

# **Effects of Psychosocial Stress and Depression on Cardiovascular Health in Youth: A Longitudinal Investigation**

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The Australian National University

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## **Declaration**

Research for this thesis was undertaken as part of the Lifestyle of our Kids (LOOK) Longitudinal Study. The overall LOOK project was designed by Professor Richard Telford and was collaboratively implemented by the ANU Research School of Psychology, the ANU Medical School, and the Canberra Hospital.

I, the candidate, have been a contributor to the LOOK study since 2006, and have been involved in all aspects of the research process from research design, questionnaire selection and development, data collection, data analysis and drafting of papers for publication.

I declare that this thesis is the product of my own work carried out under the supervision of Professor Don Byrne and Professor Walter Abhayaratna, with further advice received from Professor Richard Telford. Individuals who provided either material or conceptual assistance are acknowledged on the following page.

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## **Abstract**

Recent evidence suggests that cardiovascular disease (CVD) may be impacted by psychological distress, and specifically the experience of stress and depression. The evidence has been most clearly established in adults and, for the most part, limited to brief point-in-time measures of distress. With increasing recognition that early signs of psychosocial stress and depression, as well as the processes leading to CVD may begin to emerge in childhood, the question then presents itself as to whether psychological distress, experienced earlier in the life course, influences early pathogenesis for CVD.

The current research sought to determine whether symptoms of psychosocial stress and depression, experienced earlier in the life course, negatively influenced a set of established behavioural and metabolic risk factors and prognostic markers for CVD. Investigations in this thesis were conceptualised within a life course framework, but with an emphasis on the paediatric stage of development. Therefore, relationships between psychological constructs and CVD risk factors and risk markers were investigated as they were likely to present in this younger age group; beginning with primordial risk factors - risk factors that may underlie conditions leading to CVD rather than to causation directly, followed by intermediary markers - those considered to be prognostically significant of later CVD.

Initially, two clusters of primordial risk factors were investigated in two separate studies. Firstly, the impact of psychosocial stress and depressive symptoms on a set of behavioural risk factors, namely physical inactivity and cardiorespiratory fitness were investigated. Findings from this study indicated that a change in depressive symptoms within a child had a direct impact on their cardiorespiratory fitness and that children identified with more symptoms of stress and depression were more likely to be less physical activity and less fit. In the second study, investigations examining the influence of psychosocial stress and depressive symptoms on a set of metabolic primordial risk factors, namely percent body fat and insulin resistance, revealed a dose-response



relationship between insulin resistance and depressive symptoms, whereby boys with higher levels of insulin resistance also reported more symptoms of depression, and a direct (longitudinal) effect indicating that boys who increased in depressive symptoms also became fatter.

In Study 3 and Study 4, investigations were extended to include a set of intermediary risk makers of CVD, those considered to be prognostically significant of later CVD. The effect of psychosocial stress and depressive symptoms on arterial stiffness and blood pressure were investigated in study 3; and on endothelial function in study 4. Findings from these studies demonstrated that children who became more depressed also had increases in diastolic blood pressure and mean arterial pressure; and that those becoming more stressed had a reduction in pulse pressure; but thus far did not uncover a direct effect of psychosocial stress or depression on arterial stiffness or endothelial function in our cohort.

Overall, this thesis builds a case for the impact of psychosocial stress and depressive symptomology on CVD risk among growing children. The implications for these findings in terms of intervention and further research are discussed.

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# **PREFACE**

## **Problem Statement**

Cardiovascular disease (CVD) is a leading cause of mortality and a primary health concern in developed nations (Australian Bureau of Statistics, 2015; World Health Organisation, 2015). While the clinical manifestations of CVD are most commonly observed in adulthood, evidence indicates that its pathogenesis occurs much earlier, perhaps as young as childhood (Berenson et al., 1992; Li et al., 2004; McGill et al., 2000). Moreover, traditional risk factors, such as family history, hypertension, dyslipidaemia, and diabetes do not fully predict CVD (Flaa, Eide, Kjeldsen, & Rostrup, 2008).

One relatively novel line of investigation has been that examining the impact of psychosocial factors on CVD, with psychosocial stress and depression being among the most studied. Psychosocial stress and depression have been linked to the aetiology, development, duration, and outcome of CVD in adults (Albus, 2010; Blumenthal et al., 2003; Glozier et al., 2013; Rozanski, Blumenthal, & Kaplan, 1999; Van der Kooy et al., 2007), and there is an emerging case to suggest that depression is an independent risk factor for CVD (Hare, Toukhsati, Johansson, & Jaarsma, 2014; Kuper, Marmot, & Hemingway, 2002; Lett et al., 2004; Rozanski, Blumenthal, & Kaplan, 1999; Wulsin & Singal, 2003). Further evidence indicates that psychosocial stress may influence the development of a range of cardiovascular diseases through measureable changes associated with the stress response (Gu, Tang, & Yang, 2012).

Despite the compelling evidence in adults, very little is known regarding the effect of psychosocial stress and depressive symptomology experienced during childhood and adolescence, on early CVD pathogenesis. Given that early signs of psychosocial stress and depression, as well as the processes leading to CVD may begin to emerge in childhood, it is possible that early cardiovascular dysfunction and psychological problems may be causally related. Consequently, there is a need for this field of investigation to move beyond adulthood and include younger populations. The

motivation for this line of research lies in the well accepted dictums of health promotion and the accepted belief that early intervention is more effective, both in terms of prevention, as well as the economic cost to the community (Australian Institute of Health and Welfare, 1999; Cohen, Neumann, & Weinstein, 2008).

Despite the effects of psychosocial stress and depression being less evident in children and adolescents, possibly in part due to a paucity of studies, it is hypothesised that these psychological effects do not suddenly emerge as risks to CVD upon reaching adulthood; that rather psychological distress may induce the early stages of the development of CVD in children and adolescents. Testing such a hypothesis requires strong methodology and a longitudinal design. With the predictable lack of clinical events among this younger age group, investigations of any link between psychological distress and CVD in apparently healthy children are limited to investigations of relationships between early symptoms of psychological distress and risk factors or markers of cardiovascular dysfunction. Should these relationships emerge, then there may be grounds for early psychological interventions to accompany those in common practice, which target obesity and physical inactivity.

The longitudinal studies that are presented in the current research provide for a higher level of inference than those cross-sectional, but they remain observational, limiting any inference of causation. However, psychophysiological evidence that stress and depression can negatively influence the integrity of the cardiovascular system provides further support for inferences of causality. Whilst the exact mechanisms linking psychosocial stress and depression with CVD are not well understood, an extensive literature suggests a number of biologically and behaviourally plausible explanations for these links (Grippe & Johnson, 2002; Pereira, Cerqueira, Palha, & Sousa, 2013; Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2011). It is these underlying psychophysiological mechanisms that underpin the relevance of the research undertaken in the current Ph.D. thesis; the knowledge that the way we think can influence the physiology of the arteries and the heart. This may be particularly

relevant in growing children, where systemic plasticity may render a child's cardiovascular system even more susceptible to disruption than in adulthood. While this thesis does not directly investigate these mechanisms, nor does it directly assess what might be considered the primary mediators that may explain the link between the heart and mind (e.g. chemical messengers such as cortisol, adrenalin, noradrenalin), it is this line of questioning that can guide the selection of appropriate outcomes measures that are relevant to younger populations. This may include outcome measures that are considered intermediary or secondary mediators, including more integrated processes such as blood pressure and metabolic profiles, which are the outcome of effects of one or more primary mediators. Drawing on the principles of basic science and the empirical evidence of plausible biological mechanisms linking various forms of psychological distress and CVD risk, we are able to develop a framework for which to undertake the current research.

Despite the significant and valuable contributions of previous researchers, it has not been clearly articulated how psychological factors, including psychosocial stress and depressive symptomology come to influence cardiovascular health in youth. Whilst it is acknowledged that experimental investigations are required to fully elucidate the answers to these complex questions, prior to such investigations being warranted, there is the need to firstly establish significant and robust relationships between psychological factors and CVD risk factors in children and adolescents. Herein lays the value of current work, the first stage of investigation, examining whether early psychological distress is related to cardiovascular dysfunction in youth. Should relationships be demonstrated, this then begins to provide a framework for future work to set up appropriate experimentation to test the causal hypothesis. Therefore, this Ph.D. thesis seeks to articulate the potential negative effect of early symptoms of psychosocial stress and depression on a range of early primordial risk factors and intermediary markers, believed to be indicative of later CVD.

## **Aim**

The aim of this thesis is to investigate the influence of two psychological constructs, namely the experience of psychosocial stress and depressive symptoms, on a set of established risk factors and risk markers for CVD. This research takes a developmental perspective by investigating relationships between psychological constructs and CVD risk factors as they are likely to present in this younger age group. Our investigations begin with *primordial risk factors* - those risk factors that contribute to or influence the underlying pathogenic conditions leading to CVD, rather than contributing to causation directly. In the current thesis, these include physical inactivity, low fitness, obesity and insulin resistance. Subsequently, we examine the effects of psychosocial stress and depression on more direct and prognostically significant measures of cardiovascular health, our *intermediary risk markers* – these being risk markers that provide a pathway through which risk factors may lead to CVD. In the current work, markers of arterial stiffness, blood pressure and endothelial function are included.

## **Scope**

The scope of the work reported in this thesis is contained in two ways. Firstly, our investigations into stress refer to psychosocial stress only, and further to stressor exposure particularly relevant to an asymptomatic paediatric population. Whilst it is acknowledged that physical stress may also play a role in cardiovascular health, this is not the focus of the current work. Instead, the current research is grounded in clinical psychology and then draws knowledge from the biomedical sciences, placing this work very much in a biopsychosocial framework (Engel, 1980).

Secondly, our intermediary markers of CVD are limited to three; (1) arterial stiffness, (2) blood pressure, and (3) endothelial function. It is acknowledged that the selected intermediary markers are not the only clinically relevant measures of cardiovascular function and CVD risk. However, our current understanding of the

timeline of events in terms of cardiovascular dysfunction, along with the empirical evidence highlights that these indicators are often the first to be observed in humans, with evidence of their occurrence in children (Celermajer et al., 1992; Tavares, Bocchi, & Guimarães, 2012). Furthermore, psychological distress has been shown to affect both arterial and endothelial function in both adult (Cooper et al., 2011; Logan, Barksdale, Carlson, Carlson, & Rowsey, 2012; Vlachopoulos et al., 2006) and younger populations (Dietz & Matthews, 2011; Osika et al., 2011; Tomfohr, Murphy, Miller, & Puterman, 2011; Waloszek et al., 2015).

### **Thesis Overview**

To achieve the aims of this Ph.D. thesis, Chapter 1 begins by introducing the current landscape and significance of CVD in contemporary life, commencing with an introduction to the burden of disease. Both traditional and non-traditional CVD risk factors are discussed and the terms primordial risk factors and intermediary markers of CVD are defined. In Chapter 2, further comment on psychological risk factors, along with a definition of psychosocial stress and depression is provided. In Chapter 3, the literature investigating the relationships between psychosocial stress, depression and CVD is critically reviewed, beginning with the more substantiated evidence among adults and then with a focus on the paediatric literature. Chapter 4 then seeks to go beyond these associations, by presenting the potential mechanisms linking psychosocial stress and depression with CVD, with the aim of constructing a plausible framework for which to conduct the current research. In Chapter 5, the Lifestyle of our Kids (LOOK) Study is introduced and the methodology of the current thesis is presented, along with hypotheses. Chapters 6 to 9 present the empirical studies, which test our hypotheses. In Chapters 6 and 7, the effects of stress and depression on primordial risk factors, including physical activity and fitness (Chapter 6), and adiposity and insulin resistance (Chapter 7) are investigated. These effects are investigated using a longitudinal design, following our cohort of preadolescent children through to

adolescence. Among these studies, we provide evidence for a significant effect of psychosocial stress and depressive symptoms on physical activity, fitness, fatness and insulin resistance. In Chapters 8 and 9, based on the evidence from earlier studies that psychosocial stress and depressive symptoms effect primordial risk factors, we turn our investigations to prognostically significant measures of cardiovascular health, including arterial stiffness and blood pressure (Chapter 8) and endothelial function (Chapter 9). Investigations are longitudinal but this time with a focus on adolescence, and thus far did not uncover a direct effect of psychosocial stress or depressive symptoms on our measure of arterial stiffness or endothelial function. We provide some evidence for an effect of increasing depressive symptoms on greater diastolic blood pressure and mean arterial pressure, along with preliminary evidence for an effect of increasing psychosocial stress on reduced pulse pressure. In the final discussion in Chapter 10, the implications of the current findings are considered, including the contributions made by to the current knowledge base, but also highlighting several priorities for future research, including the need to clarify causal relations between cardiac vagal control and depression. Considerations for methodological improvements, in terms of current measurement instruments among paediatric populations are provided, along with practical implications and how this work might be translated into clinical practice.



## **CHAPTER 1**

# **CARDIOVASCULAR DISEASE: TYPES, RISK FACTORS AND POULATION BURDEN OF DISEASE**

### **Population Burden of Cardiovascular Disease**

Cardiovascular disease (CVD), a broad term that refers to any disorder affecting the heart and blood vessels (Mann, Zipes, Libby, & Bonow, 2015), is a leading cause of death worldwide, with an estimated 17.3 million deaths each year (World Health Organisation [WHO], 2015). In Australia, CVD accounts for almost 30% of all deaths, which amounted to 43,946 deaths in 2012 (Australian Bureau of Statistics [ABS], 2015).

While the disease can present in any part of the cardiovascular system, there are three main types of CVD that most contribute to CVD related mortality and morbidity, these being (1) coronary heart disease (CHD), a disease of the blood vessels supplying the heart muscle, (2) cerebral vascular disease, a disease that affects the blood vessels supplying the brain and can result in stroke, and (3) peripheral artery disease, a disease of blood vessels supplying the arms and legs. Based on the latest available statistics, in 2008 CHD accounted for 49% (22,500 individuals) of all CVD deaths and 16% of deaths from all causes in Australia (Woodall & Senes, 2008).

Although the CVD related mortality rates have fallen since the 1970's (largely due to improvements in detection and clinical management of the disease), CVD remains one of the biggest burdens on our economy. In 2004 and 2005, close to six billion dollars in health care expenditure was spent for CVD, representing 11% of the total health expenditure in Australia (Woodall & Senes, 2008). In addition to economic costs, CVD places a significant strain on the community in terms of further health, social, and emotional costs (Australian Institute of Health and Welfare [AIHW], 1999).

## CHAPTER 1

Given these statistics, CVD was identified as one of the National Health Priority Areas in 1996 in recognition of the severe impact it has on the health and wellbeing of the Australian population. It is perhaps not surprising then that CVD has become a focal point for research, including a large body of literature investigating the aetiology and primary prevention of the disease. Imperative to this work has been the finding that much of the risk for CVD is attributable to potentially modifiable risk factors (Danaei et al., 2009; Ezzati et al., 2007; Wilson, 1994; Yusuf et al., 2004).

### **Traditional and Primordial Risk Factors for Cardiovascular Disease**

A number of non-modifiable risk factors for CVD have been identified, including age, sex, family history of CVD and ethnicity (Daniels, Pratt, & Hayman, 2011; Ezzati et al., 2007). While there is no doubt that CVD is a disease of aging, with increasing age constituting the largest attributable risk (Tuomilehto, 2004), most individuals who develop CVD do so because of a combination of modifiable risk factors. These modifiable risk factors are often classified as either traditional or primordial.

Traditional risk factors are those derived from large, historical, prospective and retrospective cohort studies, and more recently from established prospective adult and child cohort studies (Assmann & Schulte, 1987; Doyle, Dawber, Kannel, Heslin, & Kahn, 1962; Dawber, Kannel, Revotskie, Stokes, Kagana, & Gordon, 1959; Doll & Peto, 1976; Feinleib, 1981; Heiss et al., 1991; Kannel, Castelli, Gordon, & McNamara, 1971; Rose et al., 1977; Stampfer, Hu, Manson, Rimm, & Willett, 2000; Wilson, 1994; Wong & Levy, 2013; Yusuf et al., 2004). Traditional risk factors include smoking, high blood pressure (hypertension), high cholesterol and diabetes. When the evidence is taken together, these risk factors only account for approximately 50% of the risk for CVD.

Seminal research from studies such as the Framingham Study (Dawber, Meadors, & Moore, 1951; Wong & Levy, 2013) and others (Fried et al., 1998; Rosengren et al., 2004; Stampfer et al., 2000; Yusuf et al., 2004) have led to the

identification of additional primordial risk factors. These risk factors tend to cluster in categories of behavioural (e.g. physical inactivity, low fitness, and poor diet), metabolic (e.g. insulin resistance, impaired glucose tolerance, and obesity), and psychological (e.g. psychosocial stress, social isolation, depression; Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2007; Hubert, Feinleib, McNamara, & Castelli, 1983; Kannel & McGee, 1979). In recent times, these factors are commonly referred to as primordial risk factors, as they pertain to the underlying conditions leading to causation of CVD, rather than to causation directly.

The identification of primordial risk factors has increased our understanding of the circumstances leading to CVD. Influential research in this area emerged from the landmark INTERHEART study, a large case-control study undertaken across 52 countries, involving more than 10,000 participants (Yusuf et al., 2004). Findings from the INTERHEART study demonstrated that just over 90% of population attributable risk for acute coronary syndrome presentations could be explained by nine risk factors, those being smoking, abnormal lipids, hypertension, diabetes, obesity, diet, physical inactivity, alcohol consumption, and psychosocial factors (Yusuf et al., 2004). Further work arising from the INTERHEART study demonstrated that the identified risk factor of psychosocial distress accounted for approximately 30% of the attributable risk of acute myocardial infarction (Rosengren et al., 2004). This finding is consistent with a rapidly growing body of evidence supporting a link between psychosocial factors and CVD. It is these psychosocial risk factors, and specifically, psychosocial stress and depression, that are of interest in the current work. Overall, the findings reported here have had a considerable impact on both the prevention and treatment of CVD in clinical practice.

Further developments in our understanding of the causes and the course of CVD have come as a result of advances in technology, such as non-invasive measurement instruments that can detect prognostically significant changes in the vasculature (Martin & Anderson, 2009; Mattace-Raso et al., 2006; Ras, Streppel, Draijer, & Zock, 2013; van den Oord et al., 2013; Vlachopoulos, Aznaouridis, &

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Stefanadis, 2010). These technological advances include the ability to detect; (1) changes in vessel structure (i.e. increased intima media thickness), (2) mechanical changes (i.e. decreased arterial distensibility or increased stiffness), and (3) physiological changes (i.e. decreased flow mediated vasodilation, indicative of endothelial dysfunction). These measurable or detectable changes in the vascular, indicative of vascular dysfunction are classified as *intermediary risk markers*, as they represent a potential pathway through which primordial risk factors may lead to CVD.

Non-invasive measurement instruments constitute an important advancement in the field of cardiology, allowing for an individual's level of CVD risk to be objectively identified and then potentially modified through (preventive) intervention. Emerging evidence has highlighted the prognostic significance of measures of arterial stiffness (Cecelja & Chowienczyk, 2012; Mitchell et al., 2010) and endothelial dysfunction (Ras et al., 2013) as important intermediary risk factors for CVD and it is these specific risk markers that form part of the empirical investigations undertaken in this thesis.

In summary, a number of well-established risk factors, both traditional and primordial have been identified for CVD. One of the more novel findings has been that identifying psychosocial risk factors in the aetiology and prognosis of CVD. In addition, a number of prognostically significant intermediary markers, which may mediate the relationship between primordial risk factors and subsequent disease development, have also been recognised. Of relevance to the current work, and on the basis of a rapidly accumulating body of credible evidence, it has become apparent that a number of these primordial risk factors and intermediary markers are identifiable in children (Berenson & Srivivasan, 2005), adding support for the hypothesis that CVD risk in adulthood is firmly founded in childhood, and further foreshadowing the issue of CVD prevention.

### **Evidence for a Life Course Approach to CVD Prevention**

To date, early CVD prevention efforts have primarily focused on reducing primordial risk factors in adults through lifestyle and behaviour modifications, and by encouraging health promoting behaviours. Although a necessary and important part of health promotion, there are some limitations to this approach. Firstly, at this point of intervention, which often occurs during the fifth decade of life or beyond, it is likely that the individual at risk already has advanced atherosclerosis (Baber et al., 2015; Strong et al., 1999; Tuzcu et al., 2001). Secondly, health behaviours and lifestyles during adulthood, which are established over earlier decades of the lifespan, may be difficult to change (Marcus et al., 2006). While the evidence on CVD risk factors described previously has largely been drawn from the adult literature, there is now direct evidence that the pathophysiological processes leading to the disease may begin much earlier in childhood for some individuals. This evidence has resulted from several classic and large-scale, prospective cohort studies.

### **Risk Factor Profiles in Children and Cardiovascular Disease Pathology**

Findings from pathology studies from Korean War casualties (Joseph, Ackerman, Talley, Johnstone, & Kupersmith, 1993; Strong, 1986), along with outcomes from long-term epidemiological studies, such as the Bogalusa Heart Study (Berenson et al., 1992) and the Pathological Determinants of Atherosclerosis in the Young (PDAY) Study (Wissler et al., 1998) have provided direct evidence of the early development of atherosclerosis via autopsy studies. In these studies, both fatty streaks (an accumulation of lipid filled macrophages within the intima of the artery, which is considered an early atherosclerotic change) and fibrous plaques (a more advanced stage of atherosclerosis) were evident in the aorta and coronary arteries of children. In both the Bogalusa Heart Study and the PDAY Study, the prevalence and extent of these lesions were strongly associated with traditional cardiovascular risk factors, including increases in blood pressure and serum concentrations of total cholesterol,

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low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (Berenson et al., 1998; McGill et al., 2000).

