leading to an overestimation of the predictive effect of cardiovascular reactivity (i.e., publication bias).

For example, in the study of SBP responses to psychological stress tests and the prediction of future SBP levels in child participants, the fail-safe N, representing the number of unpublished, non-significant studies (Clark-Carter, 2010; Rosenthal 1991) to render the findings as non-significant was 204. In addition, the critical numbers of unpublished and non-significant studies (Clark-Carter, 2010; Rosenthal 1991) were calculated; the review found that the critical number of studies is 60. Therefore, in this case, the critical number of studies is 60 and the fail-safe N is 204, so file-drawer issues are a potential problem (see appendix table 2.5). These unreported findings may have reduced effect sizes. Fourthly, the review did not examine whether the single or combined tasks differentially predicted future cardiovascular risk status; the review found that only seven studies examined the predictive value of cardiovascular reactions to multiple stressors. However, some studies used active coping tasks combined with active coping tasks, whilst some used active coping tasks combined with passive coping tasks, and others still combined active coping tasks and physical stressors. So comparisons were not made. Finally, meta-regression provides more precise estimates of effects with large numbers of studies compared to small numbers of studies (Borenstein, Hedges, & Rothstein, 2007); therefore some analyses may have included too few studies to show any relationship between cardiovascular reactivity and cardiovascular outcomes.

2.7 Conclusion

This meta-regression suggests that SBP reactivity predicts future SBP, particularly in children and over a short follow-up period. In addition, DBP reactivity was a good predictor of future DBP. Preclinical CHD, hypertension status and cardiac events were not predicted by cardiovascular reactivity. In addition, there were no differences between active and passive coping tasks in the prediction of future BP, preclinical CHD, and cardiac events. However, SBP reactions to passive coping tasks provided better prediction of future hypertension status than SBP reactions to active coping tasks.

In conclusion, these results lend support to the "Reactivity Hypothesis": the magnitude of cardiovascular reactivity contributes to increased cardiovascular risk status, particularly future high BP levels. These results also support the causal trait model (e.g., SBP responses to psychological stress predict future BP) and the situation specific model (i.e., SBP responses to passive coping tasks afforded better prediction of development of hypertension than SBP responses to active coping tasks). As mentioned in the discussion above [section 2.5.1.1], few studies have examined whether haemodynamic reactions to psychological stressors predict cardiovascular risk status. Further, only seven studies have examined the predictive value of cardiovascular reactions to multiple stressors (Trieber et al., 2003), and so were not included in the present review. Moreover, most studies that have assessed the contribution of cardiovascular reactivity to the prediction of future BP have been conducted in North Americans and Europeans. Therefore, the studies described in this thesis will explore the predictive value of haemodynamic responses (SBP, DBP, HR, CO, and TPR) to active and passive coping tasks over a one year of follow-up in both Thai and UK samples. These empirical studies, described in chapters 5 and 6, will determine differences in the predictive values of cardiovascular responses to active and passive coping tasks, and combined tasks and single tasks in healthy Thai and UK adult participants. The methods used to examine the contribution of haemodynamic reactions to psychological stress tests to future BP levels are discussed in the next chapter.

CHAPTER 3
Research Methodology

This chapter focuses on the research methodology used for investigating physiological responses to psychological laboratory stressors in this thesis. The chapter describes the target population of the studies, inclusion and exclusion criteria, the psychological factors assessed, physiological measurements, and the choice of psychological stress tests (i.e., a mental arithmetic task, a speech task, and a cold pressor task). Two studies were conducted, one in Thailand and one in the United Kingdom; these are described separately. The first study in Thailand was designed to establish the protocol and provide some initial data. However, recruitment proceeded very well and there was little attrition at follow-up, so these data are presented in full in chapter 5. The second study used a modified version of the first study's protocol to test the Reactivity Hypothesis in UK individuals.

3.1 Thailand study

3.1.1 Participants

A convenience sampling technique was used; participants were recruited from students and staff at Thammasat University and people living in the local community by poster advertisement, emails and personal contact (i.e., word of mouth) from 2010 to 2011. The participants ranged in age from 18-65 years and included male or female healthy adults. In addition, all participants gave informed consent before participation of the study. Before data collection, the study protocol approval was obtained from the Ethics Committee of Thammasat University. All procedures were carried out with the written informed consent of the volunteers.

3.1.2 Inclusion and Exclusion Criteria

The participants had no known history of CVD or surgery including a prior myocardial infarction and percutaneous coronary intervention or coronary artery bypass graft, history of neurological disorder (i.e., prior convulsions, or head injury that resulted in concussion), peripheral vascular disease, history of stroke or symptomatic cerebral ischaemia (cerebrovascular accidence), chronic renal failure or liver disease, history of psychiatric problems that are diagnosed and treated in physical medicine. Participants who had a current fever or high temperature prior to or during the experimental test were also excluded from the current study because those conditions may affect cardiovascular reactivity or raise resting

BP. Further, participants who were currently pregnant were excluded because stress responses in pregnant women may affect birth outcomes and maternal/fetal health development (Christian, 2010). Participants who reported having a history of any circulatory disorder including Raynaud's Disease were excluded from the study because Raynaud's disease and circulatory diseases may exacerbate extreme spasm of blood vessels in response to cold pressor (Freedman, Sabharal, Desai, Wenig, & Mayes, 1989; Zamora, O'Brien, Rutherford, & Weil, 1990).

3.1.3 Medical History, Parental History of Cardiovascular Status, and Psychosocial Health Questionnaires

Participants completed a series of medical and family history questionnaires, which included risk factors and parental history of CVD (hypertension status and CHD). In addition, the participants were asked to complete a set of psychological health questionnaires including a measure of anxiety and depression (HADS). Given that certain risk factors, such as a family history of CVD, current cigarette smoking status, and hypertension status, increase the risk of developing CVD and hypertension (Roger et al., 2011; Ockene & Miller, 1997; Padwal, Straus, & McAlister, 2001), they were assessed in this study. The study defined a positive family history of CVD as myocardial infarction, coronary revascularization, or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative, or essential hypertension in one or both biological parents or siblings (Lloyd-Jones et al., 2004; Treiber, Turner, Davis, & Strong, 1997). In these studies, current cigarette smoking status is defined as currently smoking cigarettes or recently quit smoking (i.e., within the previous 6 months; Birch, McLaren, & George, 2005; Thomson, Gordon, & Pescatello, 2009). In addition, history of hypertension status is defined as current hypertension status or high BP (SBP > 140 mmHg or/and DBP > 90 mmHg) or taking hypertensive medicine.

Depression and Anxiety Questionnaire

The 14-item Hospital Anxiety and Depression Scale (HADS) was administered to all participants to measure subclinical depression and anxiety symptoms since it has good psychometric qualities and has been translated into Thai. HADS was developed by Zigmond and Snaith (1983) as a self-administrated health questionnaire. It has been used in hospital patients and out-patients, including those in community setting (Snaith, 2003). The HADS has created, validated, translated, and widely used in more than 25 countries (Herrmann,

1997). It is comprises 14 items that are answered on a four-point rating scale; this can be used to provide measures of anxiety (seven items), depression (seven items) or emotional distress (all 14 items). The scores are ranging from 0 to 21 for each scale. Higher scores indicate greater depression or anxiety. The HADS has been divided into four ranges; normal (0-7 point); mild (8-10 point); moderate (11-15 point); and severe (more than 16 point; Zigmond & Snaith, 1983). In the present study, a cut-off of ≥ 8 on the depression and anxiety subscales of the HADS was used to indicate an individual who had depressive or anxiety symptoms.

The HADS has been found to have good internal consistency with Cronbach alpha coefficients for the anxiety subscale ranging from 0.68 to 0.93 (mean = 0.83) and for the depression subscale ranging from 0.67 to 0.90 (mean = 0.82) (Bjelland, Dahl, Haug, & Necklmann, 2002). The Thai translation of HADS also has good reliability and validity for both the anxiety or depression subscales. The sensitivity of anxiety subscales of Thai HADS subscale was 100%, and specificity was 86.0% against Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. For the depression subscale, sensitivity was 85.71% and specificity was 91.3%. Additionally, this version of the HADS demonstrated good internal consistencies with Cronbach alpha coefficients of 0.86 for the anxiety scale and 0.83 for the depression scale (Nilchaikovit, Lortrakul, & Phisansuthideth, 1996).

3.1.4 Apparatus and Measurement

Thai individuals were invited to a temperature-controlled laboratory at the Physiotherapy Department at Thammasat University. Participants were asked to refrain from drinking coffee, tea or caffeinated beverages, or smoking for at least two hours prior to the study based on previous advice and findings (Mort & Kruse, 2008; Shapiro et al., 1996). Participants in this study were assessed while they completed three psychological tests. Following the application of instrumentation for physiological recording, volunteers were seated on a comfortable chair with back and arm supports.

Haemodynamic Measurement

New technologies have been recently introduced to assess BP and haemodynamic indices on a beat-to-beat basis from the finger; these include the Finapres and Portapres that provides a clearer understanding how mental stress affects the cardiovascular system. The Finapres and Portapres devices have been validated (Finapres Medical System, 2010a; 2010b). A portable

version of Finapres called the Portapres Ambulatory Continuous Non Invasive BP Monitor was used to continuously monitor haemodynamic function in this study (Portapres®; TNO-TPD, Finapres Medical Systems, Biomedical Instrumentation, Amsterdam, the Netherlands).

The Portapres was used to non-invasively measure participant's BP and cardiac activity (TPR, CO and HR). Accuracy and precision of changes in BP as measured with the Finapres have been shown sufficiently reliable for research purposes (Imholz, Wieling, van Mortfrans, & Wesseling, 1998; Langewouters, Settels, Roelandt, & Wesseling, 1998). Additionally, beat-to-beat BP recording via Finapres has demonstrated an accurate estimate of means and variability of intra-arterial BP via radial BP at rest and during laboratory testing (Parati, Casadei, Groppelli, Rienzo, & Mancia, 1989). The arterial pressure signal was measured through appropriate size finger cuffs wrapped around the middle phalanx of the middle and fourth fingers of the participant's left hand and alternatively every 30-minutes. The Portapres signal was calibrated following the procedure recommended by the manufacturer. The height adjustment sensor and reference were positioned according to the manufacturer's instructions. Beat-to-beat continuous BP was then calculated from SBP and DBP signals by using the procedure incorporated in the Beatscope® software program and implementing the Modelflow® model. Physiological responses were monitored throughout the study which lasted about one hour.

Thai participants were seated in a comfortable armchair and in an upright position with their feet on the floor. In order to reduce anticipatory anxiety and the effects of unfamiliarity of the laboratory setting, there was a 20-minute resting baseline period whist wearing appropriate-sized BP monitor finger cuffs on two adjacent fingers (on the left 3rd and 4th fingers; Finapres Medical System, 2010a). Following the baseline period, participants were engaged in three psychological stress tests: a mental arithmetic task; a speech task and a cold pressor test.

3.1.5 Psychological Laboratory Stress Task

Following the baseline period (20-minutes), participants completed the psychological stress tests. All acute psychological tasks were presented while the participant was sitting upright in a comfortable chair. The study focused on either active or passive coping tasks using the definition from chapters 1 and 2; active coping tasks are defined as those where a participant copes with the situation through mental performance. In contrast, passive coping tasks are defined as those where an individual has no control over the situation outcomes or no ability

to control the situation (Hijzen, Jan Der Gugten, & Bouter, 1984; Koolhass et al., 1999; Obrist, 1976). Therefore, mental arithmetic tasks and speech tasks were classified as active coping tasks and the cold pressor task was classified as a passive coping tasks. The tasks were presented in serial, non-random order to Thai participants: a mental arithmetic task, a speech task, and finally a cold pressor task.

The Mental arithmetic task

Mental arithmetic has been frequently used as a laboratory stressor (Carroll et al., 2012; Flaa, Eide, Kjedsen, & Rostrup, 2008; Tuomisto, Majahalme, Kahonen, Fredrikson, & Turjanmaa, 2005; Uchino, Holt-Lunstad, Bloor, & Campo, 2005). Prospective studies have found that BP responses to mental stress were positively associated with follow-up BP. Speaking during mental arithmetic tasks adds more complexity; it requires some effort, calculating and speaking simultaneously, and affects performance (Linden, 1991). Therefore, a five minute, serial subtraction task was used; participants were requested to subtract the number "13" repetitively starting from "1079" as quickly and accurately as possible while mistakes were corrected by the experimenter. During this task, a metronome was set at a frequency of 2Hz to elicit time pressure. This task was chosen on the basis of past studies indicating that it elicits a beta-adrenergic pattern of activation in most participants (Cacioppo & Berntson, 2007).

The speech task

Mental stress can be found in the stressful or frustrating events of everyday life such as speaking in public. In addition, the social dimensions of the situation (e.g., social interaction) and cardiovascular reactivity have been indicated as a risk factor for the development of hypertension (Gerin, et al., 2000; detailed in chapter 1). Therefore, a speech task was used in the thesis because this task has been used as stressful social situation in previous studies (Lepore, 1995; Lepore & Revenson, 2006). Further, stressful speech occurs frequently in daily life, and speech protocols are relatively easy to administer. Feldman, Cohen, Hamrick, and Lepore (2004) found that speech tasks led to be a high threat appraisal, negative emotion and cardiovascular reactivity. Further, the speech task has become a commonly used stressor to exacerbate cardiovascular reactions, and those responses have been used to predict CVD and high BP (Carroll et al., 2012; Friedmann, Thomas, Kulick-Ciuffo, Lynch, & Suginohara, 1982; Girdler et al., 1996; Lynch, Long, Thomas, Malinow, & Katcher, 1981; Matthews et al., 1998; Westenberg et al., 2009). A speech task is composed of two major parts: the speech

preparation, which manipulates the role of cognitive preparation in the speech production by providing participants with the opportunity to think about what they would say, and the speech delivery. Therefore, a speech task protocol was used in which participants were given instructions to read and prepare a speech on an assigned topic (i.e., a salesman who refused to honour an advertised sale price) for two minutes and speak for three minutes. A video camera was set up to record during the task; participants looked at the camera and talked continuously during the speech. This protocol has been employed in past research (Light, Turner, Hinderliter, Girdler, & Sherwood, 1994; Saab, Matthews, Stoney, & McDonald, 1989; Turner, Sherwood, & Light, 1991) and has been shown to elicit beta-adrenergic cardiovascular reactivity.

The Cold pressor task

The cold pressor task is a cardiovascular reactivity test that has been used since the 1930s and involves immersing the hand or foot into an ice water (Hines, 1937, 1940). The cold pressor test was applied as a passive coping task, and has been identified as a possible marker for the detection of high BP, hypertension and CHD (Carroll, Davey Smith, Sheffield, Willemsen, & Sweetnam, 1996; Kasagi, Akahoshi, & Shimaoka, 1995; Seneviratne, Linton, Wilkinson, Rowe, & Spice, 1983; Tousoulis et al., 2007). The cold pressor task evokes vascular tone and an increase in vascular resistance via alpha-receptor activation (Kelsey, Patterson, Barnard & Alpert, 2000; Sherwood, Allen, & Obrist, 1986; Sherwood, Dolan, & Light, 1990).

In the Thai study, participants were required to immerse their right hand in a bucket of ice cold water maintained at 2-3°C. Participants were asked to place their hand in the ice cold water for two minutes. Zeltze, Fanurik, and Lebaron (1989) reported that immersing a hand up to above a wrist (about 5 centimeters proximal to the ulnar styloid process) was sufficient to produce a cold pressor pain response. Therefore, the participants were asked to put their right hand in the cold water approximately 3-5 centimetres above their wrist joint.

3.1.6 Procedure

Initial Assessment

Prior to arrival, participants were requested to refrain from drinking alcohol, caffeine or smoking for two hour prior to the session. Upon arrival at the laboratory, participants were given an information sheet. The participants then gave written informed consent to participate in the research. A set of questionnaires were presented to the participants including, parental

history of cardiovascular status, and the HADS. The individuals were measured weighted and height and BMI were then calculated. Partipants were seated upright in a comfortable chair with back and arm supports. The Portapres continouse BP monitor was perform to measure BP, HR, CO, and TPR. The finger BP cuffs were then attached at left 3rd and 4th fingers and a reading taken to acquaint individuals with the sensation of finger cuff inflation beat-to-beat for 30 minutes at left middle finger first and then moved automatically to a ring finger for a 30-minute. There was then a 20-minute formal baseline rest period for Thai participants. After the resting peroid, the volunteers then underwent a set of mental stressors (i.e., mental arithmetic, speech and cold pressor tasks), followed by an eight minute recovery period during which they completed after each task.

Follow-up Assessment

Individuals who completed the initial assessment were contacted by telephone or email and invited to attend a 20-minute follow-up assessment for re-evaluation of BP between December 2011 and February 2012. Those who agreed to participant were asked to refrain from caffeine, alcohol and smoking for at least two hours before the follow-up session.

To start the session, participants were asked to sit quietly a comfortable chair with back and pillow supports while resting BP and HR readings were obtained. With respect to standard protocols for BP measurement (Pickering et al., 2005; Shapiro et al., 1996), an appropriately sized BP cuff was attached to the left upper arm during resting period. BP was administrated by DINAMAP® PRO Series 100 monitor, which is an automated oscillometric non-invasive BP device. The monitor corresponds to comparisons with intra-aortic values within American National Standard Institute / Association of Medicine Instrumentation standards for accuracy (a mean difference of ± 5 mmHg, and a standard deviation of ± 8 mmHg). The BP monitor was assessed using the guidelines of the International Protocol of the European Society of Hypertension and it met the guidelines for clinical use in an adult population (Reinders, Reggiori, & Shennan, 2006), and has been approved by the British Hypertension Society (BHS, 2004). The automated BP monitor was set to read and record BP at 5, 10, 15, and 18 minutes of the 20-minute resting period. A summary of the experimental protocol of the Thai study is displayed below in figure 3.1.

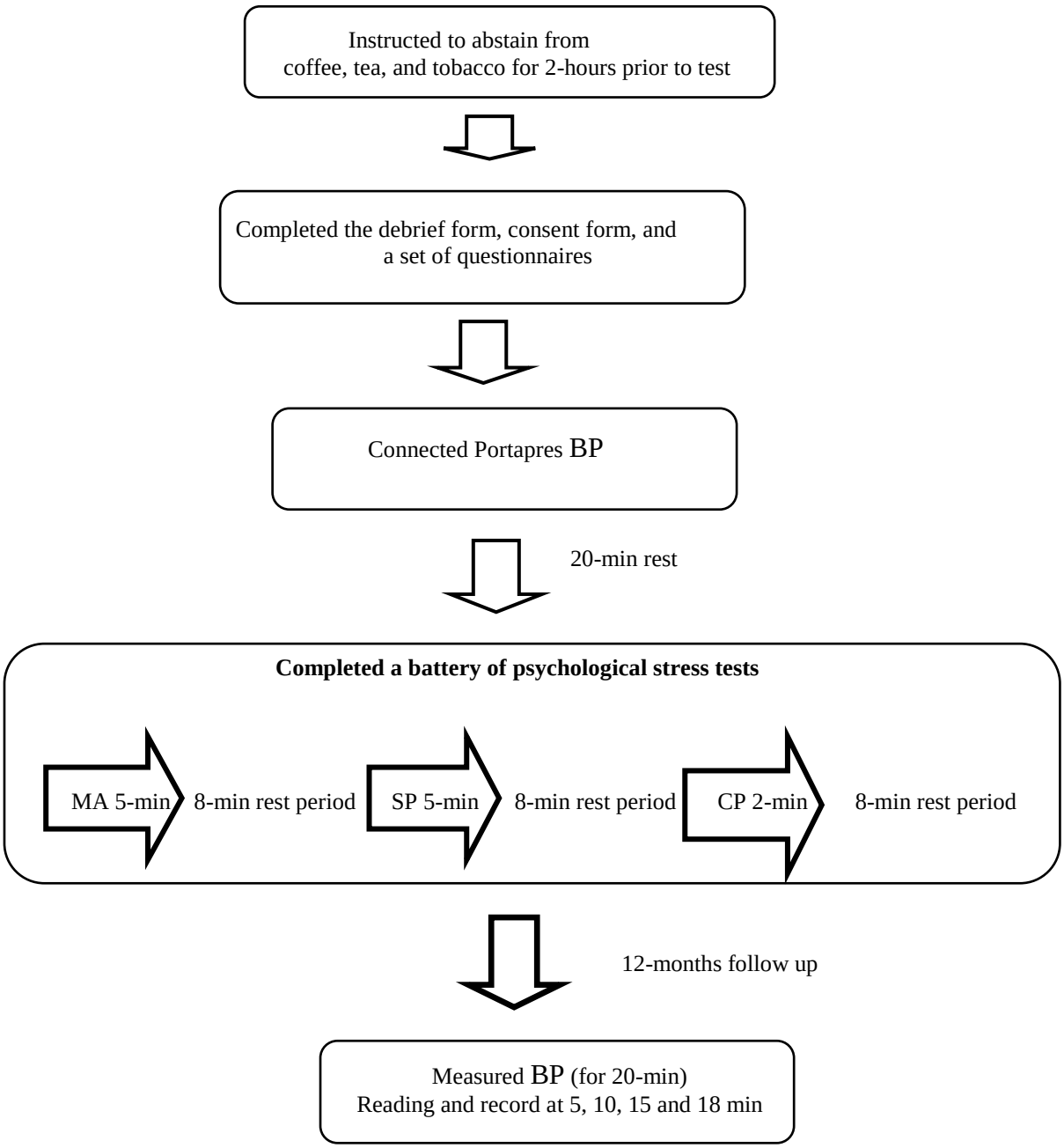


Figure 3.1 Summary of diagram shows stages of experimental protocol in Thailand

MA, mental arithmetic; SP, Speech; CP, cold pressor

3.2 The United Kingdom study

3.2.1 Participants

The UK participants were recruited after the study protocol was approved from the Ethics Committee of University of Derby. Participants consisted of students and staff from the University of Derby and adults from the surrounding local community recruited though poster advertisement, emails and personal contract (i.e., word of mouth) from March to September 2011 after the Thai study was completed and the protocol amended. The participants ranged in age between 18 and 65 years and included male and female adults. All the participants provided written informed consent for participation in the study.

3.2.2 Inclusion and Exclusion criteria

The same inclusion and exclusion criteria are applied in the UK sample as the Thai sample because these criteria may affect cardiovascular reactions to mental stressors.

3.2.3 Medical History, Parental History of Cardiovascular Status, and Psychosocial Health Questionnaires

The same Thai questionnaires were completed in English (see Medical history, parental history of cardiovascular status, psychosocial health questionnaires and Hospital Anxiety and Depression Scale (HADS). In addition, the UK participants were asked to complete the Social Readjustment Rating Scale; Holmes-Rahe Life Stress Inventory (Holmes & Rahe, 1967) after one year follow-up (see below).

The Social Readjustment Rating Scale; Holmes-Rahe Life Stress Inventory

In the UK study, the Social Readjustment Rating Scale (Holmes–Rahe Life Stress Invetory) was added to the follow-up session. BP levels increased in the Thai sample after one year of follow-up possibly because Thailand had experienced a natural diaster (flood) and this might have affected BP levels. Accordingly, life stress events were assessed in the UK sample.

The Social Readjustment Rating Scale consists of 43 items presented as a checklist about life events that have occurred within the last 12 months rated from 11 to 100. The checklist items represent common situations arising from changes in family circumstances, marriage, occupation, economic or financial events, group and peer relationships, education, religion and health; for example, death of a spouse scores 100 units and a minor violation of the law scores 11 units. A total score of 150 units or less is interpreted as good, with a low

susceptibility to stress-induced illness. A score between 150 and 299 is interpreted as medium susceptibility to develop a stress-related health disorder and a score of 300 or more is interpreted as a high susceptibility to stress-related illness.

In the UK study, the association between BP levels at one-year follow-up and the total score of life event stress was examined along with the interaction of reactivity and life events on future BP.

3.2.4 Apparatus and Measurement

The UK participants were asked to perform three psychological stress tests in a light and temperature-controlled psychology laboratory at University of Derby, UK. Participants were instructed to abstain from tobacco and caffeine (e.g., coffee, tea) for two hours prior to their appointment.

Haemodynamic Measurement

In a laboratory testing session, two non-invasive BP monitors were connected to the UK participants; one was a Portapres continuous BP (as mentioned previously in Thai study) and another was an automated BP at right upper arm. The study also used an Omron® M6 Comfort BP monitor (HEM-7211) (Omron Healthcare B.V., Kruisweg, Hoofddorp, The Netherlands). A semi-automatic oscillometeric BP monitor was then used during a 15-minute resting period which recorded BP at 5, 9, and 13 minute intervals, whereas the haemodynamic data was observed and recorded at beat-to-beat intervals for detection of SBP, DBP, HR, CO, and TPR during baseline, tasks and the recovery periods. The participants were asked to sit quietly for 15-minutes (during baseline period) and then three laboratory stressors were completed.

3.2.5 Psychological Stress Task

Participants in this study were tested using the same three psychological tests in Thailand. In contrast to the Thai study, the order of testing was randomised. A 20-minute baseline period in Thailand was changed to only 15-minutes in the UK, because data in Thailand has demonstrated an increased BP 15 minutes into rest possibly due to boredom and anticipation of the upcoming tasks. To avoid the anticipation of psychological stress tests that might cause

effects on haemodynamic reactions to psychological tasks, the baseline period was shortened to 15 minutes.

After the 15-minute rest period, participants were asked to complete a series of three psychological tasks (i.e., mental arithmetic, speech, and cold pressor) that were randomised and counterbalanced to avoid the upward drift in cardiovascular reactivity seen in the Thai study (see chapter 5). The same standardized mental stress protocols that were used in the Thai study were used in this UK study; however, the cold pressor task was modified.

For the initial study in Thailand, only a few Thai participants immersed their hands in 2-3^{o}C water for a duration of two minutes. Additionally, in the Thai study the tank was filled with cold water with no water circulation that would allow some heat build up around the hand during immersion (Zeltze et al., 1989). Therefore, the cold pressor task was designed with circulating water. Mitchell, MacDonald, and Brodie (2004) examined four cold pressor trials with varying differences in temperature, namely 1°C, 3°C , 5°C, and 7°C. Pain intensity and tolerance times were recorded for each trial. The study found that there was a longer tolerance times and less pain intensity in water temperatures of 7°C and 5°C than with water at a temperature of 1°C. However, this study revealed no differences in pain between the temperatures of 5°C and 7°C. Therefore, the cold pressor task in the UK was adjusted to 7°C to encourage participants to keep their hands in the tank for a longer period to allow more BP measures to be taken. The protocol also is likely to provide better measures of pain tolerance (total time their hands were immersed in the cold water tank) as possible floor effects should be eliminated or reduced. The participants were instructed to try to hold their hand in the cold water for as long as possible and then the tolerance time was recorded when the participants removed their hand from the cold water.

3.2.6 Performance and Perception of Task

It is already known that the performance on the acute laboratory tasks might be associated with increased haemodynamic response patterns (Garcia-Leon, Paso, Robles, & Vila, 2003; Richter & Gendolla, 2006; Sherwood, Royal, & Light, 1993). Those studies reported that effect of task difficulty or perception of task difficulty was associated with heightened cardiovascular response during performance of the task. Therefore, in the UK study, measures of performance on the mental arithemtic task and self-reported percieved stress in each task were included. Performance was assessed by recording the number of correct

responses to the mental arithmetic task. In addition, pain tolerance (defined as the total time participants immersed their hand in the cold water tank) was assessed. Tolerance time (von Baeyer, Piira, Chambers, Trapanotto, & Zeltzer, 2005) was assessed using a stopwatch to record the total duration of hand immersion.

Further, immediately after all tasks were completed, the participants were asked to complete a post-test questionnaire to rate each task using the following question: "How stressful was the … task". Self-reported perceived stress was measured using a numerical scale (0-10) with 0 corresponding to "not stressful" and 10 corresponding to "very stressful".

3.2.7 Procedure

Initial Assessment

The protocol for the initial assessment was the same as in the Thai study except for the differences noted above: the baseline period was reduced from 20-minutes to 15-minutes and resting BP was monitored with an Omron cuff device in addition to the Portapres; the order of tasks was randomized; the water used in the cold pressor tank was changed to 7^{o}C circulating; and performance and stress measures were obtained after each task. To understand the experimental protocol in the UK study, a summary of the process is displayed below in figure 3.2.

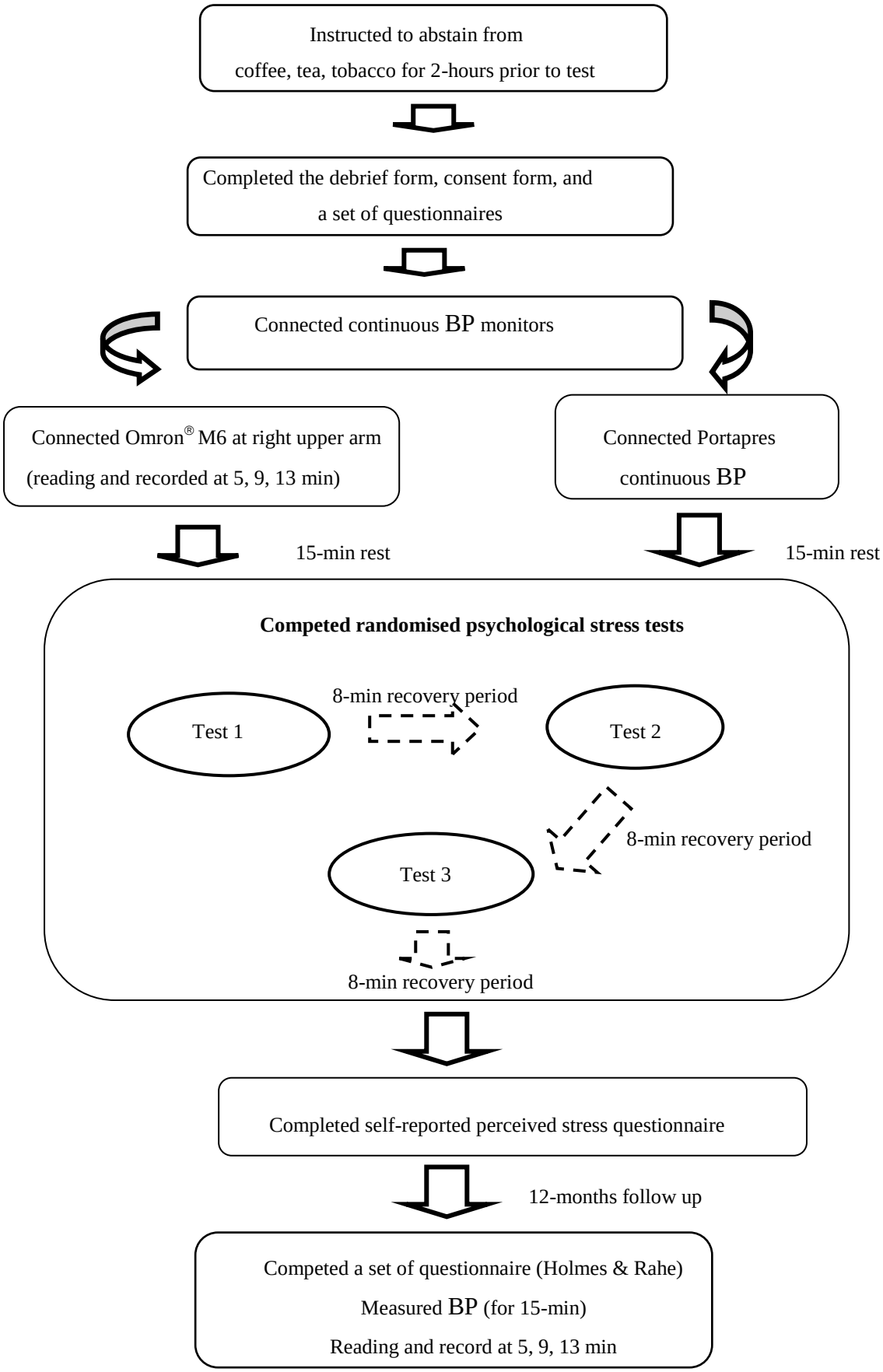


Figure 3.2 Summary of diagram shows stages of experimental protocol in the UK

Follow-up Assessment

The protocol for follow-up was altered in two ways in the UK study. First, participants were asked to complete the life events scales questionnaire (Holmes & Rahe, 1967) about major stressful events over the past 12 months. Second, resting BP was measured by an Omron® M6 Comfort BP monitor (HEM-7211) (Omron Healthcare B.V., Kruisweg, Hoofddorp, The Netherlands), which is an automated BP monitor and records brachial BP using the oscillometric method with a pressure range of 0-299 mmHg and pulse rate range of 40-180 bpm. According to the 2010 European Society of Hypertension (ESH) international protocol revision, it was validated (Topouchian et al., 2011), and it has been approved by the British Hypertension Society and the BP monitor (BHS, 2004). Appropriated arm cuff size was connected on the left semi-flexed arm at the heart level as recommended by the manufacturer. BP was measured and recorded after 5, 9, and 13 minute of rest in the resting position and was computed as the average.

In the next chapter, the cross-sectional relationships between anxiety and depression and cardiovascular responses to laboratory stressors are reported in the UK and Thai samples.

CHAPTER 4

Anxiety and Depression Symptomatology and Cardiovascular Responses to Laboratory Stressors

As previously discussed in chapter 1, cardiovascular reactivity has been posited as one mechanism linking anxiety and depression to hypertension status. Although the main focus of the PhD was the Reactivity Hypothesis, measures of depression and anxiety were taken at initial baseline in both the Thai and UK studies. These measures afford the test of a new hypothesis that gained support during the course of this PhD, the blunted cardiovascular reactivity hypothesis (Phillips, 2011; Phillips, Hunt, Der, & Carroll, 2011), which proposed that cardiovascular reactivity is inversely related to anxiety and depression. Thus, analyses of initial, cross-sectional data relating symptoms of anxiety and depression to cardiovascular reactivity in the Thai and UK samples are presented here.

4.1 Introduction

A considerable number of studies have identified symptoms of anxiety and depression are associated with cardiovascular responses to mental stressors (Carlson et al., 1989; Carroll, Phillips, Hunt, & Der, 2007; Matthews, Nelesen, & Dimsdale, 2005; Phillips et al. 2011; Schwerdtfeger & Rosenkaimer, 2011; Young, Nesse, Weder, & Julius, 1998). Some studies observed increased cardiovascular responses to laboratory behavioural stressors in depressed individuals (Betensky & Contrada, 2010; Gramer & Saria, 2007), other studies report no relationship and others report that attenuated cardiovascular responses to laboratory stressors were associated with increased depression scores (de Rooij, Schene, Phillips, & Roseboom, 2010; Young et al., 1998). Early evidence supported the hypothesis that exaggerated responses to stress were associated with depression. In particular, a meta-analysis of 11 studies from 1887 to 2001 suggested that there were small to medium (according to Cohen, 1992) positive correlations between measures of cardiovascular reactivity and depressive symptom; however, these effect sizes did not reach the conventional criteria ($p < .05$) for statistical significance because of a relatively small number (n = 11) of heterogeneous studies of variable quality (Kibler & Ma, 2004). Other more recent studies have provided limited support for this hypothesis. For example, 55 healthy male and female participants with high-normal scores on the Centre for Epidemiological Studies Depression Scale had heightened adrenergic responses, namely high DBP reactions to a speech task, compared with participants with low levels of depressive symptoms (Hamer, Tanaka, Okamura, Tsuda, &

Steptoe, 2007). In another study of 60 healthy young women who performed a speech task, depressive symptoms were positively associated with increases in plasma norepinephrine and higher SBP, DBP, HR, and CO responses (Light, Kothandapani, & Allen, 1998). Similarly, 65 healthy female participants with high scores on the Beck Depression Inventory demonstrated increased SBP and DBP response to mental stressor (Betensky & Contrada, 2010). These studies suggest that there may be a weak, positive relationship between depressive symptoms and cardiovascular reactivity. However, this conclusion was drawn from studies with small numbers of participants ($n < 100$). There are fewer studies that have examined the relationship between anxiety and cardiovascular reactivity. Gramer and Saria (2007) found that normotensives ($n = 52$) with high anxiety on the Social Anxiety Scale exhibited greater HR reactivity than those with low anxiety scores. In addition, 50 young healthy participants with high anxiety on the State-Trait Anxiety Inventory were associated with greater SBP and DBP reactions to an anger recall and cold pressor tests than a low anxiety group (Pointer et al., 2012). Thus, there is some evidence that anxiety may also be associated with exaggerated cardiovascular responses to stress.

Other studies have reported no differences in cardiovascular reactivity between depressed and non-depressed participants (Guinjoan, Bernabo, & Cardinali, 1995; Taylor et al., 2006). For example, Taylor et al. (2006) examined cardiovascular reactions to the Trier Social Stress Test, a standardized social and cognitive stressor consisting of an anticipatory period and a test period in which individuals have to perform a public speaking task and mental arithmetic in front of an audience (Kirschbaum, Pirke, & Hellhammer, 1993). Fifty-nine older depressed patients (using the Beck Depression Inventory and by interview with the Hamilton Depression Inventory) and 20 non-depressed patients matched for age and cardiovascular risk (i.e., they had similar baseline total low-density lipoprotein, high-density lipoprotein, triglyceride, BP, HR, and BMI) were tested. The study revealed no significant differences in BP reactivity between depressed and non-depressed individuals. One possible explanation for the lack of association is the small sample size ($n < 60$) and consequent lack of power to detect possible effects.

Other more recent studies that examined the depression and anxiety – reactivity relationship have found that anxiety and depressive symptoms are associated with blunted physiological reactivity (Carroll et al., 2007; Phillips et al., 2011; Schwerdtfeger & Rosenkaimer, 2011). In the largest study to date, Carroll et al. (2007) used the HADS to assess depressive symptoms

in 1608 adults. Depression scores were negatively associated with SBP and HR reactions to the PASAT. In a second large study of 725 Dutch male and female healthy participants, de Rooij et al. (2010) reported that those with high depressive or anxiety symptoms (measured by HADS) exhibited higher SBP, DBP, and HR reactions to mental stress (i.e., Stroop test, mirror-tracing test, and speech test) than those with low depressive and anxiety symptoms. Further, in a study of CAD patients, York et al. (2007) found that 21 patients with CAD and high depression scores (measured by the Beck Depression Inventory) had smaller haemodynamic responses (SBP, DBP, and HR) to a speech task than 99 CAD patients with low depression scores. Prior studies also support the notion that anxiety symptoms are associated with blunted cardiovascular responses to laboratory stressors. Young et al. (1998) assessed trait anxiety (measured by State and Trait Anxiety Inventory) in 832 healthy male and female participants, and measured their cardiovascular reactions to a mental arithmetic task. They found that participants with higher levels of trait anxiety had lower cardiovascular reactivity than participants with low levels of anxiety. So, a number of studies do not support a hyper reactivity hypothesis; rather, they suggest that blunted physiological reactivity is related to anxiety and depression. Indeed, Chida and Hamer (2008) reviewed studies of chronic psychological factors and acute psychological response to laboratory stress in healthy participants from 1950 to 2008, and found that cardiovascular (SBP, DBP, and HR) reactivity was inversely related to anxiety, neuroticism, and negative affect, and depressive mood or hopelessness, albeit more modestly (the only significant relationship was with SBP reactivity).

Recently, it has been suggested that high cardiovascular reactivity may not always be related to negative health outcomes and behaviours and, further, that low reactivity may be related to negative health outcomes; the blunted reactivity hypothesis (Phillips & Hughes, 2011). In a number of analyses, Phillips (Phillips, 2011; Phillips et al., 2011) found lower cardiovascular reactivity was prospectively related to poorer self-reported health, increased depressive symptoms, and increased risk of obesity; others have reported similar findings (Binder & Holsboer, 2012; Carroll, Phillips, Ring, Der, & Hunt, 2005; De Rooij & Roseboom, 2010; Roemmich, Smith, Epstein, & Lambiase, 2007) to support blunted cardiovascular reactivity and poor health outcomes. Phillips (2011) therefore suggested that blunted cardiovascular reactivity may be a physiological marker of motivational dysregulation shared by people with depression and obesity (Carroll, Phillips, & Lovallo, 2012; Phillips 2011; Phillips et al., 2011).

As described above, anxiety and depression appear to be related to physiological responses in many research studies. While some studies report a positive association between those factors and cardiovascular reactivity, more recent and larger studies have found negative relationships. However, most studies only included simple measures of cardiovascular reactivity, namely SBP, DBP, and HR. Many researchers (e.g., Carroll et al., 2007; Phillips, 2011) have suggested that assessing haemodynamic responses would help provide mechanistic information about the association between symptoms of anxiety and depression, and cardiovascular reactivity. To date, there are few published studies that have examined haemodynamic responses (including CO and TPR) to psychological stress tests in relation to anxiety and depressive symptoms in healthy volunteers (Light et al., 1998; Matthews et al., 2005). Matthews et al. (2005) found depressive symptoms (defined as the Center for Epidemiological Studies Depression scale) were related to higher systematic vascular resistance reactions to a mirror tracing task, whereas CO, HR, and stroke volume reactions were not, in 91 healthy male and female participants. In addition, Light et al. (1998) found that SBP, DBP, HR, and CO reactions to a speech task were positively associated with depressed symptoms (measured by the Beck Depression Inventory) in a sample of 53 women. However, the two studies that compared haemodynamic responses in depressed participants and healthy individuals (Salomon, Clift, Karlsdottir, & Rottenberg, 2009; Straeva-Meuse et al., 2004) found that individuals with depression had lower SBP and CO reactivity than non-depressed individuals. Thus, the findings from these studies are inconsistent, with some suggesting a vascular mechanism and others a myocardial mechanism linking psychological factors with reactivity. In addition, these studies used a variety of different measures of depression (e.g., clinical diagnosis or questionnaire), a range of different mental stressors and have limited sample sizes that make comparisons between them difficult.

Furthermore, the type of coping task (i.e., active and passive coping tasks) may be important. Most studies examined a single task with cardiovascular reactivity; two studies investigated both active and passive coping tasks in healthy participants (Pointer et al., 2012; Schwerdtfeger & Rosenkaimer, 2011). Pointer et al. (2012) reported that state anxiety (measured by the State-Trait Anxiety Inventory) was positively associated with SBP and DBP responses to both active and passive coping tasks (anger recall and cold pressor) among 50 African American adults. In contrast, Schwerdtfeger and Rosenkaimer (2011) found that BP responses to an active coping task (namely public speaking) were negatively associated with depressive symptoms (measured by the Beck Depression Inventory), whereas BP

responses to a passive coping task (cold pressor) were not related to depressive symptoms. However, only 55 people participated in the study and nine of those were excluded from the analysis of the cold pressor task, i.e., the sample was smaller than for the active coping task analysis and so there was less power to detect effects. In a second passive coping task, viewing a video of their speech performance, depression was negatively associated with BP responses. Schwerdtfeger and Rosenkaimer (2011) argued that it is the self-relevance of the task, rather than passive vs. active coping, that account for the pattern of their findings. Given the reduced power to detect effects using the cold pressor task, further studies comparing active and passive coping tasks are warranted. Two studies examined depressed patients and non-depressed patients on cardiovascular reactions to stress tests (Guinjoan et al., 1995; Straneva-Meuse, Light, Allen, Golding, & Girdler, 2004). Guinjoan et al. (1995) found that SBP, DBP, and HR reactions to mental arithmetic and cold pressor tasks were not different between 18 depressed patients (measured by the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised: DSM-III-R critera of major depression, melancholic type) and 18 healthy control participants. Straneva-Meuse et al. (2004) compared cardiovascular reactions to mental arithmetic, speech, cold pressor, and orthostatic challenge tasks between 17 depressed patients being treated with buropion (an atypical antidepressant), 17 depressed patients being treated with paxetine (a selective serotonin reuptake inhibitor), and a group of 15 unmedicated or non-depressed controls (measured by the Structured Clincal Interview based on the DSM-IV) (Straneva-Meuse et al., 2004). They found that these treatment groups exhibited lower SBP, and CO reactions to mental arithmetic and speech tasks than control group, but not in cold pressor or orthostic tasks. Given the small sample sizes of previous studies, and the small-medium effects found in previous larger, epidemiologic studies (that just used active tasks), future studies should recruit larger samples ($n > 100$), to ascertain the relationships between cardiovascular responses to active and passive coping tasks, and anxiety and depression symptoms.

Taken together, these studies suggest a more comprehensive assessment of the relationships between haemodynamic responses (i.e., TPR and CO) to a variety of mental stressors, and measures of depression and anxiety symptoms would be useful. Furthermore, these studies are limited to relatively homogenous samples in European countries or North America; that is, those studies included individuals from different ethnic backgrounds (see chapter 1, section 1.4). In addition, few studies have examined associations between cardiovascular reactivity and emotional stress in Asia; and those have frequently recruited mixed-ethnic

groups, e.g., Indian and Chinese (Bishop & Robinson, 2000; Why et al., 2003). For example, Why et al. (2003) examined the relationships between trait hostility and haemodynamic reactions to mental arithmetic, number reading, and anger recall tasks among 254 Singaporean police men in from a mixed-ethnic background; these included Indians, Malays and Chinese. Hostility was associated to SBP responses to the anger recall task in Indians but not Chinese or Malay participants. Therefore, further examination of relationships between psychological factors and cardiovascular reactivity in homogeneous Asian samples is warranted. In the current studies, the associations between anxiety and depressive symptoms, and cardiovascular reactivity in Thailand and the UK samples were examined. The HADS measure was used as it is a well recognised measure of anxiety and depression, and it has been transtated into Thai. Furthermore, the HADS has good reliability and validity in both UK and Thai populations (see details in chapter 3; Research Methodology). Moreover, to date there are no studies that have examined differences in cardiovascular reactivity between Thai or South East Asian samples and Western samples. Further, few studies have compared cardiovascular responses to mental stressors between Asian and Caucasian participants. Those studies found that Asians had lower haemodynamic reactions to laboratory stress tests than Caucasians (Shen, Stroud, & Niaura, 2004; Stoney, Hughes, Kuntz, West, & Thornton, 2002; Suchday & Larkin, 2004). For example, Shen, Stound, and Niaura (2004) examined cardiovascular responses across four tasks (speech, serial subtraction, mirror tracing, and handgrip) in 43 Asian Americans and 77 Caucasians. They found that the Asian Americans showed lower SBP and HR reactions to all four tasks than the Caucasians. Accordingly, differences in BP, HR, TPR, and CO responses to three stressors between Thai and UK participants were examined.