In addition to traditional risk factors, it is now clear that such well identified primordial CVD risks as obesity (Cote, Harris, Panagiotopoulos, Sandor, & Develin, 2013; Friedemann, Heneghan, Mahtani, Thompson, Perera, & Ward, 2012; Haas, Liepold, & Schwandt, 2011; Park, Sovio, Viner, Hardy, & Kinra, 2013; Spiotta & Luma, 2008; Twisk, Kemper, van Mechelen, & Post, 1997), elevated blood lipids (Ayer & Sholler, 2012; Daniels, 2001; May, Kuklina, & Yoon, 2012; Reed, Warburton, & McKay, 2007; Twisk et al., 1997;), higher than normal blood pressure (Ayer & Sholler, 2012; Reed et al., 2007), both Type 1 and Type 2 diabetes (Morrison, Glueck, Woo, & Wang, 2012; Schnell, Cappuccio, Genovese, Standl, Valensi & Ceriello, 2013; Velasquez-Mieyer, Perez-Faustinelli, & Cowan, 2005), and low physical activity and fitness (Froberg & Andersen, 2005), are evident to an apparently increasing degree in children.

Adding further support for a life course approach to CVD prevention is the compelling evidence based on pooled data of several large cohort studies (i.e. Bogalusa Heart Study [Berenson, 2001]; the Cardiovascular Risk in Young Finns Study [Raitakari et al., 2003]; the Childhood Determinants of Adult Health Study [Gall, Jose, Smith, Dwyer, & Venn, 2009]; the Coronary Artery Risk Development in Young Adults [Friedman et al., 1988]; and the Muscatine Study [Davis, Dawson, Riley, & Lauer, 2001]), which found that elevated risk factor levels in youth are highly predictive of pre-clinical or intermediary markers of cardiovascular health (i.e. increased carotid intima-media thickness; CIMT) in adulthood (Juonala et al., 2010; Magnussen et al., 2009). Similar findings for the predictive association between a range of CVD risk factors (e.g. body fatness, blood pressure, cholesterol) in childhood and adolescence and intermediary markers (i.e. CIMT and arterial stiffness) indicative of increased CVD risk in adulthood have been reported (Ferreira et al., 2004; Hartiala et al., 2012; Juonala et al., 2005; Mahmood, Levy, Vasan, & Wang, 2014). Therefore, based on this body of

evidence, there can be no doubt that the development of CVD risk in adulthood is firmly founded in childhood; thus, building an argument that CVD prevention needs to begin earlier in life, taking a life course approach to match the life course of the disease.

While the evidence presented so far supports a life course approach to both research into- and the prevention of- CVD, it is important to highlight that there is a current lack of data linking absolute levels of risk factors in childhood to incident CVD in adulthood. Similarly, there is a notable lack of randomised control trials data indicating that reduction of risk factors in childhood prevents cardiovascular events in adulthood. This lack of evidence is perhaps not surprising, given the difficulties and expense associated with the type of studies needed to provide such data, which require very long-term prospective studies with large cohorts of children adequately screened for CVD risk at intake, then followed through to early adulthood and beyond. Even so, the weight of the evidence so far has led some experts to call for a more proactive approach in childhood to the prevention of CVD. The rationale behind such calls likely being; (a) that risk-factor modification should occur prior to the widespread development of atherosclerosis, and (b) that health compromising behaviours, and therefore CVD risk factor profiles, may be more amenable to change at this younger age (Catalano, Berglund, Ryan, Lonczak, & Hawkins, 2004; Epstein, Valoski, Kalarchian, & McCurley, 1995; Prochaska, DiClemente, & Norcross, 1992).

Efforts to achieve the primordial and primary prevention of CVD through focused interventions with children are, of course, not new. This is perhaps most evident in terms of intervention efforts aimed at the prevention and treatment of childhood obesity (Dietz & Gortmaker, 2001; Freedman, Dietz, Srinivasan, & Berenson, 1999; Sothorn, 2004; Steinberger & Daniels, 2003; Story, 1999), along with interventions for other equally well established risk factors for CVD, including diet, physical inactivity, and smoking (Daniels et al., 2011; Metcalf, Henley, & Wilkin, 2012; Pahkala et al., 2013). In light of the rapidly growing body of evidence supporting a link between psychosocial factors and CVD, it is suggested that a similar preventative

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approach, focused on improving psychological risk profiles may also prove to be beneficial. While the evidence to support such a claim is currently lacking in the literature due to an absence of methodologically strong studies, it is argued that, based on the evidence linking adult CVD with lifestyles and experiences occurring early in life, including those psychological in nature (Korkeila et al., 2010), that addressing psychosocial risk factors may provide a novel approach to primordial prevention. However, the credibility of such an approach to prevention is dependent on the availability of sound evidence, both epidemiological and clinical, to guide the targets of health promoting interventions and the forms they take (Green, 2000; Juneau, Jones, McQueen, & Potvin, 2011). As previously indicated, this evidence is currently lacking in the CVD literature.

What is apparent on reviewing the CVD risk factor literature, however, is that in addition to the demonstrated associations between psychological risk factors and later development of CVD, is the consistent evidence of an association between those psychological risk factors and a range of behavioural and metabolic risk factors for CVD (Shiroma & Lee, 2010); many of which are documented in children (Jerstad, Boutelle, Ness, & Stice, 2010; Stice, Presnell, Shaw, & Rohde, 2005; Richardson et al., 2003). This evidence, linking psychosocial stress and depression to both CVD and to CVD risk factors demonstrates that psychological risk factors - and specifically, depression and psychosocial stress, where the evidence is most compelling - may influence risk for CVD via both behavioural pathways, through a negative influence of health behaviours and lifestyle factors related to CVD, and via more direct biological pathways.

For instance, psychosocial stress and depression may influence cardiovascular risk indirectly through an influence on health compromising behaviours, such as physical inactivity (Jerstad et al., 2010), and subsequent low fitness (Gerber, Lindwall, Lindegard, Borjesson, & Jonsdottir, 2013), or via poor diet control, which may influence obesity (Richardson et al., 2003; Stice et al., 2005). Childhood and adolescence is an



important period in terms of health behaviour, as it is this period where the foundations for health behaviours are most clearly laid, rendering this earlier life stage an influential and potentially sensitive time for the development of health promoting behaviours. The literature investigating the link between psychosocial stress and depression and these primordial risk factors (e.g. physical activity, fitness, obesity) is reviewed at more length in the corresponding empirical chapters.

In addition to behavioural pathways, psychosocial stress and depression may have a more direct impact on cardiovascular health via biological pathways, including an influence on autonomic and neuroendocrine mechanisms involved in mediating the stress response (d'Audiffret et al., 2010; Grippo & Johnson, 2009; Huffman, Celano, Beach, Motiwala, & Januzzi 2013; Rozanski et al., 1999). Alterations in neuroendocrine and autonomic functioning, resulting from chronic activation of these systems, may lead to a cascade of deleterious effects on the cardiovascular system, thus setting up the hormonal milieu which may lead to insulin resistance, and to further dysfunctional changes in the cardiovascular system, including high blood pressure, arterial stiffness and endothelial dysfunction. In Figure 1, the potential pathways that may link psychosocial stress and depression with CVD are presented. Although several other risk factors not listed may also contribute to disease risk, the primordial risk factors and intermediary risk markers outline in Figure 1 constitute the pathways of association that will be investigated in this thesis. The aim being to articulate the influence of early symptoms of psychosocial stress and depression and, (a) primordial risk factors, including physical inactivity, low fitness, increased adiposity and insulin resistance, and (b) intermediary markers of CVD risk, namely, elevated blood pressure, arterial stiffness and endothelial dysfunction.

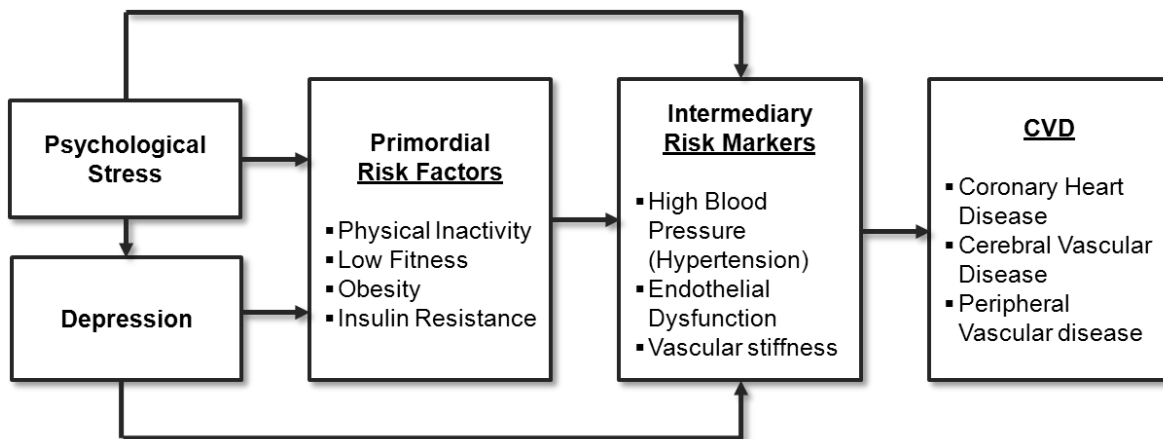


Figure 1. The potential pathways of influence between psychosocial stress and depression with risk factors and risk markers for cardiovascular disease.

### Chapter Conclusions

Cardiovascular diseases are among the most widespread and costly health problems currently facing our Nation and the developed world. However, it is now acknowledged that much of the risk for CVD is preventable. Extensive research in the field of cardiovascular medicine has successfully identified an important set of risk factors for CVD, which are thought to account for most of the risk for disease. These findings have led to intervention efforts that aim to reduce risk factor profiles among adults. However, there is now evidence to support earlier intervention, even among children and adolescents, where the pathological processes leading to eventual CVD are thought to originate. One important development, and the focus of the current work, has been the identification of psychological risk factors for CVD, including both psychosocial stress and depression. Whilst much of the evidence supporting a link between psychological factors and risk for CVD has come from research in adults, there is a new and emerging literature investigating these relationships in children and adolescents. This literature, along with the more comprehensive adult literature, is critically reviewed in a subsequent chapter. But prior to reviewing the literature, the following chapter introduces and defines the psychological risk factors investigated in the current work.

## **CHAPTER 2**

### **PSYCHOLOGICAL RISK FACTORS FOR CARDIOVASCULAR DISEASE**

In the CVD literature, a range of psychological factors have been investigated in reference to cardiovascular function and CVD risk. These have included stress, depression, anxiety, hostility, anger, and social isolation (Bunker et al., 2003; Everson-Rose & Lewis, 2005; Glozier et al., 2013). However, the research undertaken in this thesis limits its investigation to two psychological factors, those being psychosocial stress and depression (and specifically pre-clinical depression). The selection of these constructs is informed by two considerations, (1) the developmental relevance of these factors to children and adolescents, and (2) the available empirical evidence. In considering the former, psychosocial stress has featured heavily in the developmental psychology literature and is often implicated in the development of both psychopathology and chronic disease (Compas, Orosan, & Grant, 1993; Dube et al., 2009; Grant et al., 2006; Middlebrooks & Audage, 2008; Miller, Chen, & Parker, 2011; Miller, Chen, & Zhou, 2007). Similarly, internalising disorders, including depressive presentations, are thought to be one of the more prominent presentations in children and adolescents (Lawrence et al., 2015), making it a suitable candidate for any investigation involving youth. Moreover, like stress, depressive symptoms, and in particular, depression of a clinical level, can have far reaching and debilitating effects on a child's current and future psychological and physical health (Fergusson, Horwood, Ridder, & Beautrais, 2005; Keenan-Miller, Hammen, & Brennan, 2007; Kessler et al., 2010), thus providing further evidence of its utility in any study examining associations and determinants of disease.

In view of the latter consideration, it was observed in the empirical literature that the most compelling body of evidence linking psychological factors to a range of CVD

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risks and diseases related to depression and stress (Bunker et al., 2003; Glozier et al., 2013; Frasure-Smith & Lespérance, 2005, 2006, 2010; Hare, Toukhsati, Johansson, & Jaarsma, 2014; Hemingway & Marmot, 1999; Kuper, Marmot, & Hemingway, 2002; Nicholson, Kuper, & Hemingway, 2006; Rosengren et al., 2004; Van der Kooy et al., 2007; Wulsin & Singal, 2003), again highlighting the relevance of these constructs in relation to CVD risk.

### **Prevalence of Depression and Occurrence of Psychosocial Stress in Youth**

It is acknowledged that the credibility of any investigation into the potential contribution of psychological factors on later disease development in younger populations relies on the assumption that children and adolescents are sufficiently exposed to experiences of psychosocial stress and depression, of a type that may negatively influence the cardiovascular system. Despite popular belief that childhood is a relatively carefree time, there is evidence that both children and adolescents experience stressors in the form of ongoing daily hassles (Byrne, Davenport, & Mazanov, 2007; Byrne, Thomas, Burchell, Olive, & Mirabito, 2011; Jewett, 1997) and stressful life events (Kraag, Zeegers, Kok, Hosman, & Abu-Saad, 2006). Some children are also burdened with the experience of more severe trauma or adversity, including poverty, family violence, abuse and neglect (Felitti et al., 1998; May-Chahal & Cawson, 2005).

Similarly, there is evidence to indicate that both children and adolescents quite commonly manifest symptoms of depression, with some experiencing depression of clinical severity. In a major epidemiological study investigating the prevalence of diagnosable depressive disorders, Zalsman, Brent and Weersing (2006) reported a prevalence of 1% to 2% in pre-pubertal children, 3% to 8% in adolescents, and 20% as an end-of-adolescence “lifetime” estimate. This was essentially consistent with the figures of 2.8% for children under 13 years old, and 5.6% among those 13 to 18 years

old reported by Jane Costello, Erkanli, and Angold (2006), and with the 3% of Australian youth aged 6 to 17 years reported in Sawyer et al. (2001).

### **Psychosocial Stress: A Definition**

Defining stress has been notoriously difficult in the field of stress science due to the divergent use of the term across disciplines, but also owing to the difficulties in teasing stress apart, either conceptually or operationally, from other psychopathology constructs (Coyne & Racioppo, 2000; Dohrenwend & ShROUT, 1985). The pioneering work of Cannon (1929) and Selye (1946), regarding the stress response, has greatly influenced how stress has been defined and studied over many decades, particularly in reference to disease. Cannon's work focused on how organisms adapt and survive in the face of stress, which led him to devise the term *homeostasis*;

*"The body's process of maintaining the required stability in the functioning of bodily systems so that life and health can continue."*

(Cannon, 1929, p. 400).

Selye's work added the consequences of stress, specifically the additional focus on how stress degrades homeostatic systems and leads to death, which he termed the *general adaptation syndrome*, which is defined as:

*"The predictable way the body responds to stress involving three stages;*

*(1) alarm stage, (2) resistance stage, (3) exhaustion stage"* (Selye, 1946,

p. 121).

Since the seminal work of Cannon (1929) and Selye (1946), stress research has slowly moved away from physiologically oriented stimulus-response paradigms towards a model that emphasizes the psychological processes and the psychological

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impact of stress. Some of the most influential work undertaken in this area was by Lazarus, who argued that the concepts of cognitive appraisal and coping are required in order to explain how exposure to certain kinds of (stressful) events and conditions leads to certain kinds of (stress) responses, and to account for individual differences in those responses (Lazarus & Folkman, 1984).

Based on contemporary stress science, and in line with a process framework, the term stress has generally been broken down in to three main subcategories. These being; (1) *stress as a stimulus*, often termed stressors, which refers to events or sets of circumstances in the environment that may be interpreted as a threat, (2) *stress as an appraisal*, which includes a psychological processing aspect whereby an individual determines the level of threat or challenge of the stressor in relation to their ability and resources to cope, and (3) *stress as a response*, which represents the physiological stress response. A summary of these three components of the stress process is presented in Figure 2.

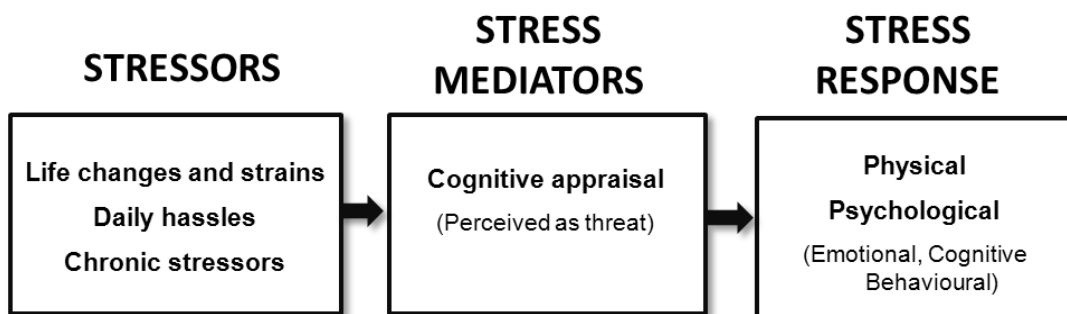


Figure 2. Components of the stress process, involving stimulus (input), mediating processes, and response (output).

Historically, psychologists have conceptualised stress with an approach that focusses on either; (a) the occurrence of stressors (e.g. stressor exposure), measured in terms of a wide range of stressors, including major life events (e.g. loss of a loved

one, parental divorce), catastrophic events (e.g. earthquakes, terrorist attacks) and chronic circumstances (e.g. living in poverty, living with a chronic illness), (b) the individual's appraisal of these stressors (e.g. the individual's perception of threat and ability to cope with the threat), or (c) a process that incorporates both stressor exposure and individual appraisals. Inherent to this process approach is the acknowledgment that continuous interactions and adjustments – called “transactions” – occur between the person and environment, each affecting- and being affected by- the other (Sarafino & Smith, 2011).

Traditionally, researchers from the biomedical fields have characterised stress as anything that activates either the sympathetic nervous system (SNS) or the hypothalamus-pituitary-adrenocortical axis (HPA-axis), be that stimulus psychological or biological in nature, resulting in investigations that primarily focus on the stress response. Despite debate over the best way to define stress, there is no dispute regarding the individual's aim during this process – to achieve and maintain homeostasis. As a result, the current research will adopt an integrative definition of stress, in line with Cohen, Kessler, and Underwood Gordon (1995), which describes stress as;

*“The processes and environmental circumstance and conditions that threaten, tax, exceed or harm the adaptive capacity of an individual, either psychologically or biologically, which in turn, places the individual at risk for disease” (p. 3).*

This definition is most similar to the process conceptualisation of stress and will inform the measurement of psychosocial stress in the current work. Central to this description, and relevant to our investigations with aspects of the cardiovascular system, is the departure from homeostasis, which in turn activates compensatory activity within the individual, be that psychological or biological. These demands may

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occur in terms of changes in the social environment, or in persistent environmental conditions that present an ongoing challenge or threat, or alternatively, as changes within the individual, both physically and psychologically.

At this point, the author reiterates that the current work is firmly based on a psychological perspective, which then draws from fields relating to the biomedical sciences, with a specific focus on the cardiovascular system; the aim being, to investigate the effects of psychosocial stress on aspects of cardiovascular health. Taking this into consideration, the measurement of stress in the current work, therefore has an emphasis on psychological processes that occur in response to the psychosocial environment, including exposure to environmental and life events that are relevant to a paediatric population and how these are perceived. As a result, and to further clarify the use of terms used throughout this work, the term *psychosocial stress* is used as an umbrella term meant to capture times when an individual has been exposed to a stimulus that is psychosocial in nature, that results in the individual making an appraisal of that stressor. An emphasis is placed on the transaction between person and environment, and specifically on the degree to which the individual appraises these environmental demands as threatening, challenging or harmful (Lazarus & Folkman, 1984). It is acknowledged that a number of strengths and limitations are inherent in this approach to examining stress and these are discussed further in Chapter 5, where the methodology for the current work is introduced. The stimulus (or input) in this process is referred to as a *stressor*, and although stressors can be both physical and psychological in nature, the current thesis limits the scope of investigation to psychological stressors. The use of the term *stress response* will be reserved for the cascade of physiological changes that occur in response to a stressor. Finally, the term *stress* will be used in its broadest sense to refer to the interactive process involving the three main subcategories outlined in Figure 2, those being; (1) stress as a stimulus (the input), (2) stress as an appraisal (the processing system), and (3) stress as a response (the output).



### **Depression: A Definition**

In adults, depression has repeatedly been identified as a risk factor for CVD (Frasure-Smith & Lespérance, 2010; Hare et al., 2014; Janszky, Ahnve, Lundberg, & Hemmingsson, 2010; Van der Kooy et al., 2007). Typically, depression has been operationalised in the empirical literature in three main ways; (1) as a *symptom*, (2) as a *syndrome*, and (3) as a *clinical disorder*. As a symptom, sadness is one subjective state commonly associated with depression, and represents a mood state experienced by most individuals at different times in their life. As a standalone symptom, sadness is not generally considered pathological. Alternatively, the syndrome of depression comprises sets of symptoms that are known to co-occur, as tested empirically to form a syndrome. Clusters of symptoms like this begin to become more relevant to health and wellbeing than a standalone symptom like sadness, and may have a greater impact on functioning. Finally, clinical disorders are when the clinical syndrome is characterised by a particular symptom picture that reflect diagnostic categories, such as those presented in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V; American Psychiatric Association [APA], 2013) or in the International Classification of Diseases (ICD-10; WHO, 1992).

Stated simply, depressive disorders involve disturbances of emotion that affect an individual's entire mental life (Merikangas et al., 2010b). There are two types of mood disorder. These are bipolar disorders, which are not addressed in the current work, and depressive disorders, which have two major subtypes; (1) Major Depressive Disorder (MDD), marked by a single episode or recurrent episodes of depression; and (2) Dysthymia (DD), which involves a chronic disturbance of mood (APA, 2013).

Major depressive disorder is among the most commonly diagnosed mood disorders in children and adolescents (Lawrence et al., 2015; Merikangas, et al., 2010a). Criteria for MDD set out by the APA's DSM-V, includes essential features of either depressed mood or loss of interest or pleasure over a two week period, experienced nearly every day, as well as four or more of the following symptoms,

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experienced nearly every day: “*significant weight loss or weight gain or a decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive inappropriate guilt; diminished ability to think or concentrate or indecisiveness; recurrent suicidal ideation or a specific plan for completing suicide or a suicide attempt*” (APA, 2013, p. 160-161). These symptoms must cause clinically significant distress or impairment in normal functioning and not be attributable to the physiological effects of a substance or to another medical condition (APA, 2013). Developmental differences may be evident in the way these symptoms are expressed among children compared to adults. However, research investigating symptom patterns at varying ages have been inconsistent (Weiss & Garber, 2003) and therefore researchers have had to rely largely on adult definitions of depression.