4.2 Purpose and Hypothesis of Study

4.2.1 Aims

The aims of the present study were:

a) to examine the differences in haemodynamic reactivity (cardiac and vascular reactivity), and HADS anxiety and HADS depression scores between participants from Thailand and the UK.
b) to examine cardiovascular reactivity to active and passive coping tasks (i.e., mental arithmetic, speech, and cold presor tasks) in participants from the UK and Thailand;

c) to explore the associations between anxiety and depression, on the one hand, and haemodynamic reactions to psychological stress tests, on the other, in participants from Thailand and the UK;

The present cross-sectional analyses were designed to evaluate the myocardial and vascular responses of healthy normotensive adults to three specific challenges: evaluated mental arithmetic, speech, and the cold pressor tasks. The evaluated mental arithmetic task involves simple subtraction for five minutes focusing on speed and accuracy. The speaking stressor is a social-evaluative active coping challenge that requires participants to prepare and described how they would respond to a customer complaint. The inhibitory-passive coping challenge was the cold pressor test, which involves immersing the right hand in cold water for two minutes.

4.2.2 Hypotheses

The following specific hypotheses of study were tested:

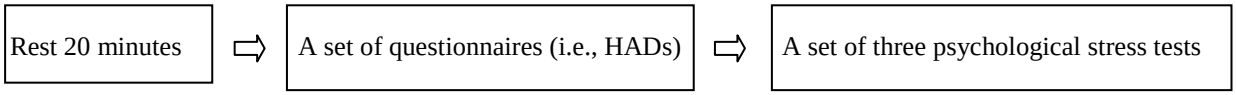
1. there would be differences in haemodynamic reactivity (cardiac and vascular reactivity), and HADS anxiety and HADS depression scores between participants from Thailand and the UK;
2. there would be significant differences in cardiovascular reactions to active coping tasks and passive coping tasks in participants from Thailand and the UK;
3. negative correlations would be found between HADS anxiety and HADS depression scores, and cardiovascular reactions to laboratory stressors in Thailand or the UK;
4. negative relationships between HADS anxiety and HADS depression may be stronger using the active, compared to the passive coping tasks, although this prediction was based on only two previous studies (Pointer et al., 2012; Schwerdtfeger & Rosenkaimer, 2011);

4.3. Materials and Method

In the previous chapter (chapter 3) the methods of investigation, including participants, inclusion and exclusion criteria, details of measures and the procedures, were outlined. Briefly, 125 Thai and 109 UK participants completed a HADS, and completed a mental arithmetic task, a speech task, and a cold pressor task while BP, HR, TPR, and CO were assessed. However, five UK participants and six Thai individuals revealed at entry to be

taking antihypertensive medication were excluded. Therefore, 119 Thai and 104 UK samples were recruited. A brief summary of protocols is provided below.

Thai participants



The UK participants

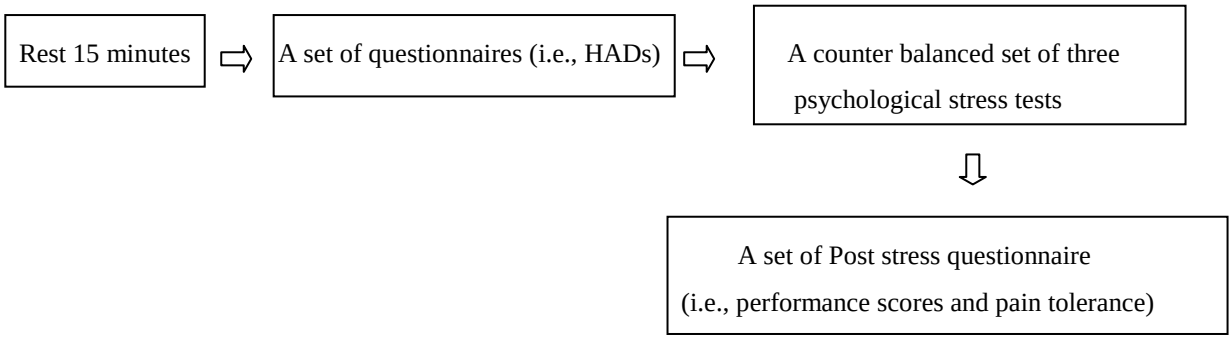


Figure 4.1 Summary of diagram shows stages of experimental protocol in the Thai and UK samples

4.4 Data Analysis

Baseline values were computed by averaging the values from five to 18 minutes in Thai and from five to 13 minutes in the UK participants. The dependent variables were SBP, DBP, HR, CO, and TPR reactions to laboratory induced psychological stress tests. Cardiovascular reactivity scores were calculated by subtracting initial baseline cardiovascular values from task levels for each cardiovascular index (Girdler et al., 1996; Hughes & Stoney, 2000; Musante, et al., 2000).

Using the HADS scores as continuous data, independent samples *t*-tests were used to indicate whether participants in the UK differed from Thai samples on HADS (depression and anxiety scores). If there were no differences the two samples would be analyzed together; if differences were found then attention would focus on the Thai sample followed by the UK sample. Also, multivariate analyses of variance (MANOVAs) were conducted to test the main and interactive effects of country and stressor type on cardiovascular reactivity. In addition, Chi-square test were used to assess whether the number of participants who had

symptoms of depression or anxiety differed from these who did not have symptoms in the UK and Thai samples; a cutoff of ≥ 8 on the depression and anxiety subscales of the HADS was used to create to binary variables (Snaith, 2003; Zigmond & Snaith, 1983). These analyses were conducted to test hypothesis 1.

Next, ANOVAs were used to examine whether the mental stress tasks provoked significant changes in cardiovascular activity. In addition, differences in haemodynamic reactions to the active and passive coping tasks were compared by ANOVA with task type (i.e., mental arithmetic, speech, and cold presor tasks) serving as a within subjects factor (hypotheses 2).

Then, correlations between HADS-Depression and HADS-Anxiety scores, and traditional risk factors and cardiovascular responses were calculated with Pearson's correlation (hypotheses 3). To examine association between possible confounding variables (i.e., current cigarette smoking status, family history of CVD, sex, age, and BMI), and cardiovascular responses to the mental arithmetic task, the speech task, and the cold pressor task, partial correlational analysis was conducted. Specially, in the UK, the study examined association between self-reported perceived stress, performance scores on the mental arithmetic task and pain tolerance on the cold pressor task, and cardiovascular reactivity. Partial correlational analyses were then performed.

To test for mediation, the study followed the steps described by Baron and Kenny (1986). The study first identified whether cardiovascular reactivity was correlated with HADS anxiety or depression scores, and then examined whether cardiovascular reactivity predicted potential mediator variables by regression. Next, regression analysis was used to examine whether cardiovascular reactivity predicted HADS anxiety or depression scores after mediator were entered at step one. Finally, a Sobel test, where appropriate, was conducted to determine the extent to which potential mediator variables (i.e., self-reported perceived mental arithmetic stress, self-reported perceived speech stress, self-reported perceived cold pressor stress, performance scores on the mental arithmetic task, and pain tolerance on the cold pressor task) mediated the relationships between cardiovascular reactivity and anxiety or depressive scores.

Finally, differences cardiovascular reactions to the psychological stress tests in participants with and without depressive and anxiety symptoms (based on the HADS cut-off scores of 8)

were compared using ANOVA. Further, ANCOVA was used to correct for potential mediators, including baseline cardiovascular activity and traditional risk factors.

4.5 Results

4.5.1 Comparison of Anxiety and Depression and Cardiovascular Reactivity between the Thai and UK Samples: Overview

Of the 223 participants who performed the stress protocol and completed data on the HADS, 104 were from the UK and 119 were from Thailand. The distribution of trait anxiety and depression for the entire population by country are presented in table 4.1. There was a significant difference in mean trait anxiety by country, with participants in the UK demonstrating higher trait anxiety than Thai participants. There was no significant difference in mean trait depression between the UK and Thai samples. In the UK sample anxiety scores were higher than a normative, non-clinical UK sample (mean = 6.14, t (114) = 3.82, $p <$ .001), whereas the depression scores did not differ from the normative sample (Crawford, Henry, Crombie, & Taylor, 2001). No normative data was available from Thailand.

Table 4.1 Independent samples *t* -test on HADS anxiety and depression scores comparing the Thai and UK and participants

	Thai participants N = 119 (mean ± SD)	**UK participants** N = 104 (mean ± SD)	***t*-test (221)**
HADS anxiety scores	5.40 ± 2.69	7.62 ± 3.85	-5.020***
HADS depression scores	3.27 ± 2.64	3.38 ± 2.86	-0.765

*** $p < .001$

The analyses testing country difference in haemodynamic reactivity to the stressors are presented in table 4.2. Thai participants showed significant greater haemodynamic reactivity to all tasks than UK individuals, except HR reactions to cold pressor, CO responses to speech and cold pressor tasks, and TPR responses to mental arithmetic task in the MANOVA, $F(15,207) = 3.843$, $p < .001$, *partial eta*^{2} = .218. Further, the MANCOVA on cardiovascular reactivity revealed a significant main effect of country in all tasks, after adjusted for baseline cardiovascular activity, sex, family history of CVD status, current cigarette smoking status, BMI, and age (see appendix tables 4. 1 and 4.2 for relationships between potential co-variates and cardiovascular reactivity; for SBP reactivity, $F(3,213) = 6.830$, $p < .001$, *partial eta*^{2} =

.088; for DBP reactivity, $F(3,213) = 6.535$, $p < .001$, *partial eta*^{2} = .050; for HR reactivity, $F(3,213) = 3.522$, $p = .016$, *partial eta*^{2} = .047; for CO reactivity, $F(3,213) = 4.599$, $p = .004$, *partial eta*^{2} = .061; for TPR reactivity, $F(3,213) = 2.797$, $p = .041$, *partial eta*^{2} = .038).

Table 4.2 Mean and standard deviation changes scores in haemodynamic variables by country

Variable	Thai participants N = 119 (mean ± SD)	UK participants N = 104 (mean ± SD)	*F (test)*	*eta*^{2}	*F (test) after adjustment*[#]	*Partial eta*^{2} *after adjustment*[#]
SBP reactivity (mmHg)						
- mental arithmetic	20.92 ± 11.06	14.78 ± 11.06	17.127***	0.021	3.912***	0.113
- speech	26.40 ± 13.03	17.68 ± 12.87	25.146***	0.028	4.144***	0.119
- cold pressor	30.13 ± 13.183	24.39 ± 12.55	11.003**	0.009	2.368*	0.072
DBP reactivity (mmHg)						
- mental arithmetic	12.01 ± 8.19	9.66 ± 6.60	5.501*	0.008	1.602	0.050
- speech	14.96 ± 8.43	10.69 ± 6.54	17.507***	0.020	3.844**	0.111
- cold pressor	18.02 ± 9.39	13.61 ± 7.53	14.661***	0.015	3.218**	0.095
HR reactivity (bpm)						
- mental arithmetic	8.58 ± 7.20	5.16 ± 5.80	14.991***	0.031	4.009***	0.115
- speech	7.87 ± 7.61	4.88 ± 6.73	9.511**	0.023	3.388**	0.099
- cold pressor	4.13 ± 7.22	3.17 ± 6.07	1.141	0.004	2.668*	0.080
CO reactivity (l/m)						
- mental arithmetic	0.75 ± 0.77	0.41 ± 0.86	9.863**	0.028	3.494**	0.102
- speech	0.57 ± 0.76	0.49 ± 0.83	0.583	0.002	4.319***	0.123
- cold pressor	0.23 ± 0.70	0.35 ± 0.93	1.252	0.005	6.925***	0.184
TPR reactivity (dyne-sec.cm-^{5})						
- mental arithmetic	49.32 ± 105.56	68.19 ± 139.80	1.313	0.005	1.791^{+}	0.055
- speech	134.51 ± 155.84	80.35 ± 133.84	7.639**	0.022	4.001***	0.115
- cold pressor	224.21 ± 174.18	142.46 ± 186.17	11.463**	0.024	4.794***	0.135

[#] after adjusted for age, sex, BMI, family history of CVD status, current cigarette smoking status, and baseline cardiovascular activity

$^{+}$ $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$

Since some previous studies (e.g., de Rooij et al., 2010) have categorised depression and anxiety scores, categorization of anxiety and depression is presented here using cut point scores of eight. Chi-square test revealed that 47 out of 104 (45.19%) of the participants from the UK were categorised as having anxiety, and 24 out of the 119 (20.17%) Thai participants fell into the anxiety category. Depression was indicated in six participants out of 104 (5.77%) the UK and 10 participants out of 119 (8.40%) in the Thai sample. Chi-square tests of

significance indicated that there was a statistically significant difference in the proportion of UK and Thailand participants in the anxiety category, $\chi^2 = 16.01$, $p < .001$, but not in the depression category; $\chi^2 = 0.58$, $p = .447$.

Given that the two samples were from different populations and there was heterogeneity in anxiety, the remainder of the analyses will be reported separately for each sample; the chapter will first report the findings from the Thai sample and then the findings from the UK sample.

4.5.2 Thai Study

4.5.2.1 Relationships between Cardiovascular Reactivity and HADS Anxiety and Depression Scores in the Thai Participants

The relationships between cardiovascular reactions to mental stressors and HADS anxiety and depression scores in Thailand were examined. First, the study examined whether the tasks used provoked cardiovascular reactions. In the Thai participants, each task was associated with significant and substantial increases in SBP, DBP, HR, CO, and TPR during the three psychological stress tests (see table 4.3).

Table 4.3 Baseline and task cardiovascular activity in the Thai participants (N = 119)

	The Mental arithmetic task (mean ± SD)	**The speech task (mean ± SD)**	**The cold pressor task (mean ± SD)**
SBP			
Baseline (mmHg)	110.64 ± 9.28	110.64 ± 9.28	110.64 ± 9.28
Task SBP (mmHg)	131.56 ± 14.37	137.04 ± 15.47	140.77 ± 15.12
t -test (118)	-20.64***	-22.11***	-24.94***
DBP			
Baseline (mmHg)	60.28 ± 6.88	60.28 ± 6.88	60.28 ± 6.88
Task (mmHg)	72.30 ± 9.54	75.25 ± 9.57	78.30 ± 10.64
t -test (118)	-16.00***	-19.36***	-20.94***
HR			
Baseline (bpm)	77.89 ± 10.15	77.89 ± 10.15	77.89 ± 10.15
Task (bpm)	86.46 ± 12.93	85.75 ± 12.13	82.02 ± 11.39
t -test (118)	-13.00***	-11.28***	-6.24***
CO			
Baseline (l/min)	5.65 ± 1.23	5.65 ± 1.23	5.65 ± 1.23
Task (l/min)	6.40 ± 1.58	6.22 ± 1.44	5.88 ± 1.35
t -test (118)	-10.72***	-8.18***	-3.60***
TPR			
Baseline (dyne-sec.cm-^{5})	872.79 ± 202.30	872.79 ± 202.30	872.79 ± 202.30
Task (dyne-sec.cm-^{5})	922.11 ± 230.16	1007.30 ± 269.96	1097.00 ± 300.15
t -test (118)	-5.10***	-9.42***	-14.04***

*** $p < .001$

Separate repeated-measures ANOVA tests and Bonferroni post-hoc tests were conducted to compare cardiovascular responses to the mental arithmetic task, the speech task and the cold pressor task. As illustrated in table 4.4, SBP reactivity increase was significantly greater during the cold pressor task than the mental arithmetic task, and the speech task. In addition, SBP reactions to the speech task were greater than during SBP responses to the mental arithmetic task. The DBP responses to the cold pressor task were significantly larger than DBP responses to the mental arithmetic task and DBP responses to the speech task. Further, DBP reactions to the speech task were greater than during DBP responses to the mental arithmetic task. Post hoc tests using the Bonferroni also revealed that larger HR reactions between the mental arithmetic task than the cold pressor task, but not higher than HR reactions to the speech task. However, HR reactions the speech task was higher than HR reactions to the cold pressor task. CO reactivity increase was significantly greater during the

mental arithmetic task than the cold pressor task, and the speech task. In addition, CO reactions to the speech task were greater than during CO responses to the mental arithmetic task. TPR responses to the cold pressor task were larger than TPR responses to the mental arithmetic task and TPR responses to the speech task. Further, the TPR responses to the speech task were larger than the TPR responses to the mental arithmetic task. In sum, SBP, DBP, and TPR reactions to cold pressor were higher than for mental arithmetic and speech task, whereas HR and CO reaction to mental arithmetic were greater than to the cold pressor task.

Table 4.4 A comparison of cardiovascular reactivity (change) scores in the Thai participants (N = 119)

	The mental Arithmetic task (mean ± SD)	**The speech task (mean ± SD)**	**The cold pressor task (mean ± SD)**
SBP reactivity scores (mmHg)	20.92 ± 11.06 $^{a***, b***}$	26.40 ± 13.03 ^{a***,c**}	30.13 ± 13.18 ^{b***,c**}
DBP reactivity scores (mmHg)	12.01 ± 8.19 ^{a***,c***}	14.96 ± 8.43 ^{b***,c***}	18.02 ± 9.39 $^{a***, b***}$
HR reactivity scores (bpm)	8.58 ± 7.20 ^{a***}	7.87 ± 7.61 ^{b***}	4.13 ± 7.22 $^{a***, b***}$
CO reactivity scores (l/m)	0.75 ± 0.77 ^{a***,c**}	0.57 ± 0.76 ^{b***,c**}	0.23 ± 0.70 $^{a***, b***}$
TPR reactivity scores (dyne-sec.cm-^{5})	49.32 ± 105.56 ^{a***,c***}	134.51 ± 155.84 ^{b***,c***}	224.21 ± 174.18 $^{a***, b***}$

$^{a, b, c}$ significant mean differences

** $p < .01$, $^{***}p < .001$

Attention then turned to the depression and anxiety scores as continuous variables. There was a positive association between HADS depression scores and anxiety scores ($r = 0.488$, $p < .001$). While this is a significant and large correlation, separate correlations between depression and anxiety, on the one hand, and cardiovascular reactivity on the other, were calculated as the variance overlap was less than 30%.

As can be seen in table 4.5, none of the correlations between cardiovascular reactivity and whether HADS anxiety scores or HADS depression scores reached the conventional criteria for statistical significance ($p < .05$).

Table 4.5 Bivariate correlations between depression and anxiety, and cardiovascular reactivity in the Thai participants (N = 119)

Cardiovascular reactivity	HADS Anxiety Scores		HADS Depression Scores	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
The mental arithmetic task				
SBP	-0.047	.608	-0.104	.262
DBP	-0.080	.389	-0.023	.807
HR	-0.034	.713	-0.071	.440
CO	0.125	.175	0.055	.555
TPR	-0.171	.063	-0.130	.160
The speech task				
SBP	-0.036	.689	-0.078	.399
DBP	-0.046	.623	0.019	.838
HR	0.095	.302	-0.036	.695
CO	0.135	.144	-0.66	.476
TPR	-0.157	.089	0.009	.923
The cold pressor task				
SBP	-0.069	.455	-0.030	.746
DBP	-0.133	.148	-0.024	.796
HR	0.056	.544	0.065	.480
CO	0.051	.583	0.017	.854
TPR	-0.108	.241	-0.009	.924

Next, the relationships between depression and anxiety scores and traditional risk factors were examined; these are shown in table 4.6. Neither depression score nor anxiety score were related to traditional risk factors ($p > .05$). There were significant association between HADS depression scores and baseline HR activity ($r = -0.183$). However, partial correlation co-efficients were computed adjusting for baseline cardiovascular measures and all risk factors to examine if the relationships between depression and reactivity survived adjustment.

Table 4.6 Point-biserial and bivariate correlations between HADS depression and anxiety scores, traditional risk factors, and cardiovascular parameters in the Thai participants (N = 119)

Variable	Anxiety scores		Depression scores	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
Traditional risk factors				
Age	-0.006	.950	0.133	.149
BMI	-0.036	.694	0.045	.631
Sex [a]	-0.033	.724	0.061	.513
Family history of CVD [b]	0.101	.276	0.027	.773
Current cigarette smoking status [c]	-0.053	.567	0.150	.103
Baseline cardiovascular parameter				
SBP	0.082	.377	-0.002	.984
DBP	0.083	.369	0.008	.932
HR	0.043	.640	**-0.183**	**.046**
CO	-0.022	.809	-0.079	.395
TPR	-0.044	.633	0.066	.477

[a] sex: male =1 , female = 0

[b] family history of cardiovascular disease: positive =1 , negative = 0

[c] current smoking: smoking = 1, non-smoking = 0

Partial correlations with adjustment for baseline cardiovascular measures and traditional risk factors (gender, age, BMI, family history of CVD, and current cigarette smoking status) revealed that only the *negative* relationships between TPR reactions to the mental arithmetic task and depression scores were observed (r = -0.186; see table 4.7).

Table 4.7 Partial correlation between depression and anxiety, and cardiovascular reactivity controlling for age, sex, BMI, current cigarette smoking status, parental history of CVD and baseline cardiovascular measures in the Thai participants (N = 119)

Cardiovascular reactivity	**HADS Anxiety Scores**		**HADS Depression Scores**	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
The mental arithmetic task				
SBP	-0.053	.575	-0.122	.199
DBP	-0.071	.457	-0.002	.984
HR	-0.054	.572	-0.034	.722
CO	0.133	.161	0.131	.165
TPR	-0.176	.063	**-0.186**	**.049**
The speech task				
SBP	-0.045	.634	-0.101	.288
DBP	-0.036	.709	0.036	.707
HR	0.088	.356	-0.032	.722
CO	0.134	.158	-0.013	.892
TPR	-0.167	.076	-0.049	.604
The cold pressor task				
SBP	-0.064	.500	-0.059	.534
DBP	-0.123	.195	-0.020	.835
HR	0.061	.520	0.060	.529
CO	0.047	.622	0.073	.442
TPR	-0.125	.187	-0.087	.361

4.5.2.2 Symptoms of Anxiety and Depression in the Thai Participants

Using eight as the cut-off points for anxiety and depression categories, 24 (24.00%) Thai participants were categorised as anxious, whereas only 10 (9.60%) were categorized as depressed. There was no significant group difference in age, BMI, current cigarette smoking status, and family history of CVD by anxiety or depression grouping ($p > .05$). These data are displayed in table 4.8.

Table 4.8 Descriptive statistics of demographic data by HADS depression and anxiety scores in the Thai participants (N = 119)

Variable	Thais (N = 119)			
	Anxiety symptoms		Depressive symptoms	
	Anxiety (n = 24)	Non-Anxiety (n = 95)	Depression (n = 10)	Non-Depression (n = 109)
Sex				
- Male (n= 34)	8 (23.53%)	26 (76.47%)	3 (8.82%)	31 (91.17%)
- Female (n = 85)	16 (18.82%)	69 (81.18%)	7 (8.24%)	78 (91.76%)
Current smoking (n = 8)	1 (12.5%)	7 (87.5%)	1 (12.5%)	7 (87.5%)
Family history of CVD (n = 50)	10 (20.00%)	40 (80.00%)	2 (4.00%)	48 (96.00%)
	Mean ± SD		Mean ± SD	
Age (years)	31.13 ± 9.19	32.44 ± 10.31	30.30 ± 7.30	32.35 ± 10.30
BMI (kg/m^2)	22.14 ± 3.65	22.07 ± 4.80	22.36 ± 3.29	22.06 ± 4.69

Finally, ANOVAs were conducted to compare cardiovascular reactivity between participants who had HADS scores indicative of anxiety and depression pathology (see appendix tables 4.3 and 4.4). In these analyses, individuals with symptoms of anxiety had lower TPR responses to the speech task than those without symptoms of anxiety; F (1,117) = 4.067, p = .046, *partial eta*^{2} = .034. In addition, individuals with symptoms of depression had lower reactivity than those without symptoms of depression: they had lower TPR reactions to the mental arithmetic task; F (1,117) = 5.604, p = .020, *partial eta*^{2} = .046. ANCOVA revealed that these relationships remained after adjusting for baseline cardiovascular activity and traditional risk factors; individuals with symptoms of depression still had smaller TPR reactions to the mental arithmetic task than individuals without symptoms of depression; F (7,111) = 2.643, p = .015, *partial eta*^{2} = .143. Further, participants with symptoms of anxiety had lower TPR reactions to the speech task than those without symptoms of anxiety; F (7,111) = 2.642, p = .015, *partial eta*^{2} = .143.

In conclusion, neither depression nor anxiety symptoms were associated with cardiovascular responses to psychological stress tests in the Thai participants. Only TPR reactions to the mental arithmetic task were inversely associated with depressive symptoms after controlling for baseline cardiovascular activity and traditional risk factors.

4.5.3 The UK Study

4.5.3.1 Relationships between Cardiovascular Reactivity and HADS Anxiety and Depression Scores in the UK Participants

First, the patterns of cardiovascular reactions to psychological stress tests among the UK participants (N = 104) were examined. Paired sample *t*-tests indicated that each task elicited significant and substantial increases in SBP, DBP, HR, CO, and TPR during the three psychological stress tests (see table 4.9). As can be seen in table 4.9, the cold pressor task appeared to provoke the greatest BP and TPR reactions, whereas the mental arithmetic task elicited the largest HR reactions ($p < .001$).

Table 4.9 Baseline and task cardiovascular activity in the UK participants (N = 104)

	The Mental arithmetic task (mean ± SD)	**The speech task (mean ± SD)**	**The cold pressor task (mean ± SD)**
SBP			
Baseline (mmHg)	106.61 ± 14.73	106.61 ± 14.73	106.61 ± 14.73
Task (mmHg)	121.39 ± 18.20	124.29 ± 19.50	131.00 ± 18.16
t -test (103)	-13.63***	-14.01***	-19.82***
DBP			
Baseline (mmHg)	57.19 ± 10.18	57.19 ± 10.18	57.19 ± 10.18
Task (mmHg)	66.84 ± 12.15	67.88 ± 11.23	70.80 ± 12.26
t -test (103)	-14.93***	-16.68***	-18.44***
HR			
Baseline (bpm)	76.93 ± 10.73	76.93 ± 10.73	76.93 ± 10.73
Task (bpm)	82.08 ± 11.18	81.81 ± 11.34	80.10 ± 11.13
t -test (103)	-9.01***	-7.40***	-5.32***
CO			
Baseline (l/min)	6.13 ± 1.38	6.13 ± 1.38	6.13 ± 1.38
Task (l/min)	6.54 ± 1.37	6.62 ± 1.36	6.49 ± 1.28
t -test (103)	-4.88***	-6.00***	-3.90***
TPR			
Baseline (dyne-sec.cm-^{5})	764.40 ± 170.34	764.40 ± 170.34	764.40 ± 170.34
Task (dyne-sec.cm-^{5})	832.59 ± 189.13	844.75 ± 219.45	906.86 ± 251.22
t -test (103)	-4.97***	-6.12***	-7.80***

*** $p < .001$

Separate repeated-measures ANOVA tests and Bonferroni post-hoc tests were conducted to compare cardiovascular responses to the mental arithmetic task, the speech task and the cold pressor task. As illustrated in table 4.10, SBP increases were significantly greater in response to the cold pressor task than the mental arithmetic task or the speech task. In addition, SBP reactions to the speech task were greater than during SBP responses to the mental arithmetic task. The DBP responses to the cold pressor task was significantly larger than DBP responses to the mental arithmetic task and DBP responses to the speech task; there was no difference in the DBP responses to the speech task compared to the mental arithmetic task. Post hoc tests using the Bonferroni correction also revealed that there were larger HR reactions to the mental arithmetic task and the speech task than the cold pressor task. However, HR reactions to the mental arithmetic task were not different to HR reactions the speech task ($p > .05$). There were no differences in CO responses to the three psychological tasks ($p > .05$). TPR responses to the cold pressor task were larger than TPR responses to the mental arithmetic task, and the TPR responses to cold pressor were larger than the TPR responses to the speech task. There were no differences in TPR responses to the speech task versus the mental arithmetic task ($p > .05$). To summarise, the active coping tasks appeared to provoke larger HR responses, and smaller SBP, DBP, and TPR responses than the passive coping task.

So, in Thai and UK participants each task was associated with significant and substantial changes in each of the cardiovascular measures. In addition, exposure to the cold pressor task (passive coping tasks) was associated with a vascular pattern of responses, as evidenced by larger TPR responses, whereas the mental arithmetic and speech tasks (active coping tasks) provoked a cardiac pattern of responding with larger CO and HR responses in both Thai and UK samples. However, compared to the Thai sample, participants in the UK tended to display lower haemodynamic reactions to each task (e.g., SBP responses to mental arithmetic).

Table 4.10 A comparison of cardiovascular reactivity (change) scores in the UK participants (N = 104)

	The mental Arithmetic task (mean ± SD)	**The speech task (mean ± SD)**	**The cold pressor task (mean ± SD)**
SBP responses (mmHg)	14.78 ± 11.06 [a***, c*]	17.68 ± 12.87 [b***, c*]	24.39 ± 12.55 [a***, b***]
DBP responses (mmHg)	9.66 ± 6.60 [a***]	10.69 ± 6.54 [b**]	13.61 ± 7.53 [a***, b**]
HR responses (bpm)	5.16 ± 5.80 [a**]	4.88 ± 6.73 [b*]	3.17 ± 6.07 [a**, b*]
CO responses (l/m)	0.41 ± 0.86	0.49 ± 0.83	0.35 ± 0.93
TPR responses (dyne-sec.cm-^{5})	68.19 ± 139.80 [a**]	80.35 ± 133.84 [b**]	142.46 ± 186.17 [a**, b**]

[a, b, c] significant mean differences

[*] $p < .05$, [**] $p < .01$, [***] $p < .001$

Next, attention focused on the depression and anxiety scores as continuous variables. A positive association was observed between HADS depression scores and anxiety scores (r = 0.483, $p < .001$). Whilst this is a significant and large correlation, separate correlations between depression and anxiety, on the one hand, and the reactivity on the other, were calculated as the variance overlap was less than 30%.

Negative associations were found between HADS depression scores and HR and CO reactions to the mental arithmetic task (r = -0.201 and r = -0.244, respectively), and CO reactions to the cold pressor task (r = -0.199). HADS anxiety scores were negatively associated with SBP responses to mental arithmetic (r = -0.214). These are displayed in table 4.11. However, it is important to note that 30 correlation co-efficients were calculated; adjustment by Bonferroni would indicate no significant relationships. Yet these correlations all offer support for the blunted reactivity hypothesis.

Table 4.11 Bivariate correlations between HADS depression and anxiety scores, and cardiovascular reactivity in the UK participants (N = 104)

Cardiovascular reactivity	Anxiety score		Depression score	
	Correlation *r*	***p*-value**	**Correlation *r***	***p*-value**
The mental arithmetic task				
SBP	**-0.214**	**.029**	-0.043	.661
DBP	-0.042	.675	0.029	.767
HR	-0.026	.793	**-0.201**	**.041**
CO	-0.152	.123	**-0.244**	**.013**
TPR	0.053	.591	0.032	.751
The speech task				
SBP	-0.099	.319	-0.132	.183
DBP	-0.102	.304	-0.126	.203
HR	-0.055	.582	-0.099	.319
CO	0.029	.771	-0.158	.110
TPR	-0.081	.416	-0.126	.201
The cold pressor task				
SBP	-0.116	.241	-0.055	.576
DBP	-0.047	.635	0.004	.972
HR	0.029	.770	-0.044	.661
CO	0.017	.865	**-0.199**	**.042**
TPR	-0.020	.842	0.108	.274

Next, the relationships between depression and anxiety scores and traditional risk factors and baseline cardiovascular activations were examined; these are shown in table 4.12. The only significant association was between HADS depression scores and current cigarette smoking status (r = 0.251). In addition, HADS anxiety scores were negatively related to baseline DBP activity (r = -0.250), but not in HADS depression ($p > .05$). However, partial correlation co-efficients were computed adjusting for baseline cardiovascular measures and all risk factors to examine if the relationships between depression and reactivity survived adjustment.

Table 4.12 Point-biserial and bivariate correlations between HADS depression and anxiety scores, traditional risk factors, and cardiovascular parameters in the UK participants (N = 104)

Variable	Anxiety scores		Depression scores	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
Traditional risk factors				
Age	-0.154	.118	0.123	.215
BMI	0.044	.661	0.005	.958
Sex [a]	0.140	.156	-0.110	.267
Family history of CVD [b]	-0.112	.256	0.015	.883
Current cigarette smoking status [c]	0.122	.216	**0.251**	**.010**
Baseline cardiovascular parameter				
SBP	-0.136	.168	-0.116	.241
DBP	**-0.250**	**.011**	-0.166	.092
HR	0.045	.649	0.038	.701
CO	-0.035	.721	0.065	.509
TPR	-0.155	.115	-0.111	.261

[a] sex: male =1 , female = 2

[b] family history of cardiovascular disease: positive =1 , negative = 0

[c] current smoking: smoking = 1, non-smoking = 0

Partial correlations revealed that the relationships between SBP response to the mental arithmetic task and anxiety scores survived adjustment for baseline cardiovascular measures and traditional risk factors (i.e., gender, age, BMI, family history of CVD, and current cigarette smoking status). Moreover, CO responses to the mental arithmetic task were associated with anxiety, after controlling for baseline cardiovascular activations and traditional risk factors. In addition, the relationships between CO response to the mental arithmetic task and depression scores survived adjustment, but not in HR reactions to the mental arithmetic task, after controlling for baseline cardiovascular activations and traditional risk factors. Further, the relationship between depression and CO responses to cold pressor was no longer significant after adjusting for traditional risk factors and baseline CO (see table 4.13).

Table 4.13 Partial correlation between depression and anxiety, and cardiovascular reactivity controlling for age, sex, BMI, current cigarette smoking status, parental history of CVD, and baseline cardiovascular measures in the UK participants (N = 104)

Cardiovascular reactivity	**HADS Anxiety scores**		**HADS Depression scores**	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
The mental arithmetic task				
SBP	**-0.201**	**.047**	-0.101	.322
DBP	-0.035	.734	-0.004	.972
HR	-0.050	.625	-0.173	.089
CO	**-0.231**	**.022**	**-0.223**	**.027**
TPR	0.038	.710	-0.035	.731
The speech task				
SBP	-0.069	.500	-0.150	.139
DBP	-0.153	.132	-0.169	.096
HR	-0.071	.484	-0.067	.511
CO	-0.031	.760	-0.091	.371
TPR	-0.073	.475	-0.176	.084
The cold pressor task				
SBP	-0.110	.280	-0.060	.560
DBP	-0.063	.539	0.041	.690
HR	0.036	.726	0.004	.971
CO	-0.058	.573	-0.161	.114
TPR	0.038	.713	0.100	.329

Since motivation has been posited as one possible pathway linking depression to blunted cardiovascular reactivity (Carroll et al., 2007), analyses then focused on the partial correlations between HADS anxiety and depression scores after controlling for self-reported perceived stress, performance (number correct for the mental arithmetic task) and pain tolerance (the total amount of time each participant's hand remained immersed in the cold water measured with a stopwatch; see table 4.14).

The partial correlations showed that after controlling for traditional risk factors, baseline cardiovascular activations, self-reported perceived stress and performance or pain tolerance (depending on types of task), higher depression scores were still associated with lower CO responses to the mental arithmetic task (r = -0.264). Further, higher anxiety scores were related to CO reactions to the mental arithmetic task (r = -0.265). In contrast, the partial

correlations between depression and anxiety and cardiovascular reactions to the speech task or the cold pressor task were no longer significant after adjustment for self-reported perceived stress, performance tasks, traditional risk factors and baseline cardiovascular activation ($p > .05$; see table 4.14).

Table 4.14 Partial correlations between HADS depression and anxiety scores, and cardiovascular reactivity controlling for baseline cardiovascular activations, traditional risk factors, self-reported perceived stress, performance or pain tolerance (depending on task) in the UK participants (N = 104)

Cardiovascular reactivity	HADS Anxiety		HADS Depression	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
The mental arithmetic task[1]				
SBP	-0.155	.136	-0.040	.699
DBP	0.042	.689	0.090	.390
HR	-0.033	.749	-0.149	.152
CO	**-0.265**	**.010**	**-0.264**	**.010**
TPR	0.112	.283	0.046	.661
The speech task [2]				
SBP	-0.051	.621	-0.135	.192
DBP	-0.130	.210	-0.148	.152
HR	-0.055	.596	-0.055	.598
CO	-0.017	.867	-0.116	.263
TPR	-0.063	.543	-0.142	.169
The cold pressor task [3]				
SBP	-0.106	.310	-0.068	.512
DBP	-0.072	.488	0.017	.873
HR	0.011	.914	-0.034	.748
CO	-0.051	.628	-0.174	.094
TPR	0.042	.685	0.098	.345

[1] controlling for baseline cardiovascular activity, traditional risk factors, self-reported perceived mental arithmetic stress, and performance scores

[2] controlling for baseline cardiovascular activity, traditional risk factors, and self-reported perceived speech stress

[3] controlling for baseline cardiovascular activity, traditional risk factors, self-reported perceived cold pressor stress, and pain tolerance

Next, a Sobel test was conducted to see if self-reported perceived stress or performance scores on the mental arithmetic task or pain tolerance on the cold pressor task were mediators of the depression or anxiety. The first step was to regress the mediator variable (self-reported perceived stress or performance scores or pain tolerance) on the predictor (SBP, HR and CO reactions to the mental arithmetic task, and CO reactions to the cold pressor task, depending on the relationships). In the second step, the outcome variable (HADS depression or anxiety scores) was regressed on the predictor variable. Next mediation was tested; there were no evidence of mediation for any relationship (p > .05; see appendix table 4.5). So, the relationships between cardiovascular reactivity and depression or anxiety scores were not mediated by self-reported perceived stress or performance scores or pain tolerance.

4.5.3.2 Symptoms of Anxiety and Depression in the UK Participants

Finally, analyses were conducted using the anxiety and depressive symptom scores, with a cut-off of > 8 to indicate possible pathology to allow comparison with previous studies. The characteristics of participants categorized as having depression or anxiety were examined. There were no significant differences in age, BMI, sex, family history of CVD, and current cigarette smoking status by depression category (p > .05), whereas individuals categorized as anxious were significantly younger (t (99) = -2.56, p = .029). Table 4.15 displays the descriptive characteristics of the UK sample.

Table 4.15 Descriptive statistics of demographic data by HADS depression and anxiety categories in the UK participants (N = 104)

Variable	**UK participants (N= 104)**			
	Anxiety symptoms		**Depressive symptoms**	
	Anxiety (n = 47)	**Non-Anxiety (n = 57)**	**Depression (n = 6)**	**Non-Depression (n = 98)**
Sex				
- Male (n = 45)	15 (33.33%)	30 (66.67%)	4 (8.89%)	41 (91.11%)
- Female (n = 59)	32 (54.24%)	27 (45.76%)	2 (3.39%)	57 (96.61%)
Current smoking (n = 33)	15 (45.45%)	18 (54.55%)	4 (12.12%)	29 (88.88%)
Family history of CVD (n = 32)	13 (40.63%)	19 (59.38%)	2 (6.25%)	30 (93.75%)
	Mean ± SD		**Mean ± SD**	
Age (years)	28.51 ± 8.82	34.40 ± 12.94	38.50 ± 9.89	31.09 ± 11.55
BMI (kg/m^2)	25.61 ± 5.89	25.46 ± 4.39	28.88 ± 5.24	25.33 ± 5.04

ANOVAs were then conducted to compare cardiovascular reactivity between participants who had HADS scores indicative of anxiety and depression pathology (see appendix tables 4.6 and 4.7). In these analyses, individuals with symptoms of depression had lower reactivity than those without symptoms of depression: they had smaller CO reactions to the mental arithmetic task, mean (SD) = -0.62 (1.57) vs. 0.47 (0.76); F (1,102) = 10.027, p = .002, *partial eta*^{2} = .090, and the cold pressor task, mean (SD) = -0.51 (1.14) vs. mean = 0.41 (SD = 0.89); F (1,102) = 5.826, p = .018, *partial eta*^{2} = .054 than individuals without symptoms of depression. Finally, ANCOVA was used to statistically correct for baseline cardiovascular activity and traditional risk factors; individuals with symptoms of depression still had smaller CO reactions to the mental arithmetic task, F (7,96) = 3.631, p = .002, , *partial eta*^{2} = .209; and the cold pressor task, F (7,96) = 5.846, p < .001, *partial eta*^{2} = .299 than individuals without symptoms of depression.

In conclusion, among a modest sample of 104 healthy UK adults, depressive symptoms were negatively associated with HR and CO responses to the mental arithmetic task. However, only the relationship between CO responses to the mental arithmetic task and depression symptoms remained after adjustment for traditional risk factors and baseline cardiovascular activity. This relationship - depression symptoms and CO reactions to the mental arithmetic task also remained significant after adjusting for traditional risk factors, baseline cardiovascular activations, self-reported perceived stress, and performance scores. However, Sobel tests did not indicate mediation. Further, CO responses to the passive coping task, cold pressor, were negatively associated with depressive symptoms but this relationship was no longer significant after adjusting for traditional risk factors and baseline CO activity or after added with self-reported perceived stress and pain tolerance. Anxiety symptoms were inversely related to SBP responses to mental arithmetic task. This correlation remained significant after adjusting for traditional risk factors and baseline SBP. Moreover, anxiety symptoms were negatively associated with CO reactions to the mental arithmetic task after controlling for baseline cardiovascular activations, traditional risk factors, self-reported perceived stress, and performance scores; this was a significant negative correlation after adjusting for traditional risk factors and baseline.

4.6 Discussion

The main aim of the present study was to examine the relationships between depressive and anxiety symptoms on the HADS, on the one hand, and cardiovascular responses to mental arithmetic, speech and cold pressor tasks, on the other. In addition, differences in haemodynamic reactivity (cardiac and vascular reactivity), and HADS anxiety and HADS depression scores between participants from Thailand and the UK, and between active and passive coping tasks, were examined. Mental arithmetic, speech, and cold pressor tasks were chosen as they represent different types of stimuli and provoke different patterns of cardiovascular response associated with active and passive coping (Girdler, Hinderliter, & Light, 1993; Girdler et al., 1996; Sherwood, Dolan, & Light, 1990). The main findings were that, in Thai participants, none of the cardiovascular reactivity indices was associated with depression or anxiety symptoms; however, a negative relationship between depression and TPR reactions to the mental arithmetic task emerged after controlling for baseline cardiovascular activity and traditional risk factors. In the UK participants, depressive symptoms were negatively associated with HR and CO responses to the mental arithmetic task. However, only the relationship between CO responses to the mental arithmetic task and depression symptoms remained after adjustment for traditional risk factors and baseline cardiovascular activity. This relationship - depression symptoms and CO reactions to the mental arithmetic task also remained significant after adjusting for traditional risk factors, baseline cardiovascular activations, self-reported perceived stress and performance scores. However, Sobel tests did not indicate mediation. Further, CO responses to the passive coping task, cold pressor, were negatively associated with depressive symptoms but this relationship was no longer significant after adjusting for traditional risk factors and baseline CO activation or after added with self-reported perceived stress and pain tolerance. Anxiety symptoms were inversely related to SBP responses to mental arithmetic task, in the UK sample. This correlation remained significant after adjusting for traditional risk factors and baseline SBP. Moreover, anxiety symptoms were negatively associated with CO reactions to the mental arithmetic task after controlling for baseline cardiovascular activations, traditional risk factors, self-reported perceived stress and performance scores; this was a significant negative correlation after adjusting for traditional risk factors and baseline.

With respect to hypothesis 1, participants in the UK had higher anxiety scores, but not depression scores, than Thai participants. Thai participants displayed greater haemodynamic reactions to each task compared to the UK sample, (see tables 4.1 and 4.2) with few

exceptions. In addition, hypothesis 2 was confirmed: exposure to the cold pressor task (passive coping tasks) was associated with a vascular pattern of responses, evidenced by larger TPR responses, whereas the mental arithmetic and speech tasks (active coping tasks) provoked a cardiac pattern of responding with larger CO and HR responses (see tables 4.3, 4.4, 4.10, and 4.11).

4.6.1 Country Differences in Cardiovascular Reactivity, Depression and Anxiety Scores: A Comparison between Thailand and the UK

Compared with the UK participants, Thai individuals exhibited larger haemodynamic responses to psychological stress tests. There were only four exceptions (from 15) to this: HR and CO responses to cold pressor, CO responses to speech and TPR responses to mental arithmetic did not differ by country. These differences remained largely unaltered by adjustment for baseline or traditional risk factors. Indeed some differences were larger after statistical adjustment (e.g., HR responses to cold pressor). The patterning of findings does not implicate task order, which was fixed for the Thai sample and randomised in the UK sample, as accounting for these differences (see appendix table 4.8). Further, the variance in the cardiovascular reactivity data (standard deviations) was similar across both samples suggesting that there were not floor or ceiling effects. Accordingly, other explanations are needed to understand these differences. Few studies have directly compared cardiovascular laboratory stress responses between Asian and Caucasian participants (Shen, Stroud, & Niaura, 2004; Stoney, Hughes, Kuntz, West, & Thornton, 2002; Suchday & Larkin, 2004). These studies have indicated that, on the whole, Asians exhibit significantly *lower* haemodynamic reactions to laboratory stress tests than Caucasians. However, these studies were of participants living in the United States, i.e., they were studies of acculturation. In the present study, differences in cardiovascular responses to mental stress may reflect cultural differences between individuals raised and living in the UK and Thailand. It may be that Thai participants were less familiar with experimental testing and so displayed greater cardiovascular reactivity than the UK participants; conversations with the Thai participants suggested that they found participation a novel experience, and they asked more questions about the study and the equipment used. Moreover, behavioural factors may account for differences in cardiovascular reactivity by ethnicity and country. Thai participants had a lower BMI and there were a smaller proportion of current smokers than in the UK sample (see appendix table 4.9). BMI and smoking status, and other behavioural factors, have been associated with cardiovascular reactivity (Jern, Bergbrant, Bjorntorp, & Hansson, 1992;

Phillips, 2011; Phillips, Der, Hunt, & Carroll, 2009). For example, Phillips (2011) reported obese participants exhibited smaller HR reactions to the PASAT than non-obese participants. In addition, Phillips et al. (2009) found that smokers had significantly smaller SBP and DBP responses to the PASAT than ex- and non-smokers. Further, several studies have found that lower socioeconomic status is correlated with higher cardiovascular reactivity (Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998). The current studies did not collect detailed information on education, incomes and occupation but it is likely that the Thai participants had lower levels of income (although both groups were or had been undergraduate students) (the Gross Domestic Product of Thailand was worth 345.649 billion US dollars in 2011, whereas the Gross Domestic Product of the UK was 2431.589 billion US dollars; World Bank, 2012). Thus, it is likely that the haemodynamic reactivity differences found here are, at least partially, socioculturally mediated (Delehanty, Dimsdale, & Mills, 1991; Markus & Kitayaman, 1991).