Although diagnostic criteria are important for a number of reasons, it would be short sighted to discount the impact of pre-clinical levels of depression on a young person’s level of functioning. Symptom clusters exist on a continuum and a child who does not meet the full criteria for a diagnosis may still be experiencing a number of symptoms that cause significant distress. This thinking has been reflected in the empirical literature undertaken with children and adolescents, where the use of pre-clinical symptom measures of depression is commonplace (Horowitz & Garber, 2006; Kelleher et al., 2012; Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013). This is coupled with evidence that pre-clinical measures of depression are significantly and negatively related to a range of adverse psychological and physical health outcomes (Ferro & Boyle, 2014). Moreover, the APA has recently come under criticism for making use of arbitrary cut-off points for defining disorders and for lowering standards of reliability (Frances, 2012; Kraemer, Kupfer, Clarke, Narrow, & Regier, 2012), adding further weight to the utility of pre-clinical symptom measures of psychiatric disorders, particularly among children where the evidence of conspicuous diagnostic patterns of symptoms is weak (Cantwell, 1996).

In the current thesis the occurrence of symptoms relevant to MDD, and the level of distress caused by these symptoms, are assessed among children via self-report. In accordance with this mode of measurement, the current work operationalizes depression at the syndrome level, assessing clusters of symptoms that occur in subcategories, closely reflecting aspects of MDD. The subcategories used in the current work capture symptoms relating to interpersonal difficulties, ineffectiveness, anhedonia, and negative mood.

Finally, and in addition to the psychological terms already introduced, the term *psychological distress* is used in this thesis to denote the combination of psychosocial stress and depression.

### **Chapter Conclusions**

A host of risk markers for CVD are now well documented. Among these, psychological risk factors, and in particular psychosocial stress and depression, have been prominent in the literature examining CVD risk in adults. However, it is now clear that children experience both psychosocial stress and depression to a significant degree not really recognized prior to the past two decades. This chapter provided an overview of the prevalence and occurrence of both stress and depression in children and adolescence, where it was evident from large epidemiological studies that a significant proportion of children and adolescents experience clinical levels of distress. Further to this, definitions of the psychological constructs under investigation were provided, identifying how they are conceptualised and operationalized in the current thesis.

Whilst much of the evidence supporting a link between psychological factors and risk for CVD has come from research in adults, there is a new and emerging literature investigating these relationships in children and adolescents. This literature, along with the more comprehensive adult literature, is critically reviewed in the

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following chapter with a specific focus on the role of psychosocial stress and depression in the development of CVD.

## CHAPTER 3

### LITERATURE REVIEW: PSYCHOSOCIAL STRESS, DEPRESSION AND CARDIOVASCULAR DISEASE

#### Publications:

Olive, L. S., Byrne, D. G., Telford, R. D., Abhayaratna, W. P., & Telford, R. M. (2016). Childhood stress, emotional distress and cardiovascular function in adolescence. In M. Alvarenga & D. G. Byrne (Eds.). *Handbook of Psychocardiology*. Springer: Singapore.

Byrne, D. G., Olive, L. S., & Telford, R. M (2016). Stress, depression and cardiovascular risk in children. In M. Alvarenga & D. G. Byrne (Eds.). *Handbook of Psychocardiology*. Springer: Singapore.

Over the past three decades, a large and varied body of research has examined the role of both acute and chronic psychosocial stress and depression in the development of CVD. Perhaps one of the most thought provoking accumulations of evidence coming out of this research has been that documenting the causal role of depression as an independent risk factor for CVD. Whilst not all authors agree there is sufficient evidence to make such a claim, there is no debate that depression is associated with an increased incidence of new CVD (aetiology) and a worse outcome in existing CVD (prognosis). A critical review of the literature, linking both stress and depression with CVD, is presented here, beginning with the more substantiated evidence in adults, and then with a focus on the paediatric literature.

#### Depression and Cardiovascular Disease in Adults

The bidirectional associations between depression and CVD are extensively documented in the literature (for reviews see Baune et al., 2012; Bunker et al., 2003;

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Doering & Eastwood, 2011; Frasure-Smith & Lespérance, 2005, 2006, 2010; Goldston & Baillie, 2008; Hare et al., 2014; Hemingway & Marmot, 1999; Kuper et al., 2002; Nicholson et al., 2006; O'Brien, Cherbuin, & Anstey, 2014; Rugulies, 2002; Thomas, Kalaria, & O'Brien, 2004; Van der Kooy et al., 2007; Wulsin & Singal, 2003). In adults, several prognostic studies have shown that the presence of depression is associated with increased levels of both CVD related mortality (Bush et al., 2001; Davidson, Mostofsky, & Whang, 2010; Dickens et al., 2008; Frasure-Smith & Lesperance, 2008; van Melle et al., 2004) and morbidity (Frasure-Smith & Lespérance, 2010; Hemingway & Marmot, 1999; Amanda Nicholson et al., 2006; van Melle et al., 2004). For example, among myocardial infarct patients, depressive symptoms during hospitalisation have been shown to predict a three-fold increase in cardiac mortality approximately five years later (Frasure-Smith, Lesperance, & Talajic, 1995; Meijer et al., 2011; Amanda Nicholson et al., 2006). A similar increased risk of mortality associated with depressive symptoms has been demonstrated in patients admitted with unstable angina (Lesperance, Frasure-Smith, Juneau, & Theroux, 2000). Therefore, given the evidence, it is well established that depression, often of a clinical intensity, is a common consequence of a clinical episode of CVD (Williams, 2011). Consistent medical opinion now recommends routine screening for depression among those with identified clinical CVD (Colquhoun et al., 2013; Lichtman et al., 2008) to ensure effective intervention against the possible exacerbation of coronary pathology.

Moreover, there is now both extensive and quite persuasive evidence that the existence of clinical depression is causally related to an elevated risk of a clinical CVD event and to a less favourable prognosis when such an event has occurred (Barth, Schumacher, & Herrmann-Lingen, 2004; Celano & Huffman, 2011; Hare et al. 2014; Zellweger, Osterwalder, Langewitz, & Pfisterer, 2004). This link appears to hold for “... *several decades after the onset of clinical depression* ...” (Ford et al., 1998, p. 1422).

Among aetiological studies undertaken with healthy community-dwelling adult populations, apparently free of CVD at intake, the negative effect of depression on a

range of forms of CVD have been repeatedly documented, the most common being coronary heart disease (CHD; Frasure-Smith & Lespérance, 2005, 2006, 2010; Hemingway & Marmot, 1999; A. Nicholson, Fuhrer, & Marmot, 2005; Rugulies, 2002; Van der Kooy et al., 2007; Wulsin & Singal, 2003). In meta-analyses, it has been reported that on average, the presence of depression approximately doubles the relative risk for developing new CHD (Frasure-Smith & Lespérance, 2006; Rugulies, 2002). The size of these reported effects being equivalent to previously published effect sizes for established CVD risk factors, such as smoking, high cholesterol and hypertension (Rozanski & Kubzansky, 2005; Wilson et al., 1998). The cumulative evidence also points to a dose-response relationship, with several studies reporting that clinically diagnosed depression confers an increased risk for developing CVD above that of depressed mood (Rugulies, 2002; Van der Kooy et al., 2007). Among one of the first studies to demonstrate a role for depression in the development of new coronary events, was that by Barefoot and Schroll (1996). In this study, which involved a long-term cohort study with a 27-year follow-up, the authors found that high levels of depressive symptoms were associated with increased risks of myocardial infarction and early mortality (Barefoot & Schroll, 1996). Similarly, the landmark INTERHEART Study, a case-control study carried out across 52 countries, which sought to investigate the influence of a number of cardiovascular risk factors on CVD risk, identified nine risk factors of most importance in their contribution to acute coronary syndrome presentations, of which psychosocial factors were one (predominately including depression and psychosocial stress; Rosengren et al., 2004; Yusuf et al., 2004).

The consistent and robust evidence presented here, has prompted many authors to claim there is no longer any doubt that depression is an independent risk factor for CVD, and specifically CHD (Bunker et al., 2003; Glozier et al., 2013; Nicholson et al., 2006; Van der Kooy et al., 2007). However, not everyone in the field has accepted the link between depression and CVD, largely due to a lack of evidence from randomised control trials showing that improving depression leads to an improved

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prognosis for CVD (Hare et al., 2014). Nevertheless, there still remains strong evidence to support a claim for causation. This includes; (a) evidence of a strong, consistent and graded relationship between depression and CVD, arising from longitudinal investigations, employing objective and prospective assessment of CVD, (b) further evidence that this relationship was not explained by known covariates, and (c) emerging evidence of plausible biological and behavioural mechanisms that may explain the link between depression and CVD (Barton et al., 2007; Bunker et al., 2003; d'Audiffret et al., 2010; Frasure-Smith & Lespérance, 2005, 2006, 2010; Gold et al., 2005; Hemingway & Marmot, 1999; Kuper et al., 2002; Nicholson et al., 2006; O'Brien, et al., 2014; Rugulies, 2002; Thomas et al., 2004; Van der Kooy et al., 2007; Wulsin & Singal, 2003)

### **Psychosocial Stress and Cardiovascular Disease in Adults**

As with depression, psychosocial stress has also been shown to promote the progression of CVD, potentially contributing to pathological changes in the vasculature. For example, the experience of a range of stressors have been associated with, endothelial dysfunction (Mausbach et al., 2012), intimal-medial thickening (Whipple et al., 2009), arterial stiffness (Logan, Barksdale, Carlson, Carlson, & Rowsey, 2012) and atherosclerotic changes in blood vessels (Black & Garbutt, 2002; Pickering, 2007). Specific components of psychosocial stress have been investigated in relation to cardiovascular outcomes. These have included forms of *acute stress* (generally defined as stressors that occur for only a short duration; McEwen & Stellar, 1993), such as those arising from acute life events and controlled mental stress manipulated in the laboratory, *chronic stressors* (defined as stressors that may be ongoing or longer in duration; McEwen & Stellar, 1993), which may include the experience of poverty, maltreatment, abuse, and illness, and *daily hassles*, those stressors relating to day to day living, considered to be lesser in severity but persistent throughout life (Hahn & Smith, 1999; Lazarus, 1985).



### **Acute Stress and Cardiovascular Disease**

Among the literature on acute stress, there is evidence to indicate that acute life event stressors or short-term emotional stress, such as the death of a loved one (Mostofsky et al., 2012), natural disasters (e.g. earthquakes; Brown, 1999; Kloner, 2006; Leor, Poole, & Kloner, 1996), major sporting matches (Carroll, Ebrahim, Tilling, Macleod, & Smith, 2002; Kloner, McDonald, Leeka, & Poole, 2009; Wilbert-Lampen et al., 2008), and terrorist attacks (Feng, Lenihan, Johnson, Karri, & Reddy, 2006; Kark, Goldman, & Epstein, 1995; Kloner, 2006) can trigger clinical cardiovascular events among vulnerable individuals, including stroke, coronary ischemia and myocardial infarction (Mittleman & Mostofsky, 2011; Steptoe & Brydon, 2009). While these studies show association between acute cardiovascular events and emotionally important or life-threatening situations, it is difficult to determine whether stress was the trigger in these experiences, given the challenges in isolating stress from other potentially contributing factors, such as physical exertion, excessive alcohol consumption, or heat (Dahabreh & Paulus, 2011).

The studies reported here, investigating the role of stressors in triggering acute CVD events, represent the final step in the pathophysiological process leading to poor cardiovascular outcomes in susceptible individuals, such as those with vulnerable atherosclerotic plaque and chronic atherosclerotic disease (Mittleman & Mostofsky, 2011). Therefore, this type of acute stress and the associated cardiovascular outcomes should be differentiated from that of chronic stress, which may be more closely related to the slower progression of atherosclerosis and other underlying pathogenesis for CVD, and therefore render an individual vulnerable to acute clinical events on exposure to acute stress.

In addition to the acute stress literature based on observational research, experimental studies, utilising more controlled mental stress tests, have investigated acute changes in the vascular arising from exposure to acute stress. Similar to observational studies, these approaches have shown that even a brief exposure to

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mental stress can induce myocardial ischemia (Chida & Hamer, 2008; Strike & Steptoe, 2003) and can lead to a somewhat sustained reduction in endothelium-dependent vasodilation, which may be indicative of endothelial dysfunction (Ghiadoni et al., 2000; Sherwood, Johnson, Blumenthal, & Hinderliter, 1999; Spieker et al., 2002). While psychophysiological responses such as these are less clinically meaningful in isolation, in terms of disease development, they are thought to represent the way that individuals respond to daily stressors, and if elicited regularly, might have clinical relevance. The theoretical underpinnings of experimental investigations like those reported here are largely centred on the *reactivity hypothesis*, suggested in a number of adult studies (e.g. Chida & Steptoe, 2010; Lovallo, 2005). The reactivity hypothesis asserts that amplified cardiovascular responses to psychosocial stress, that are in excess of what is required of an adaptive response, contribute to the aetiology of cardiovascular pathology and disease through cumulative wear and tear on physiological response systems, and that those individuals who have greatest reactivity are at greatest risk (Chida & Steptoe, 2010; Lovallo, 2005). While these findings may prove useful in identifying methods of managing stress responsivity in the prevention of clinical events among vulnerable individuals, it remains that single episodes of acute stress are likely to be less relevant to chronic disease development. Given the evidence introduced in Chapter 1, that CVD is a chronic disease that develops over several decades, it seems likely that in order for psychosocial stress to significantly contribute to CVD pathogenesis it would also need to be of a chronic nature.

### **Chronic Stress and Cardiovascular Disease**

Associations supporting a role for long-term chronic stress in the development of CVD were evident in the INTERHEART case-control study (Rosengren et al., 2004). In this study, the risk for developing a myocardial infarction was more than doubled among individuals subjectively reporting enduring stress at work or at home (Rosengren et al., 2004). Similar findings were reported in a prospective study

investigating the impact of marital stressors on recurrent coronary events in women hospitalised for acute myocardial infarction or unstable angina pectoris, where it was found that marital stress was associated with an almost three-fold increase in risk of recurrent events. This was after adjusting for a number of potentially confounding variables (Orth-Gomer et al., 2000). Further sources of chronic stress, such as being widowed (Parkes, Benjamin, & Fitzgerald, 1969), caring for a sick spouse (Lee, Colditz, Berkman, & Kawachi, 2003), or the death of a child (Li, Hansen, Mortensen, & Olsen, 2002) have also been associated with an increased risk for CHD in a number of prospective studies.

One of the most widely studied areas of chronic psychosocial stress has been that relating to job strain, described as the combination of high job demands and low control at work (Karasek & Theorell, 1990). In a recent meta-analysis of studies investigating the impact of job strain on CHD, a small, but consistent effect on increased risk of clinical CVD event was found (Kivimäki et al., 2012). Other models of work stress have focussed on the imbalance between effort and reward (Siegrist, 1996), and unfair treatment in the work place, termed organisational injustice (Kivimaki et al., 2005) in the literature. A separate meta-analysis, investigating the impact of work stress on CVD across different work stress models, found a 50% increase risk of developing CHD among those experiencing work stress (Kivimaki et al., 2006).

### **Psychosocial Stress, Depression and Cardiovascular Disease: The Need for a Life Course Approach**

In summarising the adult literature, a large and varied body of research, from both population and clinical studies, provides evidence to suggest that both depression and psychosocial stress contribute to an increased risk of CVD over the course of the disease, including the long-term development of atherosclerosis and the acute triggering of cardiac events. What is less evident is at what stage in the life course these associations begin to emerge. However, given emerging recognition that CVD

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has its origins in childhood (Berenson et al., 1998), along with evidence confirming that many known risk factors for CVD in adults are established in childhood (Hallal et al., 2012; Ogden, Carroll, Kit, & Flegal, 2012), and that elevated risk profiles in childhood are associated with pre-clinical markers of CVD in adulthood (Hartiala et al., 2012; Juonala et al., 2010; Magnussen et al., 2009; Mahmood et al., 2014), there is reason to believe that the same line of evidence may hold true for psychological risk factors.

Given the relative health of younger populations, where participants are too young to assess disease end-points, any investigation into the impact of psychological factors on CVD risk at this earlier life stage must look to pre-clinical or intermediary markers of disease. To date, such investigations have included measures of arterial function (e.g. arterial stiffness and endothelial function) and arterial structure (e.g. CIMT). Despite the effects of psychosocial stress and depression on CVD being less evident in children and adolescents, possibly in part due to a paucity of studies, it is hypothesised that these psychological effects do not suddenly emerge as risks to CVD upon reaching adulthood, but rather that both psychosocial stress and depression may induce the early stages of the development of CVD in children and adolescents. Currently, there is only a small number of published studies investigating these associations among younger age groups, but of the few studies, initial support for this hypothesis is evident.

### **A Review of the Paediatric Literature**

#### **Psychosocial Stress and Depression during Childhood and the Risk for Cardiovascular Disease**

An emerging body of evidence in children and adolescents suggests that the course of health and chronic illness in general may be influenced by early experiences and environments (Felitti et al., 1998; Gluckman, Hanson, & Beedle, 2007; Hunter, Minnis, & Wilson, 2011; Miller et al., 2011; Saridjan et al., 2010). The experience of

early depression and other emotional distress in children may be particularly relevant to the course of chronic disease development (Miller et al., 2011; Shonkoff, Boyce, & McEwen, 2009). In support of this hypothesis, is the evidence that children and adolescents with a profile of depressive symptoms exhibit poorer levels of general physical health compared to those without depressive symptoms (Lewinsohn, Seeley, Hibbard, Rohde, & Sack, 1996; Wickrama, Wickrama, & Lott, 2009). The same was evident in a very large cohort of later-adolescents and young adults at intake, who were followed up over 37 years as part of the Cardiovascular Risk in Young Finns Study. Here it was observed that early anxiety (but not depression) was associated with measurable CVD outcomes at the end of follow-up (Janszky et al., 2010). Further evidence of a relationship between depression and autonomic markers indicative of CVD risk (e.g. heart rate variability, baroreflex sensitivity, and the cortisol awakening response), have been demonstrated among children (Bosch et al., 2009).

In another large cohort study, 14-year-old girls experiencing both anxiety and depression also exhibited a higher body mass index (BMI) and riskier insulin resistance levels than did those free of affective distress, but this was not evident in boys (Louise et al., 2012). In addition, children manifesting major (diagnosed) depression were more likely than their non-depressed siblings or those in a non-depressed control group to be regular smokers, and to be obese – they were also less likely to be physically active (Rottenberg et al., 2014); these associations providing further avenues through which depression may influence risk for CVD.

The experience of psychosocial stress in youth may also be detrimental in terms of cardiovascular health. For example, in a recent publication based on data from the 1958 British Birth Cohort Study, the psychological distress of 6,714 men and women was assessed on six occasions between the ages of 7 and 42 years to determine whether psychological distress across the lifespan was predictive of cardiometabolic risk (Winning, Glymour, McCormick, Gilsanz, & Kubzansky, 2015). Compared to those with no distress, it was found that cardiometabolic risk was higher

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among people reporting psychological distress in childhood only, and in those with persistent psychological distress across the life course.

Low childhood socioeconomic status (SES) has also emerged as an important risk factor for CVD. Although not a direct measure of specific life events, SES provides an objective measure of stressor exposure, and has been associated with measures of chronic stress (Baum, Garofalo, & Yali, 1999; Turner & Avison, 2003). Moreover, low SES may be a significant risk factor for CVD related mortality. Evidence for such a link was provided in a review paper, involving in excess of 40 studies of childhood SES and mortality in adulthood (Galobardes, Lynch, & Davey Smith, 2004; Galobardes, Lynch, & Smith, 2008). Here it was found that low childhood SES was a significant risk factor of CHD mortality in 7 of the 10 studies, and of stroke mortality in 4 of 6 studies reviewed. Although this body of research provides some corroborating evidence linking experiences of childhood chronic stress to an increased risk for later CVD, it should be noted that the effects of childhood SES were attenuated when adjusting for adult SES, and therefore limit any inference that childhood exposure to stress is critical for later disease development.

In addition to chronic stress associated with low childhood SES, it is becoming increasingly recognised that specific forms of childhood adversity may lead to a heightened risk of disease during adulthood. In prospective studies, investigating the effect of childhood adversity (i.e. maltreatment, emotional, sexual and physical abuse, and neglect) on later CVD, the risk for CVD in adulthood was almost doubled in those who had experienced childhood adversity compared to those experiencing no such adversity (Dong et al., 2004; Korkeila et al., 2010; Scott et al., 2011). Furthermore, experiencing a greater number of adversities during childhood conferred a greater risk for CVD in adulthood. The most rigorous work in this area has come from the Adverse Childhood Experiences (ACE) Study, a large-scale project that assessed childhood maltreatment retrospectively in 17,337 adults (Dong et al., 2004). The experience of adverse childhood events has the potential to result in considerable ongoing stress,

which may continue throughout life, increasing the risk for early onset depression (Scott et al., 2011), further psychological disturbance (Kessler et al., 2010; Springer, Sheridan, Kuo, & Carnes, 2007), and the development of health compromising behaviours (Benjet, Borges, Medina-Mora, & Mendez, 2013; Fuller-Thomson, Filippelli, & Lue-Crisostomo, 2013), all of which constitute risk factors for CVD (Yusuf et al., 2004).

A small number of studies in youth have also examined the effect of transient acute stress, experimentally manipulated in laboratory settings, on a range of cardiovascular outcomes, such as blood pressure reactivity. This work has less clinical relevance when considering the role of psychosocial stress in the aetiology of CVD, given that acute stress reactions may reflect an adaptive “healthy” stress response, rather than the type that is likely implicated in chronic diseases. Even so, among a small number of studies it has been demonstrated that increased blood pressure reactivity may affect pre-clinical markers of CVD. For example, associations between increased systolic blood pressure reactivity in response to a controlled mental stressor, and greater CIMT, a subclinical marker of atherosclerosis have been reported in a series of studies from the same authors (Lambiase, Dorn, & Roemmich, 2012; Roemmich et al., 2011; Roemmich et al., 2009). However, not all studies in this area have replicated these findings (Low, Salomon, & Matthews, 2009).