With respect to anxiety and depressive symptoms, participants in the UK had higher trait anxiety than Thai participants whereas depression scores were similar. It is possible that the HADS was viewed with suspicion and may be not sufficiently sensitive for Thai participants. In addition, Thaneerat et al. (2009) questioned whether the Thai-HADS could be sufficiently accurate to allow for the definite diagnosis of major depressive disorder according to criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision): DSM-IV-TR. However, the HADS has been tested for validity and reliability in other languages (including Thai), with the anxiety and depression subscales having good reliability and validity in Thai samples (Bjelland, Dahl, Haug, & Neckelmann, 2002; Herrmann, 1997; Nilchaikovit, Lortrakul, & Phisansuthideth, 1996). It might be also that cultural differences between Thai and British affect reporting of symptoms. For example, there are cultural differences in the experience of emotions, how they are interpreted and expressed (Lai & Linden, 1992; Mesquita & Walker, 2003).

Therefore, future studies are needed to replicate and explore further the results obtained in this present study. In addition, research into the possible culture differences in the associations between anxiety and depressive symptoms and cardiovascular reactivity would help illuminate the possible roles of different ethnic and cultural mediators of relationships between psychological factors and haemodynamic responses to laboratory stressors.

4.6.2 Cardiovascular Responses to Active and Passive Coping Tasks in the Thai and UK Participants

The three tasks used provoked substantial but different patterns of haemodynamic responses and were similar to those reported by others (e.g., Weinberger, Schwartz, & Davidson, 1979; Young et al., 1998); the cold pressor task (passive coping tasks) provoked larger BP and TPR responses, and smaller HR responses than mental arithmetic or speech in both the UK and Thai samples. In addition, active coping tasks (mental arithmetic and speech tasks) provoked larger HR and CO responses than cold pressor. These findings largely confirmed Hypotheses 2 and allowed for meaningful tests of the other hypotheses.

4.6.3 Cardiovascular Reactivity and HADS Depression and Anxiety Scores

With respect to depressive symptoms and haemodynamic reactivity, the results indicate that participants with more depressive symptoms exhibited less HR and CO responses to the mental arithmetic task in the UK sample. However, the relationship between depressive symptoms and CO reactions to the mental arithmetic task was maintained after statistical adjustment for conservative risk factors (i.e., gender, age, BMI, family history of CVD, and current cigarette smoking status) and baseline cardiovascular measures. These findings are consistent with a growing number of studies showing attenuated cardiovascular reactivity is associated with depressive symptoms (Carroll et al., 2007; Salomon et al., 2009; Straneva-Meuse et al., 2004). Further, CO reactions have been shown to be smaller in depressed patients, both with and without CVD, than non-depressed individuals. Differences in CO reported across studies may be related to the severity of depressive symptoms. For example, Ehrenthal, Herrmann-Lingen, Fey, and Schauenburg (2010) compared cardiovascular reactivity to anger recall and mental arithmetic tasks in 25 individuals with severely depressed without heart disease and 25 non-depressed participants. They revealed that in depressed participants showed overall reduced HR, BP and CO. Similarly, depressed individuals experienced significantly less SBP, HR, and CO reactivity during stressor protocols (speech and mirror tracing) than non-depressed individuals (Salomon et al., 2009). In a study conducted by Straneva-Meuse et al. (2004), acute psychological laboratory stressors, the PASAT, a speech task, a cold pressor task, and an orthostatic challenge were used. Lower CO responses to laboratory stressors were exhibited in participants with major depression disorders who were treated with anti-depressants (bupropion or paroxetine) relative to control group. Therefore, the present study would suggest that one mechanism linking depressive symptoms with cardiovascular responses may involve deregulation of

beta-adrenergic receptors given the important direct or indirect role they play in cardiac contractility (York et al., 2007). In Thai participants in our study, there was a negative correlation between depression scores and TPR reactions to mental arithmetic task. However, this was the only one significant correlation that emerged from 30 correlation co-efficients that were calculated. Therefore, this finding is probably a type I error.

In the case of anxiety, the present study found only two small negative correlations after controlling for traditional risk factors and baseline cardiovascular activity: this was between SBP and CO responses to the mental arithmetic task and anxiety scores in the UK sample. There was no correlation between cardiovascular responses to the speech task and anxiety scores in the Thai sample. Other investigators have also found a negative correlation between SBP responses to mental arithmetic and anxiety scores (e.g., Young et al., 1998). Symptoms of anxiety may influence cardiac function via multiple pathways. For example, Nesse, Cameron, Curtis, McCann, and Huber-Smith (1984) found decreased beta-adrenergic receptor sensitivity or decreased stimulation of the beta-adrenergic system in patients with panic disorders. In addition, decreases in the number of lymphocyte beta-adrenergic receptors have been reported in the participants with trait anxiety (using the Spielberger Trait Anxiety Scores) (Aronson, Carasiti, McBane, & Whitaker-Azmitia, 1989). Therefore, the present study on SBP responses to the mental arithmetic task offers very limited support for the hypothesis of beta-adrenergic down-regulation in people with high levels of anxiety.

Further, previous studies have also demonstrated relationships between depression or anxiety and reactivity and suggested a role for the sympathetic nervous system (Dimsdale, Mills, Patterson, Ziegler, & Dillon, 1994; Pandey, Janicak, & Davis, 1987; Townsend, Bologna, & Berbee, 1998). For example, several studies have shown that participants with depression and anxiety have decreases in the number of beta-adrenergic receptors (Aronson et al., 1989; Brown, Charney, Woods, Heninger, &Tallman, 1988; Nesse et al., 1984; Yu, Dimsdale, & Mills, 1999). In anxiety disorders, Nesse et al. (1984) reported that decreased beta-adrenergic receptor sensitivity or decreased stimulation of the beta-adrenergic system was observed in patients with panic disorders. They found that higher anxiety and depression were related to decreased numbers of beta-adrenergic receptors. Yu, Kang, Ziegler, Mills, and Dimsdale (2008) examined the relationship between mood states (assessed by using the Profile of Mood States) and beta-adrenergic report in healthy individuals. They also suggested that mood states were associated with down-regulation of beta-adrenergic receptor even in

individuals who do not have psychiatric disorders. As discussed above, active coping tasks were associated with relatively greater changes in CO and these tasks involve a beta-adrenergic mediated pattern of responses via central mechanisms (Sherwood, Allen, Obrist, & Langer, 1986). The present study provides some supporting evidence for the involvement of blunted beta-adrenergic receptor responsiveness in participants with anxiety and depression: they showed smaller CO responses, a marker of beta-adrenergic responsiveness, to the active coping task.

One possible explanation for the blunted responses in individuals with high anxiety or depression scores is that they may be less engaged in the task or experience a loss of motivation in the task. Task effort might be the first concomitant of haemodynamic reactivity (Gendolla & Richter, 2006; Koo-Loeb et al., 1998; Peter et al., 1999; Richter, Friedrich, & Gendolla, 2008; Silvia, Jones, Kelly, & Zibaie, 2011; Suzuki, Kumano, & Sakano, 2003). Previous studies evidenced that mental effort is related to changes in the immune system and these changes are mediated by changes in sympathetic nervous system activity including BP, HR and norepinephrine. High effort during mental tasks results in greater increases in HR, SBP, DBP and plasma norepinephrine levels (Peter et al., 1998; Peter et al., 1999). The present study found that after controlling for performance or self-reported perceived stress of completing the task (as appropriate for each task), the negative relationships between HADS depression and anxiety and cardiovascular reactions were observed in the UK sample. For example, the association between both HADS anxiety and depression scores and CO reactions to the mental arithmetic task were significant, after controlling for traditional risk factors, baseline cardiovascular activations, self-reported perceived stress and performance scores. However, there was little evidence of mediation probably because of the small effects. This suggests that other mechanisms may be involved such as anticipatory stress or motivation to enhance effort; although these results should be treated with caution given the large number of correlations calculated.

4.6.4 Types of Coping Tasks (Active and Passive Coping Tasks) and HADS Depression and Anxiety scores

Finally, the study tested the hypothesis that that negative relationships between cardiovascular responses and anxiety and depression scores will be stronger for the active coping tasks than the passive coping task. Indeed, only responses to one of the active coping tasks (the mental arithmetic task) were related to anxiety and depression scores after

adjusting for baseline cardiovascular activity and traditional risk factors; there were no relationships with responses to the passive coping task (cold pressor). Salomon et al. (2009) also found no association between depression and cardiovascular responses to a passive coping stressor (a mirror tracing task) in groups of participants diagnosed with depressive disorder and healthy participants. In contrast, Matthew et al. (2005) reported that depressive symptoms were positively correlated with systematic vascular resistance responses to mirror tracing in 91 volunteers. In the only other study to look at different types of task, Schwerdtfeger and Rosenkaimer (2011) examined relationships between the Beck Depression Inventory depression scores and BP and HR reactions to public speaking, cold pressor and video viewing in 55 healthy participants. They found no corelation between depression and cardiovascular reactions to a cold pressor task, whereas there were negative correlations with cardiovascular reactions to public speaking and video viewing tasks. Given that the video viewing involves passive coping and provokes vascular changes (Sherwood & Turner, 1992), Schwerdtfeger and Rosenkaimer (2011) argue that it is the self-relevant nature of the tasks that is important rather than whether they are active or passive. However, they did not assess haemodynamic responses so this conclusion should be considered as speculative. In the current study, relationships between cardiovascular reactions to the other active task (public speaking) and anxiety or depression scores were not seen, suggesting that it is not the active coping associated with the mental arithmetic task that explains the relationships observed. Straneva-Meuse et al. (2004) found that depressed patients treated bupropion or paroxetine showed lesser SBP and CO responses to active coping tasks (namely mental arithmetic and speech tasks) than non-depressed individuals, but not to a passive coping tasks (cold pressor). Active coping tasks involve a beta-adrenergic mediated pattern of responses and increase BP via central mechanisms. Increasing catecholamines, HR, SBP, stroke volume, and CO or small increasing of DBP and TPR are elicited sympathetic nervous system responses. Passive coping tasks, conversely, involve vasoconstriction through alpha-adrenergic receptor stimulation (stimulation of norepinephrine) resulting in changes in DBP and TPR (Gerin et al., 2000; Obrist et al., 1978). The present study demonstrated that the specific coping strategies may be related to responses to active tasks and involve an active coping (myocardial) mechanism. Of note, mental arithmetic was associated most notably with myocardial reactivity patterns, which is consistent with a beta-adrenergic mechanism; conversely, the passive coping task was related to vascular reactivity patterns, which is consistent with an alpha-adrenergic mechanism; the speech task was associated with a more mixed pattern (Sherwood et al., 1990).

4.7 Limitations and Strengths of the Studies

The present study has several limitations. First, causality cannot be inferred as the design is cross sectional. A prospective study with multiple assessments of the anxiety and depression over time might confirm whether negative emotional distress (namely anxiety and depressive symptoms) may lead to cardiovascular reactions to psychological stress tests (e.g., Phillips et al., 2011). Further, in the UK participants, only six (5.77%) had high levels of depressive symptoms although 47 (45.19%) participants demonstrated high levels of anxiety symptoms. In Thai individuals, only ten participants (8.40%) had depressive symptoms and 24 people (20.17%) displayed a high level of anxiety symptoms. In future research, it would be useful to study a larger group of participants with some having higher levels of depression and anxiety (or both). In addition, there are many factors that would influence on anxiety and depressive symptoms; however, the current studies screened for many (e.g., medication) and statistically controlled for others (e.g., traditional risk factors). It is not possible to directly compare haemodynamic responses to psychological stress tests between the Thai and UK samples because of protocol differences. For example, the order of the psychological stress testing was randomised in the UK sample after the initial Thai study and the temperature of the cold pressor test was increased.

Finally, reactivity scores were determined by subtracting initial baseline values (at minutes 5-18 from the Thai participants and at minutes 5-13 from the UK participants) from each task values. Thus, the reactivity scores were calculated in a different way for each study and differ from some previous research (e.g., Carroll, et al., 2012; Markovitz et al., 1998). However, several studies have used different measures of initial baseline cardiovascular activity (Georgiades, Lemne, Faire, Lindvall, & Fredrikson, 1996; Girdler et al., 1996; Hughes & Stoney, 2000; Light, et al., 1999; Markovitz et al., 1998). For example, some studies used baseline cardiovascular activity at initial testing and stress reactivity scores were subtracted by initial baseline cardiovascular activity from task levels (Georgiades, Lemne, Faire, Lindvall, & Fredrikson, 1996; Girdler et al., 1996; Hughes & Stoney, 2000; Stewart, Janicki & Kamarck, 2006). Other studies calculated BP reactivity scores by subtracting the average of the final three baseline readings from the average levels measured during mental stress (Carroll, et al., 2012; Markovitz et al., 1998; Matthews, et al., 2003; Matthews, et al., 2004), whereas other studies asked the participants to return to the laboratory on a few days later, underwent similar instrumentation and perform another task (Light et al., 1999). Accordingly, differences in the manner in which cardiovascular reactivity scores are calculated might be an

important consideration. However, studies that include multiple tasks have used similar baseline and reactivity measures (Girdler et al., 1996) to those used here. Moreover, in order to determine whether the use of initial baseline measures affected the relationships of interest in the current studies, new baseline cardiovascular measures were calculated by averaging at five, six, and seven minutes before the next task commenced (the eighth minute was excluded from this calculation as the value may increase due to anticipation). Using these new baseline measures, new cardiovascular reactivity scores were derived. Analyses revealed that there were no significant difference between original baseline cardiovascular activity and new baseline cardiovascular activity or any stress reactivity measure in the Thai sample (see appendix tables 4.10 and 4.11) or the UK sample (see appendix tables 4.12 and 4.13). In addition, initial baseline cardiovascular activity was not significantly difference from 6-minute post task cardiovascular recovery measures but did differ from 3-minute post task cardiovascular recovery measures, suggesting that recovery was not complete at 3-minute. Additional analyses examined relationships between cardiovascular reactivity and HADS depression and anxiety scores in the Thai (see appendix tables 4.14 and 4.15) and the UK participants (see appendix tables 4.16, 4.17, and 4.18). The relationships were similar to the ones described in the results section in this chapter; only data from the UK participants supported the "Blunted cardiovascular reactivity hypothesis" that low cardiovascular reactivity is associated with higher anxiety and depressive scores. Indeed, using the new baseline measures suggested that, if anything, the negative relationships between cardiovascular responses to mental arithmetic and depression and anxiety were slightly stronger than originally calculated.

The current study has several noteworthy strengths. First, this chapter is, to our knowledge, the first attempt to investigate the relationships between cardiovascular reactivity and depression and anxiety in two different countries and cultures (both in Thailand and the UK). Nearly all research studies that have examined psychological factors that may be involved in the development of CHD and hypertension have been conducted in Western countries; this limits the generalizability of their findings (Roest, Martens, Denollet, & de Jonge, 2010). The present study was conducted in both Western and Eastern samples and illustrates that there may be significant differences. The number of participants in this study was reasonably large, and used multiple tasks (i.e., a mental arithmetic task and a speech task that involve the beta-adrenergic system and a cold pressor task that perturbs the alpha-adrenergic system) with

measures of both cardiac and vascular responses that afforded a better understanding of the mechanisms relating cardiovascular reactivity to depression and anxiety.

4.8 Conclusion

These analyses demonstrate that high anxiety or depressive symptoms would appear to be characterised by blunted cardiovascular reactions to acute mental stress, particularly mental arithmetic, in UK, but not Thai, participants. Future research needs to examine potential mechanisms and examine longitudinal pathways. In the next chapter a prospective cohort study was conducted in healthy Thai participants. In that prospective study attention focused on older versions of the Reactivity Hypothesis and, so haemodynamic reactions to psychological stress tests were used to predict future BP.

CHAPTER 5

Cardiovascular Responses to Acute Psychological Stressors and the Prediction of Future Blood Pressure Based on 1 Year Follow-up: A Study in Thailand

In chapter 4 the findings of two cross-sectional analyses examining the relationships between cardiovascular reactivity and depression and anxiety in the UK and Thai samples were reported. In the UK sample, but not the Thai sample, CO responses to a mental arithmetic task were negatively associated with both anxiety and depressive symptoms after controlling for baseline cardiovascular activity, traditional risk factors and mediator variables. These results supported the "Blunted cardiovascular reactivity" hypothesis, a relatively new version and extension of the Reactivity hypothesis (Carroll, Phillips, Hunt, & Der, 2007; Carroll, Phillips, & Lovallo, 2012; Phillips, 2011; Phillips, Hunt, Der, & Carroll, 2011). Two prospective studies testing traditional versions of the Reactivity Hypothesis in Thailand and the UK are described in this chapter and chapter 6, respectively. In this chapter, the focus is on the prospective cohort study of Thai participants examining whether cardiovascular responses to psychological stress tests predict future BP since this study was completed first and was used to test the protocols that were used in the UK study (chapter 6). As described later, in practice the Thai study recruited as many participants as the UK study and there was little attrition so, surprisingly, it was the larger of the two studies.

5.1 Introduction

According to the WHO, CVD is a major health problem in many countries throughout the world. The WHO estimated that 3,615,896 people in South East Asia (population = 1,760,485,705) died from CVD in 2008, a mortality rate of 2.05 per 1000 population. This equates to 45% of the overall mortality rate in 2008 in South East Asia (WHO, 2011); in the UK, CVD was the leading cause of death accounting for approximately a third of all deaths in 2010 (BHF, 2012). The equivalent Thai mortality rates for hypertensive heart disease and CHD were 1.63 and 1.04 per 1000, respectively (Kochanek, Xu, Murphy, Minino, & Kung, 2011). Further, the projected trends in CVD mortality in South-East Asia indicate a rise by 2030; it is expected to continue to be the main cause of death (WHO, 2008).

In Thailand, the estimated mortality rate of CVD was 1.52 per 1,000 (WHO, 2008) and the total number of people who died from CVD in Thailand was 95,100 in 2004. Furthermore, an estimated 3,900 people died from hypertensive heart disease, and 25,500 people from CHD in Thailand. In addition to having a lower CVD mortality rate than other Asian countries, Thailand also has a lower CVD mortality rate than other developing countries, the USA and the UK (He et al., 2004; Ueshima et al., 2008); CVD accounted for less than 20% of total deaths (Khor, 2001). Tatsanavivat et al. (1998) have claimed that heart disease has been the leading cause of death in the Thai population for a number of years, and that CVD mortality has risen year on year in Thailand. Indeed, the trend of age-standardized mortality rates for CVD shows that there has been an increase from 27.8 to 45.5 per 100,000 between 1961 and 2000. This increase is apparent and similar for both males and females (Petcharoen, 2005).

Although CVD mortality rates are increasing in Thailand, there have been few studies of cardiovascular risk factors. In one large cross-sectional study, Tatsanavivat et al. (1998) examined the results of electrocardiogram studies in 8791 Thais from the 17 provinces of Thailand. They found that the major cardiovascular risk factors among men and women were high total cholesterol, hypercholesterolemia, high BP, BMI, fasting blood sugar, hypertension status, smoking, diabetes mellitus, and obesity; factors that have been identified in many studies of Western populations. More recently, Chongsuvivatwong et al. (2010) reported regional differences in cardiovascular risk factors that may, in part, explain differences in CVD mortality rates in Thailand; in particular, Bangkok had a higher prevalence of hypertension, elevated BMI, large waist circumference, Low Density Lipoprotein, and diabetes mellitus. Thus, the risk factors contributing to CVD mortality are similar in Thailand to those in the rest of the world, although their patterning may differ. Further, these risk factors do not fully account for CVD mortality rates.

Cardiovascular responses to psychological stress tests have been shown to be good predictors of future increases in BP and for hypertension status. Cardiovascular responses to mental stress have also been correlated prospectively with preclinical CHD and cardiac events (Georgiades, Lemne, Faire, Lindvall, & Fredrikson, 1997; Key, Taylor, & Blackburn, 1971). The Reactivity Hypothesis posits that exaggerated haemodynamic responses (i.e., BP or HR) to an aversive challenge, or engaging laboratory induced stressors predict or contribute to future BP and hypertension (Krantz & Manuck, 1984; Treiber et al., 2003). Over the past few

decades, several studies have indicated that heightened cardiovascular reactions to laboratory stressors may be a risk factor for high BP, hypertension status and CVD (Treiber et al., 2003; Chida & Steptoe, 2010). In addition, these associations are still significant after controlling for traditional risk factors (e.g., BMI, age, sex) and baseline cardiovascular measures (e.g., BP). Three large reviews have summarized support for the Reactivity Hypothesis. In the first, Treiber et al. (2003) concluded that cardiovascular reactivity to psychological stress tasks contributed to preclinical and clinical disease development (including increased BP levels, left ventricular mass, carotid atherosclerosis, and clinical CHD). The second review used meta-analyses to explore the associations between cardiovascular reactions to psychological laboratory stressors and cardiovascular risk status, including BP, hypertension, left ventricular mass, subclinical atherosclerosis and clinical cardiac events (Chida & Steptoe, 2010). Chida and Steptoe's review (2010) found that cardiovascular responses to laboratory stressors were correlated with elevated cardiovascular risk (e.g., increased high BP, hypertension). However, the combined effect sizes (across studies and measures of cardiovascular reactivity) were relatively small: the effect size for the prediction of future SBP was $r = 0.096$; for the prediction of DBP, it was $r = 0.077$; and for hypertension status, it was $r = 0.101$. However, this review only focused on psychological stress tasks; studies using the cold pressor task were not included in the review. Most recently, the thesis conducted a systematic review, meta-analysis and meta-regression to assess the relationships between cardiovascular reactivity and BP, hypertension status, preclinical CHD, and cardiac events (see chapter 2). This review (chapter 2) used meta-regressions to evaluate whether these relationships differed by type of mental stress task (i.e., active and passive coping tasks), duration of follow-up (a shorter and longer term of follow-up), and age of participants (adults and children). This review also found that greater BP reactivity was associated with subsequent high BP (SBP and DBP levels). In addition, SBP responses to passive coping tasks were a better predictor of future hypertension status than SBP responses to active coping tasks; there were no differences in the prediction of future BP. SBP reactivity was a better predictor of future SBP in studies with a shorter follow-up compared to a longer follow-up, and in studies of children compared to adults. Taken together, these reviews provide evidence that cardiovascular reactivity predicts future BP levels. The meta-regressions in chapter 2 and Chida and Steptoe's meta-analysis (2010) suggests that a number of study characteristics, including age of participants, type of task and duration of follow-up, may strengthen or weaken these predictions. These characteristics are described in more

detail below. Further, the results of the meta-regression in chapter 2 are contrasted with studies where direct comparisons of those characteristics are made. This provides a rationale for the study described in this chapter.

First, the meta-regression analysis found that passive coping tasks afforded a better prediction of hypertension status than active coping tasks. This contrasts with previous reviews (Krantz & Manuck, 1984; Treiber et al., 2003) implicating cardiovascular responses to active coping tasks as being stronger predictors. However, studies using active and passive coping tasks included in the meta-regression may have differed in important ways (e.g., year of study, sophistication of equipment). Few prospective studies have used both active and passive coping tasks. For example, Girdler et al. (1996) examined cardiovascular responses to both active and passive coping tasks and assessed BP after two years in 40 healthy participants. They reported that only cardiovascular reactions to passive coping tasks, a speech preparation and a cold pressor task, predicted future BP, after controlling for baseline BP; cardiovascular reactions to an active coping task (namely a speech delivery) did not predict future BP. More recently, Flaa, Eide, Kjeldsen, and Rostrup (2008) investigated SBP, DBP, and HR reactions to mental arithmetic (active coping) and cold pressor tasks (passive coping) in 80 healthy men with a re-examination after 18 years. In contrast to Girdler et al. (1996), they found that SBP and DBP reactions to both task were significant predictors of future BP, after adjusting for traditional risk factors (resting SBP, family history of hypertension status, and BMI at entry). Moreover, cardiovascular reactions to the mental arithmetic task appeared to be better predictors of future BP than cardiovascular reactions to the cold pressor task. Similarly, Markovitz, Raczynski, Wallace, Chettur, and Chesney (1998) found that cardiovascular responses to active coping tasks were better predictors of future BP than cardiovascular responses to passive coping tasks in a sample of over 3000 health participants. Thus the findings from the small number of prospective studies are rather mixed but lend more support for the use of active coping tasks.

Second, most studies have used simple cardiovascular indices, BP and HR, to index reactivity. A comprehensive assessment of cardiovascular functions such as CO and TPR permits determination of test-retest reliability of haemodynamic patterning, and affords distinction of haemodynamic patterning of responses to active and passive coping tasks (Kasprowicz, Manuck, Malkoff, & Krantz, 1990; Light, Turner, Hinderliter, Girdler, &

Sherwood, 1994; McKinney et al., 1985; Sherwood, Dolan, & Light, 1990). In addition, the patterns of haemodynamic reactions to psychological stress tests have been used to predict cardiovascular risk status, e.g., heighted BP and hypertension status (Jennings et al., 2004; Matthews, Salomon, Brady, & Allen, 2003; Steptoe & Marmot, 2005a). However, haemodynamic reactions, notably TPR and CO, have been used in few extensive prospective cohort studies to predict future CVD events (including increase future BP). As mentioned in chapter 2, only five studies using haemodynamic parameters were included in the meta-regression models of future BP levels and the prediction of preclinical CHD (two for the prediction of future BP levels, and three for preclinical CHD). The first studies that reported TPR and CO as cardiovascular parameters of future BP were started in the mid-1990s (Girdler et al., 1996; Papavassiliou, Treiber, Strong, Malpass, & Davis, 1996) and only ten studies have applied these parameters as predictors of future BP, preclinical CHD, and essential hypertension (Jennings et al., 2004; Kapuka et al., 1999; Matthews, Salomon, Brady, & Allen, 2003; Steptoe & Marmot, 2005b). For example, Matthews et al. (2003) reported the results of a prospective study of the relationships between cardiovascular responses to reaction time, mirror tracing, cold pressor applied to the forehead and stress interview tasks in 149 girls and boys among multiethnic children (African American and white American children). BP, HR, TPR, CO, pre-ejection period, and stroke volume were measured during the performance of four mental stress tasks and used to predict future BP with short follow-up periods. Future SBP and DBP levels three years later were predicted by SBP, DBP, CO, and stroke volume changes during mental stress tasks. Girdler et al. (1996) found that only SBP and HR reactions to passive coping tasks (a cold pressor task and a speech preparation task) predicted future SBP levels; CO and TPR reactivity did not and cardiovascular responses to the active coping task did not. Moreover, the findings presented in chapter 2 suggested that haemodynamic measurement should be used to predict future BP levels.

Third, the review did not examine whether single or multiple tasks afforded better prediction of cardiovascular risk status (i.e., increased BP). Earlier prospective cohort studies examined cardiovascular responses to a single task as predictors of future cardiovascular risk status (Armstrong & Rafferty, 1950; Eich & Jacobsen, 1967; Harland, Osborne, & Graybiel, 1964). However, aggregation of cardiovascular responses across multiple tasks might improve reliability and generalizability, as a more diverse range of situations are sampled (Schwartz et

al., 2003). Several studies have found that an aggregated responsivity across different tasks is more reliable and valid than reactivity scores from a single task (Davig, Larkin, & Goodie, 2000; Kamarck, 1992; Kamarck, Debski, & Manuck, 2000; Swain & Suls, 1996; Turner, Sherwood, & Light, 1994). For example, Kamarck et al. (2000) demonstrated that aggregating cardiovascular responses across tasks (namely a marksmanship task (target), a visual short-term memory task (scanning), a psychomotor task (tracking), a Stroop Color-Word Conflict test, a speech preparation task, and a speech delivery task) increased the reliability and led to an increase in the laboratory–to–life generalisability. Furthermore, Trieber et al. (2003) suggested that aggregated cardiovascular responses to multiple tasks might be more strongly associated with the prediction of development of hypertension than cardiovascular responses to single tasks. Moseley and Linden (2006) examined whether aggregate measures of cardiovascular reactivity were better predictors of BP over three years and ten years follow-up than cardiovascular responses to single tasks. Their data supported the hypothesis that the predictive values of the aggregated reactivity scores over three laboratory stressors (namely an isometric handgrip task, a mental arithmetic task, and a recall of an anger-provoking situation task) were stronger than elevated cardiovascular responses to a single task. Given the small number of studies that have used multiple stressors, the current study examined the use of aggregate measure of cardiovascular responsivity to predict future BP.

Finally, somewhat surprisingly, the review found that a shorter follow-up period (defined as less than ten years of follow-up) was a better predictor of future SBP levels by SBP reactions to psychological stress tests than a longer follow-up time. Thus, the relatively short follow-up period may not be problematic in these studies in the Thai and UK samples.

In summary, to date a fair amount of evidence supports the "Reactivity Hypothesis"; heightened BP or haemodynamic responses to laboratory stressors predict future BP (Chida & Steptoe, 2010; Gasperin, Netuveli, Dias-da-Costa, & Pattussi, 2009; Gerin et al., 2000; Treiber et al., 2003). However, to date no single prospective study has examined features of the task (active and passive coping tasks *and* single and multiple tasks) along with a range of haemodynamic measures of reactivity (including CO and TPR). In the only prospective study in Asia, Kasagi, Akahoshi, and Shimaoka (1995) found that SBP responses to cold pressor predicted hypertension 28 years later in 824 men and women from Nagasaki, Japan; this

finding is similar to that from the many Western prospective studies that have examined cardiovascular responses to cold pressor tests. The current study is the first study in Thailand to explore whether cardiovascular responses to a range of psychological stress tests (cold pressor, mental arithmetic, and a speech task) can predict future BP.

5.2 Purpose of the Study

The aims of the present study were:

a) to establish protocols for active and passive coping tasks (i.e., mental arithmetic, speech, and cold pressor tasks) to be used in chapter 6 in this thesis;
b) to assess the patterning of cardiovascular responses to psychological stress tests in the Thai participants;
c) to examine whether measures of responses to laboratory-based challenges are useful in predicting one year BP among initially normotensive participants;
d) to determine the unique contribution of cardiovascular responses parameters to the prediction of follow-up resting BP after adjustment of traditional clinical predictors of BP (e.g., initial resting BP, initial BMI, initial age, gender, parental history of CVD, and current cigarette smoking status).

The following specific hypotheses of study were tested:

1) haemodynamic reactions to active coping tasks will differ from haemodynamic reactions to passive coping tasks in normotensive healthy Thai individuals;
2) haemodynamic reactions to active and passive coping tasks (i.e., mental arithemetic, speech, and cold presor tasks) will predict future BP in healthy Thai participants over a one year period;
3) haemodynamic reactions to multiple tasks will afford a better prediction of future BP one year later than haemodynamic reactions to single tasks in healthy Thai participants.

5.3 Materials and Method

In the previous chapter, chapter 3, research methodology, including participants, inclusion and exclusion criteria, details of measure and procedures, were outlined. These are summarized below in figure 5.1.

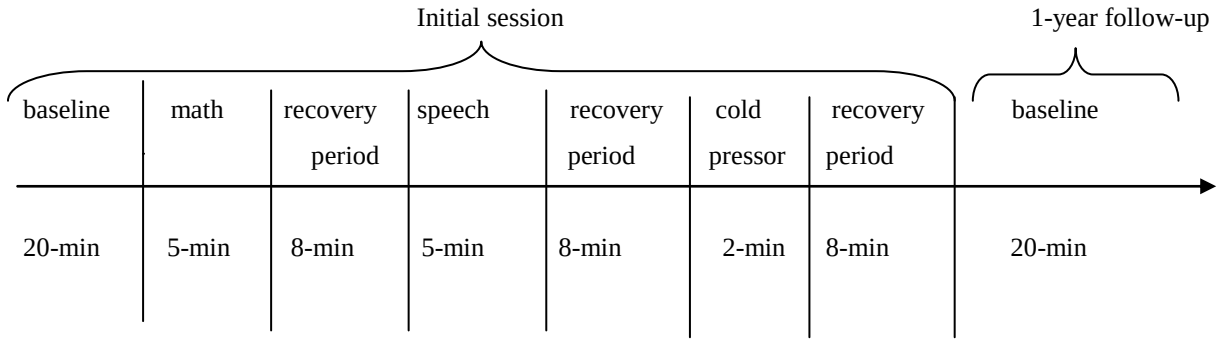


Figure 5.1 Summary of diagram shows stages of experimental protocol in Thai participants

5.4 Data Analysis

5.4.1 Data reduction

BMI was computed as weight in kilograms divided by height in meters squared (kg/m^2). Data for resting BP, HR and cardiac performance (CO and TPR) were collected on a minute-by-minute and calculated between five to 18 minute readings because cardiovascular measures may increase in anticipation of the upcoming task. The study therefore excluded the two last readings from the computation of average baseline levels. Haemodynamic responses scores (i.e., SBP, DBP, HR, CO, and TPR) for each task were calculated as the mean task level minus the mean baseline levels (Girdler et al., 1996; Hughes & Stoney, 2000).

Aggregated measures from the three mental stressors were calculated for responses to several types of stress (i.e., mental arithmetic, speech and cold pressor tasks). The calculation of cardiovascular responses scores were transformed into z-scores from each participant and then averaged to produce the aggregate measure of responses for each parameter (i.e., SBP, DBP, HR, CO, and TPR) (Treiber et al., 2001).

At the follow-up assessment, resting SBP, and DBP from the last four readings (minutes 5, 10, 15 and 18) obtained during resting period were averaged.

5.4.2 Statistical Analysis

A total of 133 Thai participants were recruited at initial session; however, eight participants with data that contained outliers (±2 SD away from the mean) and six individuals who were taking antihypertensive medications were removed from the analyses. Therefore, results were based on 119 participants at entry and 107 participants at follow-up.

Independent samples *t* tests or Mann-Whitney tests were performed to indicate whether participants in the follow-up differed from those who did not participate in the follow-up after a one year. Paired-sample *t* tests were performed to examine changes in BP and other continuous variables from baseline to follow-up. Initial repeated measures ANOVAs were conducted to assess whether the mental stressor elicited significant changes in cardiovascular activity in the Thai participants. Pearson correlations coefficients were calculated between all pairs of cardiovascular responses to tasks. Further, Pearson correlations were used to examine relationships between traditional risk factors, baseline cardiovascular activity or cardiovascular responses to psychological stress tests at the time of the initial session and BP level after one year of follow-up. Finally, a series of hierarchical regression analyses were performed to determine whether cardiovascular responses to mental stress predicted BP over 12 months independently of other variables (e.g., BMI, age, gender, parental history of CVD, current cigarette smoking status, and baseline cardiovascular activity).

5.5 Results

5.5.1 Demographic and Cardiovascular Characteristics of Stress Responses

The demographic and resting cardiovascular characteristics of the sample at baseline and follow-up are presented in table 5.1. The average time of follow-up was 13.55 (range 12.17 – 15.05) months.

A total of 119 healthy volunteers (34 men and 85 women) participated in October 2010-December 2010 at the physiotherapy laboratory, Thammasat University. One hundred and seven participants (89.92%) agreed to participate in the follow-up assessment (from December 2011 to February 2012) including 31 men and 76 women. A total of 12 (9.60%) participants were not reexamined; two did not want to participate (relocated to another place), and ten did not answer any email or calls. There were no significant differences in initial resting BP, CO, TPR, BMI, gender, current cigarette smoking status or family history of CVD between those who attended the follow-up and those who did not. However, those who attended follow-up had significantly higher initial resting HR (78.61 ±10.11 bpm) than those who did not participate (71.39 ±8.37 bpm) in the follow-up; t (117) = 2.38, p =.019). Furthermore, participants who participated at follow-up showed lower DBP responses to the cold pressor task (17.31 ± 8.90 mmHg) than those who did not attended follow-up (24.37 ± 11.53; t (117) = -2.53, p = .013) (see appendix table 5.1).

Paired *t*-tests were then used to compare initial values with follow-up values; these indicated that resting SBP (t (106) = -1.64, p = .103) had not changed significantly over the follow-up period, whereas resting DBP (t (106) = -6.40, p < .001) had increased significantly from initial period to one year follow-up. They were on average 31.43 years old (SD = 9.44) at the first visit. The mean (SD) change in SBP was 1.62 (10.29) mmHg, and in DBP was 4.41 (7.65) mmHg. Table 5.1 displays the demographic and baseline cardiovascular at the initial and follow-up assessment.

Table 5.1 Characteristics of Thai participants who completed baseline and follow-up sessions (n = 107)

Characteristic	**N**	**%**	**Mean**	**SD**
Sex				
- Male	31	28.97		
- Female	76	71.03		
Current cigarette smoking status	6	5.61		
Family history of CVD status	46	42.99		
Age at initial (years)			31.43	9.44
BMI at initial study (kg/m^2)			22.20	4.73
SBP at initial session (mmHg)			111.01	9.15
DBP at initial session (mmHg)			60.58	6.86
SBP at follow-up session (mmHg)			112.63	9.81
DBP at follow-up session (mmHg)			64.99	8.77

5.5.2 Cardiovascular Responses to Laboratory Stressors

As described previously in chapter 4, cardiovascular responses to psychological stress tests were displayed in tables 4.3 and 4.4. The analyses conducted here were with participants who completed follow-up (n = 107); the patterning of haemodynamic responses was similar to that reported in chapter 4 (which included the whole sample; i.e., those participants who attended the initial session regardless of whether they did or did not attend follow-up). In summary, participants had greater BP and TPR reactions to the cold pressor task than the mental arithmetic task and the speech task, and greater HR and CO reactions to the mental arithmetic task than the cold pressor task and the speech task. Similar patterns of haemodynamic responses to psychological stress tests were found in analyses that included participants who completed both the baseline and follow-up sessions. Cardiovascular reactions to the speech task seemed to be a combination of vascular and myocardial responses; i.e., the speech task

seemed to be a mixed task eliciting responses that were somewhere between the usual responses to an active coping and a passive coping task. The haemodynamic profiles of elevations in BP and TPR during cold pressor appeared to be predominantly due to an increase in vascular resistance. In contrast, the active coping tasks (the mental arithmetic and speech tasks) were associated with a relatively modest increase in HR and CO. The changes of haemodynamic the baseline and task period for the mental arithmetic task, the speech task, and the cold pressor task are shown in tables 5.2 and 5.3.

Table 5.2 Baseline and task cardiovascular activity in the Thai participants who participated in the initial and follow-up sessions (n = 107)

	The mental arithmetic task (mean ± SD)	**The speech task** (mean ± SD)	**The cold pressor task** (mean ± SD)
SBP			
Baseline (mmHg)	111.01 ± 9.15	111.01 ± 9.15	111.01 ± 9.15
Task (mmHg)	132.21 ± 14.55	137.35 ± 15.77	140.38 ± 15.23
t -test (106)	-19.46***	-20.51***	-23.37***
DBP			
Baseline (mmHg)	60.58 ± 6.86	60.58 ± 6.86	60.58 ± 6.86
Task (mmHg)	72.25 ± 9.11	75.23 ± 9.22	77.89 ± 10.11
t -test (106)	-15.42***	-18.78 ***	-20.11***
HR			
Baseline (bpm)	78.62 ± 10.11	78.62 ± 10.11	78.62 ± 10.11
Task (bpm)	87.38 ± 13.02	86.69 ± 12.17	82.85 ± 11.42
t -test (106)	-12.37***	-10.58 ***	-5.92***
CO			
Baseline (l/min)	5.71 ± 1.23	5.71 ± 1.23	5.71 ± 1.23
Task (l/min)	6.48 ± 1.58	6.29± 1.46	5.94 ± 1.37
t -test (106)	-10.24***	-7.59 ***	-3.38**
TPR			
Baseline (dyne-sec.cm-^{5})	865.79 ± 198.36	865.79 ± 198.36	865.79 ± 198.36
Task (dyne-sec.cm-^{5})	914.79 ±227.08	998.70 ± 264.06	1080.86 ± 284.72
t -test (106)	-4.72***	-8.62 ***	-13.32***

** $p < .01$, *** $p < .001$

Table 5.3 A comparison of cardiovascular reactivity (change) scores in the Thai participants who participated in the initial and follow-up sessions (n = 107)

	The mental Arithmetic task (mean ± SD)	**The speech task (mean ± SD)**	**The cold pressor task (mean ± SD)**
SBP responses (mmHg)	21.20 ± 11.27 [a***,c***]	26.33 ± 13.28 [b*, c***]	29.37 ± 13.00 [a***,b*]
DBP responses (mmHg)	11.67 ± 7.83 [a***,c***]	14.65 ± 8.07 [b***, c***]	17.31 ± 8.90 [a***,b***]
HR responses (bpm)	8.76 ± 7.33 [a***]	8.08 ± 7.90 [b***]	4.23 ± 7.40 [a***,b***]
CO responses (l/m)	0.76 ± 0.77 [a***,c*]	0.58 ± 0.79 [b***, c*]	0.23 ± 0.71 [a***,b***]
TPR responses(dyne-sec.cm-^{5})	49.01 ± 107.30 [a***,c***]	132.92 ± 159.53 [b***, c***]	215.08 ± 166.99 [a***,b***]

[a, b, c] significant mean differences

[*] $p < .05$, [***] $p < .001$

To determine whether haemodynamic responses to the three mental stress tasks were related, intertask correlations based on the reactivity scores were computed for all cardiovascular measures. Pearson product-moment correlation coefficients were calculated between responses to all pairs of tasks; these are displayed in table 5.4. The majority of intertask correlations were significant. In addition, the correlations of responses to mental arithmetic and the speech task were stronger than correlations between either active coping task (mental arithmetic or speech) and the cold pressor task. The strength of these correlations affords calculation of an aggregate responsivity measure (as discussed in the introduction; see page 11-12).

Table 5.4 Intertask correlations for reactivity scores in the Thai participants who participated in the initial and follow-up sessions (n = 107)

Variable	Speech	Cold pressor
SBP		
Mental arithmetic	0.748***	0.598***
Speech		0.678***
DBP		
Mental arithmetic	0.809***	0.640***
Speech		0.710***
HR		
Mental arithmetic	0669***	0.364***
Speech		0.495***
CO		
Mental arithmetic	0.662***	0.371***
Speech		0.619***
TPR		
Mental arithmetic	0.636***	0.455***
Speech		0.521***

*** $p < .001$

5.5.3 Correlations of Classical Predictors with Future BP

Next, the correlations between traditional risk factors and BP (n = 107) over one year follow-up were examined (see table 5.5) in order to determine which factors which serve as covariates in regression models. Gender, BMI, SBP, DBP, and CO at the initial assessment were significantly correlated with SBP at follow-up. In addition, gender, BMI, and initial baseline BP activity were associated with DBP at follow-up. Consequently, initial baseline cardiovascular activity was included in step one, and traditional risk factors were included in step two of hierarchical linear regression models.

Table 5.5 Point-biserial and bivariate correlations between traditional risk factors and baseline cardiovascular activity, and resting SBP and DBP at follow-up after one year in the Thai participants who participated in the initial and follow-up sessions (n = 107)

Variables at entry	Follow-up			
	Resting SBP	*p* - value	Resting DBP	*p* - value
Traditional risk factors				
Sex [a]	**0.240**	**.013**	**0.204**	**.035**
Age	0.097	.320	-0.008	.934
BMI	**0.309**	**.001**	**0.272**	**.005**
Family history of CVD status [b]	-0.034	.732	-0.025	.798
Cigarette smoking [c]	0.025	.802	0.055	.577
Baseline cardiovascular activity				
SBP	**0.413**	**< .001**	**0.359**	**< .001**
DBP	**0.247**	**.010**	**0.569**	**< .001**
HR	-0.143	.141	0.110	.259
CO	**0.212**	**.029**	0.046	.639
TPR	0.001	.992	0.186	.055

[a] sex: male =1, female = 0

[b] family history of CVD: positive =1 , negative = 0

[c] cigarette smoking status: current smoking = 1, non-smoking = 0

Bivariate correlations between cardiovascular reactions to psychological stress tests at initial testing and resting SBP and DBP at follow-up after a one-year period are presented in table 5.6. SBP at follow-up was related to SBP responses to the mental arithmetic task alone; however, the correlation between SBP reactions to the mental arithmetic task and SBP at follow-up was small (Cohen, 1992). Future SBP was also associated with SBP responses to the cold pressor task and the aggregated SBP responsiveness over three tasks. In addition, DBP at follow-up was associated with SBP reactions to mental arithmetic, but these correlations did not reach the conventional criteria for statistical significant ($p < .05$), with the exception of SBP responses to the mental arithmetic task and future SBP levels ($r = 0.250$).

Table 5.6 Bivariate correlations between haemodynamic reactivity and resting SBP and DBP at follow-up after a one year follow-up in the Thai participants who participated in the initial and follow-up sessions (n = 107)

Variable	Follow-up			
	Resting SBP	*p* -value	Resting DBP	*p* -value
The mental arithmetic task				
Δ SBP	**0.250**	**.009**	0.173	.075
Δ DBP	0.072	.458	0.017	.860
Δ HR	0.149	.125	0.040	.680
Δ CO	0.103	.289	0.052	.596
Δ TPR	-0.071	.465	-0.047	.630
The speech task				
Δ SBP	0.051	.603	0.026	.794
Δ DBP	0.079	.418	0.010	.919
Δ HR	0.085	.387	0.065	.505
Δ CO	-0.007	.945	-0.067	.495
Δ TPR	-0.124	.203	-0.004	.964
The cold pressor task				
Δ SBP	0.164	.091	-0.045	.643
Δ DBP	0.066	.498	-0.052	.596
Δ HR	0.138	.158	-0.029	.769
Δ CO	-0.013	.895	-0.125	.198
Δ TPR	0.000	.998	-0.071	.470
Aggregate responsiveness				
SBP	0.181	.062	0.063	.522
DBP	0.081	.410	-0.008	.935
HR	0.151	.120	0.029	.770
CO	0.032	.740	-0.059	.544
TPR	-0.080	.413	-0.049	.619

Δ, responses

5.5.4 Prediction of Longitudinal Changes in SBP after a One Year of Follow-up

A series of hierarchical regression analyses were performed to determine the contribution of cardiovascular responses to the prediction of follow-up resting SBP. At step one, initial resting cardiovascular parameters were entered into the regression model. Cardiovascular responses to a single psychological stress test (i.e., mental arithmetic, speech, and cold pressor tasks) and the aggregated cardiovascular responsivity were entered into the regression

model at step two for cardiovascular responses that showed a significant association with future BP levels ($p < .05$); thus, SBP responses to mental arithmetic were the only measure of reactivity to be entered.

As can be seen in table 5.7, initial baseline SBP entered at step one accounted for 17.0% of the variance in follow-up SBP levels. SBP responses to the mental arithmetic task accounted for an additional 6.2% of the variance ($\beta = 0.248$, SE = 0.075; $p = .005$).

Table 5.7 Results of hierarchical linear regression analyses predicting one year SBP from baseline resting SBP and SBP responses to mental arithmetic data in the Thai participants who participated in the initial and follow-up sessions (n = 107)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
1 year SBP							
Step 1				0.170	21.444***	0.170	21.444***
Baseline SBP	0.441	0.412	4.631***				
Step 2				0.231	15.647***	0.062	8.349**
SBP responses to MA	0.216	0.246	2.889**				

MA, mental arithmetic

** $p < .01$, *** $p < .001$

Next, hierarchical regression was performed to determine the contribution of cardiovascular responses to the prediction of follow-up resting SBP levels. At step one, initial resting baseline BP activity were entered into the regression model. At step two, a set of traditional risk factors (i.e., initial age, initial BMI, sex, current cigarette smoking status, and family history of CVD) were entered into the regression model, and at step three cardiovascular responses to psychological stress test were entered. The findings are presented in table 5.8. Initial baseline SBP entered at step one and accounted for 17.0% of the variance in follow-up SBP. The traditional risk factors accounted for an additional 10.3% of the variance; only BMI was significantly related to follow-up SBP. At step three, SBP responses to the mental arithmetic task accounted for an additional 5.5% of the variance ($\beta = 0.240$, SE = 0.073; $p = .005$), together accounting for 32.8% of the variance in follow-up SBP levels.

Table 5.8 Results of hierarchical linear regression analyses predicting one year SBP from baseline resting SBP, traditional risk factors, and SBP responses to mental arithmetic data in the Thai participants who participated in the initial and follow-up sessions (n = 107)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
1 year SBP							
Step 1				0.170	21.444***	0.170	21.444***
Baseline SBP	0.441	0.412	4.631***				
Step 2				0.273	6.251***	0.103	2.837**
Sex [a]	2.993	0.139	1.426				
Age	0.108	0.104	1.134				
BMI	0.518	0.250	2.836**				
FH [b]	-0.996	-0.051	-0.558				
Smoking [c]	-1.521	-0.036	-0.392				
Step 3				0.328	6.889***	0.055	8.071**
SBP responses to MA	0.209	0.240	2.841**				

FH, family history of CVD

[a] sex: male =1, female = 0

[b] family history of CVD: positive =1 , negative = 0

[c] cigarette smoking status: current smoking = 1, non-smoking = 0

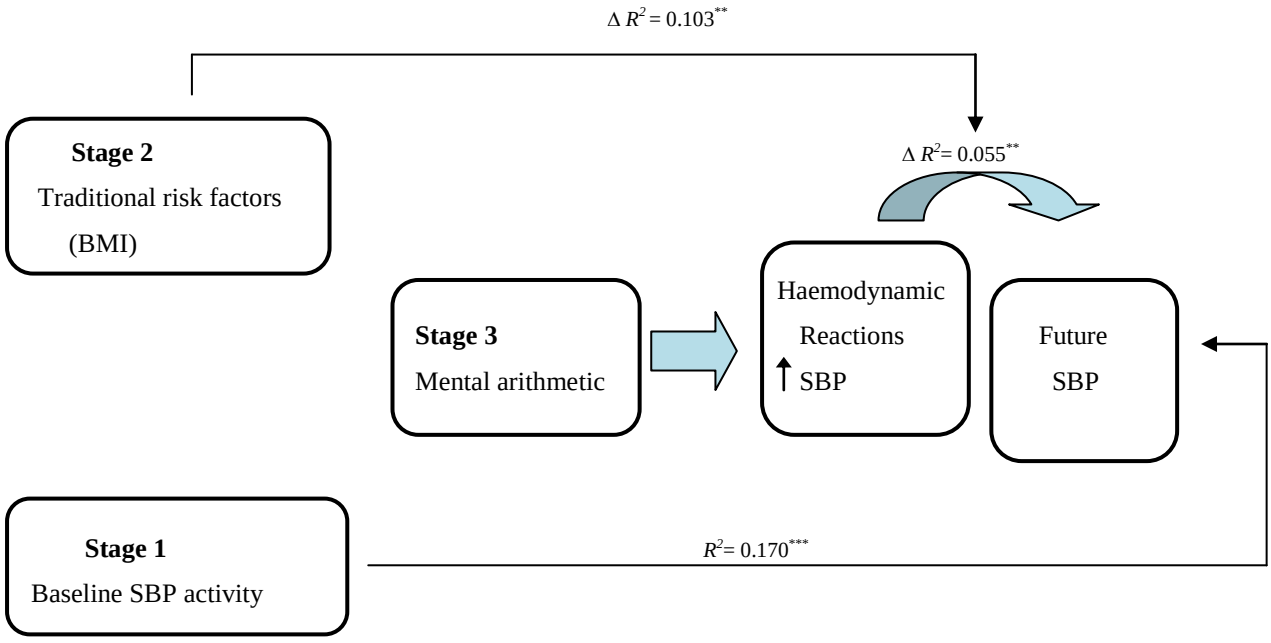
** $p < .01$; *** $p < .001$

In summary, these results suggest that SBP responses to mental arithmetic have predict follow-up SBP over one year above and beyond that of traditional risk factors, albeit modestly.

5.5.5 Prediction of Longitudinal Changes in DBP after a One Year of Follow-up

Turning to the prediction of future DBP, hierarchical regression was performed to determine the contribution of cardiovascular responses to the prediction of follow-up resting DBP. At step one, initial resting cardiovascular parameters were entered into the regression model. Cardiovascular reactions to psychological stress were entered into the regression model at step two. In the hierarchical regression analysis, none of the measures of cardiovascular reactivity predicted future DBP; cardiovascular reactivity was unrelated to future DBP in the bivariate correlations (see table 5.6).

In conclusion, the results suggest that SBP responses to mental arithmetic (active coping task, a single task) are significant independent predictors of future SBP levels, but not of future DBP levels in the Thai sample. The pooled hierarchical regression results are summarized in Figure 5.2, with arrows designating the presumed relationships among the variables. It shows that in the first regression, future SBP levels were regressed on baseline SBP activations, R^2 = 0.170. In the second regression, adjusted future resting SBP levels regressed on traditional risk factors (BMI), ΔR^2 = 0.103. In the third regression, adjusted future increased SBP levels was regressed on SBP responses to the mental arithmetic task; ΔR^2 = 0.055 (total model R^2 = 0.328). In brief, future SBP levels are best predicted by a model that includes baseline SBP, traditional risk factors and SBP reactions to the mental arithmetic task, accounting for 32.8% of the variance.



** $p < .01$, *** $p < .001$

Figure 5.2 Summary of pooled regression results relating SBP reactivity and the prediction of future SBP

Finally, regression models were re-run using alternate baselines as described and discussed in chapter 4. Results from the new regression analyses were very similar to those presented here; SBP responses to mental arithmetic task predicted future SBP, even after controlling for

baseline SBP activity and traditional risk factors (see appendix tables 5.2 and 5.3). There no other significant cardiovascular reactivity measures that predicted cardiovascular outcomes.

5.6 Discussion

The first aim for this study with Thai participants was to establish the protocol; this was consequently modified and used in the UK individuals, as described below. The second aim was to assess the patterning of cardiovascular responses to psychological stress tests in the Thai participants. As expected, the cold pressor task was associated with a vascular pattern of response, evidenced by larger TPR responses, whereas the mental arithmetic and speech tasks provoked a cardiac pattern of responding with larger CO and HR responses. The third aim was test whether cardiovascular responses to laboratory-based challenges are useful in predicting one-year follow-up BP among initially normotensive Thai participants. And the final study aim was to examine cardiovascular responses to laboratory stressors as predictors of changes in resting BP over a one year of follow-up independently of traditional risk factors of BP in healthy Thai adults. The results of this study support the Reactivity Hypothesis, which contends that cardiovascular reactions to acute psychological stress play a role in the development of hypertension or subsequent BP. However, only SBP responses to serial subtraction predicted follow-up SBP levels, after adjustment for baseline cardiovascular activity and traditional risk factors; they explained 5.5% of the variation of future SBP levels. In fact, the total regression model explained 32.8% of the variance of SBP after one-year follow-up. It is also noteworthy that none of the cardiovascular response measures to the speech or the cold pressor task were related to future SBP. Cardiovascular reactivity did not predict future DBP in the regression models.

5.6.1 Haemodynamic Reactions to Active Coping Tasks and Passive Coping Tasks

It has been noted that different types of psychological tasks provoke different patterns of haemodynamic response. In the current study, exposure to the cold pressor task was associated with a vascular pattern of response, evidenced by larger TPR responses, whereas the mental arithmetic and speech tasks provoked a cardiac pattern of responding with larger CO and HR responses, in a similar manner to the analyses of the slightly larger sample reported in chapter 4. These results are consistent with those reported by Sherwood, Davis, Dolan, and Light (1992), who examined cardiovascular responses during active and passive coping tasks. They found that patterns of response differed in the two types of coping

condition, with the active coping tasks being associated with relatively larger increases in BP, HR and CO and the passive coping conditions eliciting large changes in TPR while CO fell. These findings confirmed Hypotheses 1. Moreover, the current study suggests that Thai individuals respond to standardized mental stress tasks with large cardiovascular responses, and in a similar manner to Europeans and North Americans (see chapter 4 for a further discussion).

5.6.2 Haemodynamic Reactions to Active and Passive Coping Tasks and the Prediction of BP Over a One Year Period

The second hypothesis of the present study is that haemodynamic responses to both active and passive coping tasks will predict future BP. However, only SBP responses to mental arithmetic, an active coping task, predicted future SBP; cardiovascular responses to the passive coping task (cold pressor) were unrelated to future SBP or DBP. These findings contrast to those by Girdler et al. (1996) who found that SBP responses to a cold pressor were the best predictor of future SBP over two years in 40 normotensives, even after controlling for initial resting SBP, gender, and parental history of hypertension. The current findings accord with a larger study by Markovitz et al. (1998). They examined cardiovascular responses to video game, star tracing and cold pressor tasks in 3320 male and female participants. Only SBP responses to the video game task (an active coping task) were associated with increased SBP over a five-year period; cardiovascular reactions to the cold pressor (a passive coping task) did not predict future SBP. Further, Flaa et al. (2008) reported that SBP responses during stress explained 9.4% of the variance in follow-up BP; the effects were more marked when cardiovascular reactions to mental stressor (a mental arithmetic), rather than cold pressor, were used. Thus, the results from the current study accord with the larger studies that assessed cardiovascular responses to both active and passive coping tasks.

5.6.3 Haemodynamic Reactions to Multiple Tasks and Single Tasks and the Prediction of Future BP One Year Later

The final hypothesis of the present study is that haemodynamic responses to mulitple tasks will afford a better prediction of future BP one year later than haemodynamic reactions to single tasks. Aggregating physiological responses to multiple tasks of different types increases the reliability of the reactivity response and these aggregate responses have been found to be good predictor of future BP (Matthews et al., 1993; Moseley & Linden, 2006;

Tuomisto, Maiahalme, Kahonen, Fredrikson, & Turjanmaa, 2005). Those studies have found a strong positive relationship between the aggregated cardiovascular reactions and the prediction of future BP or hypertension status. However, the results in this study revealed aggregated cardiovascular did not predict follow-up resting BP. It should be noted that, most previous prospective studies (e.g., Moseley & Linden, 2006; Matthews et al., 1993) that used multiple tasks have combined responses to psychological and physical stressors; these may have elevated the predictive power of the aggregated responsivity measures because of the known relationship between exercise responses and hypertension (Palatini, 1998). In contrast, Tuomisto et al. (2005) aggregated responses to multiple psychological stressors but only aggregated responses within a particular task type, e.g., active coping tasks. Measures to active and passive coping tasks were aggregated in the present study, which may have reduced the reliability of the responsivity measures, particularly as haemodynamic responses to the cold pressor task were relatively modestly correlated to those elicited by the active coping tasks. However, Kamarck and Lovallo (2003) note that although aggregating across different types of psychological stressors or response may be conceptually problematic, frequently tasks evoke similar patterns of psychological effort and commensurate the central nervous system mediated changes in cardiovascular activation. Thus, for example, "It may not be meaningful to distinguish between "mental arithmetic reactivity" and "public speaking reactivity" under such circumstances" (page 11).

For haemodynamic reactivity, both CO and TPR responses to psychological stress tests were not significant predictors of follow-up BP levels. These findings are consistent with other studies that used haemodynamic reactivity (including, CO and TPR) to predict future BP. For example, Girdler et al. (1996) found that only SBP and HR reactivity significantly predicted BP levels at two-year follow-up; TPR and CO reactivity did not predict. Matthews et al. (2003) found that aggregated SBP, DBP, CO, and stroke volume responsivity across four tasks (reaction time, mirror tracing, cold pressor and stress interview tasks) predicted future BP over three years follow-up whereas aggregated TPR reactivity did not. Thus, although there are theoretical reasons to suspect that haemodynamic responses to stress may be good predictors of future BP, to date there is little empirical evidence to support this notion and the current study failed to offer any additional support.

5.7 Study Limitations

A few limitations of this study can be noted, which might have affected the results of the study. Firstly, the duration of the baseline resting periods was long (20 minutes resting), and the participants appeared to anticipate the upcoming task; BP levels rose in the final five minutes of the rest period. Therefore, to avoid increases in baseline cardiovascular activity, the initial resting period was modified from 20 minutes to 15 minutes in the UK study (chapter 6). Secondly, the order of the psychological stress tests was set (mental arithmetic followed by speech and cold pressor) and not randomized. Further, the results showed an upward drift in cardiovascular reactivity. Therefore, the ordering of the tasks might account for relationships with future BP; it might be that cardiovascular reactions to a first mental stress (regardless of test type) are predictive. To prevent the effects of the upward drift in cardiovascular reactivity and eliminate order effects, the protocols in the UK were changed from a fixed set of the psychological stress tests to randomise the order of the psychological stress tests. Thirdly, with respect to the tasks, the temperature of cold pressor test was changed from 2-3°C in the current study to 7°C in the UK study because some participants were unable to keep their hand in the water for two minutes, therefore the theshold time was too short (Wolf & Hardy 1941). In addition, the performance on the laboratory tasks might be associated with increased haemodynamic responses (Garcia-Leon, Paso, Robles, & Vila, 2003; Richter & Gendolla, 2006; Sherwood et al., 1992; Sherwood, Royal, & Light, 1993); task difficulty, and effort have been associated with heightened cardiovascular responses. Thus, self-reported perceived stress and performance scores were assessed in the UK participants after they completed all tasks. Further, at the follow-up period, individuals in the UK were asked to complete a self-administered life event stress scale (Holmes & Rahe, 1967). In addition, initial baseline was used to calculate the cardiovascular reactivity measures. There are multiple ways in which to calculate baseline and reactivity measures as discussed in chapter 4; regression models were re-run using alternate baselines as described and discussed in that chapter. Results from the new regression analyses were very similar to those presented here; only SBP responses to mental arithmetic task predicted future SBP, even after controlling for baseline SBP activity and traditional risk factors.

When the results of follow-up BP after one year are compared with initial resting BP, only DBP had increased significantly (by 4.41 mmHg). In contrast, SBP showed a more modest (and non-significant) increase (by 1.62 mmHg). Different BP monitors were used for initial

(Portapres) and follow-up (Dinamap) resting BP readings and the use of these different monitors may account for the differences in the changes in SBP and DBP. Several studies have found that oscillometric BP methods tend to underestimate SBP and overestimate DBP compared with intra-arterial measurements (Langewouters, Settels, Roelandt, & Wesseling, 1998; Manios et al., 2007; Umana, Ahmed, Fraley, & Alpert, 2006). Further, Dorlas et al. (1985) found that readings from the Finapres continuous BP monitor were 7 mmHg higher for SBP and 9mmHg lower for DBP, compared to the oscillometric method (Dinamap). In addition, Epstein, Huffnagle, and Bartkowski (1991) found that the there was no significantly difference in SBP from Finapres and Dinamap monitors but DBP values from the Dinamap monitor were higher than from the Finapres monitor. Although values between the two types of BP correlate strongly (Kawahara, 1990), using the same BP monitor would allow more accurate determination of change in resting BP over time; the same BP monitor was used to assess resting BP in the UK study.

Another factor that might explain the increases in DBP is white coat hypertension. White coat hypertension is defined as BP values that are higher than normal when measured in the medical environment (average daytime BP by 24-hour ambulatory BP is SBP < 135 mmHg and/ or DBP < 85 mmHg, while office BP is SBP ≥ 140 mmHg and/ or DBP ≥ 90 mmHg; Celis & Fagard, 2004). In Thailand, the prevalence of white coat hypertension is approximately 20% among mild hypertensive (Sermswan, Uboldejpracharak, Suthichaiyakul, Sukontasarn, & Buranakitcharoen, 2002). Therefore the measurement of BP at follow-up (using the oscillometric method) may be subject to overestimation due to the effects of white coat hypertension.

Further, Thailand was subject to a natural disaster between baseline and follow-up assessment. Thailand floods occurred during the 2011 from July to December. Further, severe flooding zones occurred in 65 of Thailand's 77 provinces and damage was widespread and severe in many locations including Rangsit Campus of Thammasat University in Pathum Thani province (Aon Benfield, 2012) where the study took place. Accordingly, participants' follow-up BP was assessed within two months of the flood. Much research suggests that exposure to traumatic stress events may contribute to high BP, both chronically and acutely. For example, a meta-analysis of 34 studies indicated that participants who were diagnosed with posttraumatic stress disease had higher resting baseline BP than individuals without a

posttraumatic stress disease diagnosis; additionally, posttraumatic stress disease was associated with elevation in BP over time (Buckley & Kaloupek, 2001). Many research studies have also suggested that exposure to trauma is associated elevated BP levels and increased cardiovascular responses to stress (Bryant, Harvey, Guthrie, & Moulds, 2000; Buckley, Holohan, Greif, Bedard, & Suvak, 2004; Forneris, Betterfield, & Bosworth, 2004; Gerin, et al., 2005; Low, Salomon, & Matthews, 2009; Shalev et al., 1998). For example, Gerin et al. (2005) assessed the impact of the 11 September 2001 (9/11) attacks in New York City before and after the events in the different sites in the USA. They found BP was increased in the two months after the 9/11 attack compared with the two months before 9/11. Therefore the effects of stressful life events (Holmes & Rahe, 1967) on cardiovascular responses and subsequent BP levels were examined in the UK study. It is hypothesized that higher levels of life events would predict higher BP levels after one year, both as a main effect and in interaction with cardiovascular reactivity.

5.8 Value of Study and Future Direction

Despite the limitations noted previously, the study extends previous research that has been completed in European or North American countries; BP reactivity significantly improved prediction models of future BP in a Thai sample. Through such investigation methods, vulnerable Thai participants may be more easily identified and directed toward appropriate screening. In addition, in the hierarchical regression models of the prediction of future SBP levels, the study found that of the conventional risk factors included in regression models, BMI was a significant positive predictor of future SBP. Previous studies have reported that BMI is an importance risk factor for hypertension status (Chiang, Perlman, & Epstein, 1969; Gelber, Gaziano, Manson, Buring, & Seeso, 2007; Havlik, Hubert, Fabsitz, & Feinleib, 1983; Kotsis, Stabouli, Papakatsika, Rizos, & Parati, 2010; Narkiewicz, 2006; Skarfors, Lithell, & Selinus, 1991). It is also well know that baseline SBP and DBP are the strongest predictors of future hypertension (Leitschuh, Cupples, Kannel, Gagnon, & Chobanian, 1991). For instance, Yong, Kuller, Rutan, and Bunker (1993) examined the BP changes in 202 males and females in a high school. They found that initial resting BP and BMI are predictive of BP changes over 30 years follow-up. Therefore, the association between BMI and future BP should be a considered in future studies examining the contribution of new or purported risk factors including cardiovascular reactivity. In addition, future research should examine the role of cardiovascular responses to acute psychological stressors in the prediction of future BP in

non-Western samples. In the current study 5.5% of the variability in future SBP was accounted for by SBP reactivity; a contribution similar to the 2 to 12% found in previous Western studies (e.g., Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Light et al., 1999; Light, Dolan, Davis, & Sherwood, 1992; Matthews et al., 1993; Newman, McGarvey, & Steele, 1999). Although this was smaller contribution than the combined traditional risk factor contribution, which accounted for 10.3% of the variability, it was similar to the contribution from BMI (7.9%) both in the current study and in previous studies (Gelber et al., 2007; Hajjar & Kotchen 2003). In Thailand, Lwin-Mm-Khin, Tassanee, Oranut, and Chaweewon (2011) reported that obesity (BMI $\geq$ 30 kg/m^2) was a significant risk factor for hypertension (odds ratio = 7.42, 95% CI = 1.68-32.87) after adjusting for the effect of other variables using multivariate logistic regression. Thus, SBP reactivity may be a clinically important risk factor for hypertension in the Thai population.

5.9 Conclusion

In conclusion, the findings support the hypothesis that cardiovascular responses to psychological stress tests have implications for the development of future BP. In addition, SBP reactions to mental arithmetic were the best predictor of future SBP. In the next chapter a prospective cohort study was conducted in healthy UK participants. In the UK study, the protocol was modified and focused on life stress events, in addition to reactivity, and the prediction of future BP.

CHAPTER 6

Cardiovascular Responses to Acute Psychological Stressors and the Prediction of Future Blood Pressure: A Prospective Longitudinal Study in the United Kingdom

In the previous chapter (chapter 5) results from a prospective study completed in Thailand were presented and discussed. The findings offered some support for the Reactivity Hypothesis; SBP reactions to mental arithmetic predicted future SBP in the Thai participants. However, there were a number of weaknesses within the study, including a non-random task order and anticipation during the rest period. Further, measures of performance, perceived stress, and pain were not taken. Measures of life stress were not included in that study and more recent versions of the Reactivity Hypothesis have suggested that cardiovascular reactivity may play a causal role in the development of hypertension in combination with life stress and hassles (Light et al., 1999; Linden & Feuerstein, 1983; Pike et al., 1997; Vermeersch, T'Sjoen, Kaufman, Vincke, & Bracke, 2010). Accordingly, a second prospective study was completed in the UK taking these weaknesses and limitations into account.

6.1 Introduction

Over the past few decades, cardiovascular responses to mental stress test have been linked to a broad range of CVD outcomes, including BP levels. According to a review by Gerin (2000; detailed in chapter 1), the way in which cardiovascular reactivity is linked to hypertension has changed conceptually from the earliest prospective studies that were completed in the 1930s. In the earliest studies cardiovascular reactivity was conceived as a marker of future hypertension (Hines & Brown, 1932, 1936); it was proposed that people who had the largest cardiovascular responses to mental stress test would be most likely to develop hypertension. In addition, this model of cardiovascular reactivity was viewed as a person-based trait; the type of mental stress test was not perceived to be important. Later models suggested that cardiovascular reactivity may play a causal role in the development of hypertension. The casual model of cardiovascular reactivity posits that the nature of the eliciting stimulus (active and passive coping tasks) is a determinant of the cardiovascular responses. Further, this model focuses on dimensions of the situation that may elicit larger or exaggerated cardiovascular responses. For example, Flaa, Eide, Kjedsen, and Rostrup (2008) examined whether cardiovascular responses to mental arithmetic (an active coping task) and cold

pressor (a passive coping task) predicted future SBP after 18 years follow-up. SBP responses to the active coping task (mental arithmetic) were a better predictor of future BP than SBP responses to the passive coping task (cold pressor). More recently, cardiovascular reactivity research has used a person-by-situation interaction model. For example, Light et al. (1999) found that the interactive effects of cardiovascular responsivity over two tasks (cold pressor and reaction time tasks) with positive versus negative family history of hypertension (a person factor) and with subjective rating of daily stress levels (a situation factor) predicted future BP levels in young men after a ten year of follow-up. They found that men with the highest future BP levels had high stress reactivity, a family history of hypertension and high levels of daily stress. Therefore, the present study posited that cardiovascular reactivity may play a causal role in the development of hypertension in combination with high levels of stress.

However, cardiovascular reactivity may not be independent of background stress, be it chronic stress, life events or daily hassles. Stressful life events have been associated with cardiovascular reactivity but the relationship has been inconsistent (Carroll, Phillips, Ring, Der, & Hunt, 2005; Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012; Low, Salomon, & Matthews, 2009; Musante et al., 2000). Some studies have observed increased cardiovascular reactivity in participants exposed to life stress events (Lepore, Miles, & levy, 1997; Matthews, Gump, Black, & Allen, 1997; McEwen & Stellar, 1993). For example, Lepore et al. (1997) found that the number of life stressors lasting nine or more months was positively related to SBP, DBP and HR reactivity over two tasks (mental arithmetic and speech tasks) in 150 participants; the number of episodic stressors (number of stressors lasting less than one month) and intermediate stressors (number of stressors lasting one to eight months) was not related to cardiovascular reactivity. Other studies have reported a negative relationship between chronic stress and cardiovascular reactivity (Jorgensen & Houston, 1989; Matthews, Gump, & Owens, 2001; Phillips, Carroll, Ring, Sweeting, & West, 2005). For example, Matthews et al. (2001) found that participants who reported high levels of chronic stress had lower SBP responsivity to mental arithmetic and public speaking tasks than those reporting low chronic stress levels. Similarly, Phillips et al. (2005) found that cardiovascular reactions to the PASAT were negatively associated with the frequency of exposure to life events during the past 12 months in 608 participants. Finally, some studies report that there is no relationship between chronic stress and cardiovascular reactivity (Cacioppo et al., 2000; Roy, Steptoe, & Kirschbaum, 1998; Vingerhoets, Ratliff-Crain, Jabaaij, Menges, & Baum, 1996).

For example, Roy et al. (2000) found that impact of life events within the past 12 months was not associated with cardiovascular reactivity in firefighters, except in combination with social support. Given these discrepancies, the relationship between cardiovascular reactivity and life events was assessed in the current study.

6.2 Purpose of the Study

The present study had three objectives. The first objective was to assess the patterning of cardiovascular responses to mental stress tests (i.e., a mental arithmetic task, a speech task, and a cold pressor task) in healthy adults in the UK who completed initial and follow-up assessment sessions. The second objective was to examine whether cardiovascular reactivity predicted changes in resting BP over a one year period, after controlling for baseline cardiovascular activity and traditional risk factors. The final objective was to examine whether life events were related to cardiovascular reactivity and whether they moderated the relationships between cardiovascular reactivity and future BP.

The following specific hypotheses of study were tested:

1) Haemodynamic reactions to active and passive coping tasks (i.e., mental arithemetic, speech, and cold presor tasks) will predict future BP in the UK participants over a one year period.
2) Aggregated haemodynamic responsitivity to multiple tasks will afford a better prediction of future BP one year later than haemodynamic reactions to single tasks in healthy UK participants.
3) Stressful life events will be associated with cardiovascular reactivity.
4) Stressful life events will moderate the prediction of future BP by cardiovascular reactivity.

Therefore, the present study was designed to clarify relationships between cardiovascular reactions to mental stressors and future BP.

6.3 Materials and Method

The method of this study is described in detail in chapter 3; it was similar to the method of the Thai study (see chapter 5) that was used to establish the protocol and ensure that cardiovascular responses could be consistently assessed. Differences between the two protocols are highlighted below.

The inclusion and exclusion criteria in chapter 3 were administrated. In brief, all participants were asked to complete a questionnaire on demographic and medical history information, including information of parental history of CVD. The participants were then connected to the Portapres continuous BP at left 3rd and 4th fingers to assess haemodynamic activity, and resting BP was measured using an automated BP monitor (Omron® M6 Comfort BP monitor (HEM-7211)) on the right arm. Initial baseline haemodynamic activity was recorded for 15 minutes. A set of psychological stressors whose order was randomized, were completed. The temperature of the cold pressor task was increased from 2-3°C to 7°C in this study. Performance scores on the mental arithmetic and pain tolerance were recorded during these tasks. After all tasks, each participant was asked to complete a post-test questionnaire assessing perceived stress in each task. One year later, participants were invited to return to re-evaluate resting BP (three readings at minutes 5, 9 and 13 of a rest period) using the same Omron BP monitor used during initial assessment. In addition, participants completed a life stress events questionnaire (Holmes & Rahe, 1967). A flowchart of the summarized procedures is displayed in figure 6.1.

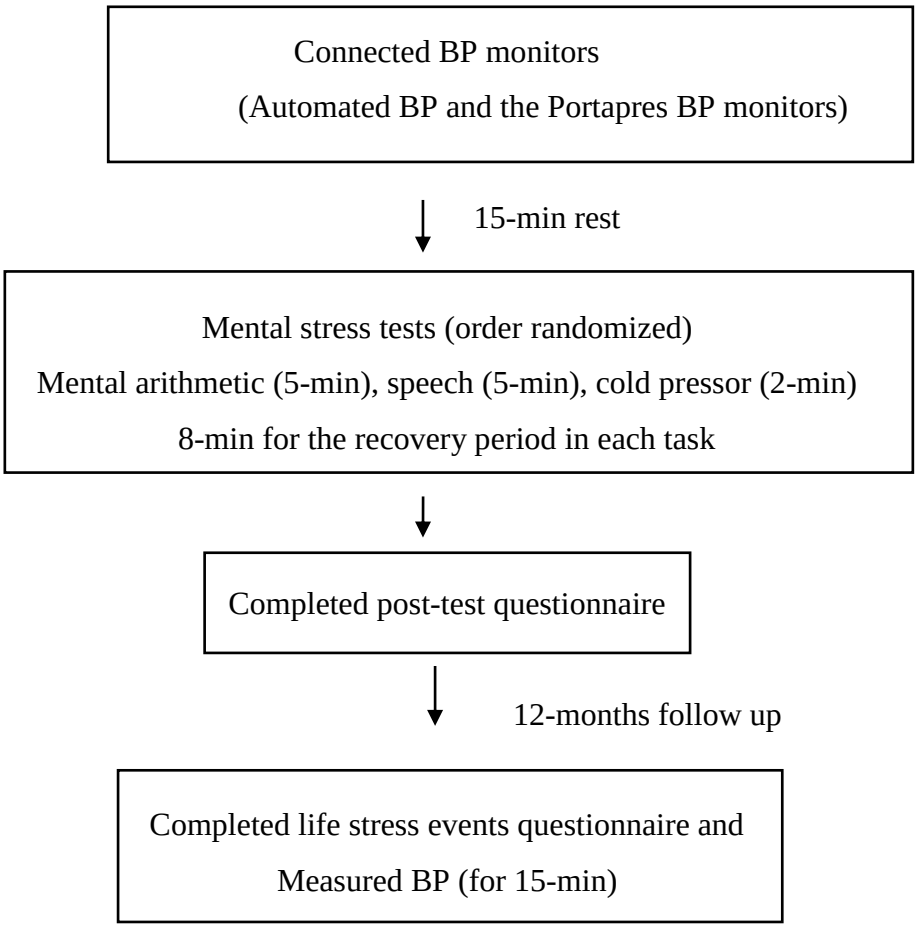


Figure 6.1 Summary of experimental protocol in the UK

6.4 Data Analysis

6.4.1 Data Reduction

Resting haemodynamic parameters (HR, CO, and TPR) were created by averaging data from minute 5 to minute 13 of the resting period. In addition, Resting BP activity was created by averaging data from the three readings (minutes 5, 9, and 13) during resting period. Cardiovascular reactivity scores were computed by subtracting resting values (baseline minute 5 to minute 13) from the average task values (Girdler et al., 1996; Hughes & Stoney, 2000). Follow-up resting BP was created by averaging the three BP readings (minutes 5, 9, and 13).

6.4.2 Statistics Analysis

A total of 124 UK participants were recruited for the initial testing session; 97 participants returned for follow-up (78.23% follow-up). However, 15 individuals whose data contained outliers (±2 SD from the mean) and five participants who were taking antihypertensive medications were removed from the analyses. Therefore, analysis was based on 104 participants at entry and 77 at follow-up. Data were analyzed using the statistical package SPSS version 19.0 for Windows.

Independent samples *t*-tests or Mann-Whitney tests were used to indicate whether participants who attended the follow-up differed from eligible nonparticipants. Paired samples *t*-tests were performed to analyze possible changes in continuous variables (e.g., BP) from entry to follow-up. To evaluate the effectiveness of three laboratory stressors for eliciting cardiovascular reactivity, one-way repeated measures ANOVAs were conducted.

To measure intertask relationships between reactivity measures, Pearson correlations coefficients were calculated between all pairs of cardiovascular responses to tasks. Further, Pearson correlations were calculated to examine correlations between future resting BP levels and traditional risk factors of CVD (i.e., age, sex, current cigarette smoking status, family history of CVD status, and BMI), performance scores on the mental arithmetic task, self-reported perceived stress, pain tolerance to the cold pressor task, and life stress events, and future resting BP levels. In addition, the relationships between cardiovascular reactivity and the stressful life events were examined.

To evaluate the utility of cardiovascular reactivity for predicting future BP, a series of hierarchical liner regression analyses for follow-up resting future SBP and DBP were performed. Regression analyses were conducted to determine the unique contribution of cardiovascular reactivity to the prediction of follow-up resting BP after adjustment for baseline cardiovascular activity and traditional risk factors (e.g., initial resting cardiovascular parameters, initial BMI, initial age, gender, family history of CVD status, and current cigarette smoking status) and self-reported perceived stress, performance scores on mental arithmetic or pain tolerance to cold pressor. Therefore, the hierarchical linear regression analyses of future BP assessed the predictive power of resting cardiovascular measurements (model one); the traditional risk factors of sex, age, BMI, parental history of CVD status, and current cigarette smoking status (model two); performance scores on the mental arithmetic task, pain tolerance to the cold pressor task, and self-reported perceived stress at entry (model three); and the cardiovascular responses during psychological stressors (model four).

Moderator analysis was undertaken to determine whether the associations between cardiovascular reactivity and future BP were moderated by stressful life events. Cross-product terms (using z-scores) were used to test two-way interactions in each model. Accordingly, the mean baseline of cardiovascular parameter value was entered first; traditional risk factors, self-reported perceived stress, and performance scores were entered at step two and step three; at step four, cardiovascular reactivity, and life stress events were entered. Finally, the interaction (multiplicative) term of the moderator (life stress events) X cardiovascular reactivity was entered at step five.

6.5 Results

6.5.1 Demographic and Cardiovascular Characteristics of Stress Responses

Characteristics of the participants at baseline and follow-up are shown in table 6.1. A total of 104 eligible participants participated in the initial examination; they were aged 32.61 ±11.80 years (range 18-63 years). Seventy-seven eligible individuals (74.04 %) attended follow-up. The duration of follow-up was on average 10.22 months (SD = 1.91). Participants reported a relatively low level of stress (mean ± SD = 111.13 ± 73.57), compared to the cut point score of 150 for chance of suffering from stress as defined by Holmes & Rahe (1967). A comparison of eligible participants who did or did not participate in follow-up revealed no significant differences in gender, age, current cigarette smoking status, family history of CVD, BMI, initial resting cardiovascular values, and cardiovascular reactivity ($p > .05$), with

two exceptions. Nonparticipants had higher CO responses to the cold pressor task (mean ± SD = 0.69 ± 0.85 vs. 0.24 ± 0.93; t (102) = 2.24, p =.027) and lower TPR responses to the cold pressor task (mean ± SD = 87.13 ± 94.84 vs. 161.86 ± 205.98; (t (95) = -2.51, p = .014) than participants who attended follow-up (see appendix table 6.1).

Paired-samples t tests revealed that none of resting SBP and resting DBP was significantly increased over ten months of follow-up (p > .05).

Table 6.1 Descriptive of the individuals at entry and after ten months of follow-up (n = 77)

Characteristic	N	%	Mean	SD
Sex				
- Male	34	44.16		
- Female	43	55.84		
Ethnicity				
- White	37	48.05		
- Mixed/multiple ethnicity	3	3.90		
- Asian	25	32.47		
- Black/African	7	9.09		
- Other ethnicity (e.g., Arab)	5	6.49		
Family history of CVD status	26	33.77		
Current cigarette smoking status	22	28.57		
Performance scores on mental arithmetic			23.42	14.95
Pain tolerance of cold pressor (seconds)			86.85	40.71
Self-reported perceived stress				
- Mental arithmetic			6.18	2.49
- Speech			5.30	2.58
- Cold pressor			6.39	3.15
Total life stressful events			111.13	73.57
Age at initial (years)			32.61	11.80
BMI at initial study (kg/m^2)			24.97	4.75
SBP at initial test (mmHg)			115.57	12.57
DBP at initial test (mmHg)			65.87	8.06
SBP at follow-up session (mmHg)			113.71	12.56
DBP at follow-up session (mmHg)			66.77	8.12

6.5.2 Haemodynamic Patterns of Cardiovascular Reactions to Mental Stress Tests

The patterns of cardiovascular reactions to psychological stressors were described in chapter 4. Briefly, in the UK individuals who participated in both the initial and follow-up sessions, the cold pressor task elicited higher BP and TPR reactions than mental arithmetic and speech, whereas the mental arithmetic task and the speech task provoked the greater HR reactions than the cold pressor task (see tables 6.2 and 6.3).

Table 6.2 Baseline and task cardiovascular activity in the UK participants who participated in the initial and follow-up sessions (n = 77)

	The mental arithmetic task (mean ± SD)	**The speech task** (mean ± SD)	**The cold pressor task** (mean ± SD)
SBP			
Baseline (mmHg)	106.97 ± 14.68	106.97 ± 14.68	106.97 ± 14.68
Task (mmHg)	121.63 ±19.44	125.17 ± 19.81	132.08 ± 19.55
t -test (76)	-12.35***	-13.58 ***	-16.96***
DBP			
Baseline (mmHg)	56.91 ± 10.14	56.91 ± 10.14	56.91 ± 10.14
Task (mmHg)	66.88 ± 12.41	68.09 ± 11.43	71.24 ± 12.94
t -test (76)	-13.30***	-15.32 ***	-15.62***
HR			
Baseline (bpm)	77.02 ± 10.64	77.02 ± 10.64	77.02 ± 10.64
Task (bpm)	82.42 ± 11.19	82.47 ± 11.28	80.66 ± 11.24
t -test (76)	-8.66***	-7.27 ***	-5.88***
CO			
Baseline (l/min)	6.08 ± 1.37	6.08 ± 1.37	6.08 ± 1.37
Task (l/min)	6.44 ± 1.33	6.52 ± 1.30	6.32 ± 1.13
t -test (76)	-3.76***	-4.77 ***	-2.23*
TPR			
Baseline (dyne-sec.cm-^{5})	770.44 ± 161.31	770.44 ± 161.31	770.44 ± 161.31
Task (dyne-sec.cm-^{5})	842.96 ± 187.33	854.80 ± 216.86	932.30 ± 248.95
t -test (76)	-4.33***	-5.32 ***	-6.90***

* $p < .05$, *** $p < .001$

Table 6.3 A comparison of cardiovascular reactivity (change) scores in the UK participants who completed initial and follow-up sessions (n = 77)

	The mental arithmetic task (mean ± SD)	**The speech task (mean ± SD)**	**The cold pressor task (mean ± SD)**
SBP responses (mmHg)	14.65 ± 10.41 ^{a***,c*}	18.20 ± 1176 ^{b***,c*}	25.11 ± 12.99 ^{a***,b***}
DBP responses (mmHg)	9.97 ± 6.58 ^{a***}	11.18 ± 6.40 ^{b**}	14.33 ± 78.05 ^{a***,b**}
HR responses (bpm)	5.39 ± 5.46 ^{b*}	5.45 ± 6.58 ^{a*}	3.64 ± 5.43 ^{a*,b*}
CO responses (l/m)	0.36 ± 0.85	0.44 ± 0.80 $^{a+}$	0.24 ± 0.93 $^{a+}$
TPR responses (dyne-sec.cm-^{5})	72.53 ± 147.13 ^{a**}	84.36± 139.26 ^{b**}	161.86 ± 205.98 ^{a**,b**}

$^{a, b, c}$ significant mean differences

$^{+}$ $p < .1$, * $p < .05$, ** $p < .01$, $^{***}p < .001$

To determine whether responses to the three mental stress tasks were correlated with one another, intertask correlations based on the haemodynamic responses were computed; these coefficients are displayed in table 6.4. The majority of intertask correlation coefficients were significant; DBP reactions to the cold pressor were not related to DBP reactions to the mental arithmetic task.

Table 6.4 Intertask correlations for cardiovascular reactivity in the UK participants who participated in the initial and follow-up sessions (n = 77)

Variable	**Speech**	**Cold pressor**
SBP		
Mental arithmetic	0.494***	0.249*
Speech		0.407**
DBP		
Mental arithmetic	0.438***	0.173
Speech		0.283**
HR		
Mental arithmetic	0.657***	0.369**
Speech		0.454***
CO		
Mental arithmetic	0.591***	0.494***
Speech		0.597***
TPR		
Mental arithmetic	0.394***	0.308**
Speech		0.325**

$^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

6.5.3 Correlations of Traditional Risk Factors and Future BP

Attention then focused on relationships between traditional risk factors and BP in order to assess which variables might serve as covariates in subsequent regression models. Bivariate correlation analyses were computed between follow-up BP and traditional risk factors (age, gender, BMI, current cigarette smoking status, and family history of CVD), mediator variables (performance, pain tolerance to cold pressor task, and perceived stress), and stressful life events (see table 6.5). Analysis of the correlation reveled that follow-up SBP was significantly associated with male gender and positive family history of CVD. Follow-up DBP was associated with older age, male gender, and positive family history of CVD. With respect to mediator variables, only self-reported perceived speech stress was negatively associated with follow-up DBP levels. The stressful life events scores were also negatively associated with follow-up DBP levels but not SBP levels. Initial resting BP and CO activity were significantly associated with SBP at follow-up. In addition, the initial resting BP and TPR activity were related to follow-up DBP levels. Accordingly, these variables were included in step one, step two, and step three of the predictive regression models of future BP, respectively.

Table 6.5 Point-biserial and bivariate correlations between traditional risk factors at initial session, and BP at ten months follow-up in the UK participants who participated in the initial and follow-up sessions (n = 77)

Variable	**Follow-up**			
	Resting SBP	*p* - value	Resting DBP	*p*-value
Age	0.132	.253	**0.294**	**.009**
Gender [a]	**-0.380**	**.001**	**-0.375**	**.001**
Current cigarette smoking status [b]	-0.111	.335	0.192	.095
Family history of CVD status [c]	**0.286**	**.012**	**0.259**	**.023**
BMI	0.106	.361	0.222	.053
Mediator variable				
Performance scores on mental arithmetic	-0.009	.936	0.199	.082
Pain tolerance to cold pressor	-0.058	.616	0.074	.523
Self-reported perceived stress				
- Mental arithmetic	-0.179	.093	-0.188	.103
- Speech	-0.163	.160	**-0.292**	**.011**
- Cold pressor	0.023	.840	-0.031	.792
Total life events	-0.197	.085	**-0.385**	**.001**
Baseline cardiovascular parameter				
SBP	**0.538**	**< .001**	**0.616**	**< .001**
DBP	**0.578**	**< .001**	**0.824**	**< .001**
HR	0.028	.812	0.045	.694
CO	**0.243**	**.034**	0.180	.117
TPR	0.174	.129	**0.267**	**.019**

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

Next, bivariate correlations between cardiovascular reactions to mental stress tests and resting SBP and DBP at follow-up were calculated; these are presented in table 6.6. SBP at follow-up was a significantly positively related to SBP responses to the mental arithmetic task and aggregated SBP responsivity over the three tasks. In addition, SBP responses to the mental arithmetic task were associated with future DBP levels. Consequently, these cardiovascular reactivity measures were included at step four of the predictive regression models (along with baseline cardiovascular measures in step one, traditional risk factors in step two, or/and mediator variable in step three and stressful life events in step four where these were potential predictors).