As previously suggested, theorists have proposed that it is the persistent adversity and ongoing chronic stress that may result in increased “wear and tear” on the cardiovascular system over time; induced by stressful experiences that over use and dysregulate stress response pathways, rather than the acute episodic stress, which is short-term. Therefore, it is maintained that it is this “weathering” over time, which may contribute to CVD development. Relevant to this thesis is whether any potential degradation of the cardiovascular system over time, can be detected via examination of measureable intermediary markers, linking psychological stress and depression with cardiovascular dysfunction. Two relevant markers that have shown

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prognostic value in adults include endothelial function and arterial stiffness (Brunner et al., 2005; Cecelja & Chowienczyk, 2012), and there is now evidence that these intermediary markers are detectable in younger populations (Sakuragi & Abhayaratna, 2010).

### **Psychosocial Stress, Depression and Intermediary Markers of CVD**

#### **Endothelial Function**

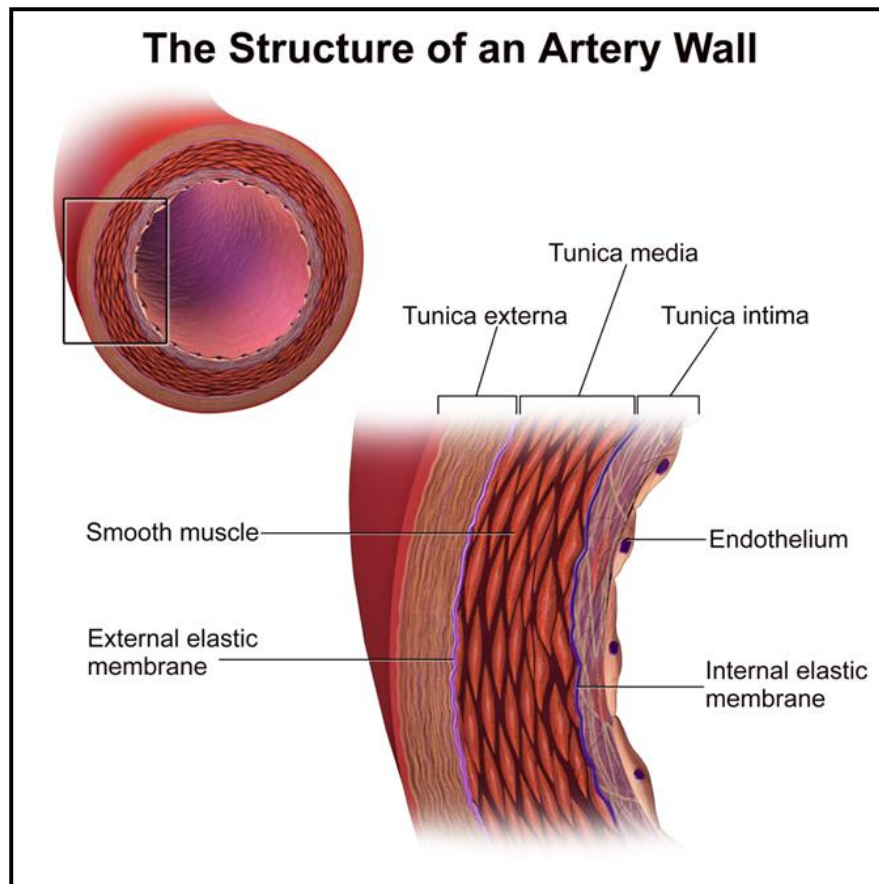
In the past, the vascular endothelium was considered to be a passive lining of cells, which divided elements of the vascular media from the flowing blood. However, over the last 30 years, it has become apparent that the endothelium plays a much larger role in maintaining vascular homeostasis. It is now understood that the vascular endothelium produces a host of chemical substances, most notably nitric oxide (NO), endothelin, prostacyclin, and angiotensinogen, which are designed to maintain homeostasis through effects on elements of blood in the lumen (the inside space of the artery), on the intimal surface (tunica intima) that is exposed to blood, within the intima itself, and on vascular smooth muscle cells in the media. Figure 3 outlines the structure of the artery wall and the location of the endothelium.

Endothelial dysfunction is generally defined as *“an imbalance between vasodilating and vasoconstricting substances produced (or acting on) endothelial cells”* (Deanfield et al., 2005, p. 7). Endothelial dysfunction is a key feature of vascular diseases, and considered to be a systemic pathological state of the endothelium.

Endothelial dysfunction is a well-established response to cardiovascular risk factors and has been implicated as one of the key determinants of early atherosclerotic disease (Brevetti, Silvestro, Schiano, & Chiariello, 2003). There is also now emerging evidence indicating that endothelial dysfunction may be a potential mechanism linking psychosocial stress and depression with CVD (Cooper et al., 2011; Toda & Nakanishi-Toda, 2011). The empirical evidence to support such claims is discussed further in



Chapter 4. In the following section, the literature investigating the influence of stress and depression on endothelial dysfunction is reviewed.



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*Figure 3. The structure of an artery wall.*

Within the adult literature, it has been shown that that endothelial function is impaired in those with a depressive disorder (Broadley, Korszun, Jones, & Frenneaux, 2002; Garcia et al., 2011; Kim et al., 2010; Lavoie, Pelletier, Arsenault, Dupuis, & Bacon, 2010) and depressive symptomology (Cooper et al., 2010; Sherwood, Hinderliter, Watkins, Waugh, & Blumenthal, 2005) compared with healthy controls. In a review conducted by Cooper et al. (2011), of 12 studies investigating the effect of depression on endothelial function the majority of studies found an association

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between greater endothelial dysfunction and depression, regardless of whether depression was assessed as depressive symptoms, MDD or remitted MDD. These findings highlight that depressed mood may have a lasting negative effect on endothelial function beyond the current episode. Moreover, in both cross-sectional and prospective studies, greater depressive severity was related to poorer endothelial function in a dose-response manner, in both healthy individuals apparently free of CVD (Fiedorowicz, He, & Merikangas, 2011; Harris, Matthews, Sutton-Tyrrell, & Kuller, 2003; van Sloten et al., 2014), as well as in patients with angina pectoris or acute coronary syndrome (Munk et al., 2012). Two studies in adults have failed to find a significant relationship (Mausbach et al., 2012; Phuong Do, Dowd, Ranjit, House, & Kaplan, 2010), both of which involved healthy adults from the community.

Three studies have investigated the relationship between depression and endothelial function in adolescents and have consistently reported the adverse impact of depressive symptoms on endothelial function (Osika et al., 2011; Tomfohr, Martin, & Miller, 2008; Tomfohr, Murphy, Miller, & Puterman, 2011; Waloszek et al., 2015). For example, initial findings from a cross-sectional investigation undertaken with adolescent girls found that depressive symptoms were associated with greater endothelial dysfunction after adjustments for age, race and contraception use (Tomfohr, et al., 2008). This association was found despite reports of only mild levels of depressive symptoms by participants, providing some evidence that even low levels of depressive symptoms are sufficient to produce negative changes in endothelial function among youth. A Swedish study by Osika et al. (2011) investigated the cross-sectional association between depressive symptoms (as part of an investigation into psychological adversity) and endothelial function in a sample of children and adolescents aged 12 to 16 years. In line with Tomfohr et al. (2008) this group reported that among girls, higher levels of depressive symptoms were associated with greater endothelial dysfunction after adjustment for age and parental education. However, these findings did not extend to boys.

Only one prospective study was identified in the child and adolescent literature, which was an extension of the work by Tomfohr et al. (2008). In this study, which included females only, it was reported that depressive symptoms were associated with increased endothelial dysfunction (Tomfohr, et al., 2011). Specifically, greater impairment in endothelial function was found during periods with greater depressive symptomology, suggesting that depressive symptoms and endothelial function co-vary within the individual. Predictive evidence for the role of depression in endothelial dysfunction was not supported in this study, with earlier depressive symptoms not found to be predictive of endothelial function six months later. In a case-control study involving 50 Australian adolescents (25 depressed, 25 healthy; aged 12 to 16 years), clinically depressed youth were found to have poorer endothelial function compared to healthy controls (Waloszek et al., 2015).

Among the studies reviewed here, there has been consistency in the method of assessing endothelial function, with all studies utilising the non-invasive EndoPAT 2000, which has emerged as a prognostically promising and reliable tool in the measurement of endothelial function (Haller et al., 2007; Hamburg et al., 2008; Kuvin et al., 2003; Mahmud, Van Uum, Kanji, Thiessen-Philbrook, & Clarson, 2008; McCrea, Skulas-Ray, Chow, & West, 2012). However, inconsistency was observed in the method of assessing depression, with some studies relying on self-report of depressive symptoms, whilst others used clinical interviews. Moreover, all but one (Osika et al., 2011) of these studies selected participants for having a high risk of developing a depressive disorder (Tomfohr et al., 2008; Tomfohr et al., 2011) or being in a current depressive episode (Waloszek et al., 2015).

Similar to depression, brief episodes of psychological stress have been shown to negatively influence endothelial function among healthy adults in a number of experimental studies (Ghiadoni et al., 2000; Gottdiener et al., 2003; Spieker et al., 2002). Currently only one study was identified in the literature that investigated these effects among younger cohorts. In this study, Chen et al. (2012) experimentally tested

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the effect of acute mental stress on vascular response in adolescents through the assessment of endothelial function. In this study adolescent males showed a greater vasoconstrictive response to a mental stressor, followed by a less vasodilatory response, and took longer to return to baseline levels compared to females, indicative of a less healthy response. The practical significance of these findings is highlighted by a recent meta-analysis, which reports that greater reactivity to - and slower recovery from - acute mental stress predicts adverse future cardiovascular health (Chida & Steptoe, 2010).

Along with experimental studies, a handful of community-based observational studies have investigated the association between a range of chronic stressors and endothelial function. Takase, Akima, Uehata, Ohsuzu, and Kurita (2004) investigated endothelial function among a sample of apparently healthy male college students, who were under intense stress to pass an examination and had chronic sleep deprivation for 4 weeks, and found decreases in flow-mediated endothelium dependent vasodilation (indicative of endothelial dysfunction). Similarly, among young medical students, a group reportedly experiencing a high frequency of stress, smoking, physical inactivity, and unhealthy nutritional habits, the main contributors to endothelial dysfunction were stress and smoking (Mancaş et al., 2008). What is evident from the literature reviewed here is a clear gap in studies among younger populations, meaning that the potential influence of psychosocial stress on endothelial function among children and adolescent is yet to be elucidated.

In summarising the literature, the findings are suggestive that endothelial function may be influenced by both psychosocial stress and depression. Much of this evidence is drawn from studies on adults and more consistently, with clinically depressed populations. It still remains to be seen, whether chronic stress and depression experienced earlier in the life course can influence endothelial function, and this is due to an absence of published studies in youth. Further long-term prospective studies are needed to determine whether any potential association between early

psychological distress and endothelial dysfunction increase the risk for developing CVD later in life.

### **Arterial Stiffness**

Arterial stiffness, which refers to the elasticity or compliance of the arteries, has also proven to be an important subclinical marker for the development of CVD (Sakuragi & Abhayaratna, 2010). Stiffening or hardening of the arteries, known as arteriosclerosis, influences how hard the heart must work to pump blood through the body, and is known to increase with age (Lee & Oh, 2010; Sun, 2015). Arterial stiffness is measured as the speed at which an aortic pulse travels between two major arteries, usually the carotid artery (located in the upper body) and the femoral artery (located in the lower body; Sakuragi & Abhayaratna, 2010). This measurement is termed pulse wave velocity (PWV).

In adults, increased arterial stiffness is associated with a higher likelihood of CVD (Mattace-Raso et al., 2006; Vlachopoulos et al., 2010). Arterial stiffness normally varies among adolescents and young adults and co-varies with gender, age and ethnicity (Alpert & Collins, 2007), however, these associations have largely been untested in children. In studies among adolescents and young adults, arterial stiffness (assessed as PWV) was found to be associated with a range of CVD risk factors, including increased body mass index (BMI), total fatness, hypertension, elevated serum triglycerides, homocysteine, and fasting insulin concentrations, as well as decreases in fitness and physical activity (Alpert & Collins, 2007; Im, Lee, Shim, Lee, & Lee, 2007; Li, Chen, Srinivasan, & Berenson, 2004). A further study undertaken with children documented an association between arterial stiffness and greater waist circumference, total body fat and BMI, as well as providing some evidence for an association with cardiorespiratory fitness (Sakuragi et al., 2009).

Psychological distress, and in particular the experience of both chronic and brief episodes of psychological stress and depression, have been associated with increases

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in arterial stiffening among adults (Logan et al., 2012; Seldenrijk et al., 2011), including younger apparently healthy adults with no established cardiovascular risk (Vlachopoulos et al., 2006). Among adolescents, significant associations between depressive symptoms and arterial stiffness were documented among 157 healthy boys and girls in the United States after adjustments for the confounding influence of age, race, gender, BMI, parent education, smoking status, physical activity, mean resting systolic blood pressure and mean resting heart rate (Dietz & Matthews, 2011). Sub-analyses in this study, which separated adolescents based on depression severity (moderate vs. severe) indicated that more severe depressive symptoms were associated with higher PWV (where higher PWV is indicative of greater arterial stiffness) compared to moderate symptoms, suggesting the possibility of a dose-response relationship. Studies like the Dietz & Matthews (2011) study, which utilise pre-clinical indicators of CVD, have the ability to detect early changes in vascular function and therefore identify early risk for the progression of atherosclerosis and map the trajectory of cardiovascular risk.

However, within the child and adolescent literature a number of important limitations exist. These include, but are not limited to, the predominant use of cross-sectional designs, making it difficult to determine the temporal sequence in these relationships, an apparent lack of clinical trials making clinical recommendations difficult; inconsistency in the approach to covariate selection, and inconsistency in the working definition of psychosocial stress and how it is measured. There is a clear need to consolidate research efforts in this area so that early risk factors can be identified and so that prevention strategies can be developed. Investigations into the associations between psychological variables and intermediate markers of CVD among younger populations have the potential to identify risk factors that may accelerate arteriosclerosis and atherosclerosis, as well as the potential to identify targets for intervention that may lead to the prevention, or at least slowing down, the development of clinical CVD. Complimentary to these investigations are studies into the

determinants of these risk factors, known as primordial risk factors. Accordingly, further investigation directed towards the evaluation of the association between states of psychological distress and cardiovascular health among younger populations appears warranted.

### **Chapter Conclusions**

Although there is now a great deal of evidence to support a link between psychological distress and CVD, most of this research has been undertaken with adults. Among the small number of published studies in youth, there is an emerging body of evidence indicating that both pre-clinical psychosocial stress and depression, and depression of a clinical level, are associated with a set of pre-clinical, intermediary markers for CVD, namely endothelial dysfunction and arterial stiffness. What is apparent from reviewing the literature is the clear need for more studies in younger populations that can further elucidate the nature of these early relationships. Currently, it is unclear what role psychosocial stress plays during the early years in terms of increasing risk for CVD. There is a particular lack of data investigating how ongoing psychosocial stress of a chronic may be implicated in the development and progression of CVD.

The most consistent evidence in terms of cardiovascular effects among youth has emerged from the study of childhood adversity, which pertains to stressors of a more severe nature that are also characteristic of chronic stress. Among adults, there is evidence of a dose-response effect, where investigations into the effects of childhood chronic stress (e.g. early adversity) on the risk for later CVD has demonstrated that exposure to a greater number of adversities increases the CVD risk. The same can be said for depression, where individuals experiencing more severe depressive symptoms or those diagnosed with clinical depression are seen to have the greatest CVD risk. These associations have also emerged in populations with a lesser severity of symptoms.

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Only through further research will we be able to elucidate the nature and importance of these relationships among children and adolescents, and therefore whether childhood psychological risk factors can reliably predict a significant level of risk for the later development of CVD, as is the case with other metabolic CVD risk factors.

The value of understanding these relationships among younger populations lies in the potential for novel and effective interventions to be developed and implemented in youth. Whether psychological interventions in youth can be successful in reducing the level of risk for later CVD is still to be determined, and may be considered premature at this stage, in the absence of consistent and robust associations between these factors in youth. A further lack of understanding relating to the underlying mechanisms that may explain how cardiovascular function comes to be influenced by psychosocial stress and depression further limits any attempt to successfully identifying appropriate targets for psychological intervention.

While the mechanisms that may potentially explain the link between psychological distress and CVD are still not fully understood, a number of plausible biological and behavioural pathways have been suggested. Many of the hypotheses in these investigations centre on the stress response in some way. Therefore, an introduction to the nature of the human stress response, along with an introduction to some of the more salient mechanistic pathways in the stress/depression-CVD link is presented in the next chapter.



## **CHAPTER 4**

# **THE HUMAN STRESS RESPONSE, DEPRESSION AND CARDIOVASCULAR DYSREGULATION: A REVIEW OF POTENTIAL MECHANISMS**

### **Context Statement**

Chronic stress response has been implicated in the pathogenesis of disease. Although a growing number of illnesses have been found to be associated with dysregulation of the stress system, the precise role of stress in their causation is usually not clear. Even so, chronic stress is often implicated in theories of both depression and CVD development. While stress and the stress response are an important part of our daily human existence, and the experience of acute stress or short-term, episodic stress is often adaptive, this is distinct from chronic stress, the grinding stress that wears people away day after day, year after year. It is stress of a chronic nature that modern psychology recognises as harmful, and which may render an individual increasingly vulnerable to chronic disease.

In this chapter, the literature investigating the potential mechanisms linking stress and depression with CVD is reviewed. This mechanistic review begins with an introduction to the evolution and basic biology of the stress response. From here the potential pathways and mechanisms that likely link stress and depression with CVD are explored, with the aim of providing both a theoretical and empirical framework for the ensuing studies presented in this thesis. Without such a foundation, indicative of biologically and behaviourally plausible mechanisms in which the cardiovascular system may be influenced by stress and depression, any investigation into their associations would be futile.

### **Stress in Humans**

In the human species, health and quality of life might be considered a balancing act to maintain homeostasis (Cannon, 1929). We are exposed to a constant barrage of ongoing environmental stimuli that destabilise homeostasis, which requires our response to attempt to restore balance. As outlined in Chapter 2, these stimuli have been referred to as “stressors” and our restorative process as “stress response”. Stress and the stress response are, therefore, part of daily human existence, complete absence of the latter coinciding only with death. However, like many characteristics and experiences vital to life, excesses can be detrimental; food, water, heat, oxygen, and physical activity being examples. The same is true for the stimuli received by the brain, for example those environmental perturbations perceived as sound, vision or feel. When a threshold is exceeded tissue damage may occur in the receptive organs (e.g. the ear, eye or somatic tissue) or even in the controlling regions in the brain.

There is another form of stress to which we are exposed on a daily basis, the direct input to our phylogenetically “higher” centres of the brain involved in conscious thought; cognition, problem solving, human interaction and the associated centres influencing emotion. We are exposed to this psychosocial stress throughout life (Kraag et al., 2006; Turner, Wheaton, & Lloyd, 1995; Wittchen, Nelson, & Lachner, 1998), both in the awake and sleep states, and the stress response is correspondingly activated (Chida & Hamer, 2008). As for the forms of stress alluded to above, there is a threshold at which the extent of this stress, and its stress response may threaten health. In order to understand this, we need to review the very nature of the stress response, our life-saving means by which we can restore homeostasis following exposure to a stressor. In other words, we need to understand the “double edged sword” of stress response; how a normally positive and homeostatic restorative process, if uncontrolled, can damage human cells and tissue and produce organic and systemic dysfunction.

This Ph.D. thesis concerns one set of stressors that can be categorised as psychological; and the following review is confined to the means by which our stress

reaction impacts upon one system, the cardiovascular system. This review begins with a discussion on the evolutionary basis of the general stress response, followed by an overview of the neuroendocrine responses to psychosocial stress and their effects on cardiovascular function, and finally the literature investigating the the potential pathways linking psychosocial stress and depression with CVD is reviewed.

### **The Nature of Human Stress Reaction: An Evolutionary Perspective**

Over millions of years, animal life has evolved and diversified in predatory roles as well as prey, leading to the specialisation and adaptation of the stress response. Among humans, for literally thousands of generations our species rightfully feared being the dinner of large predatory animals and since most of the threats to human survival were once physical, the stress response has evolved accordingly; designed to help us move quickly to fight off a predator or escape from a dangerous situation. As a result, and matching the context of our evolutionary past, the stress response was transitory, homeostasis being restored once the stressor was removed. Jumping forward to the present day, it is not difficult to see that the types of environments in which we now live, along with the situations to which humans must now adapt, differ substantially from the circumstances our species experienced for the bulk of its evolutionary existence (James, 1991; Eaton, Konner, & Shostak, 1988). The threats we face in contemporary life have shifted in emphasis from a predominantly physical to a predominantly psychological emphasis. Moreover, as the complexity of social interaction in our Western Society increases, psychological stressors are likely to present themselves with greater frequency. Consequently, not only has the nature of the stressor changed dramatically, but so has the action following the response.

Physical activity “fight or flight” no longer applies like it once did, and the neuroendocrine based stress response, setting up the systems for power output, is “bottled up” in a physically inactive environment. For example, it is not often helpful to run away from the boss, or fight the person who cut in on you in the supermarket

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queue. As a result, the physiological changes occurring with a “fight or flight” response; the increased heart rate and cardiac output, the increased blood sugars and the increased muscle blood flow, are not put to physical use. Thus, rendering restoration of homeostasis and “calm” is a protracted affair, which may well contribute to the “chronic” stress that modern psychology recognises as harmful. It is this difference between the “transient stress response” and “chronic stress response” that we can discuss in terms of their relationships to our health, and in particular CVD (Antoni et al., 2006; James & Brown, 1997; Sapolsky, 1994).

### **The Spectrum of Psychological Stress: “Healthy” and “Unhealthy” Stress**

Before discussing the basic physiology involved in the stress response, the distinction between “healthy” and “unhealthy” stress needs to be made. Stress and the stress response are an important part of daily human existence. As we navigate our environments, we are inevitably exposed to a range of stressors, and our stress response has evolved accordingly, helping us to respond effectively and appropriately to a range of threatening environments and stimuli. “Healthy stress” is an adaptive response to daily stressors, characterised by transient increases in stress hormones and associated physiological reactions to charge up muscular power production. On the other hand, “unhealthy stress” occurs when stress is repetitive, usually without any physical reactivity, and prolonged or even chronic. It is this chronic, uncontrolled stress response, which may render an individual increasingly vulnerable to chronic disease, and of particular interest in this thesis, to CVD.