Table 6.6 Bivariate correlations between haemodynamic responses and resting SBP and DBP at follow-up after ten months follow-up in the UK participants who participated in the initial and follow-up sessions (n = 77)

Variable	Follow-up			
	Resting SBP	*p* - value	Resting DBP	*p*-value
The mental arithmetic task				
Δ SBP	**0.370**	**.001**	**0.258**	**.023**
Δ DBP	0.180	.118	0.101	.384
Δ HR	0.180	.078	0.013	.909
Δ CO	0.202	.686	0.037	.747
Δ TPR	-0.047	.217	-0.015	.899
The speech task				
Δ SBP	0.142	.217	0.092	.428
Δ DBP	0.049	.670	-0.007	.950
Δ HR	0.194	.091	0.031	.789
Δ CO	-0.020	.861	-0.076	.510
Δ TPR	0.058	.614	0.051	.658
The cold pressor task				
Δ SBP	0.115	.321	0.085	.464
Δ DBP	0.049	.673	-0.003	.979
Δ HR	0.166	.150	0.021	.853
Δ CO	-0.033	.778	-0.026	.822
Δ TPR	0.183	.111	0.067	.565
Aggregate responsivity				
SBP	**0.269**	**.018**	0.186	.104
DBP	0.126	.273	0.041	.725
HR	0.221	.053	0.027	.815
CO	0.060	.604	-0.024	.833
TPR	0.090	.438	0.047	.688

Δ, responses

6.5.4 Correlations of Stressful Life Events and Cardiovascular Reactivity

In order to test Hypothesis 3, the relationships between cardiovascular reactivity and stressful life events were examined (see table 6.7). Participants who reported high stressful life events showed smaller increases in SBP, DBP and HR reactions to mental arithmetic. Thus, SBP, DBP, and HR responses to the mental arithmetic task were included in the hierarchical liner

regression models. There were no relationships between stressful life events and cardiovascular responses to cold pressor or the speech task.

Table 6.7 Pearson correlations coefficients between life events and cardiovascular reactivity in the UK participants who participated in the initial and follow-up sessions (n = 77)

Cardiovascular reactivity	**Stressful life events**	
	Correlation *r*	*p*-values
The mental arithmetic task		
- SBP	**-0.293**	**.010**
- DBP	**-0.230**	**.044**
- HR	**-0.236**	**.038**
- CO	-0.064	.578
- TPR	0.139	.228
The speech task		
- SBP	-0.120	.300
- DBP	-0.134	.244
- HR	-0.141	.221
- CO	0.020	.864
- TPR	-0.008	.947
The cold pressor task		
- SBP	0.002	.989
- DBP	-0.102	.378
- HR	0.053	.644
- CO	0.152	.186
- TPR	-0.110	.339

6.5.5 Prediction of Longitudinal Changes in SBP Over Ten Months Later

The study then focused on whether cardiovascular reactivity predicts follow-up BP. A series of hierarchical regression analyses were performed to determine the contribution of cardiovascular reactivity to the prediction of follow-up resting SBP. At Step one, initial resting cardiovascular parameters were entered into the regression model. Cardiovascular reactivity to acute psychological stress was entered into the regression model at step two if those cardiovascular reactions were significantly associated with future BP in bivariate analyses. Therefore, SBP responses to mental arithmetic and aggregated SBP responsiveness (over the three tasks) were included in regression models predicting future SBP levels.

As can be seen in table 6.8, initial baseline SBP entered at step one accounted for 28.9% of the variance in follow-up SBP. SBP responses to the mental arithmetic task accounted for an additional 5.8% of the variance in follow-up SBP (β = 0.249, SE = 0.117; p =.013). By comparison, aggregated SBP responsivity to the predictor model resulted in smaller increases in R^2 with values equivalent to only 2.7% of the variance of follow-up SBP (β = 0.167, SE = 1.682; p =.094); however, the prediction of follow-up SBP did not reach the conventional criteria ($p < .05$; see table 6.9).

Table 6.8 Results of hierarchical linear regression analyses predicting future SBP from baseline resting SBP activity and SBP responses to mental arithmetic data in the UK participants who participated in the initial and follow-up sessions (n = 77)

Regression model	*B*	*β*	*T*	R^2	*F*	Δ R^2	Δ *F*
10 months SBP							
Step 1				0.289	30.518***	0.289	30.518***
Baseline SBP	0.538	0.538	5.524***				
Step 2				0.347	19.658***	0.058	6.542*
SBP responses to MA	0.300	0.249	2.558*				

MA, mental arithmetic

*$p < .05$, ***$p < .001$

Table 6.9 Results of hierarchical linear regression analyses predicting future SBP from baseline resting SBP activity and aggregated SBP responsivity over three tasks data in the UK participants who participated in the initial and follow-up sessions (n = 77)

Regression model	*B*	*β*	*T*	R^2	*F*	Δ R^2	Δ *F*
10 months SBP							
Step 1				0.289	30.518***	0.289	30.518***
Baseline SBP	0.538	0.538	5.524***				
Step 2				0.316	17.083***	0.027	2.881+
Aggregated SBP responsivity	2.855	0.167	1.697+				

+ $p < .1$, *** $p < .001$

In the next hierarchical regression model used to predict future SBP, five traditional risk factors (age, sex, BMI, current cigarette smoking status, and family history of CVD), and mediator variables (i.e., performance scores, pain tolerance, and self-reported perceived stress) included in initial steps in order to determine the independent effects of cardiovascular reactivity. Thus, at step one, baseline cardiovascular activity was included, at step two

traditional risk factors (i.e., initial age, initial BMI, sex, initial current cigarette smoking status, and family history of CVD) were entered, and then SBP reactivity or aggregate cardiovascular responsivity were entered at step three. These findings are presented tables 6.10 and 6.11.

As can be seen in table 6.10, initial baseline SBP activity predict future SBP, accounting for 28.9%. The traditional risk factors accounted for an additional 12.5% of the variance; sex and family history of CVD were significantly related to follow-up SBP. At step three, SBP responses to the mental arithmetic task accounted for an additional 4.5% of the variance (β = 0.113, SE = 0.224; p =.020); all predictors together accounting for 45.9% of the variance in follow-up SBP levels. By comparison, aggregated SBP responsivity did not independently predict follow-up SBP.

Table 6.10 Results of hierarchical linear regression analyses predicting ten months SBP from baseline resting SBP activity, traditional risk factors, and SBP responses to mental arithmetic data in the UK participants who participated in the initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months SBP							
Step 1				0.289	30.518***	0.289	30.518***
Baseline SBP	0.538	0.538	5.524***				
Step 2				0.414	8.253***	0.125	2.990*
Sex [a]	-7.287	-0.290	-2.554*				
Age	-0.114	-0.107	-1.054				
BMI	-0.274	-0.103	-0.899				
FH [b]	5.715	0.217	2.311*				
Smoking [c]	-5.097	-0.184	-1.850+				
Step 3				0.459	8.364***	0.045	5.703*
SBP responses to MA	0.270	0.224	2.388*				

FH, family history of CVD; MA, mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

+ p <.1, * p <.05, *** p <.001

Table 6.11 Results of hierarchical linear regression analyses predicting ten months SBP from baseline resting SBP activity, traditional risk factors, and aggregated SBP responsivity over three tasks data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months SBP							
Step 1				0.289	30.518^{***}	0.289	30.518^{***}
Baseline SBP	0.538	0.538	5.524^{***}				
Step 2				0.414	8.253^{***}	0.125	2.990^{*}
Sex [a]	-7.287	-0.290	-2.554^{*}				
Age	-0.114	-0.107	-1.054				
BMI	-0.274	-0.103	-0.899				
FH [b]	5.715	0.217	2.311^{*}				
Smoking [c]	-5.097	-0.184	-1.850^{+}				
Step 3				0.434	7.555^{***}	0.020	2.388
Aggregated SBP responsivity	2.487	0.145	1.545				

FH, family history of CVD

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

$^{+}$ p <.1, * p <.05, *** p <.001

In addition, the present study examined whether mediator variables (self-reported perceived stress, performance scores, and pain tolerance) altered the relationships between cardiovascular activity and future BP. Consequently, baseline cardiovascular activity was entered in step one, the traditional risk factor were entered in step two, and mediator variables were entered in step three. Cardiovascular reactivity was entered in step four. As can be seen in table 6.12, the mediator variables entered at step three were not significantly related to follow-up SBP. At step four, SBP responses to the mental arithmetic task accounted for an additional 4.7% of the variance (β = 0.235, SE = 0.114; p =.016), similar to the proportion of variance accounted for in the model without the mediator variables (4.5%; see table 6.10).

Table 6.12 Results of hierarchical linear regression analyses predicting ten months SBP from baseline resting SBP activity, traditional risk factors, performance, self-reported perceived stress and SBP responses to mental arithmetic data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months SBP							
Step 1				0.289	30.518***	0.289	30.518***
Baseline SBP	0.538	0.538	5.524***				
Step 2				0.414	8.253***	0.125	2.990*
Sex [a]	-7.287	-0.290	-2.554*				
Age	-0.114	-0.107	-1.054				
BMI	-0.274	-0.103	-0.899				
FH [b]	5.715	0.217	2.311*				
Smoking [c]	-5.097	-0.184	-1.850+				
Step 3				0.446	6.840***	0.032	1.937
Performance scores	-0.171	-0.203	-1.795+				
Self-reported perceived stress	-0.847	-0.168	-1.510				
Step 4				0.492	7.224***	0.047	6.151*
SBP responses to MA	0.283	0.235	2.480*				

FH, family history of CVD; MA, mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

+ p <.1, * p <.05, *** p <.001

In summary, these results suggest that SBP responses to mental arithmetic have predict follow-up SBP over ten months above and beyond that of traditional risk factors or/and mediator variables (i.e., performance scores and self-reported perceived stress), albeit modestly.

6.5.6 Prediction of Longitudinal Changes in DBP after Ten Months

A similar series of hierarchical regression analyses were conducted to determine the contribution of cardiovascular reactivity to the prediction of follow-up resting DBP. As shown in table 6.6, only SBP responses to the mental arithmetic task were associated with future DBP. Therefore, SBP responses to the mental arithmetic task were entered in step two. However, in the hierarchical regression analysis, SBP responses to the mental arithmetic task did not improve the prediction of future DBP (see tables 6.13, 6.14, and 6.15).

Table 6.13 Results of hierarchical linear regression analyses predicting ten months DBP from baseline resting DBP activity, traditional risk factors and SBP responses to mental arithmetic data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months DBP							
Step 1				0.678	158.060***	0.678	158.060***
Baseline DBP	0.818	0.824	12.572***				
Step 2				0.678	77.976***	0.000	0.000
SBP responses to MA	0.000	0.000	0.005				

*** p <.001

Table 6.14 Results of hierarchical linear regression analyses predicting ten months DBP from baseline resting DBP activity, traditional risk factors and SBP responses to mental arithmetic data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months DBP							
Step 1				0.678	158.060***	0.678	158.060***
Baseline DBP	0.818	0.824	12.572***				
Step 2				0.701	27.375***	0.023	1.077
Sex [a]	-0.109	-0.007	-0.082				
Age	0.077	0.113	1.606				
BMI	-0.140	-0.083	-1.006				
FH [b]	1.519	0.090	1.330				
Smoking [c]	1.278	0.072	1.009				
Step 3				0.701	23.155***	0.000	0.054
SBP responses to MA	-0.013	-0.016	-0.232				

FH, family history of CVD; MA, mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

*** p <.001

Table 6.15 Results of hierarchical linear regression analyses predicting ten months DBP from baseline resting DBP activity, traditional risk factors, performance scores and self-reported perceived stress, and SBP responses to mental arithmetic data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months DBP							
Step 1				0.678	158.060***	0.678	158.060***
Baseline DBP	0.818	0.824	12.572***				
Step 2				0.701	27.375***	0.023	1.077
Sex [a]	-0.109	-0.007	-0.082				
Age	0.077	0.113	1.606				
BMI	-0.140	-0.083	-1.006				
FH [b]	1.519	0.090	1.330				
Smoking [c]	1.278	0.072	1.009				
Step 3				0.705	20.325***	0.004	0.455
Performance	0.211	0.065	0.806				
Self-reported perceived stress	0.036	0.066	0.807				
Step 4				0.705	17.817***	0.000	0.043
SBP responses to MA	-0.012	-0.015	-0.207				

FH, family history of CVD; MA, mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

*** p <.001

In summary, these results suggest that SBP responses to mental arithmetic predicted follow-up SBP above and beyond that of traditional risk factors and mediator variables, albeit modestly. Cardiovascular reactivity did not independently predict follow-up DBP.

6.5.7 Interaction of life stress events with Cardiovascular Responses to Acute Laboratory Stressors and the Prediction of Future BP

Moderation analyses was undertaken to determine whether the interaction of stressful life events and cardiovascular reactivity might predict of future BP; in particular, causal versions of the reactivity hypothesis suggest that reactivity might only predict future BP in high stress environments. A set of hierarchical regression models were conducted. Again, at step one, initial resting BP activity were entered into the regression model; at step two, traditional risk factors were entered; at step three, performance, and self-reported perceived stress were

entered; and at step four, cardiovascular responses to mental stress test and stressful life events scores were entered. Finally, the interaction of stressful life events and cardiovascular reactivity were entered. However, interaction between stressful life events and cardiovascular reactivity did not add to the prediction of future SBP or DBP, with or without inclusion of performance scores and self-reported perceived stress in the regression models (see appendix tables 6.2, 6.3, 6.4, 6.5, 6.6, and 6.7).

Finally, regression analyses were re-run using alternate baselines as described and discussed in chapter 4. Results from the new regression analyses were very similar to those presented here; SBP responses to mental arithmetic task predicted future SBP, even after controlling for baseline SBP activity, traditional risk factors and mediator variables (i.e., performance scores and self-perceived stress) (see appendix tables 6.8, 6.9, and 6.10). There were no other significant cardiovascular reactivity measures that predicted cardiovascular outcomes.

6.6 Discussion

The present study investigated haemodynamic reactions to psychological stressors (namely mental arithmetic, speech and cold pressor tasks) as predictors of future BP levels over a ten months period in 77 UK participants. There is only one published prospective studies (Girdler et al., 1996) that has evaluated the contributions of haemodynamic responses to both active and passive coping tasks in the prediction of future resting BP in adult participants. Furthermore, the current study examined the contribution of reactivity and life stress to the prediction of future BP. Stepwise hierarchical liner regression included baseline cardiovascular parameters, traditional risk factors (age, gender, family history of CVD, current cigarette smoking status, and BMI) and, where appropriate, mediator variables (i.e., self-reported perceived stress, performance scores on the mental arithmetic task, and pain tolerance to the cold pressor task), that permitted evaluation of the independent contribution of cardiovascular reactivity. Finally, causal models of reactivity were examined through the inclusion interaction terms for stressful life events and cardiovascular reactivity.

6.6.1 Haemodynamic Responses to Active and Passive Coping Tasks and the Prediction of Future BP

In a mixed-ethnic, mixed-gender sample of normal BP adults (as defined SBP ≤ 140 mmHg and/or DBP ≤ 90 mmHg), cardiovascular reactivity to laboratory challenges predicted follow-

up resting BP levels ten months later (hypothesis 1). Specifically, future SBP levels were predicted by SBP responses to the mental arithmetic task (an active coping task), after controlling for baseline cardiovascular activity. Further, SBP reactions to the mental arithmetic task remained a significant predictor of follow-up SBP, even after adjustment for significant traditional risk factors, mediator variables, and baseline SBP activity. Interestingly, haemodynamic reactions to the speech task and the cold pressor task were not predictors of future SBP. Further, aggregated responsivity measures to the three stress tasks did not predict follow-up SBP after controlling for both baseline SBP activity, and baseline SBP activity along with significant traditional risk factors. Moreover, future DBP levels were not independently predicted by any measure of cardiovascular reactivity, although SBP responses to mental arithmetic were correlated with future DBP in bivariate analyses.

The results showed that only cardiovascular responses to the mental arithmetic task predicted future SBP levels in accord with previous studies (Carroll et al., 2001; Carroll, Phillips, Der, Hunt, & Benzeval, 2011; Markovitz, Racanski, Wallace, Chettur, & Chesney, 1998). However, in contrast to previous studies, no relationships between future BP levels and cardiovascular responses to the cold pressor task or speech task were observed (Carroll et al., 2012; Flaa et al., 2008; Girdler et al., 1996; Matthews et al., 1998). Although self-reports of perceived stress were higher for the mental arithmetic task than the speech task, they did not differ from those for the cold pressor task (see table 6.1). This suggests perceived stress does not offer a simple explanation for the better prediction afforded by SBP responses to mental compared with the other two tasks, although the relatively lower ratings for the speech tasks might partially explain why the speech task was less predictively useful. Other measures, such as effort and coping, should be included in future studies. The mental arithmetic task (active coping task) provoked a pattern of responses consistent with beta-adrenergic activation (namely, large CO and HR responses), whereas the cold pressor task (passive coping task) provoked a pattern of responses with alpha-adrenergic activation (namely large TPR responses; Gregg, James, Matyas, & Thorsteinsson, 1999; Montoya, Brody, Beck, Veit, & Rau, 1997). Markovitz et al. (1998) suggested that BP responses to stressors eliciting primarily beta-adrenergic cardiovascular responses may be more predictive at follow-up BP changes. Thus, the cold pressor task may be a less useful stress task when measuring cardiovascular reactions in order to predict future BP levels. For the speech task, a plausible explanation for its lack of independent predictive power is that the speech task might provoke a mixed alpha- and beta- adrenergic response since it involved both preparation and speech

(Hurwitz et al., 1993, Al'Absi et al., 1997; Llabre, Klein, Saab, McCalla, & Schneiderman, 1998; Saab, et al., 1992; Zanstra, Johnston, & Rasbash, 2010). However, the patterning of haemodynamic responses in the present study suggests that speech was an active coping task that provoked SBP, HR and CO responses of a similar magnitude to the mental arithmetic task. Inspection of the haemodynamic patterns during speech delivery and speech preparation phases indicated that SBP, DBP, HR and TPR responses during the talking phase of the speech task were significantly greater than the speech preparation (see appendix table 6.11) and bivariate correlations suggested that SBP and HR reactions to speech delivery were more strongly associated with future SBP levels than responses to the preparation but again these relationships did not reach the criteria for statistical significance (r =.192, p = .095 and r =.208, p=.069 for SBP and HR responses, respectively; see appendix table 6.12); regression analyses found that these reactions were not independent predictors of future BP. So, it is unclear why cardiovascular responses to the speech task were not predictive when other studies have indicated that they are predictive, and social tasks have been argued to potentially be more important models of everyday life and better predictors of future BP (Kamarck, Peterman & Raynor, 1998; Larkin, Semenchuk, Frazer, Suchday, & Taylor, 1998). Chida and Steptoe's review (2010) found evidence that only cardiovascular responses to cognitive tasks afforded prediction of future BP; public speaking and stress interviews did not predict but there were far fewer associations for those tasks. Thus, the most likely explanation might be the relatively small number of participants in the current study that reduced the chance of detecting effects; i.e., the study did not have sufficient power to detect effects (e.g., for the prediction of future SBP by SBP responses to mental arithmetic, retrospective statistical power = 0.25 for a 2-tailed alpha = .05).

Using the Portapres BP monitor in the present study permitted determination of CO and TPR in addition to HR and BP. However, only SBP reactions were predictors of future BP; underlying haemodynamic changes were not predictive. So the mechanisms linking BP reactivity and future BP may not involve specific haemodynamic responses; the mechanisms involved may be more general, e.g., inflammation, endothelial dysfunction, and platelet aggregation (Beevers, Lip, & O'Brien, 2001; Hamer, Gibson, Wuononvirta, Williams, & Steptoe, 2006; Isowa, Ohira, & Murashima, 2004; Musumeci, Baroni, Cardillo, Zuppi, & Folli, 1989; Musumeci et al., 1987; Oparil, Zaman, & Calhoun, 2003; Robinson, Khankin, Karumanchi, & Humphreys, 2010).

6.6.2 Haemodynamic Responses to Multiple and Single Tasks and the Prediction of Future BP

Many researchers have recommended using multiple tasks to create aggregated measures of cardiovascular responsivity (Treiber et al., 2003; Kamarck & Lovallo, 2003); accordingly, this was proposed as part of hypothesis 2. However, in the current study aggregated cardiovascular responsivity across multiple tasks were not predictors of future BP levels.

Only one published study has examined whether aggregate measures of responsivity to psychological stress tasks afford better prediction of future BP or hypertension than cardiovascular responses to single tasks. Carroll et al. (2012) found that aggregated SBP responsivity across speech, Stroop, and mirror tracing tasks was a similar strength predictor of self-reported hypertension at five year follow-up as SBP responses to the speech and Stroop tasks; SBP responses to mirror tracing were not an independent predictor of hypertension status. Several other studies have found a strong positive relationship between laboratory-induced cardiovascular reactivity and the prediction of future BP or hypertension status. However, those studies used psychological stressors and physiological stressors (Georgiades, Lemne, De Faire, Lindvall, & Fredrikson, 1997; Matthews, Woodall, & Allen, 1993; Moseley & Linden, 2006; Treiber et al., 2001). For example, Matthews et al. (1993) evaluated BP change during standardized mental (namely, serial subtraction, mirror image tracing), and physical challenges (namely, handgrip exercise) to prediction resting BP status over 6.5 years among middle-aged and children. They found that elevated BP responses to a combination of mental and physical challenges were related to resting BP status, and they also suggested that aggregated BP responsivity over multitasks which are combined between mental and physical challenge may be an important marker of future BP status. Therefore, it might that it is aggregate measures which combine responses to psychological and physical stressors that are the best predictors of future BP although more studies that aggregate responses to multiple psychological stress tasks are needed to verify this. Future studies are needed to ascertain whether aggregate responses to psychological stressors offer any better prediction than responses to single tasks or multiple versions of the same task.

6.6.3 Stressful Life Events and Cardiovascular Reactivity and the Prediction of Future BP

The present study examined the association between cardiovascular reactions and life events (Hypothesis 3). Several previous studies have found that high numbers of life events are associated with attenuated cardiovascular reactivity (Jorgensen & Houston, 1989; Musante et al., 2000; Phillips et al., 2005). In the present study, SBP and HR responses to mental

arithmetic were negatively related to the severity of life events, even after controlling for traditional risk factors or/and mediator variables (performance scores and self-reported perceives stress) (see appendix tables 6.13 and 6.14). Phillips et al. (2005) explained that life stress events may be related to blunted cardiovascular reactivity because of an "inoculation effect"; a high frequency of life events may result in a gradual decline on their effects on the cardiovascular system due to habituation. Alternatively, individuals who have high frequency or severity of life events may appraise the acute stress tasks as less stressful (more trivial) and consequently show decreased cardiovascular reactions to them. However, the present study found no evidence that this was the case; ratings of perceived stress for each task were unrelated to life events in the current study.

Moderation analyses was undertaken to examine whether the combination of stressful life events and high cardiovascular reactivity would predict future BP (Hypothesis 4). However, there was no evidence of moderation. The present study used a relative small number of participants (n = 77) who reported modest stressful life event severity, thus the study may lack power or sensitivity to detect effects. The Social Adjustment scale (Holmes & Rahe, 1967) includes 43 stressful life events but many (n = 5) were not endorsed by any participant suggesting that they may not occur in their lives. Alternate measures of background stress may be more useful, for example, socioeconomic status (Lynch, Everson, Kaplan, Salonen, & Salonen, 1998). Therefore, further studies need evidence to support a person-by-situation interaction model, in particular with stressful life events or negative life stress (Light et al., 1999).

6.7 Limitations of Study

There are a number of limitations with the current study. First, the present study had a relatively small sample size (n = 77) and a short period of follow-up (only a ten months period). Therefore, research is needed using larger sample sizes and with a longer follow-up study to determine whether similar relationships exist between stress-induced reactivity and future BP. Second, the average SBP and DBP values at the follow-up session were not significantly higher than the values at the initial session: BP did not increase over the ten months of follow-up ($p > .05$; see appendix table 6.15). This differs from the findings described in chapter 5 of Thai participants; however, different BP monitors were used in that study, whereas the Omron BP monitor was used at both sessions in the current study of UK participants. Comparison of Omron and Portapres monitors in the current study revealed that

the Portapres readings of SBP and DBP were significantly lower than the Omron readings. Previous estimates of both SBP and DBP by Portapres BP may have underestimated BP when compared with brachial artery pressure (Pickering et al., 2005). Taken together these findings suggest the BP rises over time seen in chapter 5 may have been due to the underestimation of BP by the Portapres at the initial baseline. In addition, initial new baseline cardiovascular activity was used to calculate the cardiovascular reactivity measures as discussed in chapter 4; regression models were re-run using alternate baselines as described and discussed in that chapter. Results from the new regression analyses were very similar to those presented; SBP responses to mental arithmetic task predicted future SBP, even after controlling for baseline SBP activity, traditional risk factors and mediator variables (i.e., performance scores and self-perceived stress). These analyses suggest that the predictive relationships observed are not sensitivity to different methods of calculating baseline cardiovascular activity.

6.8 Conclusion

In the UK study, SBP reactions to mental arithmetic task (an active coping task) predicted future SBP, after controlling for baseline SBP activity, traditional risk factors and mediator variables. However, haemodynamic reactivity, both CO and TPR responses to mental stress tests were not significant predictors of follow-up BP levels. These findings are consistent with other studies that used haemodynamic reactivity to predict follow-up BP. Therefore, haemodynamic responses to mental stress may be helpful in determining patterns of haemodynamic responses to mental stress test rather than predicting follow-up BP. In addition, responses to mental arithmetic task, which provoked a beta-adrenergic response with an increased CO, afforded better prediction of future SBP than cold pressor (passive coping task) which provoked an alpha-adrenergic response with an increased TPR. Thus, these findings are consistent with Falkner, Kushner, Onesti, and Angelakos (1981) and Flaa et al. (2008) who suggested that changes provoked by mental arithmetic may support the notion of a hyperkinetic circulation state. Finally, the interaction of background life stress and high cardiovascular reactivity did not predict follow-up BP levels so an Interaction version of the Reactivity Hypothesis was not supported. Rather a situation/task specific version of the Reactivity Hypothesis was supported; SBP reactions to mental arithmetic were an independent predictor of future SBP, suggesting a possible role for reactivity in the development of hypertension status. However, it is not clear the causal role that reactivity plays from these or other prospective studies; further attention to the pathways linking reactivity to hypertension is warranted.

CHAPTER 7
General Discussion and Conclusion

7.1 Introduction

This thesis focused on cardiovascular responses to psychological stress tests and the prediction of future BP in healthy UK and Thai samples. Specifically, three research questions were addressed:

1. How large are changes in cardiovascular parameters to psychological stress tests in UK and Thai participants?
2. What relationships are there between cardiovascular reactivity and psychological factors, specifically depression and anxiety?
3. Can cardiovascular responses to single or multiple, active or passive psychological stress tasks predict hypertension and raised BP over a one year follow-up?

In order to answer these questions a systemic review with meta-regressions and meta-analyses was completed to determine whether cardiovascular responses to psychological stress test predict future BP levels (SBP and DBP), hypertension status, preclinical CHD and CVD states (cardiac events) (Question 3, described in chapter 2). Second, cross-sectional analyses were conducted to determine whether cardiovascular reactivity is associated with depressive and anxiety symptoms in Thai and UK participants, and life events in UK participants (Question 2, details in chapter 4 and 6). Comparisons of the magnitude of cardiovascular responses to multiple psychological stressors in UK and Thai samples were made in chapter 4 (Question 1). Finally, prospective cohort studies were conducted to examine whether cardiovascular reactivity predicts future BP levels after one year of follow-up in Thai and UK samples (Question 3, details in chapters 5 and 6).

In this chapter, the key findings from these studies are presented and discussed in light of past work, the limitations and future directions of the current work are assessed, and implications of these findings for future research and clinical practice are evaluated.

7.2 Key Findings

7.2.1 Haemodynamic Reactions to Psychological Stress Tasks in the UK and Thai samples

The three psychological stress tasks used in this thesis, cold pressor, mental arithmetic, and speech, provoked large and significant increases in BP, HR, CO, and TPR in both the UK and Thai samples. These increases were as expected; these tasks are the most commonly used and have consistently been found to provoke substantial cardiovascular reactions (Gregg, James, Matyas, & Thorsteinsson, 1999; Sherwood, Davis, Dolan, & Light, 1992; Willemsen, Ring, Carroll, Clow, & Hucklebridge, 1998). However, compared with the UK participants, Thai individuals exhibited larger haemodynamic responses to the three psychological stress tests on 11 of 15 measures of reactivity in a sample of 114 Thai and 109 UK participants (see chapter 4). There were only four exceptions to this: HR and CO responses to cold pressor, CO responses to speech and TPR responses to mental arithmetic did not differ by country from which the sample was tested. These differences remained largely unaltered after adjusting for baseline or traditional risk factors. The patterning of findings did not implicate task order, which was fixed for the Thai sample and randomised in the UK sample, as accounting for these differences (see appendix table 4.8). Further, the variance in the cardiovascular reactivity data (standard deviations) was similar across both samples suggesting that there were not floor or ceiling effects.

Few studies have directly compared cardiovascular laboratory stress responses between Asian and Caucasian participants (Shen, Stroud, & Niaura, 2004; Stoney, Hughes, Kuntz, West, & Thornton, 2002; Suchday & Larkin, 2004), and those that have, have suggested that Asians exhibit significantly *lower* haemodynamic reactions to laboratory stress tests than Caucasians. However, those studies were of participants living in the United States, whereas the current study examined differences between individuals raised and living in the UK and Thailand. Thus, this thesis was interested in national and cultural differences whereas previous studies have been more concerned with acculturation. It may be that Thai participants living in Thailand were less familiar with experimental testing and so displayed greater cardiovascular reactivity than the UK participants, whereas Asians living in the USA may be more familiar (or similarly familiar) with experimental testing. Alternatively, socioeconomic status might offer a cogent explanation. Several studies have found that lower socioeconomic status is correlated with higher cardiovascular reactivity (Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998) and it is likely that the Thai participants had lower levels of income than UK participants. Thus, it is likely

that the haemodynamic reactivity differences found here are, at least partially, socioculturally mediated (Delehanty, Dimsdale, & Mills, 1991; Markus & Kitayaman, 1991).

Analyses revealed differences between the Thai and UK participants. Thai participants had lower BMIs, were less likely to smoke, and were more likely to be women, than UK participants. These factors may account for differences in cardiovascular reactivity. For example, the study found that BMI was related to TPR responses to cold pressor and speech tasks supporting previous findings; the degree of obesity (e.g., BMI) has been found to be inversely related to systemic vascular resistance patterns, characterised by higher total peripheral resistance and vasoconstrictor responses to psychological stress tests (Jern, Bergbrant, Bjorntorp, & Hansson, 1992). After statistically adjusting for age, sex, BMI, family history of CVD, current smoking status and baseline cardiovascular activity, differences between Thai and UK participants in cardiovascular responses to psychological laboratory stress tests were, in many, cases reduced. However, these demographic differences did not fully account for statistical differences in cardiovascular reactivity, i.e. the differences remained statistically significant. Given these findings and the fact that these studies were not designed to examine differences between Thai and UK participants (with slightly different methodologies), further studies comparing individuals from different ethnic backgrounds are needed to substantiate the differences found here and elucidate potential mechanisms if these differences are found to be robust.

7.2.2 Psychological Factors and Cardiovascular Responses to Laboratory Stressors

The findings of this thesis support the "Blunted Cardiovascular Hypothesis" in that lower cardiovascular reactivity were associated with psychosocial factors (namely, anxiety and depressive symptoms). In this thesis, negative cross-sectional relationships between cardiovascular reactivity, and anxiety and depressive symptoms were found: lower cardiovascular responses to mental stress test were related to higher depressive or anxiety symptom levels. Negative cardiovascular reactions to acute psychological stress are associated with high anxiety and depressive symptoms (measured by HADS) in the UK participants. Depressive symptoms are negatively associated with CO reactions to the mental arithmetic task, after controlling for baseline cardiovascular activity, traditional risk factors (i.e., age, sex, BMI, current cigarette smoking status, and family history of CVD) and mediator variables (i.e., self-reported perceived stress, and performance scores) in the UK participants. With respect to anxiety symptoms, CO reactions to the mental arithmetic task

are negatively associated with anxiety symptoms after controlling for baseline CO activity, traditional risk factors, self-reported perceived stress and performance scores on the mental arithmetic task. Further, in the UK study, SBP and HR responses to mental arithmetic were negatively related to the severity of stressful life events, even after controlling for traditional risk factors or/and mediator variables (performance scores and self-reported perceives stress; descripted in chapter 6). However, the combination of stressful life events and high cardiovascular reactivity did not predict future BP. In brief, in the UK study, lower cardiovascular responses to the mental arithmetic task are associated with higher levels of psychological factors (i.e., anxiety, depression, and stressful life events) after controlling for confounding factors (i.e., baseline cardiovascular activity, traditional risk factors, self-reported perceived stress, performance scores).

In Thai individuals, TPR response to the mental arithmetic task was negatively associated with depressive symptoms after controlling for baseline cardiovascular activity and traditional risk factors; none of the other 29 relationships were significant. Thus, this finding might be a type I error (described in chapter 4) because of the α-level which was set at .05. Another reason for this finding relates to performance and perceived stress as possible pathways linking depression or anxiety to cardiovascular reactivity. The results in the UK sample indicated that the negative correlations between CO responses to mental arithmetic and depression and anxiety were statically significant after controlling for performance and perceived stress. In the Thai study, performance and perceived stress was not measured and so these variables were not included in partial correlations. Further, cultural differences between the Thai and UK samples may affect cardiovascular reactivity. Many studies have suggested that sociocultural factors are associated with cardiovascular responses to mental stress (Delehanty et al., 1991; Markus & Kitayaman, 1991). For example, Why et al. (2003) found that hostility was associated with SBP responses to the anger recall task in Indians but not Chinese or Malay participants. Therefore, further examination of relationships between psychological factors and cardiovascular reactivity in different Asian samples should be examined.

Results from the UK study supported the "Blunted cardiovascular reactivity" hypothesis (Phillips, 2011; Phillips, Hunt, Der, & Carroll, 2011). One possible explanation for the blunted cardiovascular reactivity observed in participants with high levels of anxiety or

depression symptoms is that they may be less engaged in the task or have reduced motivation (Capa, Audiffren, & Rogot, 2008; Phillips, 2011). However, in the UK study, the negative relationships between HADS depression and anxiety, and CO reactions to mental arithmetic remained statistically significant after controlling for self-reported perceived stress and performance, in addition to traditional risk factors and baseline cardiovascular activity. However, the significant relationship between SBP reactions to mental arithmetic and anxiety was reduced and no longer significant after the addition of perceived stress and performance but, Sobel tests did not indicate mediation. So, the study provided little evidence that motivation was the mechanism linking blunted reactivity to anxiety and depression.

It is possible that there was little evidence of mediation because of the small effects observed, i.e. for mediation to have been observed the mediators would have had to have accounted for most for the variance shared between cardiovascular reactivity and depression or anxiety. Alternatively, the measures of performance and self-reported percieved stress may be poor indices of motivation or effort; although performance and perceived stress have been associated with motivation and effort, they are proxy measures of them. Accordingly, future studies need to assess the effort participants mobilised during task performance and anticipatory measures of motivation; for examples by using measures of active motivation (Capa et al., 2008; Gendolla, 2006), by using incentive tasks (Richter & Gendolla, 2006), mental effort (Gerin, Pieper, Marchese, & Pickering, 1992; Peter et al., 1998; Wright & Kirby, 2003), and cortisol levels for an anticipation task (Gregg et al., 1999; Westenber et al., 2009). For example, Wright and Dismukes (1995) reported that HR responses to a scanning task was greater in the difficult than easy condition for high-ability participants, whereas in low-ability participants, HR reactivity was greater in the easy than difficult condition. Further, Wright and Kirby (2001) reviewed evidence relevant to an integrative analysis regarding the determinants of cardiovascular reactions to behavioural challenges. They concluded that sympathetically mediated cardiovascular adjustment varies with task engagement.

A second explanation involves beta-adrenergic activation that in the UK study; the results indicated that participants with more anxiety symptoms exhibited less SBP and CO responses to the mental arithmetic task. Further, participants with depressive symptoms showed less CO responses to the mental arithmetic task in the UK sample, after statistical adjustment for conservative risk factors (i.e., gender, age, BMI, family history of CVD, and current cigarette

smoking status) and baseline cardiovascular measures. These findings are consistent with a growing number of studies showing attenuated cardiovascular reactivity is associated with anxiety and depressive symptoms (Salomon, Clift, Karlsdottir, & Rottenberg, 2009; Straneva-Meuse, Light, Allen, Golding, & Girdler, 2004; York et al., 2007). These results suggest that mechanisms linking anxiety and depressive symptoms with cardiovascular responses may involve deregulation of beta-adrenergic receptors, given the important role they play in cardiac contractility (Nesse, Cameron, Curtis, McCann, & Huber-Smith, 1984; York et al., 2007; Young, Nesse, Weder, & Julius, 1998). Further, several studies have shown that participants with depression and anxiety have decreases in the number of beta-adrenergic receptors. For example, Aronson, Carasiti, McBane, & Whitaker-Azmitia (1989) found decreased numbers of beta-adrenergic receptors are associated with participants' trait anxiety (using the Spielberger Trait Anxiety Scores); depressed patients also have been shown to have fewer beta-adrenergic receptor sites (Pandey, janicak, & Davis, 1987). Further, active coping tasks were associated with relatively greater changes in CO and these tasks involve a beta-adrenergic mediated pattern of responses via central mechanisms (Sherwood, Allen, Obrist, & Langer, 1986). The UK study provides some supporting evidence for the involvement of blunted beta-adrenergic receptor responsiveness in participants with anxiety and depression: they showed smaller CO responses, a marker of beta-adrenergic responsiveness, to the active coping task. Moreover, results from the UK study accord with the only other previous study that assessed haemodynamic reactions to stress, and anxiety and depressive symptoms. Straneva-Meuse et al. (2004) found that participants with major depression disorders exhibited lower SBP, and CO reactions to mental arithmetic and speech tasks than unmedicated or non-depressed controls. So, myocardial mechanisms may, at least partially, be responsible for the relationships between depression and anxiety, and blunted cardiovascular reactivity.

7.2.3 Haemodynamic Reactions to Mental Stress Tests and the Prediction of Future BP

The two prospective analyses found some evidence supporting the reactivity hypothesis; the evidence allowed some assessment of the various versions of the hypothesis (marker, causal trait, situation-cause and person by situation interaction). According to bivariate analyses, SBP responses to the mental arithmetic task were associated with future SBP in Thai sample. In the UK study, SBP responses to the mental arithmetic task and aggregated SBP responsivity over the three tasks were related to future SBP. In addition, SBP responses to the mental arithmetic task were associated with future DBP levels in the UK study. However,

haemodynamic reactivity (namely CO and TPR) was not predictive in the UK or Thai studies. These findings largely confirmed BP reactivity as a marker for hypertension risk; i.e., SBP responses to mental arithmetic were associated with future SBP.

Further, the two prospective cohort studies (chapters 5 and 6) indicated that even after adjusting for traditional risk factors (i.e., baseline cardiovascular activity and traditional risk factors (sex, age, BMI, family history of CVD, and current cigarette smoking status)) in multiple regression models, cardiovascular responses to stress contributed significantly to the prediction of future SBP, i.e., BP reactivity was an independent predictor of future SBP. Specifically, after controlling for traditional risk factors and initial baseline SBP activity, SBP reactions to the mental arithmetic task remained a predictor of future SBP both in the UK and Thai samples. In addition, aggregated SBP responsivity across three mental stress tests predicted future SBP in UK participant; however, the prediction of follow-up did not reach the conventional criteria ($p > .05$). With respect to the prediction of future DBP levels, after adjusting for initial baseline cardiovascular activity or traditional risk factors, none of the cardiovascular reactivity indices predicted future DBP levels, in the UK and the Thai samples. These findings therefore, are in line with previous prospective studies that have found BP responses to active coping tasks to be predictive of future BP (Flaa, Eide, Kjeldsen, & Rostrup, 2008; Carroll et al., 2003; Carroll, Phillips, Der, Hunt, & Benzeval, 2011; Markovitz, Racanski, Wallace, Chettur, & Chesney, 1998). Collectively, these results accord with previous findings that cardiovascular reactions to active coping tasks predict future BP levels. For example, Markovitz et al. (1998) found that cardiovascular responses to active coping tasks (video games) were better predictors of future BP over five years follow-up than cardiovascular responses to passive coping tasks (cold pressor) in healthy participants. Further, the findings in chapters 5 and 6 offer some support to the notion that cardiovascular reactivity is a casual trait in the development of hypertension because likely confounding risk factors were statistical controlled. Additionally, the proportion of variances in future BP accounted for by cardiovascular responses parameters after adjustment for controlling for standard risk factors ranged from 2 to 12% in previous research (Light et al., 1999; Matthews, Woodall, & Allen, 1993; Murphy, Alpert, Walker, & Willey, 1991; Newman, McGarvey, & Steele, 1999; Tuomisto, Maiahalme, Kahonen, Fredrikson, & Turjanmaa, 2005) which was similar to the amount of variance accounted for in the studies in this thesis (range = 4.5–6.2%). Thus, BP reactivity appears to be a modest, independent predictor of future SBP.

Further, the systematic review described in chapter 2 revealed that SBP and DBP reactions to mental stress tests independently predicted future SBP and DBP, respectively. In contrast, HR, CO and TPR reactivity did not predict future BP levels. In the two prospective studies presented in the thesis, only SBP reactions to the mental arithmetic task independently predicted future SBP; no measures of reactivity predicted future DBP. Thus, there was no evidence that HR, CO, and TPR reactivity predicts future BP in this thesis. It is already known that CO and TPR index myocardial and vascular responses to psychological stressors. In addition, many researchers have suggested that using a more comprehensive assessment of haemodynamic parameters would be useful (Phillip, 2011; Treiber et al., 2003). However, these studies found no evidence supporting this suggestion. Moreover, the present studies (chapters 5 and 6) showed simple measurement of BP responses to mental stress are sufficient to predict future BP levels. It is possible that the non-invasive methods to assess haemodynamic changes were not sufficiently reliable to afford prediction of future BP. The use of the non-invasive methods for monitoring CO and BP are not the "gold standard" (Bogert & van Lieshout, 2005; Stover et al., 2009). Bogert and van Lieshout (2005) reviewed that changes in stress and tone of smooth muscle in the arterial wall and in haematocrit affect the diameter of an artery under a cuff wrapped around the fingers at a given pressure. Some studies found that the Finapres meets the Association for the Advancement of Medical Instruments accuracy for SBP and DBP (Imholz, Wieling, Langewouters, & van Montfrans, 1991; Schutte, Huisman, van Rooyen, Malan, & Schutte, 2004; Silke & McAuley, 1998). However, others studies found that Portapres did not reliably estimate absolute values of CO (Hirschl et al., 1997; Jansen et al., 2002; Jellema et al., 1999; Pitt, Marshall, Diesch, & Hainsworth, 2004; Remmen et al., 2002). Accordingly, changes in BP may be more reliably assessed by Portapres than changes in CO or TPR. The systematic review described in chapter 2 revealed that CO and TPR reactivity (assessed by impedance cardiogram) did not predict future BP levels, suggesting that reliability issues with CO and TPR changes assessed by the Portapres are an unlikely explanation for the lack of predictive relationships observed in chapters 5 and 6. However, the use of impedance cardiography is a relatively recent addition to testing; only two prospective studies (with four data sets) that used CO and TPR reactivity as predictors were included in meta-regression models (Girdler et al., 1996; Steptoe & Marmot, 2005b). Even so, the mechanisms linking cardiovascular reactivity and future BP might be better explained other pathophysiological factors, i.e., the mechanisms linking BP reactivity and future BP may not involve specific haemodynamic responses. The mechanisms may be more general, e.g., inflammation, endothelial dysfunction, and platelet aggregation

(Beevers, Lip, & O'Brien, 2001; Hamer, Gibson, Wuononvirta, Williams, & Steptoe, 2006; Isowa, Ohira, & Murashima, 2004; Musumeci, Baroni, Cardillo, Zuppi, & Folli, 1989; Musumeci et al., 1987; Oparil, Zaman, & Calhoun, 2003; Robinson, Khankin, Karumanchi, & Humphreys, 2010). For example, Steptoe, Willemsen, Owen, Flower, and Mohamed-Ali (2001) found SBP, DBP, and HR responses to colour-word and mirror were positively associated with IL-6 concentration (an inflammatory cytokine). Steptoe et al. (2003) also found that SBP responsivity to colour-word and mirror tasks was associated with the magnitude of stress-induced increases in leukocyte and monocyte platelet aggregates in 37 healthy men. Hamer et al. (2006) found that BP responses to speech and mirror tracing tasks were associated with plasma C-reactive protein, von Willebrand factor antigen, and leukocyte-platelet aggregates. Accordingly, these alternate mechanisms should be explored in future prospective studies.

Haemodynamic Reactions to Active and Passive Coping Tasks and the Prediction of Future BP

Many studies have reported that active coping tasks elicit beta-adrenergic with an increase in CO responses via activation of the sympathetic nervous system (Iwanaga, Liu, Shimomura, & Katsuura, 2005; Light, 1981; Liu, Iwanaga, Shimomura, & Katsuura, 2007; Sherwood et al., 1990), whereas passive coping tasks elicit alpha-adrenergical mediated vasoconstriction with an increase in TPR (Girdler, Hinderliter, & Light, 1993; Girdler et al., 1996; Sherwood, Dolan, & Light, 1990). Therefore, it has been assumed that cardiovascular responses to active coping tasks might be better predictors of future BP than cardiovascular responses to passive coping tasks (Markovitz et al., 1998). However, there have been few studies that test this assumption. These results from previous studies are inconsistent; the meta-regressions presented in chapter 2 found that cardiovascular responses to passive coping tasks afforded a better prediction of *hypertension status* than cardiovascular responses to active coping tasks. However, cardiovascular responses to active and passive coping tasks did not differentially predict *future BP*. One explanation is individual differences in haemodynamic responses to mental stress tests interact with type of task, to provoke alpha- and/or beta-adrenergic responses (Sherwood et al., 1990). For example, active coping tasks provoked a pattern of responses consistent with beta-adrenergic activation (increases in CO and HR responses), whereas passive coping tasks provoked a pattern of responses with alpha-adrenergic activation (increases in TPR responses); however, a few studies have found that BP responses to active coping tasks may be elicited via increases in systematic vascular resistance,

presumably eliciting alpha-adrenergic activity, rather by than cardiac performance (Waldstein, Bachen, & Manuck, 1997). Another important factor to consider is pathophysiology of hypertension (detailed in chapter 1). Specifically, there is evidence that younger adults with heightened BP have increased peripheral resistance, and smaller increases in cardiac index (Mayet & Hughes, 2003), whereas patients with hypertension have high peripheral vascular resistance but normal or reduced cardiac index and stroke volume (Foëx & Sear, 2004; Mayet & Hughes, 2003). In addition, the number and type of covariates included in analytic models has changed over time along with a change in focus from passive coping tasks to active coping tasks. Thus, the current review findings should be interpreted cautiously with regards to the haemodynamic patterning of the tasks, the number and type of covariates, and the prediction of cardiovascular outcomes.