Expanding on the previous section of this chapter, our stress system was not designed for situations that evoke ongoing activation of this stress response, such as those common to modern life; events such as ongoing financial difficulties, work place bullying, undergoing a divorce, or caring for spouse with diminishing health. It is these circumstances that can give rise to ongoing worry and rumination, which can serve as a stressor in themselves, thus exacerbating the stress response (Brosschot, Gerin, &

Thayer, 2006; Gianferante et al., 2014; Zoccola & Dickerson, 2012). When the stress response is repeatedly triggered, even by stimuli that may be trivial to some but monumental to others, pathological promoting conditions may arise. The process by which individuals attempt to restore stability or homeostasis is termed allostasis (Sterling & Eyer, 1988). The term *allostatic load* or *overload* (McEwen & Stellar, 1993) then refers to:

*“The wear and tear that results from either too much stress or from inefficient management of allostasis, e.g. not turning off the response when it is no longer needed (McEwen, 1998; McEwen & Wingfield, 2003; Sterling & Eyer, 1988),...not turning on an adequate response in the first place, or not habituating to the recurrence of the same stressor, and thus dampening the allostatic response.” (McEwen, 2006, p. 368).*

A summary of the forms of allostatic load outlined by McEwen (1998, 2006) are summarised in Figure 4. In the next section the basic physiology of the human stress response is introduced, highlighting the physiological reactions involved in an “unhealthy” stress response. This discussion is focused further, on how an “unhealthy” stress reaction impacts upon one system, the cardiovascular system.

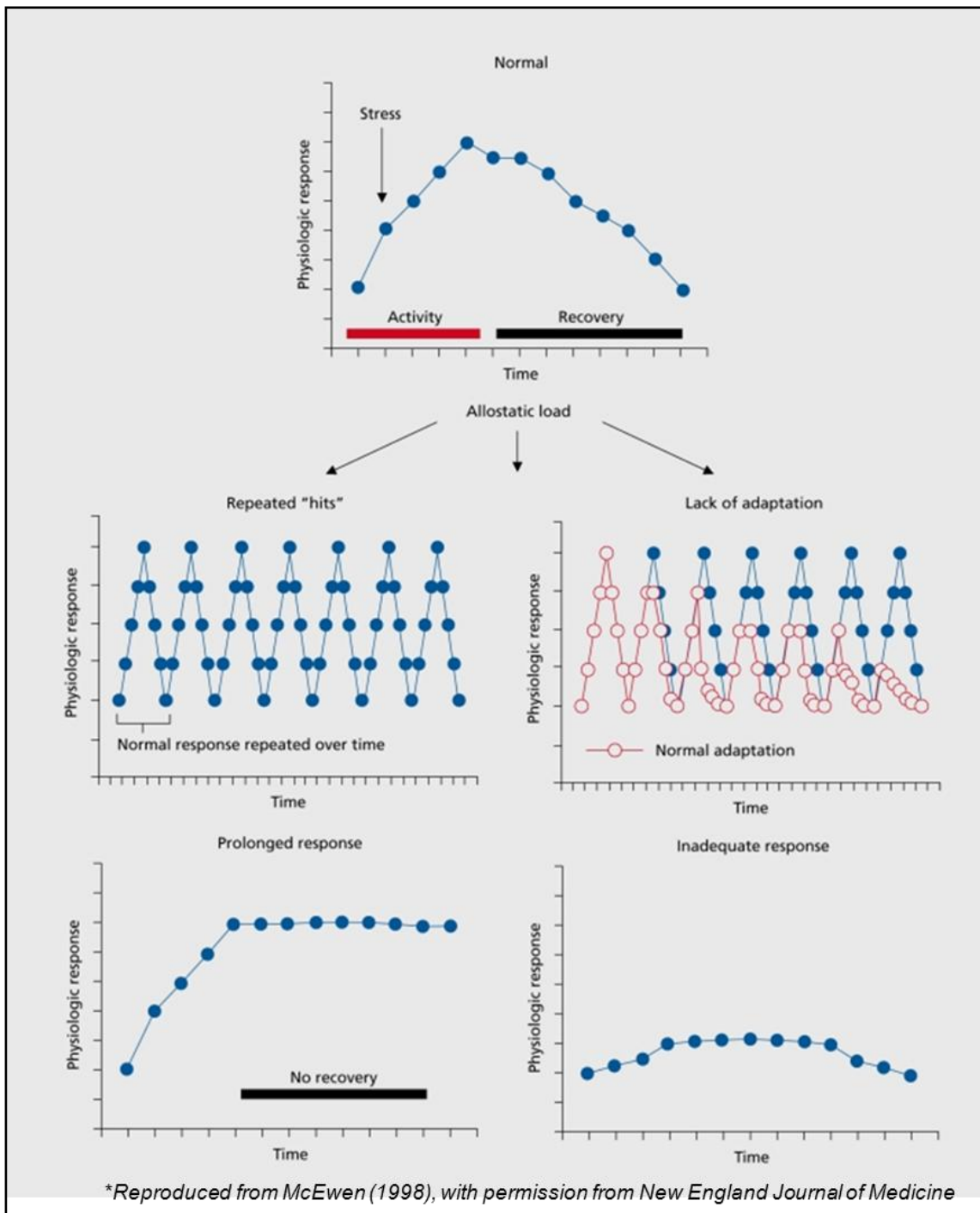


Figure 4. Examples of allostatic load resulting from stressor exposure.

### **An Introduction to Basic Stress Physiology**

As previously introduced, stress in the current thesis is conceptualised within a psychological framework and in line with a process definition, as described by Cohen et al. (1995), which emphasises the interaction between individuals and their environment. This definition acknowledges stress as a process involving inputs (stressors), outputs (stress response) and mediating activities (appraisals and coping). In a preceding section of this chapter, it was introduced how this “process” has been shaped by past and unfolding evolutionary determinants. This discussion now turns to the physiology involved in this process, with a brief introduction to basic stress physiology. Beginning in the brain, an overview is provided of the neural processes involved in our response to psychosocial stress – the interaction between individual and their environment - and the subsequent initiation of a stress response. An introduction to basic stress physiology provides the foundation for further inquiry into the functional pathways linking the brain and the cardiovascular system, and therefore, the potential mechanisms that may underlie and support the hypothesis that cardiovascular risk factors and markers can be influenced by psychosocial stress and depression.

### **Psychosocial Stress and Neural Processes**

The stress response begins in, and is orchestrated by the brain, which also stands as a target organ for stress hormones (McEwen, 2009). Environmental stimuli are received by the brain through our sensory receptor systems, which convey information to their respective sensory areas of the thalamus, primary sensory cortices, and higher order sensory cortices. Important cognitive-evaluative processes also occur during exposure to a psychosocial stressor, which shapes our response to environmental demands (McEwen, 2007). This initial cognitive-evaluative process occurs in the prefrontal and frontal cortices. Information is simultaneously transmitted to parts of the limbic system, including the amygdala, an area of the brain that

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contributes to the processing of emotion, which then interprets the images, sounds and sensations (Phelps & LeDoux, 2005). Further input is provided by the hippocampus and related cortical and subcortical storages, which are implicated in explicit memory formation and retrieval (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000). The hippocampus assigns meaning to our perceptions and provides contextual information. Additional involvement comes from the cingulate gyrus, which helps form connections that create our awareness of emotions (Lane et al., 1998). Of particular relevance to our understanding of psychosocial stress, is that the involvement of these brain areas in the processing of stimuli means that internal stressors in the form of distressing memories may further trigger a stress response and this can occur in the absence of external stimuli (Jacobs & Nadel, 1985). Associated with the individual's emotions and behaviours are a host of centrally and peripherally activated physiological responses, or reactivity, the nature of which is determined by the way that a stressor is perceived as a threat by these higher order processes in the brain (Dickerson & Kemeny, 2004; Tomaka, Blascovich, Kelsey, & Leitten, 1993).

**Stressors perceived as threatening.** Once a stimulus is perceived as stressful (e.g. a threat to the organism), the amygdala rapidly sends a distress signal to the hypothalamus, which acts like the command centre communicating with the rest of the body via the autonomic nervous system. The immediate response to a stressor involves all three stress response neural axes, these being; (1) the sympathetic nervous system, which functions to produce generalised arousal within end organ targets, (2) the parasympathetic nervous system, which functions to inhibit, slow and restore bodily functions, and (3) the neuromuscular nervous system (Everly & Lating, 2012). This neuroendocrine response occurs via the hypothalamus, which stimulates the release of neurotransmitters noradrenalin and acetylcholine, leading to direct innervations via sympathetic, parasympathetic and somatic nervous systems. This physiological response (triggered by the limbic system) results in an increase in heart



rate and blood pressure, which defines hemodynamic reactivity. The major effects of autonomic neural innervations on target organs are immediate but not potentially chronic. Therefore, in order to maintain high levels of stress arousal for prolonged periods, additional physiological stress axes must be activated.

### **The Autonomic and Neuroendocrine System Response**

The body's principal physiological responses to stress stimuli are mediated, at the most basic level, by two main systems, (1) the sympathetic-adrenal-medullary (SAM) system and (2) the hypothalamic-pituitary-adrenal axis (HPA-axis).

**Sympathetic-adrenal-medullary system.** In concert with direct neural innervations, the first component of the stress response involves the SAM system. In this system, the hypothalamus stimulates the adrenal medulla, which in turn responds by releasing the catecholamines adrenalin and noradrenalin, into the blood stream. This release of adrenaline and noradrenaline stimulates an increase in generalised adrenergic somatic activity in humans (Folkow & Neil, 1971; Wenger et al., 1960).

The autonomic nervous system plays a crucial role in the control of arterial pressure and therefore in the regulation of blood flow in humans. It does so via the richly innervated sympathetic nerves of the heart, which project to the myocardium, coronary arteries, and conduction system. This allows the cardiovascular system to maintain effective delivery of blood to the capillary beds (perfusion) of the body's organs, by meticulously regulating arterial pressure via continuously altering cardiac output and/or systemic vascular resistance. For example, activation of the sympathetic arm of the autonomic nervous system, and specifically, adrenergic receptors (e.g. alpha 1 receptors) by adrenaline or noradrenaline in the arteries of the heart results in vasoconstriction, and therefore increased vascular resistance, increased heart rate, increased blood pressure, increased cardiac output, and decreased heart rate variability, all of which define hemodynamic reactivity. Changes in autonomic balance

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(e.g. between sympathetic and parasympathetic activity) in turn increase or decrease blood flow through the organs, affecting the function of the target organ, peripheral resistance and arterial pressure (Charkoudian & Rabbitts, 2009).

As the initial adrenalin subsides, the hypothalamus activates the second component of the stress response system – the HPA-axis.

**Hypothalamic-pituitary-adrenal axis.** The HPA-axis consists of the hypothalamus, the pituitary gland, and the adrenal glands. In response to a stressor that is still perceived as a threat, hypothalamic neurons from the paraventricular nucleus increase the synthesis and release of corticotrophin-releasing hormone and arginine vasopressin. Corticotrophin-releasing hormone travels to the anterior pituitary gland and stimulates the secretion of adrenocorticotrophic hormone. Adrenocorticotrophic hormone in turn signals the adrenal glands to secrete glucocorticoids (e.g. cortisol in humans) and mineralocorticoids (Everly & Lating, 2012). Glucocorticoids modulate activity of the HPA system by providing feedback to the pituitary, hippocampus and hypothalamus (Herman, Ostrander, Mueller, & Figueiredo, 2005).

Glucocorticoids have direct effects on the heart and blood vessels, mediated by both glucocorticoid (Walker, 2007) and mineralocorticoid receptors (Frey, Odermatt, & Frey, 2004). Glucocorticoid secretion, in the absence of reactive physical activity, may be associated with adverse cardiovascular outcomes, including an increased amount of free fatty acids in circulation, which in the absence of muscular activity, are then available for ectopic fat distribution (liver, muscle, and central adipocytes), as well as the potential for endothelial inflammation and excessive clotting (Walker, 2007). Findings on the effect of excess glucocorticoids on the vascular endothelium suggest that this excess leads to an overproduction of reactive oxygen species (ROS), which thereby disturbs nitric oxide availability in the vascular endothelium, in turn giving rise to vascular complications (Iuchi et al., 2003). Furthermore, glucocorticoid excess affects lipid metabolism, which may result in increased low density lipoprotein cholesterol

(LDL-C) and decreased high density lipoprotein cholesterol (HDL-C; Boers et al., 2003; Fraser et al., 1999); and pleiotropic action of glucocorticoids, which stimulates processes leading to increased blood pressure and insulin resistance (Lifton, Gharavi, & Geller, 2001); all factors that may adversely impact on cardiovascular function (Yusuf et al., 2004).

Following activation of the stress system, and once the perceived stressor has subsided, feedback loops are triggered at various levels of the system (that is, from the adrenal gland to the hypothalamus and other brain regions such as the hippocampus and the frontal cortex) in order to shut the HPA-axis down and return to a set homeostatic point (Lupien, McEwen, Gunnar, & Heim, 2009). However, among individuals under ongoing chronic stress or in people with depression, abnormalities in these feedback loops, involving the prefrontal cortex, the amygdala and the HPA-axis are evident (Gillespie & Nemeroff, 2005; McEwen, 2000; Nestler et al., 2002; Sapolsky, 2000). It is under these circumstances that a healthy stress response may become an unhealthy damaging stress response. The consequences of these alterations are widespread and in terms of cardiovascular function, may include coagulation alterations, endothelial injury and hypertension (Flaa et al., 2008; Grippo & Johnson, 2009; Lett et al., 2004; O'Connor, O'Halloran, & Shanahan, 2000; Rozanski Blumenthal, & Kaplan, 1999).

The physiological responses described here comprise the human stress response, our life-saving means by which we can restore homeostasis following exposure to a stressor. A growing number of chronic diseases have been found to be associated with dysregulation of the stress system (O'Connor, Moynihan, & Caserta, 2014), including the development of CVD (O'Connor et al., 2000).

However, the precise role of stress in the causation of CVD is currently not clear, nor concretely established. What determines how and when a healthy stress reaction may become a potentially damaging one is complex and likely to be influenced by individual genetics, epigenetics and environmental factors, all of which are known to

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play a role in the aetiology of CVD and other chronic presentations related to stress dysregulation, such as depression. The diathesis-stress model (Zuckerman, 1999) provides a model linking stress, the stress response and genetics that is consistent with individual variation in vulnerability to a stressor described here.

In this chapter, the physiological responses to a stressor have been described in terms of “healthy” and “unhealthy”. Depression is of course a separate issue, with symptoms that might well be described as the opposite of the healthy “fight or flight” response to a stressor. However, individuals with depression express many of the same detrimental physiological effects as those associated with the chronic, unhealthy responses to stress, which lead to stress system dysregulation. The relationship between stress and depression is now explored, and with this, the potential role for depression in the development of CVD.

### **Stress and Depression**

Of relevance to the current discussion and the work undertaken in this thesis, is the link between chronic stress and the development of depression. Chronic stress has been associated with the development of depression in certain individuals and under certain circumstances (Kessler, 1997; Tafet & Bernardini, 2003). While it is acknowledged that depression is a complex disorder that results not only from environmental factors but also from genetic influences (Flint & Kendler, 2014; Sullivan, Neale, & Kendler, 2000), chronic stress may lead to the eventual exhaustion of these defence systems, dysregulation of the stress system and depression (Fuchs & Flügge, 2011; Tafet & Bernardini, 2003). For example, abnormalities in the function of the HPA-axis have been described in people with depression, including HPA-axis hyperactivity in major depression (Bhagwagar, Hafizi, & Cowen, 2005; Knorr, Vinberg, Kessing, & Wetterslev, 2010; Owens et al., 2014; Tafet & Bernardini, 2003); but hypoactivation of the stress system has also been documented in people with seasonal depression and post-traumatic stress disorder (Gold & Chrousos, 2002; Meewisse, Reitsma, De Vries,

Gersons, & Olf, 2007). Although the precise pathophysiology underlying these links remains unknown (Tsankova et al., 2006), the increased activity of the HPA-axis in major depression is thought to be related to impaired feedback inhibition by endogenous glucocorticoids on the HPA-axis; and that this impaired feedback inhibition is due to altered or decreased glucocorticoid receptor function (Pariante & Lightman, 2008; Paslakis et al., 2011).

Consequently, the neurophysiological changes experienced by depressed individuals would be anticipated to be similar to those in chronically stressed individuals, and so with similar effects on cardiovascular function. The next section includes a discussion of the potential mechanisms underlying the prognostic significance of stress and depression.

### **Mediators of the Effect of Stress and Depression on CVD**

A number of plausible biological mechanisms have been proposed, which may link psychosocial stress and depression with cardiovascular disease. Dysfunction of the autonomic nervous system and HPA-axis we consider as the over-riding or “Master” mediators of the link between psychology and CVD. Their disruption, in terms of an “unhealthy” stress response, can produce localised target tissue effects, to reduce arterial elasticity and impair endothelial function and to increase platelet activity, aggregation and produce coagulation abnormalities. Chronic HPA-axis and autonomic nervous system activity can also lead to immune dysfunction, including increased production of pro inflammatory cytokines (Kang et al., 2008; Pongratz & Straub, 2014). A schematic diagram of the potential mediating pathways and mechanisms linking psychosocial stress and depression associated with CVD is presented in Figure 5. Finally, we consider the influence of genetic and behavioural factors, which are likely to exert their influence on the relationship between stress, depression and CVD, and so need to be considered carefully in any study of associations.

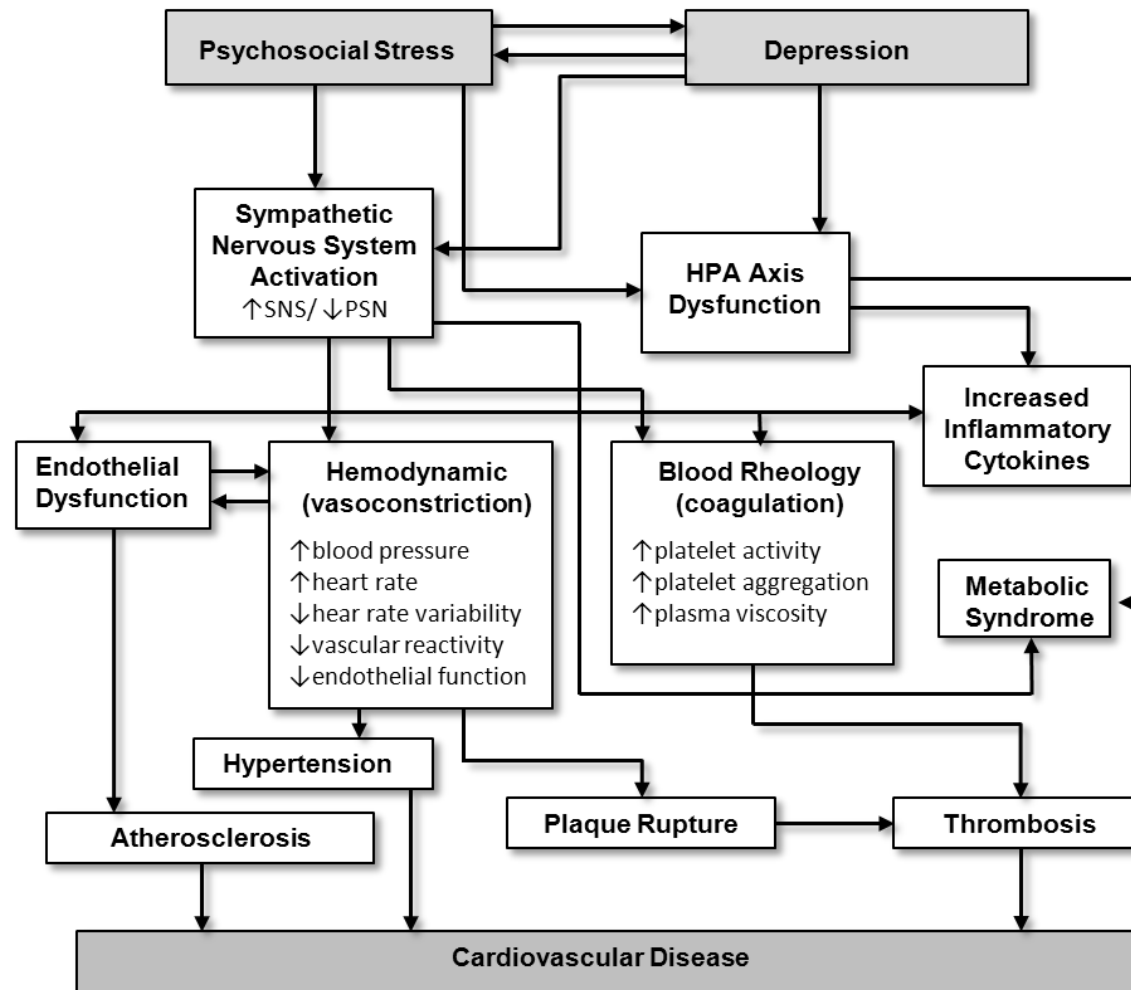


Figure 5. Potential mediating pathways and mechanisms linking psychosocial stress, depression and cardiovascular disease.

**A. Autonomic Nervous System and the HPA-Axis: the “Master” Mediators****(a) Disruption of the autonomic nervous system**

The discussion so far has highlighted the role of a chronic low level hyperactive sympathetic system and a hypoactive parasympathetic system, as characteristic of stressed and depressed individuals (Dao et al., 2010; Glassman, Bigger, Gaffney, & Van Zyl, 2007; Kemp et al., 2010). Also as previously introduced, the heart is richly innervated by nerves from both the sympathetic and parasympathetic nervous systems rendering it sensitive to abnormal activity.

Evidence for a link between psychological distress and autonomic imbalance has largely arisen from investigations involving heart rate variability (HRV). Heart rate variability, a measure of the beat-to-beat fluctuation in heart rate, and therefore considered to reflect the balance between sympathetic and parasympathetic regulatory control of the heartbeat, is a key measure of autonomic regulation and has been used as an indicator of good cardiac function (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). Low HRV, is suggestive of excessive cardiac sympathetic modulation, inadequate cardiac parasympathetic modulation, or both (Lahiri, Kannankeril, & Goldberger, 2008; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Thayer et al., 2012; Thayer, Yamamoto, & Brosschot, 2010) and has been repeatedly documented among depressed individuals (Dao et al., 2010; Kemp et al., 2010), including young depressed girls (Tonhajzerova et al., 2010). Low HRV is also a known risk factor for a number of clinical cardiac presentations, including ventricular arrhythmias in patients with coronary heart disease and for cardiac sudden death (Curtis & O'Keefe, 2002; Huikuri & Makikallio, 2001; Tsuji et al., 1996). Furthermore, a decline in HRV has been linked to an increased risk of myocardial infarction and insufficient blood flow to the coronary arteries (Laghrissi-Thode, Wagner, Pollock, Johnson, & Finkel, 1997), as well as an increase in the relative risk for CVD (Dekker et al., 2000; Dekker et al., 1997).

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An upsurge in chronic low-level sympathetic activity, due to either excessive cardiac sympathetic modulation, inadequate cardiac parasympathetic modulation, or both, will in turn, elicit a chronically raised concentration of circulating catecholamines, adrenaline and noradrenaline, in the periphery. Increased levels of these catecholamines have been seen in individuals exposed to chronic psychosocial stress and among those with depression (Barton et al., 2007; Gold et al., 2005). This chronic low-grade increase in sympathetic activity can result in vasoconstriction, platelet activation, hypertension and arrhythmia (Esler & Kaye, 2000; Esler, 1998; Fisher & Paton, 2012; Johnson, Feig, Nakagawa, Sanchez-Lozada, & Rodriguez-Iturbe, 2008; Manolis, Poulimenos, Kallistratos, Gavras, & Gavras, 2014; Oparil, Zaman, & Calhoun, 2003), all factors associated with an increased risk for CVD and CVD related mortality. Autonomic dysfunction has also been associated with increased levels of pro-inflammatory cytokines in depressed patients (Frasure-Smith, Lesperance, Irwin, Talajic, & Pollock, 2009; Kop et al., 2010b) and the potentially damaging effects of this response are discussed later in this chapter.

### **(b) Disruption of the HPA-axis**

As previously introduced depression and chronic stress have been associated with dysregulation of the HPA-axis (Schulman, Muskin, & Shapiro, 2005), which can result in hypersecretion of glucocorticoids and subsequent hypercortisolism (Carroll et al., 2007; Gold, Goodwin, & Chrousos, 1988; Gold, Machado-Vieira, & Pavlatou, 2015). This is often demonstrated by assessing circulating cortisol, which is found to be higher among people with depression (Bhagwagar et al., 2005; Gold et al., 1988; Murphy, 1997; Owens et al., 2014; Parker, Schatzberg, & Lyons, 2003; Sachar, Hellman, Fukushima, & Gallagher, 1970); as are levels of corticotrophin-releasing hormone in cerebrospinal fluid and in the paraventricular nucleus of the hypothalamus (Nemeroff et al., 1984).



Elevated levels of plasma cortisol have been shown to promote the development of atherosclerosis (Kaplan, Pettersson, Manuck, & Olsson, 1991) and hypertension (Whitworth, Brown, Kelly, & Williamson, 1995). In addition, high plasma cortisol has been shown to accelerate injury to the vascular endothelial cells, leading to endothelial dysfunction through alterations to the nitric oxide (NO) system (Rogers, Bonar, Estrella, & Yang, 2002; Turner et al., 2005; Wallerath et al., 1999). In addition to endothelial dysfunction, increased sympathoadrenal activity, resulting from increased cortisol may lead to vasoconstriction, platelet activation, and elevated heart rate and rhythm disturbances. All being changes that are highly deleterious to the cardiovascular system, predisposing to atherosclerosis, thrombogenesis and coronary disease (Badimon, Padró, & Vilahur, 2012; Scott, 2004).

## **B. Mechanistic Target Tissue Effects of HPA-Axis and Autonomic Nervous System Disruption**

### **(a) Endothelial dysfunction**

The vascular endothelium plays a crucial role in regulating vascular tone and vasomotor function. Endothelial dysfunction is considered an early marker of cardiovascular dysfunction and a risk factor for the development of CVD (Anderson et al., 1995; Kinlay & Ganz, 1997; Matsuzawa et al., 2013; Ras et al., 2013). Healthy vascular endothelium can be characterised by vasodilator, anti-adhesive, anti-inflammatory and anti-coagulant properties (Clapp et al., 2004). In contrast, endothelial dysfunction is characterised by reduced dilator function, increased inflammatory cell and platelet adhesion (Goldsmith, Blann, Patel, & Lip, 2000), and increased coagulation activity (Bombeli, Mueller, & Haeberli, 1997). As introduced in Chapter 3, psychosocial stress and depression have been associated with impaired endothelial function, where endothelial dysfunction has been documented in individuals experiencing symptoms of stress and depression who were otherwise healthy

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individuals (Broadley et al., 2002; Ghiadoni et al., 2000; Sarabi & Lind, 2001; Sherwood et al., 1999), and in those at risk for CVD (Cardillo, Kilcoyne, Cannon, & Panza, 1998; Pizzi, Manzoli, Mancini, & Costa, 2008) or with established CVD (Sherwood et al., 2005; Yeung et al., 1991). These associations are potentially mediated via the effects of a chronically elevated autonomic nervous system and hormone secretion on arterial function.

In a normal state, the autonomic nervous system and the endothelium work together to maintain vascular tone, with a balance between the vasodilating factors (e.g. NO) released by the endothelium and vasoconstricting factors from sympathetic nerve terminals (Amiya, Watanabe, & Komuro, 2014). The balance between these opposing forces acts on the vascular smooth muscle cells, which lies between the autonomic nervous system nerve terminals and the endothelial cells lining the blood vessel lumen, to maintain the appropriate vessel tone (Burnstock, 1990). However, alterations in the balance between these two systems may lead to detrimental effects on the cardiovascular system.

Over activation of the autonomic nervous system may directly impair endothelial function and enhance endothelium-mediated atherogenic processes (Davignon & Ganz, 2004). For example, the increased level of circulating catecholamines, associated with an increased sympathetic drive, which is also often seen in depressed patients (Barton et al., 2007), may contribute to structural changes in the endothelial cells along the arterial wall (Loesch, Maynard, & Burnstock, 1992), including the induction of macrophages into the abluminal space (Coutinho, Durieu-Trautmann, Strosberg, & Couraud, 1991). Further to these effects, circulating catecholamines may also increase the uptake of low-density lipoproteins by endothelial cells (Born, 1991). High levels of circulating catecholamines are also associated with an upregulation of immunoreactivity (Coutinho et al., 1991) and associated inflammatory processes. Inflammation, which has been associated with both depression and acute coronary syndromes (Black & Garbutt, 2002; Corti, Fuster, & Badimon, 2003; Danesh et al.,

2000; Hansson, 2005; Patel, 2013), also impairs endothelial function (Bhagat & Vallance, 1997; Hingorani et al., 2000; Ohkawa, Ikeda, Kanbe, Kawasaki, & Shimada, 1995), and specifically, endothelial NO bioavailability (Clapp et al., 2004; Clapp et al., 2005). Healthy endothelium maintains vascular tone via NO metabolites and it is changes in bioavailability of NO on exposure to stress and depression that has been implicated as a potential mechanism explaining associations between stress, depression and CVD.

The influences of such neurohormonal inputs on the endothelium have been demonstrated through animal experimentation, including investigations into the role of psychosocial stressors, where it has been demonstrated that exposure to psychosocial stressors in primates' results in endothelial injury (Skantze et al., 1998; Strawn et al., 1991). Similarly, in humans, experiences of acute stress have been shown to bring about transient endothelial dysfunction (Ghiadoni et al., 2000; Poitras & Pyke, 2013), which if experienced repeatedly or chronically may have adverse effects on the cardiovascular system.

#### **(b) Platelet activity and blood rheology effects**

Depression and psychosocial stress have also been linked to an increased risk of cardiac thrombotic events via platelet reactivity and activation (Aschbacher et al., 2009; Musselman et al., 1996; Wittstein, 2010); platelet adhesion, activation and aggregation being recognised contributors to cardiac disease (Nancy Frasure-Smith & Lespérance, 2006).

The link between depression and platelet reactivity, and subsequent aggregation, may be mediated by serotonin, which plays a key role in platelet biology (Williams, 2012), and the serotonergic system has also been implicated in the pathogenesis of major depression (Hasler, 2010; Mann, 1999; Risch et al., 2009). In atherosclerotic arteries, where endothelial cells are unable to release NO in response to serotonin, serotonin leads to platelet aggregation and, ultimately vasoconstriction of

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arteries (Weyrich, Solis, Li, Tulenko, & Santamore, 1992). Studies among depressed individuals have documented increased platelet function, including increased serotonin response, increased platelet serotonin receptor density (Arora & Meltzer, 1989; Hrdina et al., 1997), decreased serotonin transporter binding (Nemeroff, Knight, Franks, Craighead, & Krishnan, 1994), and decreased platelet serotonin levels (Maurer-Spurej, Pittendreigh, & Misri, 2007). Yet, the aetiology of this increased platelet function in depression is not yet understood (Williams, 2012). However, given that serotonin is involved with platelet aggregation and blood clotting, and is also implicated in mood control; this renders it a prime candidate as a mediator in the link between depression and stress, and CVD.

Accompanying the potential role of platelet abnormalities, depression and psychosocial stress have been linked with other hemorheologic factors. Potentially damaging increases in blood viscosity (Brown, Giles, & Croft, 2001; Patterson et al., 1995) have been brought about by hemoconcentration and increased total plasma protein in depressed patients (Kim et al., 2005). These findings add to the bank of evidence linking depression, psychosocial stress and the development of CVD.

### **(c) Inflammation and immune dysfunction**

The link between both psychosocial stress and depression and the immune system has received a great deal of attention in recent times (Dowlati et al., 2010; Maes, 1995; Maes et al., 1997; Miller & Raison, 2016; Patel, 2013). There is now considerable evidence showing that many individuals with depressive illness (both with and without CVD) manifest elevated inflammatory markers (Howren, Lamkin, & Suls, 2009; Kop et al., 2010a; Miller, Maletic, & Raison, 2009; Pizzi et al., 2008). Several recent meta-analyses and review papers have reported that increases in production, and plasma levels of proinflammatory cytokines, particularly interleukin-6 (IL-6), interleukin-1b (IL-1b), C-reactive protein (CRP) and tumor necrosis factor-a (TNF-a) are often seen in depressed subjects compared to controls (Dowlati et al., 2010;

Howren et al., 2009; Maes, 1995). Proinflammatory cytokines have been implicated in the pathogenesis of atherosclerosis (Dantzer, Wollman, & Yirmiya, 2002) and CVD (Boekholdt & Stroes, 2012; Hedayat, Mahmoudi, Rose, & Rezaei, 2010; Kofler, Nickel, & Weis, 2005; Sarwar et al., 2012); and in turn, it has also been suggested that atherosclerotic lesions (Dantzer et al., 2002) and endothelial damage lead to the increased production and release of proinflammatory cytokines (Sprague & Khalil, 2009), creating a cycle of inflammation. As a result, a sequence of events that eventually lead to thrombus formation and vascular occlusion may be stimulated.

Interestingly, it has been suggested that increased levels of proinflammatory cytokines themselves can produce depressive symptoms, including fatigue, apathy, social withdrawal and loss of appetite (Dantzer & Kelley, 2007; Maes, 2008; Miller et al., 2009). These findings have led to the Cytokine Theory of Depression (Connor & Leonard, 1998), which states that psychosocial stress, likely in combination with genetic factors, increases cytokine production, which when specific neurobiological systems are effected (e.g. HPA-axis and serotonin function), results in depressive symptoms. Developments in this line of research therefore suggest that depression can modify immune function, via inducing increased levels of pro-inflammatory cytokines; and conversely, that immune system abnormalities may play a role in the aetiology of depression.

The influence of increased proinflammatory cytokines in the link between depression and CVD likely involves both peripheral and central nervous system mechanisms. For example, specific cytokines such as IL-1 IL-1b, IL-6, interferon- $\gamma$  and TNF- $\alpha$  contribute to central nervous system function, and can affect developing neurons by acting directly on receptors or by stimulating the release of neurotrophic factors (Mehler, Goldstein, & Kessler, 1996). Peripheral cytokines influence the release and metabolism of several neurotransmitters, including dopamine (Jarskog, Xiao, Wilkie, Lauder, & Gilmore, 1997), noradrenalin (Kabiersch, del Rey, Honegger, & Besedovsky, 1988) and serotonin (Clement et al., 1997). That these neurotransmitters

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influence sympathetic nerve outflow to the cardiovascular system (Huangfu, Hwang, Riley, & Guyenet, 1994), as well as being implicated in the pathogenesis of depression (Nosjean, Franc, & Laguzzi, 1995) provides further evidence of the depression-CVD relationship.

### **C. Genetic and Behavioural Influences**

#### **(a) Genetic influences**

In addition to the effects discussed so far, which have largely related to autonomic nervous system and neuroendocrine changes, individually inherited characteristics are likely to play a central role in the aetiology of both psychological disorders and chronic disease. Both depression and CVD are complex disorders, and have both been associated with perturbations of the synthesis of hormones and transmitter substances. As a result, genetically determined variation in the production of these substances is likely to influence the development of both depression and CVD. In support of this premise, is the evidence suggesting that both depression and CVD run in families, along with twin studies, which have provided evidence that this familial aggregation is based on an increased genetic vulnerability (Sullivan et al., 2000; Zdravkovic et al., 2004). In recent years, many studies have investigated polymorphisms in candidate genes in relation to functional characteristics of central or peripheral mechanisms, which are involved in the development of both depression and CVD. For example, genetic predispositions, such as specific serotonin transporter gene polymorphisms, coupled with gene–environment interaction, have been implicated in the development of depressive disorders and also with an increase in sympathetic nervous system activation. As previously demonstrated, this increase in sympathetic nervous system activity has been linked to increased risk for CVD (Barretto et al., 2009; Charkoudian & Rabbitts, 2009; Dekker et al., 2000).

**(b) Behavioural influences**

In addition to the biological pathways discussed here, a number of behavioural pathways appear to be involved in the relationship between psychological risk factors and CVD. A growing body of evidence suggests that depressed individuals or those experiencing ongoing psychosocial stress are more likely to exhibit unhealthy behaviours and less likely to engage in health-promoting behaviours (Bonnet et al., 2005; Jacka, Cherbuin, Anstey, & Butterworth, 2014; Jerstad et al., 2010; Kinnunen et al., 2006; Mouchacca, Abbott, & Ball, 2013; Rottenberg et al., 2014; Weinberger, Pilver, Desai, Mazure, & McKee, 2013). For example, depressed individuals are less likely to participate in health promoting physical activity (Jerstad et al., 2010; Rottenberg et al., 2014), which is of significance in terms of CVD risk. Low levels of physical activity are an independent risk factor for CVD development (Shiroma & Lee, 2010) and has been associated with a number of further risk factors for the disease, including obesity, blood pressure and glycaemic control (Adamis & Ball, 2000; Cornelissen & Smart, 2013; Kan et al., 2013; Mezuk, Eaton, Albrecht, & Golden, 2008). Conversely, regular physical activity has been shown to reduce the risk for CVD related mortality (Shiroma & Lee, 2010), and has also been associated with improvements in obesity, blood pressure, glycaemic control and lipid levels (Kokkinos & Myers, 2010; Shiroma & Lee, 2010).

Depression and ongoing psychosocial stress may also predispose an individual to excessive weight gain via poor diet (Goodman & Whitaker, 2002; Richardson et al., 2003; Stice et al., 2005). For some depressed individuals, increases in appetite are apparent and these changes in appetite can potentiate positive energy balances and therefore, increased body fat (Louise et al., 2012). While the pathways between stress and depression with overweight and obesity are likely to be multifactorial, and are thought to involve neuroendocrine changes and HPA-axis dysfunction (Dallman, 2010; Lee, Pramyothin, Karastergiou, & Fried, 2014), they likely also involve maladaptive coping behaviours, such as reduced physical activity (Ng & Jeffery, 2003), poor food

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choices and disordered eating (Peterson, Latendresse, Bartholome, Warren, & Raymond, 2012). This may include binge-eating (Peterson et al., 2012) and an increased preference for higher-fat, energy dense foods (Adam & Epel, 2007; Gibson, 2006), once again, creating the potential for a positive energy balance and therefore increases in adiposity.

In addition to physical inactivity and poor diet, the ongoing experience of chronic stress and depression may further affect cardiovascular health via their influence on cigarette smoking behaviour, sleep disturbance and poor adherence to treatment (Grandner, Jackson, Pak, & Gehrman, 2012; Minichino et al., 2013; Ziegelsteing & Elfrey, 2011). Smoking behaviour is thought to be higher among depressed patients (Degenhardt & Hall, 2001; Minichino et al., 2013) and is a well-known risk factor for CVD (Huxley & Woodward, 2011; Prescott, Hippe, Schnohr, Ho, & Vestbo, 1998). Similarly, the experience of chronic stress and depression can affect sleep quality (Alvaro, Roberts, & Harris, 2013; Breslau, Roth, Rosenthal, & Andreski, 1996), which has been associated with the occurrence of clinical CVD events (Alibhai et al., 2014; Canivet, Nilsson, Lindeberg, Karasek, & Östergren, 2014) and CVD related mortality (Mallon, Broman, & Hetta, 2002; Grandner, et al., 2012). Those who are depressed are also less likely to adhere to treatment regimens, be that adherence to medication, cardiac rehabilitation programs or suggested lifestyle modifications, such as changes in diet and exercise routine (Ziegelsteing & Elfrey, 2011). Treatment adherence may be affected by negative attitudes to treatment or to low self-efficacy in an individual's ability to successfully implement and maintain the required lifestyle changes (Ziegelsteing & Elfrey, 2011); a kind of negative cognitive bias that is characteristic of depressive presentations (Beck, 1967).

The behavioural factors reported here all pose an increased risk for developing CVD (Yusuf et al., 2004). However, it should be noted that in studies investigating behavioural pathways between psychosocial factors and CVD, not all of the risk could



be explained, indicating that alternative pathways and mediators, as has been introduced previously in the Chapter, are also at play.

### **Chapter Conclusions**

In this chapter, a basic overview of stress in humans was presented, beginning with an introduction to how the human stress response has evolved, followed by a presentation of basic stress physiology. In this chapter I have highlighted how an adaptive and “healthy” stress response, can in contrast become an “unhealthy” life-threatening response, leading to the damage of human cells and tissue, and producing organic and systemic dysfunction. This discussion concentrated on the impact these deleterious changes have on one system, that being the cardiovascular system. It became evident that, despite the fact that they are identical processes in essence, the potentially life-saving effects of rarely accounted acute stress responses are very different to those of chronic, low-level stress responses which are life threatening.

In addition, plausible biological and behavioural mechanisms, which may explain how the cardiovascular system could be influenced by the experience of psychosocial stress and depression, were reviewed. What became apparent from reviewing the literature was on the one hand, the highly integrated and sophisticated manner in which these mechanisms seemed to operate, resulting in a network of feedback regulation that is likely to be bidirectional. On the other hand, much of the literature linking chronic stress and depression and CVD was observational with little experimental work with humans, so with many uncertainties as to inferences of causation, let alone direction of causation. At the centre of much of the work investigating potential mechanisms explaining the relationship between psychological distress and CVD, is a role for the sympathetic nervous system and the HPA-axis. At the same time, the inconsistencies across studies and between individuals, regarding the nature of sympathetic nervous system reaction on exposure to psychosocial stress

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and depression likely indicates that different central nervous system pathways, and peripheral and genetic factors influencing neurotransmitter disposition, may be at play.

Although the exact mechanisms are not currently well understood, the literature reviewed in this chapter provides plausible evidence to support the hypotheses underlying the current thesis, that early markers of cardiovascular risk, including markers of arterial function, as well as metabolic dysfunction, may be influenced by the experience of psychosocial stress and depression. We now turn our attention to the empirical work undertaken in this thesis, beginning with an introduction to the research design employed in the empirical studies.

## **CHAPTER 5**

### **RESEARCH DESIGN**

#### **Context Statement**

This chapter begins by introducing the Lifestyle of our Kids (LOOK) Study. This includes an introduction to the overall aims of LOOK, along with a description of the overarching research design. The methodology specific to the current Ph.D., which forms part of the larger LOOK Study, is then discussed, providing a description of the sampling design, participant characteristics and attrition. An introduction to the measurement instruments utilised in the current thesis is presented, along with a critique and rationale for their selection. A further critical review of alternative methods of measurement considered in the current thesis is also presented. Finally, the analytical approach used in the empirical studies is described.

### **Overview of the LOOK Study**

The Lifestyle of our Kids (LOOK) study is a multidisciplinary, longitudinal cohort study based in Canberra, in the Australian Capital Territory (ACT). The overarching aims of the childhood and adolescent phase of the LOOK study were; (a) to investigate relationships between lifestyle factors and health in children, and (b) to investigate the effects of a specialised physical education intervention, introduced to half of the cohort during primary school, to determine whether quality physical education provided during primary school could significantly and positively affect current and future health. Although this Ph.D. thesis will not report on effects of the physical education intervention, it is an important design feature of the overall LOOK study and one that could potentially affect the variables under investigation in the current research. Therefore, preliminary analyses were undertaken to investigate the effect of the intervention on psychological, cardiac and metabolic variables under investigation in the proceeding studies. The results indicated that the specialist physical education intervention had no significant effect on any of the measured variables, with the exception of insulin resistance and percent body fat. As a result, subsequent investigations in the current thesis involving insulin resistance and percent body fat will account for the intervention effect by adding it as a design variable in the corresponding statistical model.