In the prospective studies completed in this thesis (chapters 5 and 6), SBP responses to an active coping task (the mental arithmetic task) predicted future SBP in both the UK and Thai samples, even after controlling for baseline BP activity, and traditional risk factors. Cardiovascular responses to the passive coping task (cold pressor) did not predict future SBP or DBP in either study. Markovitz et al. (1998) suggested that BP responses to stressors eliciting primarily beta-adrenergic cardiovascular responses may be more predictive of follow-up BP than stressors eliciting primarily alpha-adrenergic cardiovascular responses. Thus, the cold pressor task may be a less useful stress task when measuring cardiovascular reactions in order to predict future BP levels. For the speech task, a plausible explanation for its lack of independent predictive power is that the speech task might provoke a mixed alpha-adrenergic response and beta-adrenergic response because it involved both preparation and speech tasks (Al'Absi et al., 1997; Hurwitz et al., 1993; Llabre, Klein, Saab, McCalla, & Schneiderman, 1998; Saab et al., 1992; Zanstra, Johnston, & Rasbash, 2010. Indeed, the patterning of haemodynamic responses in the present studies found that speech tasks elicited both alpha-adrenergic responses (via TPR responses) and beta-adrenergic responses (via CO responses) somewhere between the responses provoked by the active (mental arithmetic) and passive (cold pressor) coping tasks (see chapters 5 and 6). Another potential explanation for the inability of cardiovascular responses to speech and cold pressor tasks to predict future BP may concern other elements of the task (such as whether performance is assessed) that may be more likely to be influenced by personality or coping styles instead (Flaa, Ekeberg, Kjeldsen, & Rostrup, 2007; Jamner, Shapiro, Hui, Oakley, & Lovett, 1993; Suls, Wan, & Costa, 1995). Fichera and Andreassi (1998) investigated the relationships among Type A

behaviour (measured the Jenkins Activity Survey; Jenkins, Zyzanski, & Rosenman, 1979), hostility (measured the Cook-Medley Hostility Scale; Cook & Medley, 1954) and cardiovascular reactions to a reaction time task and an oral IQ quiz in 96 women. Type A and high hostile women had greater SBP reactions to the reaction time task and the IQ quiz than Type B and low hostile women. Further, there were greater SBP and DBP reactions to the oral IQ quiz than to the reaction task. The researchers assumed that task difficulty may be important because the IQ quiz appeared to be more difficult than the reaction time task. In future, it may be useful to assess personality and account for differences in personality or coping styles. Thus, the findings in chapters 5 and 6 support recent models of cardiovascular reactivity that focus on dimensions of the task (details in chapter 1) as key to the predictive power of cardiovascular reactivity. However, the results from the UK study (chapter 6) did not support a person-by situation interaction model. The interaction of stressful life events and cardiovascular reactivity did not add to the prediction of future BP. However, interaction analyses may lack power or sensitivity to detect effects (e.g., for the prediction of future SBP by SBP responses to mental arithmetic, retrospective statistical power = 0.25 for a 2-tailed alpha = .05). Moreover, measure of life stress events (the Social Adjustment scales; Holmes & Rahe, 1967) may not be the best measure of background stress because some stressful life events (e.g., divorce) may not occur in the everyday events. Alternate measures of background stress may be more useful; for example, socioeconomic status has been found to moderate the relationship between BP responses to anticipated exercise and progression of carotid atherosclerosis (Lynch et al., 1998).

Alternatively studies could focus on the components of background stress that are important in everyday life. For example, research has revealed that cardiovascular reactivity has been associated with naturally occurring social interactions and, in particular, hostile interactions (Brodolo et al., 2003; Karin, Brondolo, & Schwartz, 2003). Brondolo et al. (2003) found that trait hostility was positively associated with the frequency and intensity of negative interactions and was related to increases in SBP and DBP as assessed by ambulatory BP monitoring. Moreover, the magnitude of the increases in BP in those interactions was positively associated with the degree to which those social interactions were perceived negatively. These findings are also consistent with laboratory studies that find that strong negative emotions are associated with greater cardiovascular activation to psychological stress tasks (Fredrikson, Blumenthal, Evans, Sherwood, & Light, 1989; Matthews, Owens, Allen, & Stoney, 1992). Moreover, Matthews et al. (1992) found that individuals who had

heighted cardiovascular responses to laboratory stressors exhibited greater ambulatory SBP and DBP levels during periods of stress compared to periods of low stress in everyday. Therefore, further studies need to examine the person-by-situation interaction model, using more ecologically valid measures of background stress (Light et al., 1999) and consider the most salient features of stress in daily life that could be modelled within the laboratory.

Haemodynamic Reactions to Multiple and Single Tasks and the Prediction of Future BP

Few studies have examined whether cardiovascular responses to single or multiple tasks afford better prediction of cardiovascular risk status (i.e., increased BP). In the meta-analyses and meta-regressions presented in chapter 2, comparisons between cardiovascular responses to single or multiple tasks were not made because of the small numbers of studies using multiple tasks (n = 7). However, the cohort studies (chapters 5 and 6) explored whether haemodynamic responses to aggregated responses to multiple and responses to single tasks predicted BP over 12 months in the UK and Thai samples. Compared with multiple tasks, the findings revealed that a one of the single tasks, mental arithmetic, afforded a better prediction of future SBP levels whether in the UK or the Thai samples. Although several researchers have suggested that the use of multiple tasks might increase predictive power under such circumstances (Kamarck & Lovallo, 2003; Mosley & Linden, 2006; Treiber et al., 2003; Zanstra & Johnston, 2011), there was no evidence that this was the case. Mosely and Linden (2006) found that aggregated cardiovascular responsivity over three tasks (handgrip, math, and anger-recall tasks) was a better predictor of future SBP over three years compared to cardiovascular responses to individual tasks (ranging from 7.3% to 10.6% for aggregated SBP responsivity, and 0.6% for individual stress (math). Moreover, Carroll et al. (2012) examined the association between BP reactions to Stoop colour word, mirror tracing and speech tasks, and subsequent hypertension status after five year follow-up. They reported that after adjustment for age, sex, socio-economic status, BMI, antihypertensive medication, current smoking, commitment to stress tasks and famine exposure, aggregated SBP across three tasks was positively associated with hypertension status (odds ratio = 1.019). Regarding individual tasks, SBP responses to speech and Stroop tasks were less predictive compared to aggregated tasks (odds ratio = 1.01 and 1.02, respectively). Most previous prospective studies (e.g., Moseley & Linden, 2006; Matthews et al., 1993) that used multiple tasks have combined responses to psychological (active coping tasks) and physical stressors which produce a primarily beta-adrenergic response (Butler, Kelly, O'Malley, & Pidgeon, 1983; Maisel, Harris, Rearden, & Michel, 1990; Murry et al., 1992). These may have elevated the

predictive power of the aggregated responsivity measures because of the known relationship between exercise responses (which provoked a pattern of responses with beta-adrenergic activation) and hypertension (Palatini, 1998). The only study that used aggregated responses to multiple psychological stressors is combined cardiovascular responses to active coping task with active coping tasks (video games and mental arithmetic), or passive coping tasks together (humorous film, habituation test and cold pressor; Tuomisto et al., 2005). They found that cardiovascular reactivity to active coping or passive coping tasks independently predicted future SBP (ΔR^2 = 0.06 and 0.08, respectively). Therefore, aggregated responses within a particular task type might be better predictors than aggregated responses between different task types.

Aggregating physiological responses to multiple tasks of different types of coping task may have reduced the reliability of the responsivity measures, in part, due to different haemodynamic responses to active and passive coping tasks which provoked a pattern of responses with beta-adrenergic activation and alpha-adrenergic activation, respectively. For example, Kamarck (1992) examined the haemodynamic reactions to a memory task, a psychomotor task, and a reaction time task. They reported that task aggregation across three tasks increased the internal consistency of SBP, DBP and HR measures and also improved the test-retest reliability of those responses; test-retest coefficients for aggregated SBP responsiveness scores was r = 0.79, whereas test-retest correlations for single tasks on SBP measures ranged from 0.52 to 0.71. However, they assessed the aggregated responses within a particular task type (active coping tasks). Turner, Sherwood, and Light (1994) reported that aggregated SBP responsivity over mental arithmetic and reaction time (combined active coping tasks) were higher than SBP responsivity over mental arithmetic and cold pressor tasks (r = 0.79 and 0.28, respectively). In the studies in chapters 5 and 6, the intertask correlations between SBP responses to mental arithmetic (active coping) and speech tasks (active coping) were somewhat higher than SBP responses to mental arithmetic (active coping) and cold pressor tasks (passive coping) in the UK (r = 0.49 and 0.41, respectively and Thai samples (r = 0.75 and 0.60, respectively). Thus, aggregation across multiple tasks might allow greater generalisability. In addition, the diversity of situations aggregated across multiple tasks may be a better representation of stress experienced in everyday life; the correspondence between laboratory and field measures of BP has been found to be improved

by taking into account the environmental circumstances during the ambulatory assessments and by aggregation of multiple tasks (Carroll, 2011; Matthews et al., 1992).

Cardiovascular Reactivity and the Prediction of Future BP: Thailand and UK

The Reactivity Hypothesis, which contends that cardiovascular reactions to acute psychological stress play a role in the development of future BP, was supported in the Thai and UK studies. The bivariate correlations, which assess the role of cardiovascular reactivity as a marker for hypertension risk, revealed that SBP responses to the mental arithmetic task were related to future SBP in the Thai and UK studies. However, the association was larger in the UK study (r = 0.37 than the Thai study (r = 0.25) and SBP responses to mental arithmetic was also associated with future DBP in the UK study (r = 0.26), but not the Thai study (r = 0.17). Thus, the relationships between BP reactivity and future BP appear stronger in the UK sample.

With respect to the causal trait model in the Thai study, SBP responses to mental arithmetic were predictive of follow-up SBP levels; initial baseline SBP accounted for 17.0% of the variance in follow-up SBP levels and SBP responses to mental arithmetic task accounted for an additional 6.2% of the variance (β = 0.25). After adjustment for traditional risk factors and baseline cardiovascular activity SBP responses to mental arithmetic explained 5.5 % of the variation of future SBP levels (β = 0.24). Interestingly, these results accord with findings from the UK study, SBP responses to mental arithmetic were predictive of follow-up SBP levels; initial baseline SBP accounted for 28.9 % of the variance in follow-up SBP levels and SBP responses to mental arithmetic task accounted for an additional 5.8% of the variance (β = 0.25). After statistical adjustment for traditional risk factors and baseline cardiovascular activity, SBP responses to mental arithmetic explained 4.5% of the variation of future SBP levels. (β = 0.22). Thus SBP responses predicted a similar proportion of the variance in future SBP independently of initial resting SBP and traditional risk factors in the UK and Thai studies (4.5% – 6.2%). Thus, it may suggest that the use of cardiovascular reactivity to predict future BP is not different in different countries or cultures. Further, these findings suggest mental arithmetic may be an effective stressor and diminishes the possibility that task order, which was fixed for the Thai sample, was responsible for the findings in the Thai study as task order was randomised in the UK sample. However, the proportion of variance in future SBP explained by baseline SBP activity was higher in the UK study than in the Thai

study (28.9% vs. 17.0%). It should be noted different BP monitors were used in Thai study (a Portapres monitor was used at the initial session and a Dinamap monitor was used at the follow-up session), whereas the Omron BP monitor was used at both sessions in the current study of UK participants which might account for these differences. Taken together the findings suggest that cardiovascular responses to acute psychological stressors in the laboratory may reflect reactivity in real life (Turner, Girdler, Sherwood, & Light, 1990) and maybe a risk factor for negative health outcomes e.g., increased BP (Obrist, 1981). Further, Carroll (2011) suggested that cardiovascular stress reactivity in real life is positively correlated with standardised laboratory reactivity in better designed studies and the reactions to real life stress exposures are often greater than those observed in laboratory analogues. Therefore, relationships between cardiovascular reactions to real life stress and CVD and hypertension should be the focus of further study.

Summary and Model

With respect to Reactivity Hypotheses, the findings offered some support for the hypothesis that *blunted* cardiovascular reactivity would be associated with anxiety and depressive symptoms, whereas *exaggerated* cardiovascular reactively would be associated with future BP. The figure 7.1 below summarises a model of the cardiovascular reactivity findings from this thesis. In order to complete the models, correlations between symptoms of anxiety and depression, and future BP in the UK and Thai samples were calculated. Negative correlation between anxiety and future BP were found in the UK participants (r = -0.27 for future SBP, and -0.32 for future DBP; see appendix table 7.1); however, after controlling for baseline BP and traditional risk factors, none of the associations between anxiety and future BP were significant (see appendix table 7.2). This suggests that anxiety may be indirectly related to future BP (Jonas, Franks, & Ingram, 1997; Paterniti et al., 1999).

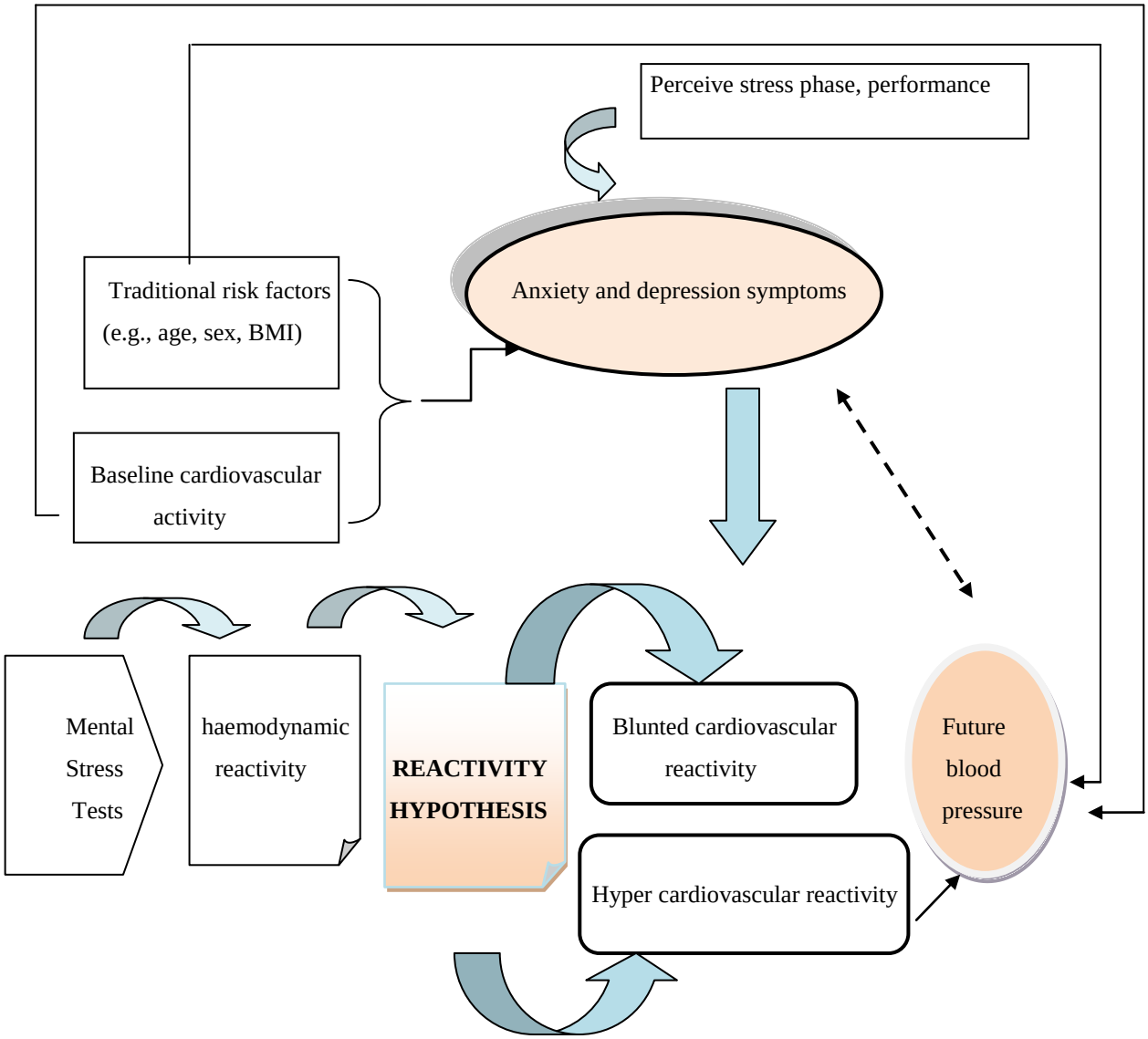


Figure 7.1 Proposed models between cardiovascular responses to psychological stress tests and future BP

The reactivity hypothesis suggests that exaggerated haemodynamic reactions to acute psychological stressors may contribute to the subsequent development of hypertension (Obrist, 1976). The present studies offers evidence that heightened cardiovascular reactions to stress may be important risk factors for hypertension, although only some stressors (mental arithmetic) and some cardiovascular measures (BP) afforded prediction of future BP. In addition, blunted cardiovascular reactivity was associated with stressful life events, anxiety and depressive symptoms. Thus, traditional versions of the Reactivity Hypothesis and the Blunted Reactivity Hypothesis were supported in the same samples. Previous work using the West of Scotland epidemiological data has reported similar findings (Carroll, Phillips, Hunt,

& Der, 2007; Carroll et al., 2003). Lovallo (2011) has suggested that both very large and very small cardiovascular responses to mental stressor are indicators of poor homeostasis and are signals of possible risk of disease. He also posited that larger than normal responses of cardiovascular and smaller than normal responses to stressor can signal dysfunction of systems and contribute to pathophysiological processes (see figure 7.2). The data presented here suggest that exaggerated and blunted cardiovascular responses are associated with negative health outcomes, and thus lend support to his proposition from within the same samples. However, the current data found no evidence that blunted cardiovascular reactivity was associated with future BP (see appendix table 7.3) and accords with findings from the five year follow-up data from the Whitehall II study of civil servants (Carroll, Davey Smith, Sheffield, & Marmot, 1995; David Sheffield, private correspondence). Thus, exaggerated cardiovascular responses appear to be associated with one group of negative health outcomes (i.e., BP and hypertension) and blunted cardiovascular responses appear to be associated with a different group of negative health outcomes (i.e., anxiety and depression). However, given the small sample sizes and limited follow-up in studies in chapters 5 and 6, future studies should examine the relationship of both blunted and exaggerated cardiovascular reactivity with a range of health outcomes both cross-sectionally and, more importantly, prospectively.

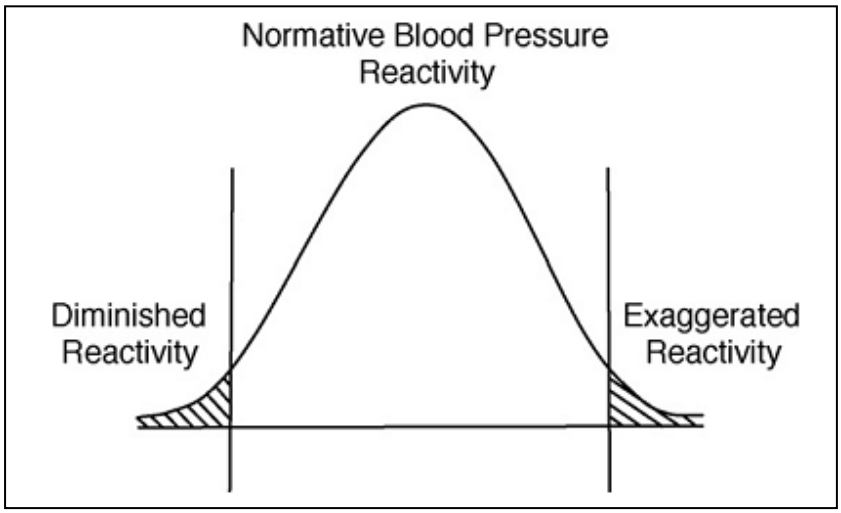


Figure 7.2 A hypothetical cardiovascular reactivity (hyper cardiovascular reactivity and hypo cardiovascular reactivity)

Mechanisms Linking Cardiovascular Reactivity and Future BP

As mentioned previously, controlling BP is a reciprocal balance between CO and peripheral resistance (Beevers et al., 2001). Further, active coping tasks generally appear to elicit sympathetic nervous system responses that stimulate cardiac and vascular beta-adrenergic receptors. In contrast, passive coping tasks involve sympathetic activation eliciting vasoconstriction (and increases in TPR) through alpha-adrenergic receptor stimulation (Obrist, 1976). Additionally, active coping tasks were associated with relatively greater changes in CO and these tasks involve a beta-adrenergic mediated pattern of responses via central mechanisms (Sherwood et al., 1986). Consequently, one mechanism for the relationship between SBP responses to mental arithmetic tasks (active coping) and future SBP may involve a beta-adrenergic mediated pattern of responses (via CO responses). The figure 7.3 below summarises the mechanisms linking cardiovascular reactivity and high BP from this thesis. The findings from this thesis suggest that cardiovascular responses to mental arithmetic may be useful in predicting BP among younger adults with a short follow-up. In addition, responses to mental arithmetic tasks, which provoked a beta-adrenergic response with an increased CO, may support the notion of a hyperkinetic circulation state (Flaa et al., 2008). Cardiovascular responses to cold pressor tasks, which primarily elicited an alpha-adrenergic response with an increased TPR, may be helpful in predicting hypertension among older adults; the systematic review in chapter 2 found that cardiovascular responses to passive coping tasks afforded a better prediction of hypertension than cardiovascular responses to active coping tasks. Future studies should continue to examine the importance of type of tasks, with younger or order adults, to determine the predictive value of cardiovascular reactivity for future BP and hypertension.

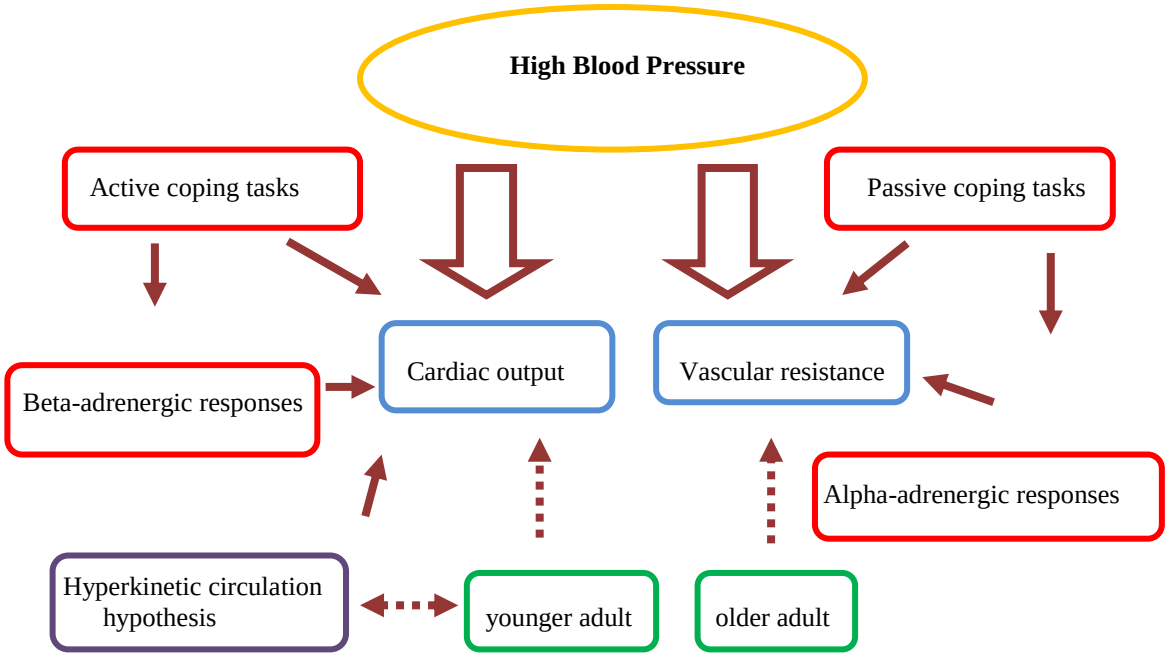


Figure 7.3 Mechanisms linking cardiovascular reactivity and high BP

Finally, the results have been demonstrated how reactivity might contribute to development of future increased BP using four cardiovascular reactivity models. Cardiovascular responses to mental arithmetic were associated with future BP which supports the reactivity as a marker for hypertension risk model. Further, after statistical adjustment for risk factors and baseline BP activity, cardiovascular reactivity was still a predictor of future BP; these results support the casual trait model of the Reactivity Hypothesis. Moreover, SBP responses to active coping tasks (mental arithmetic) afforded a better prediction of future SBP than SBP responses to passive coping tasks (cold pressor). Consequently, these results support the situation specific (and causal trait) model of cardiovascular reactivity. However, the interaction of stressful life events and cardiovascular reactivity did not predict future BP; the person-by situation interaction model was not supported. Therefore, cardiovascular reactivity appears, at least partially, to be a causal trait in the development of hypertension.

7.3 Limitations and Future Directions

The studies described in this thesis have a number of limitations including the use of laboratory measures of BP as a baseline, the focus on cardiovascular responses but not cardiovascular recovery, and the assessment of background stress. First, measures of BP within the laboratory may not be ideal. As discussed in chapters 5 and 6, individuals with

white coat hypertension may present with high BP in a laboratory setting and have normal or low BP in everyday life. Several clinical studies suggest that ambulatory BP monitoring may be a better clinical indicator of hypertension than BP readings from a single visit (Pickering, 1996; Pickering, 2000; Staessen, O'Brien, Thijs, & Fagard, 2000). Indeed, it has been recommended that individuals are not classified as hypertensive on the basis of a single clinic visit (Pickering, 2000). Therefore, cardiovascular responses to stress in a laboratory setting might be better measures of more accurate and realistic assessments of BP. Tuomisto et al. (2005) assessed cardiovascular reactions to active, passive and social task and used these to predict future BP over 9-12 years follow-up as assessed by casual BP readings and 24-hour ambulatory BP measures. SBP responses to psychological tasks were significant and strong independent predictors of future 24-hour ambulatory SBP, explaining 12% - 17% of the variance after adjustment for baseline SBP. In contrast, SBP responses to psychological tasks were weaker, although still significant, predictors of future casual SBP accounting for 4% - 8% of the variance of SBP after adjustment for baseline SBP.

Second, the anticipation of psychological stressors (anticipated stress before a task) provokes haemodynamic reactivity. Using pre-stress tasks as a baseline may reduce a substantial part of the individual differences which may occur in reaction to stress. For example, Light (1981) demonstrated that during the tasks and before the tasks (a cold pressor task, an erotic film, and a shock avoidance reaction time task), high reactors showed evidence of a greater cardiovascular reactivity even prior to the stressful events. In the Thai study (chapter 5), baseline BP levels rose in the final five minutes of the 20-minute baseline period. Therefore, in the UK study, the duration of resting periods was modified to 15-minute to reduce anticipation. Of course, anticipation of stressful tasks may be associated with the future BP. For example, Everson, Kaplan, Goldberg, and Salonen (1996) examined BP responses to the anticipation phase of an exercise stress test (a bicycle ergometer stress test) for five minutes before the exercise test in relation to future BP at four years of follow-up. SBP and DBP reactivity significantly predicted subsequent high BP after adjusting for age and resting BP (odds ratio = 1.03 and 1.07, respectively). Accordingly, examining the predictive utility of cardiovascular indices of anticipation and their psychological correlates (e.g., anxiety) may prove fruitful.

In addition to anticipation, cardiovascular recovery from stressful tasks has received some attention. Recent evidence suggests that cardiovascular recovery may be an equally strong

predictor future BP, hypertension (Moseley & Linden, 2006; Steptoe & Marmot, 2005a; Stewart & France, 2001; Stewart, Janicki, & Kamarck, 2006) and preclinical CHD (Heponiemi et al., 2007; Steptoe, Donald, O'Donnel, Marmot, & Deanfield, 2006), independently of initial resting BP and, in some cases, cardiovascular reactivity. Chida and Steptoe's (2010) meta-analysis found that poor cardiovascular recovery from stress was associated longitudinally with poor cardiovascular status (e.g., for prediction of future SBP, $r = 0.12$); the strength of these relationships was similar to those with cardiovascular reactivity (e.g., for prediction of future SBP, $r = 0.08$). However, only five articles of post-stress recovery were recruited in the meta-regression, whereas 36 articles of stress reactivity were conducted. Accordingly, further research should examine the role of cardiovascular reactivity and recovery to stress in the prediction of preclinical manifestations of increased CVD risk such as elevated BP or hypertension status. Psychophysiological mechanisms, such as preservative cognition (e.g., rumination, worry) which can prolong stress-induced increases in cardiovascular activity, should be the focus of these investigations too (Brosschot, Gerin, & Thayer, 2006; Gerin, Davidson, Christenfeld, Goyal, & Schwartz, 2006; Thayer, Friedman, & Borkovec, 1996).

The role and measurement of background stress also warrants further study. Chronic stress has been associated with cardiovascular reactivity (Carroll, Phillips, Ring, Der, & Hunt, 2005; Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012; Musante et al., 2000; Phillips, Carroll, Ring, Sweeting, & West, 2005) and may moderate the relationship between cardiovascular reactivity and future CHD (Lynch et al., 1998). Further, the possible role of socioeconomic factors that have been associated with cardiovascular risk should be examined. Several reviews of socioeconomic and CVD have concluded that psychobiological reactivity is associated with socioeconomic status: heightened cardiovascular reactivity is associated with low socioeconomic status (i.e., education, occupational status) (Kaplan & Keil, 1993; Steptoe & Marmot, 2002; Steptoe, Willemsen, Kunz-Ebrecht, & Owen, 2003). Thus, future studies involving prospective cohort study should examine whether these variables moderate the impact of cardiovascular reactivity upon the development of preclinical manifestations of cardiovascular risk such as increased BP. Further, the generalisability of cardiovascular reactivity to everyday life should be considered, and modeling the elements of everyday life that elicit the largest cardiovascular responses might be revealing in future prospective studies given their importance in studies of generalisability (Carroll, 2011).

The manner in which initial baseline cardiovascular activity is calculated differs across studies. Although the methods used here has been used in other studies using multiple psychological stress tasks, alternate methods have been used. Thus, comparison between initial baseline cardiovascular activity and average levels measured before each task were made. The results revealed that there were no significant differences in these baselines cardiovascular activity and reactivity scores regardless of the type of baseline cardiovascular activity measure used (see appendix tables 4.9, 4.10, 4.11, 4.12). Further, the relationships between cardiovascular reactivity and depression and anxiety scores were very similar regardless of how baseline cardiovascular activity was determined (see appendix tables 4.15, 4.16, and 4.17). In addition, SBP responses to mental arithmetic remained a significant and strong independent predictor of future SBP over one year follow-up in both the Thai (see appendix tables 5.2 and 5.3) and UK samples (see appendix tables 6.8, 6.9, and 6.10). Therefore, using the different baseline cardiovascular reactivity did not affect the results suggesting that the findings presented here are not sensitive to methodological or statistical features of baseline calculation.

Finally, future studies need to specify the population characteristics in the study. In this thesis, the findings are limited by small sample sizes and commensurate inadequate statistical power. Further, the studies had relatively short follow-up periods. Homogenous groups of sufficient size and longer follow-up periods will be important for future quantitative studies. These studies should also focus on the role that cardiovascular reactivity plays in the development of hypertension. Although there is suggestive evidence that cardiovascular reactivity has a casual role in hypertension development, studies have not attempted to alter cardiovascular reactivity and assess BP over time (e.g., within an randomized controlled trial), nor have studies examined whether changes in cardiovascular reactivity are associated with subsequent changes in cardiovascular reactivity (e.g., panel analysis; Berrington, Smith, & Sturgis, 2006). Finally, pathophysiological mechanisms have also not been fully elucidated (Carretero & Oparil, 2000) and should be the focus of further research.

7.4 Clinical Implications

Several studies have demonstrated that greater cardiovascular reactivity is associated with cardiovascular risk (i.e., high BP, hypertension, preclinical CHD or CVD events), and this was also borne out by the results in this thesis. Therefore, psychological stressors may help to identify individuals at risk of CVD. Previous studies have shown that an exaggerated

cardiovascular reaction to mental stress tests is associated with exercise–induced myocardial ischemia in patients with stable myocardial ischemia or patients with preclinical CHD (Goldberg et al., 1996; Kral et al., 1997; Sheps et al., 2002). Rozanski, Blumenthal, and Kaplan (1999) also suggested that mental stress testing may provide added prognostic information beyond that given by a standard exercise stress test. Further, mental stress-induced ischaemia has been prospectively related to cardiac events (Burg, Jain, Soufer, Kerns, & Zaret, 1993) and all-cause mortality in cardiac patients (Sheps et al., 2002), although BP responses were unrelated to all-cause mortality (Sheps et al., 2002). Therefore, cardiovascular responses to mental stress tests may be an alternative to exercise stress testing to the assess risk of CVD (including future increased BP levels), particularly in patients with musculoskeletal discomfort, and those unable to tolerate high workload increments (Fletcher et al., 2001).

Moreover, assessing cardiovascular responses to psychological stress may help guide therapeutic efforts to reduce high BP Attenuation of haemodynamic reactions to psychological stressor using behavioural therapy, emotional control, mediation, stress management or relaxation therapy might be one approach to reduce high BP levels. Many researchers have shown that emotional control, meditation, biofeedback control or behavioural interventions are effective inventions to reduce BP and CVD risk (Glasgow, Gaarder, & Engel, 1982; Greenhalgh, Dickson, & Dundar, 2010; Tacon, McComb, Caldera, & Randolph, 2003). Thus, attenuation of haemodynamic reactions to mental stress may potentially be used to assess the reduced the risk of CVD. Additionally, physicians should emphasize the role of psychosocial risk factors (e.g., smoking, family history of CVD) in counselling their patients (Alton, 2005; Rozanski, Blumenthal & Kaplan, 1999). Finally, controlling or reducing risk factor levels (e.g., obesity) offer opportunities for preventing hypertension and CVD.

7.5 Conclusion

The studies in this thesis represent the first to examine associations between cardiovascular reactivity and psychological factors (i.e., anxiety and depression) and future BP, in both Western and Asian countries. They add to a growing body of evidence that support the role of cardiovascular reactivity to mental stress tests in the prediction, and possible development, of future elevated BP. However, BP responses to only one of the three tasks used as stressors (the mental arithmetic task) predicted BP increases over a one year follow-up in both the UK

and Thai participants. The relationships remained after controlling for baseline cardiovascular activity and traditional risk factors. Thus, these findings suggest that BP reactions to the mental arithmetic task eliciting primarily beta-adrenergic cardiovascular responses that may be predictive of significant BP change; however, there was no indication that specific haemodynamic changes were responsible for these predictive relationships. In addition, cross-sectional analysis revealed that blunted cardiovascular responses were associated with depressive symptoms and anxiety (in the UK study); changes in CO were implicated. Future studies need to continue to examine the psychophysiological mechanisms associated with cardiovascular reactivity, and the utility of cardiovascular reactivity in predicting BP changes, hypertension status, and depression and anxiety over many years.

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Appendix 1- Ethics

INFORMATION SHEET

Do cardiovascular responses to mental stress tests predict blood pressure one-year later?

We are interested in cardiovascular responses (e.g., blood pressure and heart rate) to mental stress task. This is part of my PhD research studies. Your results will help us to understand how cardiovascular responses differ to mental stress tests. In addition, we will examine how useful these responses are in predicting future blood pressure. You involvement will be no longer than 1 hour, a 24 hour period where we measure you ambulatory blood pressure using a wearable blood pressure monitor during a weekday and be followed by a follow-up visit at 1 year where your resting blood pressure will be assessed. The research study consists of a number of stages; these stages are briefly outlined below (see a flow chart).

We will first collect information on your name, address, gender, date of birth, weight, height, medical history, current medication usage, parental history of cardiovascular disease or hypertension, cigarette smoking status, physical activity levels and psychological measures by completing questionnaires. Following this, you will be asked to perform a random order set of 3 mental stress tests. Before the tests, we will connect you to a blood pressure monitor. You will be asked to rest for 15 minutes before starting the tests. We will record physiological data during the resting period, while you complete the mental stress tasks and at the end of testing. The mental stress tasks are mental arithmetic, speech task, and cold pressor (placing hand in cold water), each of which are followed by 8 minutes for recovery period. For the speech task, a video camera will be set up and will record during this task. After all tasks are completed, you will be asked to complete questionnaire about how your feel during task. At the end of laboratory setting, you will be fitted with ambulatory blood pressure monitor for 24 hours during a regular week day; this will take blood pressure readings at regular intervals throughout the day (you will be able to turn it off or take it off during the night if it disturbs your sleep).

At 1-year follow up, you will be invited back to the laboratory to examine your blood pressure; three resting blood pressure readings will be taken.

These testing procedures have little risk associated with them. However, during the cold pressor task you may feel some discomfort as the water is close to freezing; you can remove your hand at any time if it becomes too uncomfortable.

Please do not take part if you have:
any circulatory disorders including Reynaud's Disease;
have a diagnosis of cardiovascular disease including myocardial infarction (heart attack), peripheral vascular disease, or symptomatic cerebral ischeamia (stroke);
any have known neurological disorder, prior convulsions, or head injury that resulted in concussion;
chronic renal failure or liver disease;
a history of mental health problems;
a fever (high temperature);
are pregnant;
had cardiac surgery, including percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).

If you are happy to take part in this study please indicate your consent by signing the consent form. Please note, all data are treated in the strictest of confidence, and only the researchers have access to them. When we examine the information from the physiological measures and questionnaires we will make them anonymous, and your data will remain anonymous if we discuss or publish any information from this study. The data will be stored in a locked cabinet and a password protected computer for the duration of the project. After publication, the data will be kept for five years, and then discarded confidentially.

Should you have any questions and want to know more about the outcome of the study please feel free to contact Kornanong Yuenyongchaiwat on k. Yuenyongchaivat@derby.ac.uk, or (44) 1332-592038 or my supervisor, David Sheffield, at d.sheffield@derby.ac.uk or (44) 1332-592038

DEBRIEF SHEET

Do cardiovascular responses to mental stress tests predict blood pressure one-year later?

Thank you for taking part in this study
your participation is much appreciated.

Rationale: Cardiovascular disease (CVD) is a major cause of death in Europe and the rest of the world. In addition, approximately half (48%) of total mortality from CVD are from coronary heart disease (CHD). There has been evidence to support that mental stress tests might help predict future CHD and hypertension. These studies suggest that mental stress tests might also help detect current risk but may have low sensitivity because of the measures taken (primarily blood pressure and heart rate) and the limited range of mental stress tasks used. This research study aims to examine the predictive values of a greater range of cardiovascular responses (including measures of cardiac output and peripheral resistance) to three mental stress tasks. This will enable us to determine if mental stress tasks (or combinations of tasks) might predict hypertension (or raised blood pressure) and add to the data on cardiovascular responses by assessing underlying haemodynamics.

Therefore, the aims of this research study are to assess cardiovascular responses to mental stress tests and to determine how useful these responses are in predicting future blood pressure. These results will help us to understand how cardiovascular responses to mental stress tests and the relationship between cardiovascular responses to mental stress tests (three stress tests) and resting blood pressure levels at 1-year follow-up.

We hope you found the study interesting and enjoyed taking part in the study. We would like to contact you in one year to measure your blood pressure again. If you are willing for us to contact you please tick the box below and provide contact details:

☐

Your contact details:

Name: _____ Address _____

Telephone number _____ Age _____

Gender _____ Race/Ethnic _____

If any aspect of the study has raised issues for you or has caused any upset please speak to one of the project team who will be able to provide some support or facilitate access to appropriate support. If you have any concerns about your blood pressure or any cardiac symptoms then advice can be provided from your GP or NHS direct. You can also find information from the websites: www.heartuk.org.uk or www.americanheart.org or visit NHS website on www.nhs.uk

Thank you once again for your participation in this research.

Sources of Support:

Key Staff:

- Kornanong Yuengchaiwat – researcher (441332592089)
- David Sheffield – Supervisor (441332592038).

Should you have any questions please feel free to contact Kornanong Yuenyongchaiwat on K.Yuenyongchaivat@derby.ac.uk or 0133-259-2089., or my supervisor, David Sheffield, at D.Sheffield@derby.ac.uk or 01332592038.

CONSENT FORM

Do cardiovascular responses to mental stress tests predict blood pressure one-year later?

Researchers: Kornanong Yuenyongchaiwat, Professor David Sheffield, Dr Frances Maratos and Dr Ian Baker

Please tick the following boxes if you agree to the statements:

1. I confirm that I have read and that I understand the information sheet for the study "Do cardiovascular responses to mental stress tests predict blood pressure one-year later?" and have had the opportunity to ask questions ☐

2. I understand that my participation is voluntary and I understand that I may withdraw my consent and discontinue participation at any time, without further consequences ☐

3. I agree to be connected to a blood pressure monitor during tests ☐

4. I agree to perform the mental stress tests which are mental arithmetic, speech task and cold pressor test ☐

5. I agree to take 24-hr ambulatory blood pressure during working day ☐

6. I agree to have my blood pressure and complete a two page questionnaire about my health at follow-up at one year after the initial test ☐

7. I do not have any of the conditions listed on the information sheet ☐

8. I consent that my participation is voluntary and I understand that I may withdraw my consent and discontinue participation at any time if I feel uncomfortable, or do not wish to continue for any reason, without further consequences and without indicating reason for my withdrawal. ☐

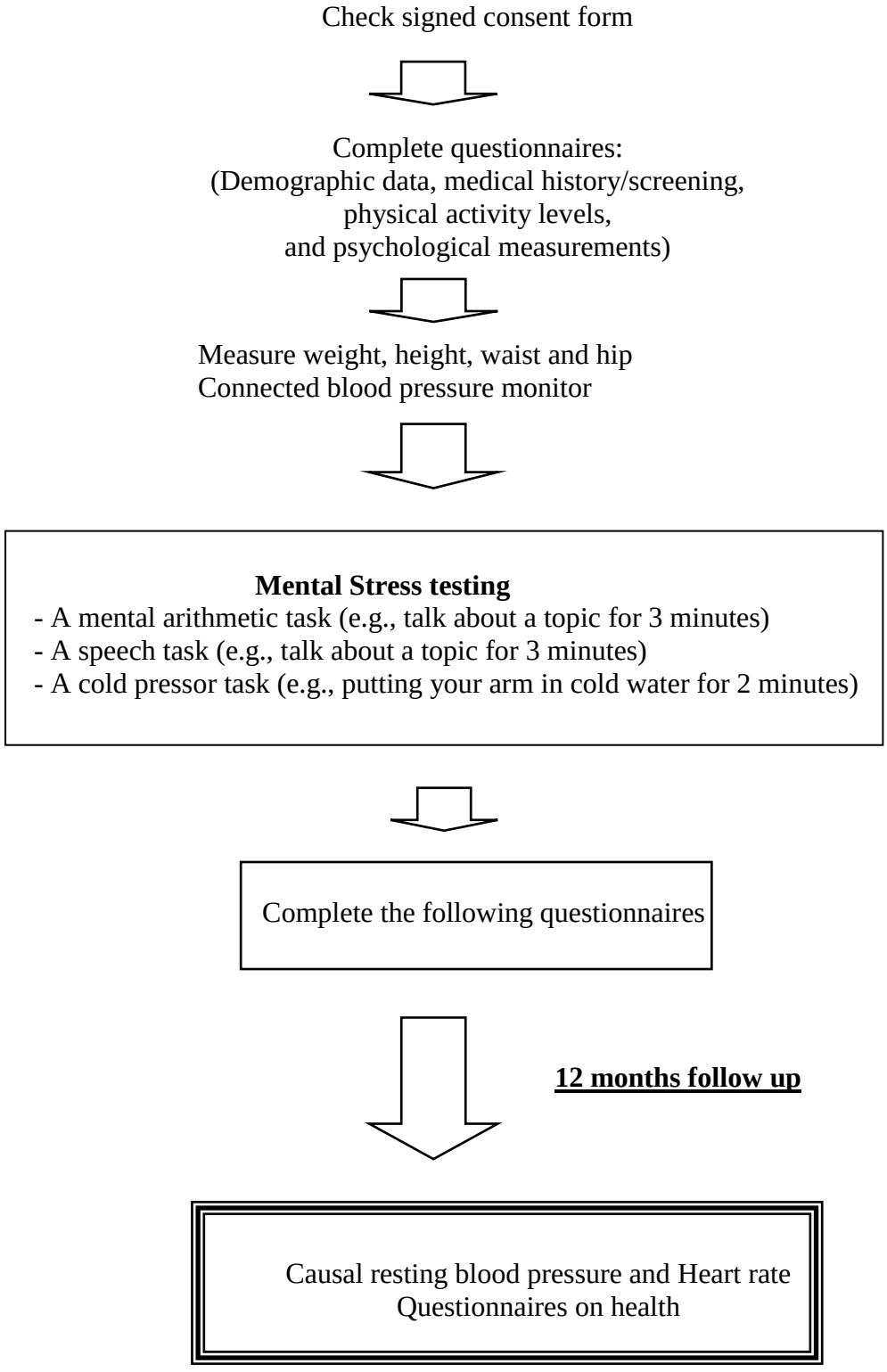
.....	.....	.....
Name of Subject	Signature	Date

.....	.....	.....
Name of Researcher	Signature	Date

Please also provide us with an identifying number or words (e.g. mothers' maiden name and year of birth, e.g. Yuengyongchaiwat1973), so we can identify your details if you decide you want to withdraw from the study. We will also use this to match your follow-up data with your data from the stress tests.