The LOOK study has four main phases; (1) the completed Childhood Phase (age 8 to 12 years), (2) the completed Adolescent Phase, (age 16 years), (3) the Young Adult Phase, and (4) the Middle and Old Age Phase. The initial childhood phase of the LOOK study commenced with a cohort of prepubescent, grade two children. These same children were followed over the course of primary school and again in high school as adolescents. Major LOOK measurement periods during the Childhood and Adolescent Phases occurred in grade 2 (baseline), grade 4, grade 6 and grade 10. Psychological data collection followed a slightly different time line with major collections occurring in grade 2, grade 3, grade 6 and grade 10. Differences in timing for

psychological data were, for the most part, to allow appropriate assessment of psychometric properties of self-report inventories developed for the LOOK study. A timeline depicting the major testing periods for the overall LOOK Study and for psychological data is provided in Figure 6. The uniqueness of the LOOK study lies in the breadth of health areas that have been measured simultaneously across a number of disciplines, and over the important developmental period of mid-to-late childhood and again in adolescence. A summary of the research areas investigated in the child and adolescent phase of the LOOK study are summarised in Figure 7.

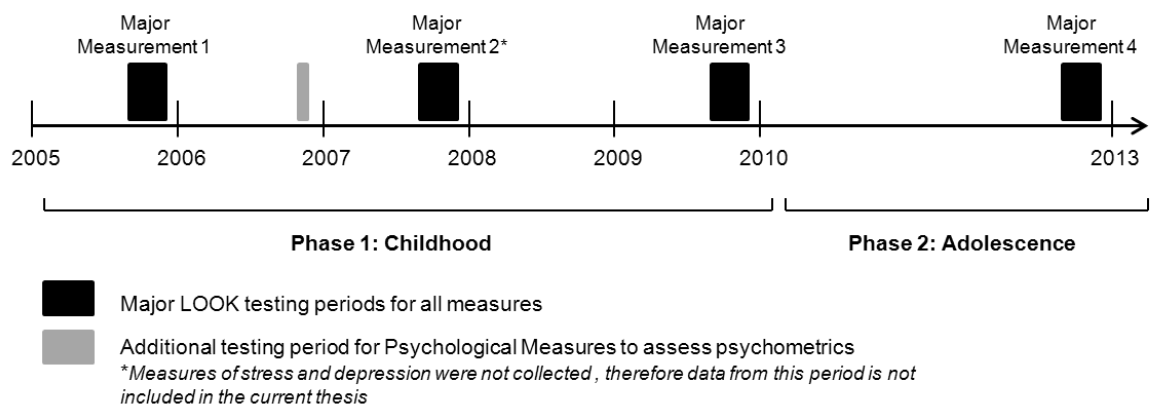


Figure 6. Time-line showing occurrence of LOOK Study data collection periods.



Figure 7. Multidiscipline research areas investigated in the LOOK Study.

### **Methodology of the Current Thesis**

The research proposed in the current Ph.D. thesis will draw from a select few areas of the LOOK Study, with a focus on relationships between psychological health, physical activity and fitness, and metabolic and cardiovascular health over the period of childhood and adolescence. For the most part, data used in the current thesis is drawn from measures collected in grade 2 (age 7 to 9 years), grade 6 (age 11 to 13 years) and grade 10 (age 15 to 17 years). All psychological and metabolic measures under investigation were repeated at each of these major measurement periods. Additional to this data, assessments of cardiovascular function, and specifically assessments of arterial stiffness and blood pressure, were available in grade 6 and grade 10. Further to these assessments, and with advancements in technology and affordability, a measure of endothelial function was added in grade 10.

In the empirical study investigating endothelial function, which is presented in Chapter 9, psychological data collected in 2006 for psychometric assessment is also utilised. This is done in order to maximise the use of longitudinal data in this investigation, which requires a different analytical approach from the other empirical studies, owing to the cross-sectional nature of the endothelial function assessment. The timing of data collection for each specific variable used in the current study is presented in Figure 8.

### **Sampling Design and Participant Characteristics**

**Recruitment process.** Thirty public primary schools from outer suburbs in the ACT, approximately matched for socioeconomic status (SES) as indicated by the Australian Bureau of Statistics (ABS) Socioeconomic Indexes for Areas (SEIFA; ABS, 2009), were approached to participate in the LOOK study. The principals of these 30 schools were invited to an information evening, which outlined the aims of the LOOK study and written information was provided to each principal. Of the 30 schools approached, 29 agreed to participate. The reason given by the declining school was

that the principal at the time of recruitment was temporarily employed and did not want to commit the permanent principal to the study without their consent.

Once the principals had accepted the invitation, consent forms were disseminated to the parents of all grade two children in participating schools. Subsequent to this, separate information nights were held at each school for parents of participating children to outline the purpose of the LOOK study, the methodology and to answer any further questions.

As previously stated, this recruitment process resulted in a sample of 853 children recruited from the 29 primary schools. This represented 96% of grade two children approached to participate. Schools were selected into the study based on class groups rather than individual students, and this “cluster” design is taken into account when investigating relationships in the ensuing studies. Schools were randomly assigned to either the intervention or control group using a randomised number table with the intervention group receiving a specialist physical education program and the control group continuing with physical education delivered by the classroom teacher<sup>1</sup>.

**Participants.** The sample at baseline consisted of 853 grade two children aged 7 to 9 years (435 boys, *M* age = 8.18; 418 girls, *M* age = 8.13). Follow-up data for the studies presented in this thesis were collected in grade 3 (379 boys, 371 girls; used only in Study 4 on endothelial dysfunction, which is presented in Chapter 9), grade 6 (261 boys, 266 girls) and grade 10 (123 boys, 146 girls).

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<sup>1</sup> The intervention is not investigated in the current thesis but rather is mentioned as it forms an important design feature of the overall LOOK study and a potentially confounding factor in the current research that needs to be accounted for.

	2005 (Grade 2)												2006 (Grade 3)												2009 (Grade 6)												2013 (Grade 10)											
Months	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
<b>Physical Activity</b>																																																
Pedometers																																																
Accelerometers																																																
<b>Fitness</b>																																																
<b>Blood Collection</b>																																																
<b>Percent Body Fat</b>																																																
<b>Cardiovascular measures</b>																																																
Arterial Stiffness & BP*																																																
Endothelial Function																																																
<b>Psychology Surveys</b>																																																

\* BP = Blood Pressure

Figure 8. Timeline of measures used in the current thesis.



**Attrition.** During the duration of the Childhood Phase of LOOK, four participating schools closed due to government restructure. As a result, attrition in the current study was mostly due to relocation of students out of area or to a non-participating school (70%), followed by child absences or technical difficulties on the day of testing (12%), and the remaining 8% withdrew from the LOOK study. Of concern would be children leaving the study because of worries relating to their experiences of stress or depression, or due to poor physical health, and specifically factors relating to the metabolic and cardiac health under investigation in the current thesis.

The effect of attrition was investigated by comparing baseline assessments of children remaining in the study compared to those who left the study (or were absent on the day of testing) at each follow-up. Table 1 shows the proportion of children lost to attrition at each year of measurement, and compares participants with non-participants across candidate variables. Compared to children remaining in the study, non-participants (e.g. children who withdrew and those who were absent from testing) were significantly fatter at grade 6 ( $p = .044$ ); had greater MAP at grade 10 ( $p = .025$ ); were more stressed at grade 6 ( $p = .002$ ) and grade 10 ( $p = .011$ ); and reported significantly more depressive symptoms at grade 6 ( $p = .013$ ). Further investigation into the effects of attrition for boys and girls separately, revealed that these trends were more predominant among girls, with the exception of depressive symptoms in grade 6. A summary of these differences for the variables found to be affected by attrition, analysed separately for boys and girls are presented in Table 2. Given these differences, the possible effects of attrition should be kept in mind when interpreting results in the empirical studies of this thesis.

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Table 1.

*Proportions of Participants and Non-Participants, and a Comparison of Their Characteristics at Two-Year and Four-Year follow-up<sup>^</sup>*

	Grade 6 (2009)		Grade 10 (2013)	
	Two-year follow-up		Four-year follow-up	
	Sample	Non-participants	Sample	Non-participants
<i>Sex (girls)</i>				
Height	69.7%	30.3%	28.7%	71.3%
Weight	69.6%	30.4%	31.7%	68.3%
BMI	69.7%	30.3%	28.7%	71.3%
<i>Psychological Measures</i>				
Psychosocial stress	61.8%	38.2%**	30.8%	69.2%*
Depression	63.9%	36.1%*	68.6%	31.4%
<i>Physical Fitness &amp; Metabolic Measures</i>				
%Body Fat	69.8%	30.2%*	33.6%	66.4%
Fitness	60.9%	39.1%	25.6%	74.4%
Physical activity	100%	0%	30.4%	69.6%
Glucose	100%	0%	30.3%	69.7%
Insulin	100%	0%	30.3%	69.7%
HOMA-IR	100%	0%	30.3%	69.7%
<i>Cardiovascular Health Measures</i>				
PWV	-	-	42.9%	57.1%
MAP	-	-	43.1%	56.9%
SBP	-	-	43.1%	56.9%
DBP	-	-	43.1%	56.9%
PP	-	-	43.1%	56.9%

<sup>^</sup>Comparisons analysed using independent sample t-test \*\* $p < .01$ ; \* $p < .05$

Table 2

*A Comparison of Participants and Non-Participants (Means and Standard Deviations in Brackets) Split by Sex for Variables Found to be Significantly Affected by Attrition*

		Participants	Non-participants	
		<i>M (SD)</i>	<i>M (SD)</i>	<i>p</i>
Psychosocial Stress	<i>Boys</i>	93.05 (21.07)	97.83 (25.40)	.051
(Grade 6)	<i>Girls</i>	96.80 (20.66)	102.29 (22.46)	.012
Psychosocial Stress	<i>Boys</i>	92.84 (21.98)	95.66 (23.24)	.261
(Grade 10)	<i>Girls</i>	94.97 (20.46)	100.88 (21.80)	.009
Depressive Symptoms	<i>Boys</i>	24.79 (4.16)	25.68 (4.40)	.048
(Grade 6)	<i>Girls</i>	24.85 (4.23)	25.89 (4.63)	.106
Percent Body Fat	<i>Boys</i>	22.6 (5.8)	22.9 (6.1)	.737
(Grade 6)	<i>Girls</i>	27.5 (6.2)	28.9 (6.7)	.053
MAP	<i>Boys</i>	77.5 (7.4)	78.6 (8.2)	.219
(Grade 10)	<i>Girls</i>	78.4 (8.0)	80.5 (8.4)	.035

### Demographic information

**Socioeconomic status.** The ABS SEIFA was used as a measure of SES (ABS, 2009). This index represents different aspects of relative socioeconomic disadvantage and/or advantage in a geographic area including economic and social resources, education and occupation as measured by the government Census. Schools participating in the LOOK study were all a part of the ACT and were relatively homogeneous in terms of SES. The average SES index of the suburbs in our study ( $M = 1085$ ,  $SD = 40$ ; range 982-1160) was higher than the average index of all towns and cities throughout Australia ( $M = 980$ ,  $SD = 84$ ; range 598-1251).

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**Racial background.** At baseline, approximately 86% of the children had one or both parents of Caucasian descent, 8% of Asian descent, 3% Australian Aboriginal or Torres Strait Islander and 1% Polynesian. No data were available on 2% of the families

**Country of origin.** From the 564 parents who provided information, 93% reported that their child was born in Australia. In terms of parent's birth place, 77% of biological mothers and 69.5% of biological fathers were born in Australia. The majority of parents were Anglo Saxon (73% of mothers and 73% of fathers), followed by other ethnic groups not listed (13% of mothers and 13% of fathers), South East Asian (4.8% of mothers and 5% of fathers), and Aboriginal and/or Torres Strait Islander (2.3% of mothers and 2.3% of fathers). The remaining parents were born in countries of the Indian Subcontinent, the South Pacific or the Middle East.

**Marital status of parents.** The majority of the fathers were aged between 40-49 years, and half of the mothers were aged between 30-39 years. Of these parents 72% were married and 10% were in a defacto relationship. A further 12% were divorced or separated and approximately 4% were single or never married.

**Employment.** In most households, fathers worked full-time (87%) more often than mothers (32%), the majority of whom were employed in a part-time capacity (44%). A much larger proportion of women (20%) reported home duties as their employment compared to men (2%).

**Parent education.** Among fathers, 43% reported having a tertiary qualification, 20% a TAFE or trade qualification and a further 20% had completed year 11 or 12 as their highest level of education. Mothers' level of education was similar to fathers with 33% completing a tertiary qualification, 23.5% a TAFE or trade qualification and 24%

completing grade 11 or 12. A larger proportion of mothers were only educated up to grade 10 or below (14%) compared to fathers (6%).

## **Measures**

The measures used to assess candidate variable in the current research are described in detail in the following sections. Therefore, the methods reported in the succeeding empirical chapters present only a brief description of these same methods to minimise any unnecessary repetition. The following section begins with a discussion and critique of stress measurement, and outlines the processes undertaken in the selection of an appropriate stress measurement tool.

**Psychosocial stress.** The measurement of stress has been plagued with conceptual difficulties, which largely stem from the “fuzziness” of the construct, as well as the considerable overlap with other similar constructs (e.g. depression, anxiety). As introduced in Chapter 2, the current research limits its investigations of stress to those of a psychosocial nature, and utilises a “process” definition of stress (Lazarus, 1990; Lazarus & Folkman, 1984) involving inputs (e.g. the stimuli or stressors themselves), mediating activities or psychological processes (e.g. appraisals and coping), and outputs (e.g. the stress response). This definition, based in contemporary stress theory, provided a framework that could inform the selection of an appropriate assessment tool that may best capture this process. In addition to being driven by stress theory, further consideration in selecting an appropriate measurement tool was based on; (1) evidence from the empirical literature, (2) the availability of appropriate stress measures, (3) developmental theory, and (4) the logistical and economic capabilities and restrictions imposed by having a large cohort and longitudinal design. As a result, a self-report measure of stress was selected, which was capable of capturing the key inputs (e.g. life events and daily encounters) and the mediating appraisal process generated by exposure to stressors. It is acknowledged that the selection of a self-

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report tool precludes any direct assessment of the output aspect of this process - the stress response. An absence of a direct assessment of stress response (e.g. biological markers), may be considered a limitation of the current research, and this is addressed later in this chapter. We begin now with a brief discussion on stress measurement in children.

***Measurement of stress in children.*** Contemporary research has provided evidence of the nature, type and context in which children may experience stress, with evidence indicating children experience both life event stress (Kraag et al., 2006) and chronic daily hassles (Jewett, 1997). Informed by available theory and evidence, and taking a child development perspective, the principle contexts in which stressors manifest during the primary school years appear to be clustered into themes, which can be identified as the parental/family environment (Kelly & Emery, 2003), the peer group environment (Heubeck & O'Sullivan, 1998) and the school environment (Lee & Cohen, 2008). Any measure of childhood psychosocial stress, should therefore be informed by, and adequately account for these themes.

Among a large body of research, stress in children has measured and investigated both the magnitude of stressor exposure in childhood and the perceived impact of such stressors on a child's health and wellbeing (Attar, Guerra, & Tolan, 1994; Cheng, Lau, & Chan, 2014; Compas, 1987; Compas, Malcarne, & Fondacaro, 1988; Dise-Lewis, 1988; Kushner, 2014; Pechtel & Pizzagalli, 2011; Tennant, 2002; Walker, Smith, Garber, & Claar, 2007). However, the measurement of stress in this field has been restricted by a number of factors, most notably, a lack of suitable measurement instruments. While scales to measure stress in children are available, many have been developed for the assessment of stress within specific populations, designed to capture very specific stressor experiences that may not be relevant to broader populations, therefore limiting their applicability to "normal" populations. This has included scales for children with obsessive compulsive disorder and Tourette

syndrome (Findley et al., 2003), asthma (Röder, Boekaerts, & Kroonenberg, 2002), mood and adjustment disorders (Williamson et al., 2003), and parental history of depression (Wagner, Abela, & Brozina, 2006). At the outset of the LOOK Study, few, if any scales had been developed specifically for apparently healthy children from a normal population. Moreover, of the few existing stress scales, many had been criticised for not being theory driven, while other older inventories were based on lists of items, which were likely outdated in terms of contemporary childhood stressor experience (e.g., Dize-Lewis, 1988). Additionally, the need for interviewer involvement in the administration of some instruments (e.g., Williamson et al., 2003), limited the convenience of those measures in large sample epidemiological research, particularly where extensive and multifaceted data collection is required.

What was apparent on reviewing the stress measurement literature was the need for a stress inventory that was appropriate for use in apparently healthy children, which was based in theory, and that appropriately addressed stressor experiences relevant to contemporary times. The Children's Stress Questionnaire (CSQ) was therefore developed and utilised in the LOOK Study, and therefore the current study. A detailed description of the development of this scale can be seen in Byrne et al. (2011).

***Children's Stress Questionnaire.*** The Children's Stress Questionnaire (CSQ; Byrne et al., 2011) is a 50-item self-report questionnaire that was developed specifically for the LOOK study to assess the occurrence and impact of a range of stressor experiences relevant to children. The CSQ assesses stressors across five domains; (1) daily hassles, (2) relationship with parents, (3) experience of transition and change, (4) problems in the school environment, and (5) family dissonance and upheaval, and items from these domains are summed together to form the CSQ Full Scale. Children are required to report their stressor experience for the last 12-months on a 5-point likert scale, ranging from 1 = *"This didn't happen to me"*, 2 = *"It happened to me but it didn't matter"*, 3 = *"It made me a bit upset"*, 4 = *"It made me quite upset"*; 5

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= "*It made me very upset*". While the literature on life events has expressed general concern regarding the 12-month timeframe for recall, Turner and Wheaton (1995) consider this to be the standard in studies of the kind reported here and appropriate in long-term longitudinal studies. This item-response scale resulted in the development of two, likely related, scales, these being a dichotomous exposure scale coded 1 = "*It didn't happen to me*" and 2 = *all other response options*, which indicates the occurrence or frequency of a stressor; and a dimensional scale based on the level of impact of the stressor (coded 2 to 5), including no-exposure (coded 1), which resulted in an item scale ranging from 1 to 5 with higher scores indicating greater impact of the stressor.

It could be argued that the usefulness of the CSQ is limited by the conjunction of measures of stressor exposure and stressor impact in the same instrument (Turner & Wheaton, 1995). For this reason, preliminary analyses in the current thesis were undertaken to investigate relationships with candidate response variables, using measures of both stressor exposure only, and self-rated stressor impact. There was remarkably little difference between results using these two metrics of stressor experience when investigating candidate relationships, indicating that the level of confounding was weak at most. Moreover, similar findings by the authors investigating the scale effects on outcomes led to similar findings, which led them to conclude that the issue of confounding is not a cause for concern in the general use of the CSQ as a research instrument (Byrne et al., 2011). Therefore, the studies undertaken in the current thesis will report on stressor experience only, as it provides a richer and more detailed description of the individual child's experience, whilst also capturing the context within which reported stressors occur. This approach has also been used successfully in other scales of stressor experience (Byrne et al., 2007) and the resulting metric has been a significant predictor of distress.



*Psychometric properties of the Children's Stress Questionnaire.* The work undertaken in the current thesis investigates stress based on the CSQ Full Scale scores rather than at the individual domain level. This approach was chosen as preliminary investigations based on analyses using domain subscales were not remarkably different from those using the CSQ Full scale and therefore it was determined that, to improve parsimony in reporting outcomes, investigations would be based on CSQ Full Scale scores only. Further supporting this decision was the superior reliability of the full scale compared to subscales.

Based on data from the LOOK cohort, the CSQ appears to have both internal consistency and test-and-retest reliability and validity, as a measure of stressor experience in children. Full scale internal reliability (Cronbach's alpha) was high at baseline and across all follow-up periods (all > .9). Subscale reliability for each year of measurement is summarised in Table 3 and ranged from .902 in grade two to .927 in grade 6.

Table 3

*Reliability Scores for CSQ Full Scale*

	Internal reliability ( $\alpha$ ) values			
	2005	2006	2009	2013
Stress Full Scale	.902	.926	.927	.911

***Methodological considerations and limitations of self-reported stressor inventories.*** Although self-report measures of stress are widely used in large-scale studies like LOOK, they can be criticised for several reasons. Here a critical discussion on self-report assessments for measuring stress is presented, and it is acknowledged up front that all currently available measures of stress (including more objective

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biological measures) may be considered limited in some way. However, through this critical discussion the defensible use of such a method is demonstrated given the recognition in the literature of the important role subjective mediating processes (e.g. appraisal of stress and coping) may play in the development of disease, including CVD (Fontana, Kerns, Rosenberg, & Colonese, 1989; Kristensen, 1996; Miller et al., 2011; Nielsen et al., 2006; Siegrist, Peter, Junge, Cremer, & Seidel, 1990).

Strategies for measuring stress have varied, but historically, self-report measures have focused on capturing a single element of the stress process, such as the input (stimuli/stressor) or output (stress reaction/response). For example, life events inventories, in the tradition originally outlined by of Holmes and Rahe (1967) dominated the literature on stress and health for several decades. This approach focuses on objectively measurable changes and occurrences within the individual's environment (the input or stimulus). This approach to measurement is limited as it only captures part of the stress process and fails to acknowledge the contribution made by the individual (e.g. the individual's appraisal of the stressor and their ability to cope), and therefore ignores individual differences. Moreover, it has been suggested that life events occur relatively infrequently and that much stress is connected with chronic or recurrent conditions that occur day to day, and that it is this type of stress that may be important in disease development (Cohen, Janicki-Deverts, & Miller, 2007; McGonagle & Kessler, 1990; Vitaliano et al., 2002).

Similarly, assessments that solely capture the reaction or output aspect of stress (e.g. the stress response) are also limited, in that they pay no attention to the contents or sources of the stress reaction, or the mediating processes (e.g. individual appraisals). In addition, all output measures of stress are likely confounded to some degree, by individual appraisals and coping, because the stress response is likely to be greater among individuals with lower levels of coping and among those who more often appraise events as stressful (Lazarus, 1990). While more direct and objective measures of the stress response are available, including the assessment of adrenal

medullary catecholamines and adrenocortical steroids (and these are clearly an important aspect with regards to the hypotheses under investigation in the current work), these methods also have their limitations, which are discussed in more detail in the following section of this chapter.