Participant number:

Flow chart diagram illustrating the stages of research study: Cardiovascular responses to mental stress tests



Appendix 2- Measures

Medical History Questionnaire

1. Do you have or have you ever had high blood pressure (BP > 140/90 mmHg) or taking antihypertensive or blood pressure lowering medication? [ ] yes [ ] no
2. Does one or both of your parents have high blood pressure (BP > 140/90 mmHg) or taking antihypertensive or blood pressure lowering medication or cardiovascular (heart) disease? [ ] yes [ ] no

   if yes,

   mother – hypertension [ ]

   father- hypertension [ ]

   mother - cardiovascular (heart) disease [ ]

   father - cardiovascular (heart) disease [ ]

3. Do you have or have you ever had a high blood glucose, or a diagnosis of diabetes and/or are receiving medical treatment for this condition? [ ] yes [ ] no
4. Do you have or have you ever had a high cholesterol level or being treated with cholesterol lowering medication [ ] yes [ ] no
5. Do you or have you ever smoke cigarettes? [ ] yes [ ] no

   If yes; 5.1 How long have your smoked? _____ years/ months

   5.2 How many cigarettes do you smoke per day? _____cigarettes

   5.3 Currently do you smoke?

   _____ continue to smoke _____ years of smoke

   _____ quit smoke _____years of quit smoke

The Hospital Anxiety and Depression Scale (HADS)

Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box ☒ in each section

I feel tense or wound up:		**I feel as if I am slowed down:**	
Most of the time	☐	Nearly all the time	☐
A lot of the time	☐	Very often	☐
Time to time	☐	Sometimes	☐
Not at all	☐	Not at all	☐
I still enjoy the things I used to enjoy:		**I get a sort of frightened feeling like butterflies in the stomach:**	
Definitely as much	☐	Not at all	☐
Not quite so much	☐	Occasionally	☐
Only a little	☐	Quite often	☐
Hardly at all	☐	Very often	☐
I get a sort of frightened feeling as if something awful is about to happen:		**I have lost interest in my appearance:**	
Very definitely and quite badly	☐	Definitely	☐
Yes, but not too badly	☐	I don't take so much care as I should	☐
A little, but it doesn't worry me	☐	I may not take quite as much care	☐
Not at all	☐	I take just as much care as ever	☐
I can laugh and see the funny side of things:		**I feel restless as if I have to be on the move:**	
As much as I always could	☐	Very much indeed	☐
Not quite as much now	☐	Quite a lot	☐
Definitely not so much now	☐	Not very much	☐
Not at all	☐	Not at all	☐
Worrying thoughts go through my mind:		**I look forward with enjoyment to things:**	
A great deal of the time	☐	As much as ever I did	☐
A lot of the time	☐	Rather less than I used to	☐
From time to time but not too often	☐	Definitely less than I used to	☐
Only occasionally	☐	Hardly at all	☐
I feel cheerful:		**I get sudden feelings of panic:**	
Not at all	☐	Very often indeed	☐
Not often	☐	Quite often	☐
Sometimes	☐	Not very often	☐
Most of the time	☐	Not at all	☐
I can sit at ease and feel relaxed:		**I can enjoy a good book or radio or TV programme:**	
Definitely	☐	Often	☐
Usually	☐	Sometimes	☐
Not often	☐	Not often	☐
Not at all	☐	Very seldom	☐

The post-test questionnaire

Read each item and circle the rating which comes closest to **how you have been feeling about each task.**

1.How stressful was the mental arithmetic procedure?

Not stressful very stressful

0 1 2 3 4 5 6 7 8 9 10

2. How stressful was the speech procedure?

Not stressful very stressful

0 1 2 3 4 5 6 7 8 9 10

3. How stressful was the cold pressor procedure?

Not stressful very stressful

0 1 2 3 4 5 6 7 8 9 10

4. How painful was the cold pressor procedure?

Not painful very painful

0 1 2 3 4 5 6 7 8 9 10

5. Which procedure did you find most stressful? Please rank with numbers 1-3 in the box next to that task.
(1= too much stressful, 2= fair, 3= too little stressful)

…… Mental arithmetic
…… Speech task
……. Cold pressor

Life Events Scale

This is a list of stressful events in your life. Sit back, take a moment, and review your life **over the past 12 months**. Go through the following list. Click on the check box of those stressful events that you have happened or are taking place in your life.

☐ Death of a spouse	☐ Divorce
☐ Change to different line of work	☐ Death of a close friend
☐ Marital separation (or separation from any major intimate relationship)	☐ Jail term
☐ Death of a close family member	☐ Personal injury or illness
☐ Major change in health or behaviour of a family member	☐ Being fired from work
☐ Sexual difficulties	☐ Marital reconciliation
☐ Gain of new family member thru birth, adoption, or remarriage	☐ Retirement
☐ Business readjustment	☐ Pregnancy
☐ Major change in finances	☐ Marriage
☐ Increase in number of arguments with spouse	☐ Trouble with boss/superior
☐ Mortgage or loan for major purchase (i.e. home, etc.)	☐ Foreclosure of mortgage or loan
☐ Changes in responsibility at work	☐ Son or daughter leaving home
☐ Outstanding Personal Achievement	☐ Spouse stops work outside of home
☐ Trouble with in-laws	☐ Going back to school
☐ Change in living condition (rebuilding, remodelling)	☐ Change in residence
☐ Change in work hours or responsibilities	☐ Change in school
☐ Revision/change of personal habits	☐ Change in recreational habits
☐ Change in church/spiritual activities	☐ Change in social activities
☐ Purchase of major items (auto, computer, etc)	☐ Change in sleeping habits
☐ Change in number of family get-togethers	☐ Change in eating habits
☐ Vacation	☐ Christmas
☐ Minor violations of the law (e.g., traffic tickets, misdemeanours)	

Appendix 3- Results

Table 2.1 Data searching based upon electronic databases

Date of searching	Database	terms	Retrieved studies	Selected studies
15/July/2009	**PsycINFO**	(mental arithmetic OR math* OR Stroop OR speak OR problem solv* OR mirror trac* OR cold pressor OR reaction time OR stress interview	**510**	
	SPORTDIscus	OR cognit* challe* OR anger recall OR speech task OR emotion* stress OR mental stress OR psycho* stress)	**153**	
				80
	CINAHL	AND (*sympathetic OR isch*emi* OR myocard* OR blood pressure OR heart rate OR cardi* OR peripheral resistance OR ventri* mass wall motion OR electrocardio* OR haemodyn* OR hemodyn* OR heart OR epinephrine OR arterosci* OR coronary heart OR heart OR isch* heart) AND (response OR react* OR change OR recovery) AND (predict* OR prospec* OR longit* OR follow-up)	**212**	
15/July/2009	**Web of Knowledge**	(mental stress OR psychological stress OR Mental arithmetic OR stroop colour OR stoop color OR speaking task OR problem solving OR mirror trace OR cold pressor OR reaction time OR stress interview OR cognitive challenge OR anger recall OR speech task OR emotion stress OR VDO) AND (sympathetic OR parasympathic OR ischemia heart OR myocardial OR blood pressure OR heart rate OR peripheral resistance OR cadiac output OR epinephrine OR ventricular mass OR wall motion abnormal OR electrocardiogram OR hemodynamic OR norepinephrine OR coronary OR myocardial ischemic OR artheroscierosis OR hypertension) AND (response OR reaction OR reactivity OR change OR recovery) AND (predict OR prospective OR longitudinal OR follow)	**768**	**72**
16/July/2009	**Cochrane library**	(mental stress OR psychological stress OR Mental arithmetic OR stroop colo* OR speak OR problem solv* OR mirror trac* OR reaction time OR cold pressor OR stress interview OR cognitive chall* OR anger recall OR speech task OR emotion stress OR VDO) AND (sympathetic OR parasym* OR ische* heart OR myocardi* OR blood pressure OR heart rate OR peripheral resistance OR cadiac output OR ventri* mass OR wall motion abnormal OR electrocardio* OR hemodynamic OR norepinep* OR epinep* OR coronary OR myocardial ische* OR artherosc*) AND (response OR reaction OR reactivity OR change OR recovery) AND (predict OR prospective OR longitu* OR follow)	**1991**	**0**

Date of searching	Database	Terms	Retrieved studies	Selected studies
16/July/2009	**PubMed**	(mental stress OR psychological stress OR mental arithmetic OR stroop colour OR stroop color OR speaking task OR problem solving OR reaction time OR stress interview OR cognitive challenge OR anger recall OR speech task OR emotion stress OR VDO) AND (sympathetic OR parasympathetic OR ische* heart OR myocardial OR blood pressure OR heart rate OR peripheral resistance OR cardiac output OR ventricular mass OR wall motion abnormal OR electrocardiography OR hemodynamic OR norepinephrine OR epinephrine OR coronary OR myocardial ischemia OR artheroscierosis OR hypertension) AND (response OR reaction OR reactivity OR change OR recovery) AND (predict OR prospective OR longitudinal OR follow)	**1554**	**79**
17/July/2009	**Medline**	(mental stress OR psychological stress OR Mental arithmetic OR stroop colour OR stoop color OR speaking task OR problem solving OR mirror trace OR cold pressor OR reaction time OR stress interview OR cognitive challenge OR anger recall OR speech task OR emotion stress OR VDO) AND (sympathetic OR parasympathic OR ischemia heart OR myocardial OR blood pressure OR heart rate OR peripheral resistance OR coronary OR ventricular mass OR wall motion abnormal OR electrocardiogram OR hemodynamic OR norepinephrine OR epinephrine OR myocardial ischemic OR artheroscierosis OR hypertension) AND (response OR reaction OR reactivity OR change OR recovery) AND (predict OR prospective OR longitudinal OR follow)	**1282**	**76**

Table 2.2 Quality checklists

	Items	#1	#2	#3
1	Was the inclusion criteria defined? 3 = clearly defined 2 = partial defined 1 = poorly defined 0 = not defined			
2	Was the subject selection clearly explained? 3 = clearly explained 2 = partial explained 1= poorly explained 0 = not explained			
3	Was there an adequate description of diagnostic criteria? 3 = clearly defined 2 = partial defined 1= poorly defined 0 = not defined			
4	Was the clinical and demographic characteristics (e.g., Age, family history, medical history, cardiovascular measures: blood pressure, etc) fully described ? 3 = fully described 2 = partial described 1 = poorly described 0 = not described			
5	Were the samples of this study directly representative of other groups? 3 = fully representative 2 = partial representative 1 = poorly representative 0 = not representative			
6	Were all individuals followed-up at the same time point? 3 = at the similar point 2 = within 6 months-1 year 1 = more than 1year 0 = not described			

	Items	#1	#2	#3
7	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed? 3 = adequate proportion (less than 20% drop-out rate) 2 = partial proportion (20-30% drop-out rate) 1 = inadequate (more than 30% drop-out rate) 0 = unknown/not addressed			
8	Was follow-up sufficiently long for the outcomes to study? 3 = > 10 years 2 = 5-10 years 1= < 5 years			
9	Was the study addressing an appropriate and clear objective? 3 = Clearly addressed 2 = partial addressed 1= poorly addressed 0 = Not addressed/ not reported			
10	Was outcome assessment blind to prognostic information? 3 = Action taken to blind assessors, or outcomes such that bias is unlikely 2 = Moderate chance of unblinding of assessors 1 = poor chance of unblinding of assessors 0 = Not mentioned			
11	Were the outcome measures used fully defined? 3 = Fully defined 2 = Partial defined 1 = Poorly defined 0 = Not defined			
12	Was the outcome appropriate? 3 = Fully appropriate 2 = Partially appropriate 1 = Poorly appropriate 0 = Not mentioned			
13	Was the prognostic variable fully defined? 3 = Fully defined including details of method of measurement. 2 = Partial defined and moderately precisely measured 1 = Poorly defined and mildly precisely measured 0 = Not defined and not precisely measured			

	Items	#1	#2	#3
14	Was the prognostic variable available for all of participants? 3 = Fully available and the cut points defined. 2 = Partial available and the cut points clearly defined 1 = Poorly available and the cut points not clearly defined. 0 = Not mentioned			
15	Was the continuous predictor variable analyzed appropriately? 3 = Fully appropriately 2 = Partial appropriately 1 = Poorly appropriately 0 = Not mentioned			
16	Was there the adequate statistical adjustment for all important prognostic factors? 3 = Fully adequate statistical adjustment 2 = Partial adequate statistical adjustment 1 = Poorly adequate statistical adjustment 0 = Not mentioned			
17	Was the task fully described? 3 = Fully described 2 = Partial described 1 = Poorly described 0 = Not mentioned			
	TOTAL SCORES			

Adapted from the Centre for Reviews and Dissemination, University of York, 2008

Table 2.3 Articles excluded

No.	References	Reason for Exclusion
1	Aderman, M. H., Ooi, W. L., Madhavan, S., & Cohen, H. (1990). Blood pressure reactivity predicts myocardial infarction among treated hypertensive patients. *Journal of Clinical Epidemiology, 43,* 859-866.	Non relevant sample
2	Armstrong, H. G., & Rafferty, J. A. (1950). Cold pressor test follow-up study for seven years on 166 officers. *American Heart Journal, 39,* 484-490.	No control baseline BP
3	Barnett, P. H., & Hines, E. A. (1963). Blood pressure and vascular reactivity to the cold pressor test. *Journal of the American Medical Association, 183,* 143-146.	Insufficient data
4	Brody, S., Veit, R., & Rau, H. (1996). Neuroticism but not cardiovascular stress reactivity is associated with less longitudinal blood pressure increase. *Personality and Individual Differences 20,* 375-380.	Non relevant measurement
5	Brydon, L., & Steptoe, A. (2005). Stress-induced increases in interlueukin-6 and fibrinogen predict ambulatory blood pressure at 3-year follow-up. *Journal of Hypertension, 23,* 1001-1007.	Overlapping study
6	Carroll, D., Ring, C., Hunt, K., Ford, G., & Macintyre, S. (2003). Blood pressure reactions to stress and the prediction of future blood pressure: Effects of sex, age, and socioeconomic position. *Psychosomatic Medicine, 65,* 1058-1064.	Overlapping study
7	Carroll, D., Davey Smith, G., Sheffield, D., Shipley, M. J., & Marmot, M. G. (1995). Pressor reactions to psychological stress and prediction of future blood pressure: Data from the Whitehall II study. *British Medical Journal, 310,* 771-776.	Overlapping study

8	Chen, Y., Dangardt, F., Osika, W., Berggren, K., Gronowitz, E., & Friberg, P. (2010). Age- and sex-related differences in vascular function and vascular response to mental stress. Longitudinal and cross-sectional studies in a cohort of healthy children and adolescents. *Atherosclerosis, 220,* 269-274.	Non relevant measurement
9	Eich, R. H., & Jacobsen, E. C. (1967). Vascular reactivity in medical students followed for 10 year. *Journal of Chronic Disease, 20,* 583-592.	No control baseline BP
10	Everson, S. A., Lynch, J. W., Kaplan, G. A., Lakka, T. A., Sivenius, J., & Salonen, J. T. (2001). Stress-induced blood pressure reactivity and incident stroke in middle – aged men. *Stroke, 32,* 1263-1270.	Non relevant sample
11	Falkner, B., Kushner, H., Onesti, G., & Angelakos, E. T. (1981). Cardiovascular characteristics in adolescents who develop essential hypertension. *Hypertension, 3,* 521-527.	Insufficient data
12	Georgiades, A., Lemne, C., Faire, U. D., Lindvall, K., & Fredrikson, M. (1997). Stress-induced blood pressure measurements predict left ventricular mass over three years among borderline hypertensive men. *European Journal of Clinical Investigation 27*, 733-739.	Combined mental and physical stress tests
13	Gianaros, P. J., Salomon, K., Zhou, F., Owens, J. F., Edmundowicz, D., Kuller, L. H., & Matthews, K. A. (2005). A greater reduction in high frequency heart rate variability to a psychological stressor is associated with subclinical coronary and aortic calcification in postmenopausal women. *Psychosomatic Medicine, 67,* 553-560.	Non relevant measurement
14	Harland, W. R., Osborne, R. K., & Graybiel, A. (1964). Prognostic value of the cold pressor test and the basal blood pressure: Based on an eighteen- year follow-up*. *American Journal of Cardiology, 13,* 683-687.	No control baseline BP

15	Hassellund, S. S., Flaa, A., Sandvik, L., Kjeldsen, S. E., & Rostrup, M. (2010). Long-term stability of cardiovascular and catecholamine responses to stress tests. An 18-year follow-up study. *Hypertension, 55,* 131-136.	Non relevant outcome
16	Jain, D., Burg, M., Soufer, R., & Zaret, B. L. (1995). Prognostic implications of mental stress-induced silent left ventricular dysfunction in patients with stable angina pectoris. *American Journal of Cardiology, 76,* 31-35.	Non relevant sample
17	Jiang, W., Babyak, M., Krantz, D. S., Waugh, R. A., Coleman, R. E., Hanson, M. M., & Blumenthal, J. A. (1996). Mental stress -- Induced myocardial ischemia and cardiac events. *Journal of the American Medical Association, 275,* 1651-1656.	Non relevant sample
18	Jokiniitty, J. M., Tuomisto, M. T., Majahalme, S. K., Kahonen, M. A., & Turjanmaa, V. M. (2003). Pulse pressure responses to psychological tasks improve the prediction of left ventricular mass: 10 years of follow-up. *Journal of Hypertension, 21,* 789-795.	Insufficient data
19	Krantz, D. S., Santiago, H. T., Kop, W. J., Bairey Merz, C. N., Rozanski, A., & Gottdiener, J. S. (1999). Prognositc value of mental stress testing in coronary heart disease*. *American Journal of Cardiology, 84,* 1292-1297.	Non relevant sample
20	Levin, A. Y., & Linden, W. (2006). Dose dissociation of emotional and physiological reactivity predict blood pressure change at 3- and 10- year follow-up? *Biological Psychology, 77,* 183-190.	Overlapping study
21	Light, K. C. Girdler, S. S., Sherwood, A., Bragdon, E. E., Brownley, K. A., West, S. G., & Hinderliter, A. L. (1999). High stress responsivity predicts later blood pressure only in combination with positive family history and high life stress. *Hypertension, 33,* 1458-1464.	Combined stressors

22	Manuck, S. B., Olsson, G, Hjemdahl, P., & Rehnqvist, N. (1992). Does cardiovascular reactivity to mental stress have prognostic value in postinfarction patients? A pilot study. *Psychosomatic Medicine, 54,* 102-108.	Non relevant sample
23	Matthews, K. A., Woodall, K. L., & Allen, M. T. (1993). Cardiovascular reactivity to stress predicts future blood pressure status. *Hypertension, 22,* 479-485.	Combined mental and physical stress tests
24	Ming, E. E., Adler, G. K., Kessler, R. C., Fogg, L. F., Matthews, K. A., Herd, J. A., & Rose, R. M. (2004). Cardiovascular reactivity to work stress predicts subsequent onset of hypertension: The Air Traffic Controller Health Change Study. *Psychosomatic Medicine, 66,* 459-465.	Non relevant stressor
25	Murdison, K. A., Treiber, F. A., Mensah, G., Davis, H., Thomspon, W., & Strong,W. B. (1998). Prediction of left ventricular mass in youth with family histories of essential hypertension. *American Journal of the Medical Sciences, 315,*118-123.	Combined mental and physical stress tests
26	Murrphy, J. K., Alpert, B. S., Walker, S. S., & Willey, E. S. (1991). Children's cardiovascular reactivity: Stability of racial blood pressure over a one-year period. *Psychophysiology, 28,* 447-457.	Overlapping study
27	Steptoe, A., Donald, A. E., O'Donnell, K., Marmot, M., & Deanfield, J. E. (2006). Delayed blood pressure recovery after psychological stress is assoicated with carotid intima-meida thickness. Whitehall Psychology Study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 26,* 2547-2551.	Non relevant outcome
28	Malpass, D., Treiber, F. A., Turner, J. R., Davis, H., Thompson, W., Levy, M., & Strong, W. B. (1997). Relationships between children's cardiovascular stress responses and resting cardiovascular functioning 1 year later. *International Journal of Psychophysiology, 25,* 139-144.	Overlapping study

29	Thomas, C. B., & Duszynski, K. R. (1982). Blood pressure levels in young adulthood as predictors of hypertension and the fate of the cold pressor test. *The John Hopkins Medical Journal, 151,* 93-100.	No control baseline BP
30	Thomas, J., Neser, W. B., Knuckles, B., Semenya, K., Thomas, D. J., & Gillum , R. F. (1988). Failure of the cold pressor test to predict hypertension in black physicians: The Meharry Cohort Study. *Journal of the National Medical Association, 80,* 1185-1187.	Insufficient data
31	Treiber, F. A., Musante, L., Kapuku, G., Davis, C., Litaker, M., & Davis, H. (2001). Cardiovascular (CV) responsivity and recovery to acute stress and future CV functioning in youth with family histories of CV disease: A 4- year longitudinal study. *International Journal of Psychophysiology 41,* 65-74.	Combined mental and physical stress tests
32	Treiber, F. A., Raunikar, A. R., Davis, H., Fernandez, T., Levy, M., & Strong W. B. (1994). 1- year stability and prediction of cardiovascular functioning at rest and during laboratory stressors in youth with family histories of essential hypertension. *International Journal of Behavioral Medicine, 1,* 335-353.	Overlapping study
33	Uchino, B. N., Holt-Lunstad, J., Bloor, L. E., & Campo, R. A. (2005). Aging and cardiovascular reactivity to stress: Longitiudinal evidence for changes in stress reactivity. *Psychology and Aging, 20,* 134-143.	Non relevant outcome
34	Wood, D. L., Sheps, S. G., Elveback, L. R., & Schirger, A. (1984). Cold pressor test as a predictor of hypertension. *Hypertension, 6,* 301-306.	Insufficient data

Table 2.4 Articles included

No.	References	Outcome
1	Carroll, D., Davey Smith, G., Sheffield, D., Willemsen, G., & Sweetnam, P. M. (1996). Blood pressure reactions to the cold pressor test and the prediction of future blood pressure status: Data from the Caerphilly study. *Journal of Human Hypertension, 10,* 777-780.	BP
2	Carroll, D., Davey Smith, G., Shipley, M. J., Steptoe, A., Brunner, E. J., & Marmot, M. G. (2001). Blood pressure reactions to acute psychological stress and future blood pressure status: A 10-year follow-up of men in the Whitehall II Study. *Psychosomatic Medicine, 63,* 737-743.	BP, Hypretension
3	Carroll, D., Phillips, A. C., Der, G., Hunt, K., & Benzeval, M. (2011). Blood pressure reactions to acute mental stress and future blood pressure status: Data from the 12- year follow-up of the West of Scotland Study. *Psychosomatic Medicine, 73,* 737-742.	BP, Hypertension
4	Del Rosario, J. D., Treiber, F. A., Harshfield, G. A., Davis, H., S., & Storng, W. B. (1998). Predictions of future ambulatory blood pressure in youth. *The Journal of Pediatrics, 132,* 693-698.	BP
5	Deter, H. C., Micus, C., Wagner M., Sharma, A. M., & Buchholz, K. (2006). Salt sensitivity, anxiety, and irritability predict blood pressure increase over five years in health males. *Clincial and Experimental Hypertension, 28,* 17-27.	BP
6	Flaa, A., Eide, I. K., Kjedsen, S. E., & Rostrup, M. (2008). Sympathoadrenal stress reactivity is a predictor of future blood pressure an 18- year follow- up study. *Hypertension, 52,* 336-341.	BP
7	Girdler, S. S., Hinderliter A. L., Brownley K. A., Turner, J. R., Sherwood, A., & Light, K. C. (1996). The ability of active versus passive coping tasks to predict future blood pressure levels in normotensive men and women. *International Journal of behavioral medicine, 3,* 233-250.	BP

8	Light, K.C., Dolan C. A., Davis, M. R., & Sherwood A. (1992). Cardiovascular responses to an active coping challenge as predictors of blood pressure patterns 10 to 15 years later. *Psychosomatic Medicine, 54,* 217-230.	BP
9	Markovitz, J. H., Racanski, J. M., Wallace, D., Chettur, V., & Chesney, M. A. (1998). Cardiovascular reactivity to video game predicts subsequent blood pressure increases in young men: The CARDIA Study. *Psychosomatic Medicine, 60,* 186-191.	BP
10	Matthews, K. A., Salomon , K., Brady, S. S., & Allen, M. T. (2003). Cardiovascular reactivity to stress predicts future blood pressure in adolescence. *Psychosomatic Medicine, 65,* 410-415.	BP
11	Matthews, K. A., Woodal, K. L., & Allen, M. T. (1993). Cardiovascular reactivity to stress predicts future blood pressure status. *Hypertension, 22,* 479-485.	BP
12	Moseley, J. V., & Linden, W. (2006). Predicting blood pressure and heart rate change with cardiovascular reactivity and recovery: Results from 3- year and 10- year follow up. *Psychosomatic Medicine, 68,* 833-843.	BP
13	Murphy, J. K., Alpert, B. S., & Walker, S. S. (1992). Ethnicity, pressor reactivity, and childrent's blood rpessure five year of observations. *Hypertension, 20,* 327-332.	BP
14	Newman, J. D., McGarvey, S. T., & Steele, M. S. (1999). Longitudinal association of cardiovascular reactivity and blood pressure in Samoan adolescents. *Psychosomatic Medicine, 61,* 243-249.	BP
15	Parker, F. C., Croft, J. B., Cresanta, J. L., Freedman, D. S., Burke, G. L., Webber, L. S., & Berenson, G. S. (1987). The association between cardiovascular response tasks and future blood pressure levels in children: Bogalusa Heart Study. *American Heart Journal, 113,* 1174-1179.	BP
16	Steptoe, A., & Marmot, M. (2005). Impaired cardiovascular recovery following stress predicts 3- year increases in blood pressure. *Journal of Hypertension, 23,* 529-536.	BP

17	Stewart, J. C., & France, C. R. (2001). Cardiovascular recovery from stress predicts longitudinal changes in blood pressure. *Biological Psychology 58,* 105-120.	BP
18	Stewart, J. C., Janicki, D. L., & Kamarck, T. W. (2006). Cardiovascular reactivity and recovery from psychological challenge as predictors of 3- year change in blood pressure. *Health Psychology, 25*, 111-118.	BP
19	Treiber, F. A., Turner, J. R., Davis, H., & Strong, W. (1997). Prediction of resting cardiovascular functioning in youth with family histories of essential hypertension: A 5- year follow-up. *International Journal of Behavioral Medicine, 4,* 278-291.	BP
20	Trieber, F. A., Turner, J. R., Davis, H., Thompson, W., Levy, M., & Strong, W. B. (1996). Young children's cardiovascular stress responses predict resting cardiovascular functioning 2 ½ years later. *Journal of Cardiovascular risk, 3,* 95-100.	BP
21	Tuomisto, M. T., Majahalme, S., Kahonen, M., Fredrikson, M., & Turjanmaa, V. (2005). Psychological stress tasks in the prediction of blood pressure level and need for antihypertensive medication: 9-12 years of follow-up. *Health psychology, 24,* 77-87.	BP, Hypertension
22	Borghi, C., Costa, F. V., Boschi, S., Bacchelli, S., De Esposti, D., Piccoli, M., & Ambrosioni, E. (1996). Factors associated with the development of stable hypertension in young borderline hypertensives. *Journal of Hypertension, 14,* 509-517.	Hypertension
23	Borghi, C., Costa, F. V., Boschi, S., Mussi, A., & Ambrosioni, E. (1986). Predictors of stable hypertension in young borderline subjects: A five-year follow-up study. *Journal of Cardiovascular Pharmacology, 8,* S138-S141.	Hypertension
24	Carroll, D., Ginty, A. T., Painter, R., Roseboom, T. J., Phillips, A. C., & de Rooij, S. R. (2012). Systolic blood pressure reactions to acute stress are associated with future hypertension status in the Dutch Famine Birth cohort study. *International Journal of Psychophysiology, 85,* 270-273.	Hypertension

25	Everson, S. A., Kaplan, G. A., Goldberg, D. E., & Salonen, J. T. (1996). Anticipatory blood pressure response to exercise predicts blood pressure in middle-aged men. *Hypertension, 27,* 1059-1064.	Hypertension
26	Kasagi, F., Akahoshi, M., & Shimaoka, K. (1995). Relation between cold pressor test and development of hypertension based on 28- year follow-up. *Hypertension, 25,* 71-76.	Hypertension
27	Matthews, K. A., Katholi, C. R., McCreath, H., Whooley, M. A., Williams, D. R., Zhu, S., & Markovitz, J. H. (2004). Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA Study. *Circulation, 110,* 74-78.	Hypertension
28	Menkes, M. S., Matthews, K. A., Krantz, D. S., Lundberg, U., Mead, L. A., Quqish, B., . . . Pearson, T. A. (1989). Cardiovascular reactivity to the cold pressor test as a predictor of hypertension. *Hypertension, 14,* 524-530.	Hypertension
29	Barnett, P. A., Spence, J. D., Manuck, S. B., & Jennings, J. R. (1997). Psychological stress and the progression of carotid artery disease. *Journal of Hypertension, 15,* 49-55.	Preclinical CHD
30	Gianaros, P. J., Salomon, K., Zhou, F., Owens, J. F., Edmundowicz, D., Kuller, L. H., & Matthews, K. A. (2005). A greater reduction in high- frequency heart rate variability to a psychological stressor is associated with subclinical coronary and aortic calcification in postmenopausal women. *Psychosomatic Medicine, 67,* 553-560.	Preclinical CHD
31	Heponiemi, T., & Elovainio, M. (2007). Cardiac autonomic reactivity and recovery in predicting carotid atherosclerosis: The cardiovascular risk in young Finns study. *Health Psychology, 25,* 13-21.	Preclinical CHD
32	Jennings, J. R., Kamarck, T. W., Everson-Rose, S. A., Kaplan, G. A., Manuck, S. B., & Salonen, J. T. (2004). Exaggerated blood pressure responses during mental stress are prospectively related to enhanced carotid atherosclerosis in middle- aged Finnish men. *Circulation, 110,* 2198-2203.	Preclinical CHD

33	Kapuku, G. K., Treiber, F. A., Davis, H. C., Harshfield, G. A., Cook, B. B., & Mensah, G. A. (1999). Hemodynamic function at rest, during acute stress, and in the field predictors of cardiac structure and function 2 years later in youth. *Hypertension, 34,* 1026-1031.	Preclinical CHD
34	Lynch, J. W., Everson, S. A., Kaplan, G. A., Salonen, R., & Salonen, J. T. (1998). Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? *American Journal of Public Health, 88,* 389-394.	Preclinical CHD
35	Matthews, K. A., Owens, J. F., Kuller, L. H., Sutton-Tyrrell, K., Lassila, H. C., & Wolfson, S. K. (1998). Stress- induced pulse pressure change predicts women's carotid atherosclerosis. *Stroke, 29,* 1525-1530.	Preclinical CHD
36	Matthews, K. A., Zhu, S., Tucker, D. C., & Whooley, M. A. (2006). Blood pressure reactivity to psychological stress and coronary calcification in the coronary artery risk development in young adults study. *Hypertension, 47,* 391-395.	Preclinical CHD
37	Papavassiliou, D. P., Treiber, F. A., Strong, W. B., Malpass M. D., & Davis, H. (1996). Anthropometric, demographic, and cardiovascular predictors of left ventricular mass in young children*. *American Journal of Cardiology, 78,* 323-326.	Preclinical CHD
38	Carroll, D., Davey Smith, G., Willemsen, G., Sheffield, D., Sweetnam, P. M., Gallacher, J. E., & Elwood, P. C. (1998). Blood pressure reactions to the cold pressor test and the prediction of ischeamic heart disease: Data from the Caerphilly Study. *Journal of Epidemiology and Community Heath, 52,* 528-529.	Cardiac events
39	Coresh, J., Klag, M. J., Mead, L. A., Liang, K. Y., & Whelton, P. K. (1992). Vascular reactivity in young adults and cardiovascular disease a prospective study. *Hypertension, 19,* II218-II223.	Cardiac events

40	Keys, A., Taylor, H. L., & Blackburn, H. (1971). Mortality and coronary heart disease among men studies for 23 years. *Archives of Internal Medicine,128*, 201-214.	Cardiac events
41	Shaffer, J. A., Wasson, L. T., Davidson, K. W., Schwartz, J. E., Kirkland, S., & Shimbo, D. (2012). Blood pressure reactivity to an anger provocation interview dose not predict incident cardiovascualr disease events: The Canadian Nova Scotia Health Survey (NSHS95) prospective population study. *International Journal of Hypertension*, 658128, doi: 10.1155/2012/658128	Cardiac events

Table 2.5 Summary of meta-analysis in cardiovascular responses to mental stress to predict cardiovascular risks in fail-safe N and the critical number

Predictor	Outcome	Fail-safe N	Critical number for drawer
SBP reactivity in child participants	SBP	204	60
SBP reactivity in adult participants	SBP	240	140
SBP reactivity with short follow-up	SBP	381	135
SBP reactivity with long follow-up	SBP	105	65
SBP response to active coping tasks	hypertension	96	65
SBP response to passive coping tasks	hypertension	73	40

Data presented from statically significant in tables 2.4 and 2.5

Table 4.1 Point-biserial and bivariate correlations between demographic data and cardiovascular parameters in both the UK and Thai samples (N = 223)

Variable	Traditional risk factors				
	Age	Sex	BMI	FH	Smoking
SBP reactivity (mmHg)					
- mental arithmetic	0.033	-0.074	-0.068	0.174**	-0.029
- speech	0.062	0.008	-0.124	0.130+	-0.104
- cold pressor	0.051	0.003	-0.113	0.027	-0.106
DBP reactivity (mmHg)					
- mental arithmetic	-0.059	-0.017	-0.108	0.067	-0.042
- speech	-0.051	0.044	-0.146*	0.028	-0.106
- cold pressor	-0.076	0.006	-0.169*	-0.033	-0.138*
HR reactivity (bpm)					
- mental arithmetic	-0.120+	0.166*	-0.149*	0.101	-0.112+
- speech	-0.015	0.155*	-0.057	0.080	-0.112+
- cold pressor	0.008	0.117+	-0.020	-0.026	-0.134*
CO reactivity (l/m)					
- mental arithmetic	-0.211**	0.140*	-0.152*	0.008	-0.105
- speech	-0.273***	0.102	-0.030	-0.029	-0.107
- cold pressor	-0.305***	0.127+	-0.077	-0.108	-0.065
TPR reactivity (dyne-sec.cm-5)					
- mental arithmetic	0.139*	-0.060	0.012	0.026	0.094
- speech	0.153*	0.092	-0.233***	0.097	0.006
- cold pressor	0.219**	-0.037	-0.155*	0.134*	-0.071

FH, family history of CVD

+ $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$

Table 4.2 Bivariate correlations between baseline cardiovascular activity and cardiovascular parameters in both the UK and Thai samples (N = 223)

Baseline CV measure	Cardiovascular responses to mental stressors		
	Mental arithmetic	Speech	Cold pressor
SBP	0.028	0.023	-0.079
DBP	-0.065	-0.125+	-0.063
HR	-0.021	-0.135*	-0.187**
CO	-0.101	-0.172*	-0.266***
TPR	-0.135*	0.131+	0.197**

+ $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$

Table 4.3 Compared between depressive and non-depressive symptoms, and cardiovascular reactivity in the Thai participants (N = 119)

Variable	**Non-depression** n = 109 (Mean ± SD)	**Depression** n = 10 (Mean ± SD)	***F (test)***	***eta²***	***F (test) after adjustment#***	***eta² after adjustment#***
SBP reactivity (mmHg)						
- mental arithmetic	21.18 ± 10.71	18.09 ± 14.71	0.714	0.001	0.580	0.008
- speech	26.25 ± 14.71	28.03 ±15.67	0.170	0.000	0.846	0.001
- cold pressor	29.89 ± 13.03	32.70 ± 15.23	0.414	0.000	0.980	0.009
DBP reactivity (mmHg)						
- mental arithmetic	11.97 ± 8.10	12.52 ± 9.60	0.041	0.000	1.033	0.019
- speech	14.79 ± 8.38	16.82 ± 9.25	0.525	0.001	1.255	0.018
- cold pressor	17.81 ± 9.22	20.29 ± 11.35	0.635	0.001	0.999	0.013
HR reactivity (bpm)						
- mental arithmetic	8.68 ± 7.28	7.44 ± 6.44	0.270	0.000	1.073	0.026
- speech	7.87 ± 7.79	7.80 ± 5.44	0.001	0.000	1.182	0.033
- cold pressor	3.97 ± 7.39	5.85 ± 5.03	0.618	0.004	1.909^{+}	0.081
CO reactivity (l/m)						
- mental arithmetic	0.72 ± 0.77	1.08 ± 0.60	1.978	0.008	2.940**	0.079
- speech	0.56 ± 0.77	0.74 ± 0.70	0.557	0.003	1.710	0.062
- cold pressor	0.21 ± 0.70	0.46 ±0.67	1.192	0.009	2.619*	0.128
TPR reactivity (dyne-sec.cm-^{5})						
- mental arithmetic	56.12 ±103.59	-24.88 ± 103.15	5.604*	0.038	2.643*	0.117
- speech	135.68 ± 157.11	121.76 ±148.27	0.073	0.000	2.147*	0.068
- cold pressor	225.19 ± 177.62	213.54 ± 138.14	0.041	0.000	4.353***	0.081

after adjusted for age, sex, BMI, family history of CVD status, current cigarette smoking status and baseline cardiovascular activity

$^{+}$ $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$

Table 4.4 Compared between anxiety and non-anxiety symptoms cardiovascular reactivity in the Thai participants (N = 119)

Variable	**Non-anxiety** n = 95 (Mean ± SD)	**Anxiety** n = 24 (Mean ± SD)	***F (test)***	***eta²***	***F (test) after adjustment#***	***eta² after adjustment#***
SBP reactivity (mmHg)						
- mental arithmetic	21.05 ± 11.85	20.42 ± 7.28	0.061	0.001	0.529	0.007
- speech	26.39 ± 13.81	26.46 ± 9.52	0.001	0.000	0.785	0.009
- cold pressor	30.43 ± 13.93	28.94 ± 9.77	0.242	0.000	0.899	0.009
DBP reactivity (mmHg)						
- mental arithmetic	12.48 ± 8.34	10.18 ± 7.44	1.520	0.004	1.246	0.023
- speech	15.49 ± 8.41	12.89 ± 8.39	1.824	0.004	1.411	0.020
- cold pressor	18.65 ± 9.61	15.52 ± 8.18	2.143	0.004	1.209	0.015
HR reactivity (bpm)						
- mental arithmetic	8.77 ± 7.30	7.80 ± 6.84	0.346	0.001	1.103	0.027
- speech	7.80 ± 7.24	8.14 ± 9.09	0.040	0.000	1.200	0.034
- cold pressor	4.42 ± 7.72	2.99 ± 4.70	0.741	0.005	1.907^{+}	0.081
CO reactivity (l/m)						
- mental arithmetic	0.72 ±0.79	0.86 ± 0.66	0.607	0.003	2.514^{*}	0.069
- speech	0.52 ± 0.74	0.79 ± 0.83	2.567	0.014	1.990^{+}	0.071
- cold pressor	0.24 ± 0.74	0.21 ± 0.52	0.022	0.000	2.515^{*}	0.123
TPR reactivity (dyne-sec.cm-^{5})						
- mental arithmetic	56.30 ± 108.98	21.67 ± 87.34	2.082	0.014	2.057^{+}	0.094
- speech	148.81 ± 158.71	77.93 ± 132.14	4.067^{*}	0.019	2.642^{*}	0.082
- cold pressor	231.03 ± 179.07	197.19 ± 153.79	0.722	0.002	4.405^{***}	0.081

after adjusted for age, sex, BMI, family history of CVD status, current cigarette smoking status and baseline cardiovascular activity

$^{+}$ $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$

Table 4.5 Sobel test results of mediated relationships among the UK participants (N = 104)

Indirect effect	a	s_a	b	s_b	z
SBP to MA → performance → anxiety	0.194	0.140	-0.006	0.024	-0.2460
SBP to MA → perceived stress → anxiety	-0.037	0.021	0.256	0.158	-1.1923
HR to MA → perceived stress → anxiety	-0.062	0.040	-0.007	0.065	0.1074
HR to MA → perceived stress → depression	-0.062	0.040	0.100	0.119	-0.7388
HR to MA → performance → depression	0.143	0.269	-0.013	0.018	-0.4281
HR to MA → performance → anxiety	0.143	0.269	-0.013	0.024	-0.3794
CO to MA → perceived stress → anxiety	0.305	0.277	0.338	0.155	0.9829
CO to MA → perceived stress → depression	0.305	0.277	0.174	0.116	0.8876
CO to MA → performance → depression	0.169	1.821	-0.014	0.017	-0.0922
CO to MA → performance → anxiety	0.169	1.821	-0.682	0.441	-0.0923
CO to CP → perceived stress → depression	0.365	0.325	0.038	0.093	0.3840
CO to CP → pain tolerance → depression	-1.319	4.453	0.004	0.007	-0.0426

These values were entered into the Sobel test calculator obtained electronically from http://quantpsy.org/sobel/sobel.htm. Available 21st September 2012.

a; unstandardized regression coefficient for the association between independent variable and mediator; s_a; standard error of a

b; unstandardized regression coefficient for the association between the mediator and the dependent variable ; s_b; standard error of b

z; zobel test

MA, mental arithmetic; CP, cold pressor

Table 4.6 Compared between depressive and non-depressive symptoms, and cardiovascular reactivity in the UK participants (N = 104)

Variable	**Non-depression** n = 98 (Mean ± SD)	**Depression** n = 6 (Mean ± SD)	***F (test)***	***eta²***	***F (test) after adjustment#***	***eta² after adjustment#***
SBP reactivity (mmHg)						
- mental arithmetic	14.75 ± 11.32	15.22 ± 5.58	0.010	0.000	1.037	0.025
- speech	17.79 ± 13.03	15.85 ± 10.87	0.127	0.000	0.590	0.014
- cold pressor	24.65 ± 12.87	20.10 ± 6.97	0.741	0.001	1.294	0.018
DBP reactivity (mmHg)						
- mental arithmetic	9.84 ± 6.60	12.53 ± 6.45	1.207	0.004	1.052	0.023
- speech	10.80 ± 6.36	8.96 ± 9.64	0.444	0.001	0.760	0.014
- cold pressor	13.79 ± 7.60	10.59 ± 5.83	1.025	0.002	1.706	0.026
HR reactivity (bpm)						
- mental arithmetic	5.26 ± 5.73	3.42 ± 7.24	0.566	0.003	1.786^{+}	0.064
- speech	4.94 ± 5.72	3.89 ± 7.37	0.138	0.001	1.089	0.048
- cold pressor	3.24 ± 6.07	1.97 ± 6.47	0.245	0.002	1.659	0.085
CO reactivity (l/m)						
- mental arithmetic	0.47 ± 7.65	-0.62 ± 1.57	10.027**	0.073	3.631**	0.170
- speech	0.52 ± 0.81	-0.03 ± 1.07	2.475	0.018	4.691***	0.189
- cold pressor	0.41 ± 0.89	-0.51 ± 1.14	5.826*	0.047	5.846***	0.261
TPR reactivity (dyne-sec.cm-^{5})						
- mental arithmetic	62.11 ± 136.57	167.46 ± 167.98	3.282^{+}	0.025	1.867^{+}	0.097
- speech	82.90 ± 131.33	38.63 ± 179.37	0.616	0.004	1.643	0.078
- cold pressor	137.70 ± 186.35	220.26 ± 180.59	1.113	0.007	1.040	0.044

after adjusted for age, sex, BMI, family history of CVD status, current cigarette smoking status and baseline cardiovascular activity

$^{+}$ $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$

Table 4.7 Compared between anxiety and non-anxiety symptoms cardiovascular reactivity in the UK participants (N = 104)

Variable	**Non-anxiety** n = 57 (Mean ± SD)	**Anxiety** n = 47 (Mean ± SD)	***F (test)***	***eta²***	***F (test) after adjustment#***	***eta² after adjustment#***
SBP reactivity (mmHg)						
- mental arithmetic	16.42 ± 10.99	12.79 ± 10.91	2.839^{+}	0.010	1.330	0.032
- speech	18.25 ±12.56	16.99 ± 13.34	0.247	0.001	0.573	0.014
- cold pressor	25.18 ± 11.09	23.43 ± 14.19	0.499	0.001	1.270	0.018
DBP reactivity (mmHg)						
- mental arithmetic	9.40 ± 5.96	9.96 ± 7.35	0.177	0.000	0.909	0.020
- speech	10.72 ± 5.61	10.65 ± 7.57	0.003	0.000	0.697	0.013
- cold pressor	13.57 ± 6.40	13.66 ± 8.78	0.004	0.000	1.687	0.025
HR reactivity (bpm)						
- mental arithmetic	4.89 ± 5.64	5.47 ± 6.04	0.254	0.001	1.763	0.063
- speech	4.43 ± 5.74	5.42 ± 7.79	0.555	0.004	1.139	0.050
- cold pressor	2.88 ± 5.29	3.52 ± 6.95	0.282	0.002	1.708	0.087
CO reactivity (l/m)						
- mental arithmetic	0.49 ± 0.77	0.32 ± 0.95	1.102	0.009	3.292**	0.158
- speech	0.40 ± 0.77	0.60 ± 0.90	1.398	0.010	4.454***	0.182
- cold pressor	0.31 ± 0.83	0.40 ± 1.04	0.236	0.002	5.343***	0.244
TPR reactivity (dyne-sec.cm-^{5})						
- mental arithmetic	56.68 ± 137.44	82.17 ± 142.84	0.856	0.007	1.853^{+}	0.096
- speech	80.32 ± 128.56	80.39 ± 141.49	0.000	0.000	1.599	0.077
- cold pressor	133.06 ± 152.32	153.86 ± 221.64	0.319	0.002	1.075	0.046

After adjusted for age, sex, BMI, family history of CVD status, current cigarette smoking status and baseline cardiovascular activity

$^{+}$ $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$

Table 4.8 Mean and standard deviation changes scores in haemodynamic variables in the ordering of the tasks (mental arithmetic followed by speech and cold pressor tasks) by country

Variable	Thai participants N = 119 (mean ± SD)	UK participants n = 17 (mean ± SD)	*F (test)*	*eta²*
SBP reactivity (mmHg)				
- mental arithmetic	20.92 ± 11.06	11.08 ± 11.71	11.614**	0.020
- speech	26.40 ± 13.03	14.16 ± 15.95	12.390**	0.020
- cold pressor	30.13 ± 13.183	26.28 ± 10.32	1.329	0.002
DBP reactivity (mmHg)				
- mental arithmetic	12.01 ± 8.19	6.59 ± 5.79	6.927**	0.017
- speech	14.96 ± 8.43	9.38 ± 6.34	6.872*	0.012
- cold pressor	18.02 ± 9.39	16.65 ± 7.04	0.331	0.000
HR reactivity (bpm)				
- mental arithmetic	8.58 ± 7.20	6.22 ± 6.41	1.639	0.005
- speech	7.87 ± 7.61	4.28 ± 6.82	3.395+	0.013
- cold pressor	4.13 ± 7.22	5.52 ± 6.52	0.567	0.003
CO reactivity (l/m)				
- mental arithmetic	0.75 ± 0.77	0.41 ± 0.60	3.097+	0.112
- speech	0.57 ± 0.76	0.44 ± 1.02	0.399	0.002
- cold pressor	0.23 ± 0.70	0.33 ± 0.65	0.313	0.002
TPR reactivity (dyne-sec.cm-^{5})				
- mental arithmetic	49.32 ± 105.56	24.36 ± 87.22	0.864	0.005
- speech	134.51 ± 155.84	59.44 ± 96.05	3.728+	0.016
- cold pressor	224.21 ± 174.18	146.32 ± 105.34	3.218+	0.009

+ $p < .1$, * $p < .05$, ** $p < .01$

Table 4.9 Demographic data by country

Variable	**Thai participants** Mean ± SD	**UK participants** Mean ± SD	**t (221)**
Age (years)	32.18 ± 10.07	31.52 ± 11.55	0.454
BMI (kg/m^2)	22.09 ± 11.55	25.53 ±5.09	-5.319***
Variable	**Thai participants** n (%)	**UK participants** n (%)	**Mann-Whitney U**
Sex			5278.500*
- Male	34 (28.57)	45 (43.27)	
- Female	85 (71.43)	59 (56.73)	
Current cigarette smoking status			4640.500***
- Smoking	8 (6.72)	33 (31.73)	
- No smoking	111 (93.28)	71 (68.27)	
Family history of CVD			5482.00^{+}
- Family history	50 (42.02)	32 (30.77)	
- No family history	69 (57.98)	72 (69.23)	

$^{+}$ $p < .1$, * $p < .05$, *** $p < .001$

Table 4.10 Independent samples *t* -test on using baseline cardiovascular activity (between 5-18 minutes), last 3 minutes (between minute 5-7), pre-task at minute 3 and pre-task at minute 6 in Thai participants (N = 119)

Variable	Cardiovascular reactivity		t (118)	Compare between baseline at 5-18 min and post-task			
	Using baseline at 5-18 min	Using pre-task at last 3 mins		Using at min 3 post-task		Using at min 6 post-task	
	(mean ± SD)	(mean ± SD)		(mean ± SD)	t (118)	(mean ± SD)	t (118)
Mental arithmetic							
- SBP (mmHg)	110.64 ± 9.28	110.96 ± 9.17	-0.80	118.71 ± 14.04	-8.15***	110.64 ± 10.75	0.00
- DBP (mmHg)	60.28 ± 6.88	60.76 ± 8.53	1.14	64.63 ± 9.37	-7.34***	60.96 ± 7.96	-1.49
- HR (bpm)	77.89 ± 10.15	77.78 ± 9.69	-0.55	77.76 ± 10.91	0.28	77.64 ± 9.91	0.59
- CO (l/m)	5.65 ± 1.23	5.64 ± 1.23	-0.53	5.77 ± 1.29	-2.60*	5.62 ± 1.21	0.91
- TPR (dyne-sec.cm-^{5})	872.79 ± 202.30	871.13 ± 206.71	-0.39	917.78 ± 238.42	-4.21***	882.47 ± 188.41	-1.55
Speech							
- SBP (mmHg)	110.64 ± 9.28	110.66 ± 11.06	0.02	123.71 ± 16.32	-10.88***	111.21 ± 10.13	-0.979
- DBP (mmHg)	60.28 ± 6.88	61.04 ± 7.89	1.70	68.06 ± 9.84	-11.91***	60.82 ± 8.24	-1.27
- HR (bpm)	77.89 ± 10.15	77.75 ± 9.90	-0.35	76.94 ± 12.41	1.22	77.61 ± 9.91	0.64
- CO (l/m)	5.65 ± 1.23	5.63 ± 1.21	-0.56	5.66 ± 1.22	-0.27	5.59 ± 1.24	1.46
- TPR (dyne-sec.cm-^{5})	872.79 ± 202.30	883.07 ± 189.90	1.70	988.08 ± 256.32	-7.34***	881.34 ± 196.11	-1.12
Cold pressor							
- SBP (mmHg)	110.64 ± 9.28	111.32 ± 10.06	1.23	123.82 ± 12.61	-12.67***	112.04 ±10.75	-1.82
- DBP (mmHg)	60.28 ± 6.88	60.91 ± 8.24	1.54	69.51 ± 10.73	-12.17***	60.54 ± 8.30	-0.55
- HR (bpm)	77.89 ± 10.15	77.64 ± 9.74	-0.56	78.68 ± 9.83	-0.83	78.45 ± 11.95	-1.13
- CO (l/m)	5.65 ± 1.23	5.60 ± 1.24	-1.17	5.47 ±1.17	2.86**	5.61 ± 1.24	0.75
- TPR (dyne-sec.cm-^{5})	872.79 ± 202.30	883.51 ± 197.13	1.42	1008.62 ± 234.55	-10.09***	879.30 ± 160.43	-0.61

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 4.11 Independent samples *t* -test and correlation on cardiovascular reactivity by baseline cardiovascular activity and pre-task at last 3 minutes (at minute 5-7) in the Thai participants (N = 119)

Variable	Cardiovascular reactivity		t (118)	*r*
	Using baseline at min 5-18 (mean ± SD)	Using baseline at last 3 mins (mean ± SD)		
Mental arithmetic				
- SBP (mmHg)	20.92 ± 11.06	20.60 ± 11.71	0.80	0.93
- DBP (mmHg)	12.01 ± 8.19	11.54 ±8.01	1.14	0.84
- HR (bpm)	8.58 ± 7.20	8.68 ±7.61	-0.55	0.96
- CO (l/m)	0.75 ± 0.77	0.76 ± 0.76	-0.53	0.99
- TPR (dyne-sec.cm-^{5})	49.32 ± 105.56	50.98 ± 107.48	-0.39	0.91
Speech				
- SBP (mmHg)	26.40 ± 13.03	26.38 ± 13.03	0.02	0.74
- DBP (mmHg)	14.96 ± 8.43	14.21 ± 8.92	1.70	0.85
- HR (bpm)	7.87 ± 7.61	8.01 ± 6.76	-0.35	0.82
- CO (l/m)	0.57 ± 0.76	0.59 ± 0.66	-0.56	0.87
- TPR (dyne-sec.cm-^{5})	134.51 ± 155.84	124.24 ± 144.78	1.70	0.91
Cold pressor				
- SBP (mmHg)	30.13 ± 13.18	29.44 ± 12.28	1.27	0.90
- DBP (mmHg)	18.02 ± 9.39	17.40 ± 9.62	1.54	0.89
- HR (bpm)	4.13 ± 7.22	4.37 ± 5.88	-0.56	0.76
- CO (l/m)	0.23 ± 0.70	0.28 ± 0.56	-1.17	0.80
- TPR (dyne-sec.cm-^{5})	224.21 ± 174.18	213.49 ± 167.76	1.12	0.88

Table 4.12 Independent samples *t* -test on baseline cardiovascular activity (between 5-18 minutes), last 3 minutes (between 5-7 minutes), pre-task at 3 minute and pre-task at 6 minute in the UK participants (N = 104)

Variable	Cardiovascular reactivity		t(103)	Compare between baseline at 5-18 mins and post-task			
	Using baseline at 5-18 mins	Using pre-task at last 3 mins		At 3 min post-task		At 6 min post-task	
	(mean ± SD)	(mean ± SD)		(mean ± SD)	t (103)	(mean ± SD)	t(103)
Mental arithmetic							
- SBP (mmHg)	106.61 ±14.73	106.37 ± 13.65	0.30	112.70 ± 13.85	-6.08***	107.18 ± 14.33	-0.99
- DBP (mmHg)	57.19 ± 10.18	56.91 ± 10.38	0.55	61.66 ±10.76	-6.91***	57.67 ± 10.91	-1.25
- HR (bpm)	76.93 ± 10.73	76.96 ± 10.27	-0.07	76.69 ± 10.26	0.45	76.73 ±10.81	0.54
- CO (l/m)	6.13 ± 1.38	6.09 ± 1.32	0.70	6.14 ± 1.22	-0.13	6.11 ± 1.29	0.38
- TPR (dyne-sec.cm-^{5})	764.40 ± 170.34	767.01 ± 145.83	-0.27	809.46 ± 209.81	-2.73**	771.54 ± 162.41	-1.16
Speech							
- SBP (mmHg)	106.61 ± 14.73	106.89 ± 13.60	-0.51	113.02 ± 15.46	-6.08***	107.28 ± 13.94	-0.95
- DBP (mmHg)	57.19 ± 10.18	57.38 ± 9.17	-0.40	61.89 ± 10.84	-6.91***	57.68 ± 10.59	-1.22
- HR (bpm)	76.93 ± 10.73	76.77 ± 10.82	0.37	75.56 ± 11.39	0.45	76.89 ± 10.66	0.09
- CO (l/m)	6.13 ± 1.38	6.10 ± 1.18	0.54	6.19 ± 1.20	-0.13	6.14 ± 1.25	-0.14
- TPR (dyne-sec.cm-^{5})	764.40 ± 170.34	763.93 ± 157.72	0.08	805.11 ± 196.20	-2.73**	765.19 ± 172.38	-0.09
Cold pressor							
- SBP (mmHg)	106.61 ± 14.73	106.82 ±14.86	-0.37	112.92 ± 18.40	-5.94***	107.31 ± 13.16	-1.01
- DBP (mmHg)	57.19 ± 10.18	57.53 ±9.50	-0.71	61.80 ± 12.37	-6.12***	57.90 ± 10.34	-1.44
- HR (bpm)	76.93 ± 10.73	76.96 ± 10.32	-0.10	75.12 ± 11.10	2.89**	76.23 ± 10.93	1.22
- CO (l/m)	6.13 ±1.38	6.14 ± 1.29	-0.13	6.00 ±1.23	-0.73	6.12 ± 1.24	0.24
- TPR (dyne-sec.cm-^{5})	764.40 ± 170.34	763.59 ± 241.57	0.05	848.63 ± 246.18	-2.55*	775.01 ± 152.28	-1.58

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 4.13 Independent samples *t* -test and correlation on cardiovascular reactivity by baseline cardiovascular activity and pre-task at last 3 minutes in the UK participants (N = 104)

Variable	Cardiovascular reactivity		t (118)	*r*
	Using Baseline at 5-18 mins (mean ± SD)	Baseline at last 3 mins (mean ± SD)		
Mental arithmetic				
- SBP (mmHg)	14.78 ± 11.06	15.02 ± 11.55	-0.30	0.74
- DBP (mmHg)	9.66 ± 6.60	9.93 ± 8.02	-0.55	0.77
- HR (bpm)	5.16 ± 5.80	5.13 ± 6.04	0.07	0.77
- CO (l/m)	0.41 ± 0.86	0.45 ± 0.83	-0.70	0.75
- TPR (dyne-sec.cm-^{5})	68.19 ± 139.80	65.58 ± 109.48	0.27	0.70
Speech				
- SBP (mmHg)	17.68 ± 12.87	17.40 ±12.93	0.51	0.91
- DBP (mmHg)	10.69 ± 6.54	10.49 ± 6.98	0.40	0.72
- HR (bpm)	4.88 ± 6.73	5.04 ±7.32	-0.37	0.82
- CO (l/m)	0.49 ± 0.83	0.52 ± 0.73	-0.54	0.79
- TPR (dyne-sec.cm-^{5})	80.35 ± 133.84	80.83 ±141.00	-0.78	0.90
Cold pressor				
- SBP (mmHg)	24.39 ± 12.55	24.18 ± 13.92	0.37	0.91
- DBP (mmHg)	13.61 ± 7.53	13.27 ± 7.80	0.71	0.80
- HR (bpm)	3.17 ± 6.07	3.13 ± 6.07	0.10	0.87
- CO (l/m)	0.35 ± 0.93	0.35 ± 0.86	0.13	0.94
- TPR (dyne-sec.cm-^{5})	142.46 ± 186.17	143.27 ± 273.23	-0.05	0.75

Table 4.14 Bivariate correlations between depression and anxiety, and cardiovascular reactivity (subtracting by task levels from average baseline pre-task levels at a 5, 6, and 7 minute) in the Thai participants (N = 119)

Cardiovascular reactivity	**HADS Anxiety Scores**		**HADS Depression Scores**	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
The mental arithmetic task				
SBP	-0.028	.761	-0.145	.115
DBP	-0.006	.944	-0.059	.527
HR	-0.034	.712	-0.114	.217
CO	0.100	.282	0.029	.757
TPR	-0.073	.430	-0.100	.281
The speech task				
SBP	0.033	.719	-0.100	.874
DBP	-0.050	.587	-0.015	.396
HR	0.171	.063	-0.079	.811
CO	0.131	.156	-0.022	.288
TPR	-0.155	.093	-0.098	.779
The cold pressor task				
SBP	-0.006	.953	-0.014	.876
DBP	-0.139	.131	-0.096	.300
HR	-0.075	.420	0.095	.303
CO	-0.018	.846	-0.028	.762
TPR	-0.134	.146	-0.035	.705

Table 4.15 Partial correlation between depression and anxiety, and cardiovascular reactivity (subtracting by task levels from average baseline pre-task levels at last 3 minutes) controlling for age, sex, BMI, current cigarette smoking status, parental history of CVD and baseline cardiovascular measures (using average baseline pre-task levels at last 3 minutes) in the Thai participants (N = 119)

Cardiovascular reactivity	**HADS Anxiety Scores**		**HADS Depression scores**	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
The mental arithmetic task				
SBP	-0.032	.738	-0.154	.103
DBP	-0.023	.807	-0.023	.805
HR	-0.053	.575	-0.084	.378
CO	0.098	.301	0.098	.300
TPR	-0.071	.456	-0.168	.075
The speech task				
SBP	0.014	.880	-0.058	.543
DBP	-0.035	.716	-0.021	.825
HR	0.158	.094	-0.001	.992
CO	0.127	.180	-0.036	.706
TPR	-0.160	.091	-0.083	.382
The cold pressor task				
SBP	-0.018	.847	-0.039	.680
DBP	-0.134	.156	-0.060	.528
HR	0.060	.528	0.113	.232
CO	-0.039	.682	0.038	.692
TPR	-0.169	.074	-0.132	.164

Table 4.16 Bivariate correlations between depression and anxiety, and cardiovascular reactivity (subtracting by task levels from average baseline pre-task levels at last 3 minutes) in the UK participants (N = 104)

Cardiovascular reactivity	**HADS Anxiety Scores**		**HADS Depression Scores**	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
The mental arithmetic task				
SBP	**-0.245**	**.012**	**-0.206**	**.036**
DBP	-0.082	.409	-0.039	.697
HR	-0.153	.120	**-0.263**	**.007**
CO	-0.140	.158	**-0.349**	**< .001**
TPR	-0.043	.666	-0.073	.459
The speech task				
SBP	-0.096	.332	-0.086	.384
DBP	-0.053	.593	-0.153	.121
HR	0.138	.162	-0.103	.299
CO	-0.090	.365	-0.162	.101
TPR	-0.126	.203	0.030	.762
The cold pressor task				
SBP	-0.139	.158	0.016	.871
DBP	-0.043	.663	0.005	.959
HR	0.108	.273	-0.075	.447
CO	-0.146	.138	-0.159	.108
TPR	-0.113	.254	-0.064	.515

Table 4.17 Partial correlation between depression and anxiety, and cardiovascular reactivity (subtracting by task levels from average baseline pre-task levels at last 3 minutes) controlling for age, sex, BMI, current cigarette smoking status, parental history of CVD, and baseline cardiovascular measures (using average baseline pre-task levels at last 3 minutes), in the UK participants (N = 104)

Cardiovascular reactivity	**HADS Anxiety scores**		**HADS Depression scores**	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
The mental arithmetic task				
SBP	**-0.231**	**.022**	**-0.232**	**.021**
DBP	-0.122	.232	-0.083	.416
HR	-0.128	.211	**-0.263**	**.009**
CO	-0.154	.130	**-0.336**	**.001**
TPR	-0.026	.803	0.066	.519
The speech task				
SBP	-0.115	.261	-0.129	.207
DBP	-0.093	.364	-0.187	.066
HR	0.128	.211	-0.113	.266
CO	-0.076	.456	-0.139	.173
TPR	-0.110	.281	0.001	.991
The cold pressor task				
SBP	-0.162	.112	-0.071	.488
DBP	-0.071	.487	-0.014	.891
HR	0.125	.218	-0.109	.287
CO	-0.139	.172	-0.108	.209
TPR	-0.151	.137	-0.131	.199

Table 4.18 Partial correlations between HADS depression and anxiety scores, and cardiovascular reactivity (subtracting by task levels from average baseline pre-task levels at last 3 minutes) controlling for baseline cardiovascular activations (using average baseline pre-task levels at last 3 minutes), traditional risk factors, self-reported perceived stress, performance or pain tolerance (depending on task) in the UK participants (N = 104)

Cardiovascular reactivity	HADS Anxiety		HADS Depression	
	Correlation *r*	*p*-value	Correlation *r*	*p*-value
The mental arithmetic task[1]				
SBP	**-0.201**	**.042**	**-0.225**	**.029**
DBP	-0.082	.432	-0.028	.787
HR	-0.144	.166	**-0.295**	**.004**
CO	-0.147	.159	**-0.367**	**< .001**
TPR	-0.027	.796	0.104	.318
The speech task [2]				
SBP	-0.109	.292	-0.126	.222
DBP	-0.103	.319	-0.187	.069
HR	0.138	.183	-0.108	.300
CO	-0.051	.623	-0.146	.157
TPR	-0.130	.209	0.004	.967
The cold pressor task [3]				
SBP	-0.140	.178	-0.069	.506
DBP	-0.069	.508	-0.024	.820
HR	0.150	.149	-0.124	.232
CO	-0.109	.296	-0.110	.290
TPR	-0.112	.282	-0.082	.433

[1] controlling for baseline cardiovascular activity, traditional risk factors, self-reported perceived mental arithmetic stress, and performance scores

[2] controlling for baseline cardiovascular activity, traditional risk factors, and self-reported perceived speech stress

[3] controlling for baseline cardiovascular activity, traditional risk factors, self-reported perceived cold pressor stress, and pain tolerance

Table 5.1 Independent samples *t* -test and Mann-Whitney test on traditional risk factors, baseline cardiovascular activity and cardiovascular reactivity comparing participant who participated and did not participant at one year follow-up

Variable	**Participants at follow-up** (n = 107) Mean ± SD	**Participants who did not participate** (n = 12) Mean ± SD	***t* (117)**
Age (years)	31.43 ± 9.44	38.83 ± 13.31	-1.88^{+}
BMI (kg/m^2)	22.20 ± 4.73	21.06 ± 2.93	0.82
Baseline cardiovascular activity			
SBP (mmHg)	111.01 ± 9.15	107.34 ± 10.22	1.30
DBP (mmHg)	60.58 ± 6.86	57.63 ± 6.74	1.41
HR (bpm)	78.62 ±10.11	71.39 ± 8.37	2.38*
CO (l/m)	5.71 ± 1.23	5.08 ± 1.02	1.72^{+}
TPR (dyne-sec.cm-^{5})	865.79 ± 198.36	935.25 ± 234.78	-1.13
The mental arithmetic task			
SBP responses (mmHg)	21.20 ±11.27	18.43 ± 8.93	0.82
DBP responses (mmHg)	11.67 ± 7.83	15.10 ± 10.56	-1.38
HR responses (bpm)	8.76 ± 7.33	6.91 ± 0.72	0.85
CO responses (l/m)	0.76 ± 0.77	0.64 ± 0.72	0.53
TPR responses (dyne-sec.cm-^{5})	49.01 ± 107.30	52.10 ± 92.63	-0.10
The speech task			
SBP responses (mmHg)	26.34 ± 13.28	26.98 ± 10.95	-0.16
DBP responses (mmHg)	14.65 ± 8.07	17.75 ± 11.22	-1.21
HR responses (bpm)	8.08 ± 7.90	6.01 ± 3.91	0.89
CO responses (l/m)	0.58 ± 0.79	0.50 ± 0.46	0.34
TPR responses (dyne-sec.cm-^{5})	132.92 ± 159.53	148.75 ± 122.59	-0.33
The cold pressor task			
SBP responses (mmHg)	29.37 ± 13.00	36.91 ± 13.33	-1.90^{+}
DBP responses (mmHg)	17.31 ± 8.90	24.37 ± 11.53	-2.52*
HR responses (bpm)	4.23 ±7.40	3.19 ± 5.54	0.47
CO responses (l/m)	0.23 ± 0.71	0.22 ± 0.63	-0.06
TPR responses (dyne-sec.cm-^{5})	215.08 ± 166.99	305.63 ± 220.72	-1.72
Variable	**Participants at follow-up** (n = 107) Mean rank	**Participants who did not participate** (n = 12) Mean rank	***Mann-Whitney test***
Sex	60.24	57.88	616.50
Current cigarette smoking status	59.34	65.92	571.00
Family history of CVD	60.58	54.83	580.00

$^{+}$ $p < .1$, * $p < .05$

Table 5.2 Results of hierarchical linear regression analyses predicting one year SBP from baseline resting SBP using average baseline pre-task levels at a 15, 16, and 17 minute) SBP responses to mental arithmetic (subtracting by task levels from average baseline pre-task levels at a 15, 16, and 17 minute) data in the Thai participants who participated in the initial and follow-up sessions (n = 107)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
1 year SBP							
Step 1				0.171	21.604***	0.171	21.604***
Baseline SBP	0.442	0.413	4.648***				
Step 2				0.244	16.779***	0.073	10.085**
SBP responses to MA	0.235	0.271	3.176**				

MA, mental arithmetic

** $p < .01$, *** $p < .001$

Table 5.3 Results of hierarchical linear regression analyses predicting one year SBP from baseline resting SBP (using average baseline pre-task levels at a 15, 16, and 17 minute), traditional risk factors, and SBP responses to mental arithmetic data (subtracting by task levels from average baseline pre-task levels at a 15, 16, and 17 minute) in the Thai participants who participated in the initial and follow-up sessions (n = 107)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
1 year SBP							
Step 1				0.171	21.604***	0.171	21.604***
Baseline SBP	0.442	0.413	4.648***				
Step 2				0.274	6.284***	0.103	2.841*
Sex [a]	2.998	0.140	1.432				
Age	0.106	0.102	1.122				
BMI	0.518	0.250	2.843**				
FH [b]	-0.977	-0.050	-0.549				
Smoking [c]	-1.359	-0.032	-0.351				
Step 3				0.340	7.283***	0.066	9.917**
SBP responses to MA	0.229	0.264	3.149**				

FH, family history of CVD

[a] sex: male =1, female = 0

[b] family history of CVD: positive =1 , negative = 0

[c] cigarette smoking status: current smoking = 1, non-smoking = 0

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 6.1 Independent samples *t* -test and Mann-Whitney test on traditional risk factors, baseline cardiovascular activity and cardiovascular reactivity comparing participant who participated and did not participant at a one year follow-up

Variable	**Participants at follow-up** (n = 77) Mean ± SD	**Participants who did not participate** (n = 27) Mean ± SD	***t* - test**
Age (years)	32.61 ± 11.80	28.41 ±10.39	*t* (102) = 1.641
BMI (kg/m^2)	24.97 ± 4.75	27.13 ± 5.77	*t* (102) = -1.92^{+}
Baseline cardiovascular activity			
SBP (mmHg)	113.71 ± 12.56	109.89 ± 9.57	*t* (102) 1.44
DBP (mmHg)	66.77 ± 8.12	72.19 ± 7.28	*t* (102) = -3.06**
HR (bpm)	77.02 ± 10.64	76.66 ± 11.18	*t* (102) = 0.15
CO (l/m)	6.08 ± 1.37	6.28 ± 1.42	*t* (102) = -0.64
TPR (dyne-sec.cm-^{5})	770.44 ± 161.31	747.18 ± 196.13	*t* (102) = 0.61
The mental arithmetic task			
SBP responses (mmHg)	14.66 ± 10.41	15.14 ± 12.92	*t* (102) = -0.19
DBP responses (mmHg)	9.97 ± 6.58	8.76 ± 6.68	*t* (102) = 0.82
HR responses (bpm)	5.39 ± 5.46	4.48 ± 6.74	*t* (102) = 0.70
CO responses (l/m)	0.36 ± 0.85	0.55 ± 0.89	*t* (102) = -0.96
TPR responses (dyne-sec.cm-^{5})	72.53 ± 137.13	55.82 ± 118.05	*t* (102) = 0.53
The speech task			
SBP responses (mmHg)	18.20 ± 11.76	16.21 ± 15.79	*t* (102) = 0.69
DBP responses (mmHg)	11.18 ± 6.40	9.31 ± 6.84	*t* (102) = 1.28
HR responses (bpm)	5.45 ± 6.58	3.27 ± 7.01	*t* (102) = 1.46
CO responses (l/m)	0.44 ± 0.80	0.64 ± 0.91	*t* (102) = -1.12
TPR responses (dyne-sec.cm-^{5})	84.36 ± 139.26	68.90 ± 118.70	*t* (102) = 0.52
The cold pressor task			
SBP responses (mmHg)	25.11 ± 12.99	22.33 ± 11.16	*t* (102) = 0.99
DBP responses (mmHg)	14.33 ± 8.05	11.57 ± 5.41	*t* (102) = 1.65
HR responses (bpm)	3.64 ± 5.43	1.82 ± 7.56	*t* (102) = 1.34
CO responses (l/m)	0.24 ± 0.93	0.69 ±0.85	*t* (102) = -2.24*
TPR responses (dyne-sec.cm-^{5})	161.86 ± 205.98	87.13 ± 94.84	*t* (95) = 2.51*
Variable	**Participants at follow-up** (n = 77) Mean rank	**Participants who did not participate** (n = 27)Mean rank	***Mann-Whitney test***
Sex	55.09	45.11	840.00
Current cigarette smoking	50.86	57.19	913.00
Family history of CVD	54.06	48.06	919.50

$^{+}$ $p < .1$, * $p < .05$, ** $p < .01$

Table 6.2 Results of hierarchical linear regression analyses predicting ten months SBP from baseline resting SBP activity, traditional risk factors, stressful life events, cardiovascular reactivity and interaction of stressful life events and SBP responses to mental arithmetic data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months SBP							
Step 1				0.289	30.518^{***}	0.289	0.518^{***}
Baseline SBP	0.538	0.538	5.524^{***}				
Step 2				0.414	8.253^{***}	0.125	2.990^{*}
Sex [a]	-7.287	-0.290	-2.554^{*}				
Age	-0.114	-0.107	-1.054				
BMI	-0.274	-0.103	-0.899				
FH [b]	5.715	0.217	2.311^{*}				
Smoking [c]	-5.097	-0.184	-1.850^{+}				
Step 3				0.460	7.232^{***}	0.045	2.856^{+}
LSE	0.005	0.029	0.292				
SBP responses to MA	0.278	0.230	2.378^{*}				
Step 4				0.465	6.458^{***}	0.005	0.605
LSE X SBP responses to MA	0.001	0.147	0.778				

FH, family history of CVD; MA, mental arithmetic; LSE, life stress events; LSE X SBP responses to MA, interaction of stressful life events and SBP responses to mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 2

[c] current cigarette smoking status: smoking = 1, non-smoking = 2

$^{+}$ p <.1, * p <.05, *** p <.001

Table 6.3 Results of hierarchical linear regression analyses predicting ten months SBP from baseline resting SBP activity, traditional risk factors, performance scores, self-reported perceived stress, stressful life events, cardiovascular reactivity and interaction of stressful life events and SBP responses to mental arithmetic data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months SBP							
Step 1				0.283	29.230***	0.283	29.230***
Baseline SBP	0.529	0.532	5.406***				
Step 2				0.409	7.973***	0.126	2.951*
Sex [a]	-6.975	-0.278	-2.424*				
Age	-0.126	-0.119	-1.154				
BMI	-0.259	-0.099	-0.850				
FH [b]	5.953	0.227	2.391*				
Smoking [c]	-4.888	-0.178	-1.765+				
Step 3				0.441	6.608***	0.032	1.893
Performance scores	-0.163	-0.194	-1.708+				
Self-reported perceived stress	-0.886	-0.177	-1.572				
Step 4				0.486	6.138***	0.045	2.821+
LSE	0.001	0.004	0.037				
SBP responses to MA	0.276	0.231	2.332*				
Step 5				0.489	5.564***	0.003	0.395
LSE X SBP responses to MA	0.001	0.120	0.629				

FH, family history of CVD; MA, mental arithmetic; LSE, life stress events; LSE X SBP responses to MA, interaction of life stress events and SBP responses to mental arithmetic task

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

+ p <.1, * p <.05, *** p <.001

Table 6.4 Results of hierarchical linear regression analyses predicting ten months DBP from baseline resting DBP activity, traditional risk factors, stressful life events, cardiovascular reactivity and interaction of stressful life events and DBP responses to mental arithmetic data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months DBP							
Step 1				0.334	37.553***	0.334	37.553***
Baseline DBP	0.894	0.578	6.128***				
Step 2				0.452	9.619***	0.118	3.020*
Sex [a]	-6.372	-0.253	-2.283*				
Age	-0.050	-0.047	-0.487				
BMI	-0.239	-0.090	-0.811				
FH [b]	4.970	0.188	2.062*				
Smoking [c]	-6.518	-0.236	-2.439*				
Step 3				0.458	7.195***	0.007	0.409
LSE	0.001	0.005	0.047				
DBP responses to MA	0.162	0.085	0.896				
Step 4				0.462	6.389***	0.003	0.428
LSE X DBP responses to MA	0.003	0.169	0.655				

FH, family history of CVD; MA, mental arithmetic; LSE, life stress events; LSE X DBP responses to MA, interaction of stressful life events and DBP responses to mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

* p <.05, *** p <.001

Table 6.5 Results of hierarchical linear regression analyses predicting ten months DBP from baseline resting DBP activity, traditional risk factors, performance scores, self-reported perceived stress, stressful life events, cardiovascular reactivity and interaction of stressful life events and DBP responses to mental arithmetic data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months DBP							
Step 1				0.331	36.634***	0.331	36.634***
Baseline DBP	0.884	0.575	60.53***				
Step 2				0.448	9.330***	0.117	2.919*
Sex [a]	-6.055	-0.241	-2.152*				
Age	-0.062	-0.058	-0.603				
BMI	-0.224	-0.086	-0.761				
FH [b]	5.210	0.199	2.148*				
Smoking [c]	-6.301	-0.230	-2.348*				
Step 3				0.476	7.599***	0.028	1.775
Performance scores	-0.161	-0.191	-1.740+				
Self-reported perceived stress	-0.756	-0.151	-1.388				
Step4				0.480	6.002***	0.004	0.274
LSE	-0.004	-0.022	-0.221				
DBP responses to MA	0.122	0.064	0.658				
Step 5				0.482	5.422***	0.002	0.283
LSE X DBP responses to MA	0.002	0.142	0.532				

FH, family history of CVD; MA, mental arithmetic; LSE, life stress events; LSE X DBP responses to MA, interaction of stressful life events and DBP responses to mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

+ p <.1, * p <.05, *** p <.001

Table 6.6 Results of hierarchical linear regression analyses predicting ten months DBP from baseline resting DBP activity, traditional risk factors, stressful life events, cardiovascular reactivity and interaction of stressful life events and SBP responses to mental arithmetic data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months DBP							
Step 1				0.519	80.918***	0.519	80.918***
Baseline DBP	0.573	0.720	8.995***				
Step 2				0.569	15.419***	0.050	1.635
Sex [a]	-0.906	-0.056	-0.571				
Age	0.119	0.175	2.075*				
BMI	-0.193	-0.114	-1.151				
FH [b]	1.579	0.093	1.146				
Smoking [c]	2.160	0.122	1.425				
Step 3				0.595	12.468***	0.025	2.125
LSE	-0.016	-0.147	-1736+				
SBP responses to MA	0.043	0.056	0.672				
Step 4				0.609	11.579***	0.014	2.406
LSE X SBP responses to MA	0.002	0.251	1.551				

FH, family history of CVD; MA, mental arithmetic; LSE, life stress events; LSE X SBP responses to MA, interaction of stressful life events and SBP responses to mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 2

[c] current cigarette smoking status: smoking = 1, non-smoking = 2

+ p <.1, * p <.05, *** p <.001

Table 6.7 Results of hierarchical linear regression analyses predicting ten months DBP from baseline resting DBP activity, traditional risk factors, stressful life events, cardiovascular reactivity and interaction of stressful life events and SBP responses to mental arithmetic data in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months DBP							
Step 1				0.516	78.907***	0.516	78.907***
Baseline DBP	0.573	0.718	8.883***				
Step 2				0.567	15.045***	0.051	1.616
Sex [a]	-0.929	-0.057	-0.579				
Age	0.121	0.175	2.063*				
BMI	-0.194	-0.115	-1.150				
FH [b]	1.553	0.092	1.112				
Smoking [c]	2.140	0.121	1.397				
Step 3				0.582	11.677***	0.016	1.248
Performance scores	0.066	0.123	1.254				
Self-reported perceived stress	0.439	0.135	1.394				
Step4				0.604	9.934***	0.022	1.820
LSE	0.054	0.070	0.815				
SBP responses to MA	-0.014	-0.131	-1.500				
Step 5				0.622	9.568***	0.017	2.941+
LSE X SBP responses to MA	0.002	0.282	1.715+				

FH, family history of CVD; MA, mental arithmetic; LSE, life stress events; LSE X SBP responses to MA, interaction of stressful life events and SBP responses to mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 2

[c] current cigarette smoking status: smoking = 1, non-smoking = 2

+ p <.1, * p <.05, *** p <.001

Table 6.8 Results of hierarchical linear regression analyses predicting future SBP from baseline resting SBP activity SBP responses to mental arithmetic (subtracting by task levels from average baseline pre-task levels at last 3 minutes) in the UK participants who participated in the initial and follow-up sessions (n = 77)

Regression model*B*	*β*	*T*	R^2	*F*	Δ R^2	Δ *F*
10 months SBP						
Step 1			0.289	30.518***	0.289	30.518***
Baseline SBP	0.538	0.538	5.524***			
Step 2			0.365	21.233***	0.075	8.782***
SBP responses to MA	0.316	0.289	2.963**			

MA, mental arithmetic

** p <.01, *** p <.001

Table 6.9 Results of hierarchical linear regression analyses predicting ten months SBP from baseline resting SBP activity, traditional risk factors, and SBP responses to mental arithmetic data (subtracting by task levels from average baseline pre-task levels at last 3 minutes) in the UK participants who participated in the initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	Δ R^2	Δ *F*
10 months SBP							
Step 1				0.289	30.518***	0.289	30.518***
Baseline SBP	0.538	0.538	5.524***				
Step 2				0.414	8.253***	0.125	2.990*
Sex [a]	-7.287	-0.290	-2.554*				
Age	-0.114	-0.107	-1.054				
BMI	-0.274	-0.103	-0.899				
FH [b]	5.715	0.217	2.311*				
Smoking [c]	-5.097	-0.184	-1.850+				
Step 3				0.474	8.878***	0.060	7.810**
SBP responses to MA	0.297	0.271	2.795**				

FH, family history of CVD; MA, mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

+ p <.1, * p <.05, ** p <.01, *** p <.001

Table 6.10 Results of hierarchical linear regression analyses predicting ten months SBP from baseline resting SBP activity, traditional risk factors, performance, self-reported perceived stress and SBP responses to mental arithmetic data (subtracting by task levels from average baseline pre-task levels at last 3 minutes) in the UK participants who completed initial and follow-up sessions (n =77)

Regression model	*B*	*β*	*T*	R^2	*F*	ΔR^2	ΔF
10 months SBP							
Step 1			0.283	29.230^{***}	0.283	29.230^{***}	
Baseline SBP	0.529	0.532	5.406^{***}				
Step 2			0.409	7.973^{***}	0.126	2.951^{*}	
Sex [a]	-6.975	-0.278	-2.424^{*}				
Age	-0.126	-0.119	-1.154				
BMI	-0.259	-0.099	-0.850				
FH [b]	5.953	0.227	2.391^{*}				
Smoking [c]	-4.888	-0.178	-1.765^{+}				
Step 3			0.441	6.608^{***}	0.032	1.893	
Performance scores	-0.163	-0.194	-1.708^{+}				
Self-reported perceived stress	-0.886	-0.177	-1.572				
Step 4			0.511	7.665^{***}	0.070	9.451^{**}	
SBP responses to MA	0.328	0.303	3.074^{**}				

FH, family history of CVD; MA, mental arithmetic

[a] sex: male =1, female = 2

[b] family history of CVD: positive =1, negative = 0

[c] current cigarette smoking status: smoking = 1, non-smoking = 0

$^{+}p < .1$, $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

Table 6.11 Paired–sample *t* test on cardiovascular responses change scores from baseline to psychological stress tests in the UK participants who completed initial and follow-up sessions (n = 77)

	mental arithmetic (mean ± SD)	**speech preparation** (mean ± SD)	**speech delivery** (mean ± SD)	**cold pressor** (mean ± SD)
SBP				
Baseline (mmHg)	106.97 ± 14.68	106.97 ± 14.68	106.97 ± 14.68	106.97 ± 14.68
Task (mmHg)	121.63 ±19.44	118.60 ± 17.14	129.78 ±22.33	132.08 ± 19.55
t -test (76)	-12.35***	-10.09 ***	-14.13***	-16.96***
DBP				
Baseline (mmHg)	56.91 ± 10.14	56.91 ± 10.14	56.91 ± 10.14	56.91 ± 10.14
Task (mmHg)	66.88 ± 12.41	62.99 ± 10.04	71.33 ± 12.84	71.24 ± 12.94
t -test (76)	-13.30***	-9.00 ***	-16.82***	-15.62***
HR				
Baseline (bpm)	77.02 ± 10.64	77.02 ± 10.64	77.02 ± 10.64	77.02 ± 10.64
Task (bpm)	82.42 ± 11.19	80.05 ± 11.26	83.94 ± 11.52	80.66 ± 11.24
t -test (76)	-8.66***	-4.28 ***	-8.49***	-5.88***
CO				
Baseline (l/m)	6.08 ± 1.37	6.08 ± 1.37	6.08 ± 1.37	6.08 ± 1.37
Task (l/m)	6.44 ± 1.33	6.48 ± 1.29	6.54 ± 1.37	6.32 ± 1.13
t -test (76)	-3.76***	-5.22 ***	-4.22***	-2.23*
TPR				
Baseline (dyne-sec.cm-^{5})	770.44 ± 161.31	770.44 ± 161.31	770.44 ± 161.31	770.44 ± 161.31
Task (dyne-sec.cm-^{5})	842.96 ± 187.33	782.83 ± 205.80	891.32 ± 263.14	932.30 ± 248.95
t -test (76)	-4.33***	-0.74	-5.12***	-6.90***

* $p < .05$, *** $p < .001$

Table 6.12 Bivariate correlations between haemodynamic responses variable at entry and resting SBP and DBP at follow-up after ten months in the UK participants who completed initial and follow-up sessions (n = 77)

Variable	Follow-up			
	Resting SBP	*p* -value	Resting DBP	*p* -value
Speech preparation				
Δ SBP	0.059	.613	-0.045	.700
Δ DBP	0.111	.338	0.078	.499
Δ HR	.0171	.138	0.000	.997
Δ CO	-0.065	.574	-0.133	.248
Δ TPR	-0.149	.197	-0.186	.105
Speech delivery				
Δ SBP	0.192	.095	0.156	.105
Δ DBP	-0.083	.471	-0.178	.176
Δ HR	0.208	.069	0.057	.122
Δ CO	0.007	.952	-0.049	.624
Δ TPR	-0.030	.799	-0.030	.674

Δ, responses

Table 6.13 Partial correlation between life events, and cardiovascular reactivity controlling for age, sex, BMI, current cigarette smoking status, parental history of CVD and baseline cardiovascular measures in the UK participants who completed initial and follow-up sessions (n = 77)

Cardiovascular reactivity	**Stressful life events**	
	Correlation *r*	*p*-value
The mental arithmetic task		
SBP	**-0.239**	**.045**
DBP	-0.210	.079
HR	**-0.291**	**.014**
CO	-0.186	.121
TPR	0.185	.123
The speech task		
SBP	-0.109	.364
DBP	-0.194	.104
HR	-0.190	.112
CO	-0.107	.376
TPR	-0.031	.799
The cold pressor task		
SBP	-0.032	.791
DBP	-0.138	.253
HR	-0.008	.950
CO	0.020	.869
TPR	-0.084	.485

Table 6.14 Partial correlations between life events and cardiovascular reactivity controlling for baseline cardiovascular activity, traditional risk factors, self-reported perceived stress, performance or pain tolerance (depending on task) in the UK participants who completed initial and follow-up sessions (n = 77)

Cardiovascular reactivity	Stressful life events	
	Correlation *r*	*p*-value
The mental arithmetic task[1]		
SBP	-0.232	.055
DBP	-0.218	.072
HR	**-0.284**	**.018**
CO	-0.161	.186
TPR	0.168	.168
The speech task [2]		
SBP	-0.110	.363
DBP	-0.195	.105
HR	-0.190	.115
CO	-0.111	.360
TPR	-0.025	.837
The cold pressor task [3]		
SBP	-0.046	.706
DBP	-0.137	.262
HR	-0.015	.903
CO	0.029	.811
TPR	-0.120	.328

[1] controlling for baseline cardiovascular activity, traditional risk factors, self-reported perceived mental arithmetic stress and performance scores

[2] controlling for baseline cardiovascular activity, traditional risk factors, and self-reported perceived speech stress

[3] controlling for baseline cardiovascular activity, traditional risk factors, self-reported perceived cold pressor stress and pain tolerance

Table 6.15 Paired- sample t tests on blood pressure in the initial and follow-up sessions in different blood pressure monitors in the UK participants who completed initial and follow-up sessions (n = 77)

Blood pressure	**Variable**		***t*-test**	***p*-value**
	Portapres BP Mean ± SD	**Omron® M6 BP** Mean ± SD		
SBP at initial session (mmHg)	106.97± 14.68	113.71 ± 12.56	*t* (76) = -5.30	< .001
DBP at initial session (mmHg)	57.91± 10.14	66.77 ± 8.12	*t* (76) = -14.70	< .001
	Omron® M6 BP at first session Mean ± SD	**Omron® M6 BP at follow-up session** Mean ± SD		
SBP (mmHg)	113.71 ± 12.56	115.57± 12.57	*t* (76) = -1.36	.179
DBP (mmHg)	66.77 ± 8.12	65.87 ± 8.06	*t* (76) = 1.64	.106
	Portapres BP at first session Mean ± SD	**Omron® M6 BP at follow-up session** Mean ± SD		
SBP (mmHg)	106.97± 14.68	115.57± 12.56	*t* (76) = -6.46	< .001
DBP (mmHg)	57.91± 10.14	65.87 ± 8.06	*t* (76) = -11.12	< .001

Table 7.1 Bivariate correlations between symptoms of anxiety and depression, and BP at follow-up in the UK and Thai samples who participated in the initial and follow-up sessions

Variable	**Follow-up**			
	Resting SBP	*p* - value	Resting DBP	*p*-value
Thai participants (n = 107)				
- HADS anxiety scores	-0.122	.212	-0.007	.941
- HADS depression scores	-0.070	.471	0.082	.403
UK participants (n = 77)				
- HADS anxiety scores	**-0.272**	**.017**	**-0.322**	**.004**
- HADS depression scores	-0.124	.284	-0.008	.944

Table 7.2 Partial correlation between HADS anxiety scores, and resting SBP at follow-up controlling for age, sex, BMI, current cigarette smoking status, parental history of CVD, and baseline cardiovascular measures in the UK participants who participated in the initial and follow-up sessions (n = 77)

Variable	**Follow-up**			
	Resting SBP	*p* - value	Resting DBP	*p*-value
- HADS anxiety scores	-0.147	.222	-0.100	.405
- HADS depression scores	-0.090	.454	-0.052	.667

Table 7.3 A comparison of cardiovascular reactivity and future BP between three groups in the UK and Thai samples who completed initial and follow-up sessions (ANCOVA analysis; controlling for baseline BP activity)

Study		**Lowest**	**Intermediate**	**Highest**
UK	SBP responses to MA and future SBP	102.93 ± 16.04 [a] ** , [b] **	118.58 ± 9.89 [a] **	118.81 ± 7.92 [b] **
UK	SBP responses to MA and future DBP	58.78 ± 7.54 [a] **	67.99 ± 7.98 [a] **	66.33 ± 4.20
Thailand	SBP responses to MA and future SBP	108.17 ± 1.90 [a] **	112.99 ± 1.08	115.96 ± 1.88 [a] **

[a, b, c] significant mean differences

* $p < .05$, *** $p < .001$