Given the limitations outlined here, the method employed in the current study sought to capture stress as a “process”, which was done with varying degrees of success. This approach to assessment was congruent with the longitudinal design of the current study and a major strength of our assessment was the ability to repeatedly assess appraisals of stress as the person-environment relationship changed over time (e.g. over eight years) and across different encounters (e.g. across the transition from primary school to high school). While a process framework informed stress measurement in the current research, it is acknowledged that limitations also exist when using this approach. For example, potentially confounding influences of genetics and other individual vulnerabilities that contribute to risk may influence appraisal processes. However, the current author argues that it is these inherent genetic and individual vulnerabilities that are of interest, as they likely play a central role in determining how stress comes to affect health and disease (de Kloet, Joels, & Holsboer, 2005). Even so, this may be seen as a limitation to the current method of assessing stress, and therefore it is acknowledged that our process framework of stress is, to some degree, more of an ideal rather than a reality, due to the compromises required to undertake research in the ‘real world’. As with all studies, some further limitations were evident in the current methods of assessing stress. These limitations are acknowledged and the author’s attempts to limit the impact of such factors are presented.

Firstly, it has been argued that measures involving checklists, similar to the CSQ, are restricted by the finite number of stressors that are presented in the questionnaire, and therefore may not capture important stressful situations if not listed. In terms of the CSQ, attempts were made to minimise this limitation during the

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development of the questionnaire by gaining input from an aged-matched group of children during the pilot testing phase of the CSQ. This process helped to provide an authentic and contemporary representation of events and stressors that were of relevance to children (see Byrne et al., 2011 for a detailed discussion).

Secondly, time frame boundaries, such as the one year recall used in the current study can prevent the reporting of significant stressful events and experiences if they fall outside this time frame. Fortunately, the longitudinal nature of the current study increased the opportunity to capture stressful events and situations occurring throughout childhood and adolescence. However, as testing did not occur every year, it is still possible that significant stressors occurring outside the testing timeframe were not captured.

Thirdly, over and under reporting of stressors can arise due to the child's miscomprehension of the items or due to personality factors. The former was addressed in the current research by having each item read out to the children with opportunities for further explanation from the researcher afforded, as required for each item. In addition, the researcher frequently provided context for stressors relevant to the child's experience. Comprehension of the response options was also aided by providing visual representations of the response scale.

Finally, self-report measures of stress among children are susceptible to recall bias and this can result in failure to remember and therefore under-report stress; or alternatively, over-report stress due to children recalling and attributing distant events inaccurately as occurring in a more proximal timeframe. This may result in children incorrectly dating distant events in a more recent time and therefore, over-reporting stress (Eisen & Goodman, 1998; Salmon, 2001). To limit this recall bias, anchors of time were provided for children when administering the CSQ, including noteworthy events such as Christmas, birthdays and school holidays.

Careful considerations of the methodological limitations during questionnaire development and administration, such as those presented here, increase the likelihood

of developing and collecting a valid and reliable measure of stress, and this appears to be reflected in the psychometric properties of the CSQ described earlier. However, it is acknowledged that self-report questionnaires are but one method available for assessing stress, and that such methods fail to capture the physiological reaction to stress, which likely mediates any relationship between stress and health (Black & Garbutt, 2002; Grippo & Johnson, 2009; Huffman, Celano, Beach, Motiwala, & Januzzi, 2013; Rozanski et al., 1999; Schwartz et al., 2003). A more direct and objective physiological assessment of the stress response was considered in the current research, however, on reviewing the empirical evidence to support the inclusion of an additional measure, and on considering the economic and logistical restriction imposed by the LOOK Study design, the decision was made not to include a physiological measure of stress. To provide support for this decision, a critical review of the physiological measures considered for inclusion in the current research is presented here.

***Measuring the stress response: A biological perspective.*** The prevailing approach of assessing the physiological stress response has been to focus on two primary outputs of the neuroendocrine stress system, including (1) adrenal medullary catecholamines, resulting from activation of the SAM system, and (2) adrenocortical steroids, resulting from activation of the HPA-axis. While there is a growing number of neuroendocrine changes that are thought to be influenced by stress, including the secretion of sex hormones, growth hormones, thyroid hormones, prolactin and insulin, the most commonly studied include corticosteroids (particularly cortisol) and their metabolites, and the catecholamines, adrenalin and noradrenalin.

*Catecholamines.* Assessment of sympathetic arousal and catecholamine secretion has played a central role in stress research. Generally, it is thought that the SAM system is activated once an individual perceives an event or situation as stressful, which results in the release of adrenalin and noradrenalin due to sympathetic nervous

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stimulation of the adrenal medulla. In the modern day, elevated catecholamine levels are more often thought to be caused by social or psychological threats rather than physical threat. Therefore, the assessment of catecholamines is thought to capture the state of sympathetic nervous system function.

Catecholamines can be measured in blood or urine. Adrenalin and noradrenalin concentrations assessed in blood change rapidly in response to stressor exposure, and therefore more readily reflect short-term and acute stress responses. Because urinary sampling can be collected over longer time periods (typically collected at regular intervals for 24 hours, several days or weeks), urinary catecholamines are useful for examining long-term stress. Acute psychological stress in healthy adults has been shown to elicit an elevation of adrenalin levels (Bassett, Marshall, & Spillane, 1987; Gerra et al., 2001), whereas chronically stressed individuals have presented with low adrenalin responsivity, which is thought to be due to habituation to constant adrenalin induced signalling (Hoagland, Callaway, Elmadjian, & Pincus, 1950). It is this chronic activation that is thought to contribute to the development of atherosclerosis and that predispose individuals to myocardial infarction (Kumari et al., 2003; Wang et al., 2007).

A number of methodological difficulties exist when using catecholamines as a proxy measure of the biological response to psychosocial stress, the most pertinent being that adrenalin responds to any experience that causes mental arousal or requires effort, regardless of whether it is perceived as a stressful or not. In addition, noradrenalin is more readily affected by physical activity and demands, rather than mental stress (Lundberg, 2011). This responsiveness of the SAM system highlights the difficulty in clearly delineating what the SAM system is actually responding to – be that a subjective appraisal of a stressor or resulting from physical effort.

*Cortisol.* Cortisol is a glucocorticoid, produced and secreted by the adrenal cortex and is a commonly used biomarker of stress (Kudielka & Wust, 2010). Accumulating evidence suggests cortisol is the main hormone responsible for stress responses (Kudielka & Wust, 2010), with additive effects exerted from corticotrophin-

releasing hormone and adrenocorticotropin. Therefore, cortisol is thought to capture the status of HPA-axis functioning, which plays an important role in converting subjective psychosocial experience into physiological changes relevant to health and disease (Steckler, Kalin, & Reul, 2005).

Cortisol can be measured from blood, urine, saliva, and now hair, with each providing a slightly different temporal window on hormonal activity. Levels of cortisol in blood and saliva are thought to reflect HPA-axis activity in the past 10-60 minutes, while urinary and hair cortisol is thought to provide a measure of HPA-axis activity over a broader timeframe. In healthy individuals, cortisol exhibits a diurnal rhythm characterised by low levels at night, a rise in the hours before waking, a sharp increase 30 to 45 minutes after waking, and a subsequent decline over the rest of the day. This pattern is an important consideration in the timing of measurement and one that can be potentially confounding.

The means of reporting cortisol has varied between studies and this may explain the conflicting findings in the literature. Some studies have assessed total or 'average' cortisol levels, while others have focussed on assessing the marked diurnal rhythm in the release of cortisol. In studies assessing elements of the diurnal cortisol rhythm, further differences exist in how cortisol is captured. Methods have included assessment of the cortisol awakening response (CAR; the size of post-awakening surge in cortisol that occurs 30-45 minutes after waking), changes in cortisol levels from morning to evening (diurnal cortisol slope), waking cortisol, bedtime cortisol and cortisol reactivity to stressors (both momentary and daily stressors). With no consistent method or agreed upon "gold standard" of measuring cortisol, what has resulted is a series of assessments that capture a different time shot of cortisol activity. As a result, there is a large degree of heterogeneity in reported findings, which makes it difficult to accurately and confidently interpret these outcomes.

For example, among studies investigating the effect of chronic psychosocial stress or childhood adversity, children have displayed both blunted (MacMillan et al.,

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2009; Ouellet-Morin et al., 2011) and elevated (Smeekens, Marianne Riksen-Walraven, & van Bakel, 2007) cortisol response to acute stress when compared to control children. In other studies, children have displayed a blunted cortisol awakening response (van der Vegt, van der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009), shallow decline in change of cortisol from morning to evening (Cicchetti, Rogosch, Gunnar, & Toth, 2010; Dozier et al., 2006; Gunnar & Vazquez, 2001), greater average daytime cortisol (using the area under the curve method; Saridjan et al., 2010; Suglia, Staudenmayer, Cohen, & Wright, 2010), and both blunted (MacMillan et al., 2009; Ouellet-Morin et al., 2011) and elevated (Smeekens et al., 2007) cortisol response to acute stress. Divergent findings in the literature, whereby some children display an increase in cortisol on exposure to stressors, while other display decreases, along with interpretative issues that arise with non-responders, have meant there is still debate over the exact interpretations of these proxy measures in explaining elements of HPA-axis functioning. In addition, and similar to the SAM system, the HPA-axis is sensitive to a variety of events that are not just psychosocial in nature, including minor concurrent physical stressors, illnesses, physical activity, daily life activities, intake of food and beverage, and time of the day tested, which may make it less useful as a specific indicator of stress.

Therefore, without precise and reliable methods of measuring stress hormones, it was questioned whether adding yet another measure to the LOOK study and placing further burden on participants was a worthwhile pursuit. Logistically, given the difficulty of incorporating a biological marker of children's stress in this large-scale multidisciplinary study, which would have required repeat sampling of the same child at each measurement period for a reliable and valid assessment to be collected, in a study where children were already burdened by numerous measurements across a number of disciplines, it was determined that such an assessment was not feasible. Although blood samples were collected as part of LOOK, and measures of catecholamines and cortisol could have been obtained from these samples, recent



evidence clearly highlights the need for multiple blood collections to obtain a reliable assessment of cortisol and catecholamine concentrations and reduce the potential for confounding influence (Cohen et al., 1995). Again, this was unfeasible in the current study due to time and economic constraints. Given that other physiological measures specific to the cardiovascular system, such as blood pressure, were already collected as part of LOOK assessments, and could therefore provide some information about the biological responsiveness to perceived psychosocial stress with no further burden, this decision to exclude a more direct physiological measure of stress appeared justified.

### **Depression**

***Children's Depression Inventory.*** The Children's Depression Inventory (CDI) is a 27-item self-report questionnaire, which assesses the presence and severity of specific depressive symptoms in children (Kovacs, 1982, 1992). In the current research, all children were given a modified (19 item) form of the CDI, with a forced-choice (symptom present or absent) response format. The original CDI has demonstrated validity and reliability (Kovacs, 1992) in assessing clinical and sub-clinical depression in preadolescent groups. Scrutiny of the overall psychological protocol by two independent ethics committees led to a non-negotiable requirement that for the present research, all items indicating conspicuous clinical depression (e.g. items pertaining to persistent crying, suicidal ideation, and worthlessness) were removed from the CDI. This was due to the belief that the inclusion of such items may have inadvertently induced an unpleasant and potentially lasting negative mood state in a very largely psychologically normal sample, which was deliberately unselected for either mental or physical dysfunction. This requirement also extended to the inclusion of response options, which therefore limited the response scale to two (symptom absent or symptom present). Because these modifications meant that the fifth subscale, negative self-esteem, was left with an unviable item content, this subscale was not included in our final modified version of the CDI. The remaining items in our

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modified version reflect a range of depressive symptoms relevant to a diagnosis of MDD, including both affective (e.g. negative mood and anhedonia) and somatic (e.g. lack of energy, aches and pains) symptoms. These remaining items could therefore be considered to reflect depressed mood but not clinical depression, with the modified scale resulting in a full scale score of depressive symptoms that ranged from 19 to 38, with higher scores indicating a greater number of depressive symptoms.

Although not a clinical scale, the authors of the CDI provide recommendations for clinically relevant scores that are likely indicative that the child is experiencing a level of depressive symptoms that could be considered clinically significant. A score of 20 or above on the original 27 item CDI questionnaire, with items measured on a 3-point scale is suggestive that the child may be experiencing depressive symptoms of a clinically level. Although a clinically significant cut-off point is difficult to determine in the current modified version of the CDI, where item response options were restricted to symptom absent or symptom present, using the same ratio as the original CDI, a cut-off point of 26 would apply in the current research, with scores equal to or higher than this indicating that the child is experiencing a level of symptoms that could be severe enough to be meet a clinical diagnosis for a mood disorder. Of course the use of this cut-off should be treated with caution and does not translate to a clinical measure per se, but it may provide descriptively useful and therefore should not absolutely preclude the use of the cut-off in characterising the sample.

Factor analysis and confirmatory factor analysis of the modified CDI were conducted to ensure reliability and validity of the current measure. Multiple indicators of goodness of fit demonstrated factor stability in line with the original factor structure of the CDI (RMSEA = 0.06; NNFI = 0.92; CFI = 0.93; Standardised RMR = 0.06; AGFI = 0.85) and demonstrated good internal reliability (Cronbach's Alpha range = 0.77- 0.86 across measurement years; see Table 4). Additionally, the modified CDI correlated significantly and positively with other LOOK assessments of psychopathology, including concurrently and prospectively with stress (all  $r > .6$ ), and prospectively with

negative affect ( $r = .3$ ) and anxiety ( $r = .4$ ) assessed two years later, providing further evidence of its convergent validity. To further assess the suitability of the modified CDI, the full original version of the CDI was also administered in grade 10. This was with exception of the item pertaining to suicidal ideation. Associations between the full scale of the original CDI version and our modified version at grade 10 were strong and significant ( $r = 0.9$ ). In addition, analyses were conducted on the effects of depression (using the original non-modified version of the CDI) with the candidate response variables of the current study (e.g. physical activity and fitness) during grade 10. These analyses revealed remarkably little difference in outcomes when using the non-modified CDI compared to using the modified version, suggesting that our modified CDI could be used as a valid and reliable measure of depressed mood in children and adolescents.

Table 4.

*Internal Reliability (Cronbach's Alpha) for CDI Full Scale at Each Year of Measurement*

	Internal reliability ( $\alpha$ ) values			
	2005	2006	2009	2013
CDI Full Scale	.833	.858	.769	.833

### **Physical activity**

**Pedometers.** Physical activity was measured using New Lifestyle pedometers (Lee's Summit, MO, USA), which record the number of steps taken per day. The validity of New Lifestyle pedometers detection mechanism has been previously demonstrated in children (Beets, Patton, & Edwards, 2005). Children wore pedometers on their hip in line with their left patella for seven consecutive days. Measurements

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taken on the first day were excluded to account for the novelty of wearing a pedometer and any subsequent artificially increased physical activity, and because they did not form a full day (24-hours).

A physical activity index was calculated using best linear unbiased predictor (BLUPS; Robinson, 1991) or “shrunken mean”. The BLUPS index is calculated for a given individual by providing a weighted combination of the population mean and the mean for that individual. The BLUPS method was chosen for its desirable statistical properties and meant that we did not have to rely on the simple mean of steps taken per day, as the distribution of the physical activity index has a known mean and variance. Using the BLUPS statistic to calculate the physical activity index also allows us to adjust for possible differences in activity due to day of the week and to maximise the use of all data “including incomplete sets of individual data, and data from subjects who did not undertake all three years of measurement. This method also provides enhanced predictive ability of an individual’s activity level compared with conventional methods.

**Accelerometers.** In the current research, accelerometers (Actigraph GT1M, Pensacola, FL, USA) were introduced in addition to pedometer assessments, to assess intensity in addition to volume of physical activity. With accelerometer data in the current study being confined to grade 6 and grade 10, and pedometers employed for the entirety of the study. Accelerometers were positioned on a belt around the waist in line with the right knee. The first day of data were discarded to minimise any potential reactivity. Daily accelerometer counts were used as a measure of volume of physical activity and cut off points for light physical activity (LPA) were defined as 101 – 2,296 counts per minute and moderate to vigorous physical activity (MVPA) classified as greater than 2,297 counts per minute based on published recommendations (Evenson, Catellier, Gill, Ondrak, & McMurray, 2008; Trost, Loprinzi, Moore, & Pfeiffer, 2011). An epoch length of 60 seconds was used and days of accelerometer data were included if

there were 10 or more hours of activity. In the absence of any established non-wear time criteria for children in the extant literature (Cain, Sallis, Conway, Van Dyck, & Calhoun, 2013), the current study deemed an hour assessment to be invalid if there were more than 30 zero counts in a row (30 minutes of non-wear time). Accelerometer data were collected on both weekdays and weekends, and at least three days data comprising at least two weekdays and one weekend day, were required for inclusion in the analyses. Actigraph accelerometers have been validated for use in both children and adolescents (Mattocks et al., 2007). Accelerometer data were analysed without the low frequency extension (LFE) function using Meterplus software, Version 4.2 (San Diego State University, USA).

**Cardiorespiratory fitness.** The 20m multistage shuttle test (MSST) was used as a measure of cardio-respiratory fitness (CRF) and has been well-established as a reliable field-test among children (Tomkinson, Leger, Olds, & Cazorla, 2003). The MSST requires children to run between two lines 20m apart in time with a recorded beep. The time between the recorded beep decreases at each level of the test. The MSST requires maximal effort and therefore performance may be influenced by the individual's motivation to do well. Even so, the MSST is a practical and commonly used method to assess CRF in large samples.

**Percent body fat.** Body composition was measured using dual energy x-ray absorptiometry (DXA, Hologic Discovery QDR Series, Hologic Inc., Bedford, MA, USA) and QDR Hologic Software Version 12.4:7 was used to generate fat mass from which percent body fat was calculated.

**Insulin resistance.** Blood samples were collected to measure glucose and insulin levels. Fasting blood samples (serum and whole blood) were taken from the forearm of overnight fasting children (water only) between 8.30 and 9.30am at the

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schools in late 2005, 2009 and 2013. Serum samples were mixed and allowed to clot for up to 30 minutes prior to centrifugation. Samples were centrifuged for 10 minutes at 2850 rpm (Spintron GT-25P, Spintron Pty Ltd, Australia) and either immediately frozen in ice and stored at -80°C for subsequent analysis, carried out at the Canberra Hospital. Care was taken to maximise consistency of laboratory handling of samples. Procedures were carried out according to instrument Manufacturers' standards and biochemical analysis was performed within acceptable limits of internal quality control. Insulin concentration (INS) was measured using microparticle enzyme immunoassay on the AXSYM (Abbott laboratories, IL 60064 USA).

The insulin resistance index by homeostasis model assessment (HOMA-IR; Katz et al., 2000; Matthews et al., 1985) was calculated from fasting plasma glucose and insulin levels with the following formula:

$$HOMA-IR = [fasting\ insulin\ (mU/L) \times fasting\ glucose\ (mmol/L)]/22.5$$

While insulin sensitivity may be a more appropriate term than insulin resistance in asymptomatic children, HOMA-IR is validated for use with children (Gungor, Saad, Janosky, & Arslanian, 2004; Huang, Johnson, & Goran, 2002), and is a method of assessment that is consistent with recent publications in children (Jeffery et al., 2007; Metcalf, Voss, Hosking, Jeffery, & Wilkin, 2008; Srinivasan, Myers, & Berenson, 2006).

**Arterial stiffness.** Increased arterial stiffness is a marker of cardiovascular aging. Carotid-femoral pulse wave velocity (PWV), a measure of arterial stiffness, is considered to be the gold standard in arterial stiffness measurement (Laurent et al., 2006; Van Bortel et al., 2012).

The theoretical underpinnings of PWV as a measure of arterial stiffness are based on the Moens-Korteweg equation;

$$PWV^2 = E \cdot h / 2\rho r;$$

Whereby;

E is the slope of the stress-strain relationship for a given vessel,

Young's modulus;

$\rho$  is the density of fluid; and

$h/2r$  is the wall thickness/diameter.

In the current study, PWV was assessed non-invasively using the SphygmoCor system (AtCor Medical, Sydney, Australia). Electrocardiogram-gated carotid and femoral waveforms were recorded using applanation tonometry. Carotid-femoral path length was measured as the difference between the surface distances joining (1) the suprasternal notch, the umbilicus and the femoral pulse and (2) the suprasternal notch and the carotid pulse. Carotid-femoral transit time was estimated in 8 to 10 sequential femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. Pulse wave velocity was calculated as the carotid-femoral path length divided by the carotid-femoral transit time, whereby higher PWV is indicative of greater arterial stiffness.

Accurate assessments of PWV are dependent on accurate measurement of the distance between recording sites; therefore, care was taken during this process. Moreover, because PWV is also determined by distending blood pressure, it is important to adjust for the effects of mean blood pressure before estimating the independent influence of arterial stiffness on outcomes of interest. In the current research, mean arterial pressure (MAP) was obtained from the pressure waveform during the assessment of carotid-femoral PWV. Therefore, adjustments for MAP were made in all analyses involving PWV.

**Blood pressure.** Supine brachial blood pressure (BP) was determined using an automated oscillometric Omron 7051T. The average of two measurements made at 1-minute intervals was recorded. Blood pressure measurements were taken in a quiet room, where children rested in the supine position for five minutes prior to measurement.

**Endothelial function.** Endothelial function was assessed non-invasively using the EndoPAT 2000 (Itamar). The EndoPAT device captures a beat to beat plethysmographic recording of the finger arterial pulse wave amplitude with pneumatic probes. A peripheral arterial tonometry (PAT) probe is attached to the index finger of each hand, one forming the test finger and the other the control. The EndoPAT examination involves three phases: (1) the baseline phase, which is recorded for 5 minutes, (2) the occlusion phase, where a blood pressure cuff is inflated to suprasystolic pressure for 5 minutes on the test arm, and (3) the reactive hyperaemia phase, which occurs after the cuff is released and the signal is recorded for 5 minutes. In a healthy individual, pulse amplitude will increase rapidly after cuff deflation, allowing increase blood flow and therefore the delivery of oxygen and removal of metabolic products. This is known as reactive hyperaemia, which is thought to be a vital response after a period of ischemia. A low response post cuff deflation is thought to indicate endothelial dysfunction.

The magnitude of flow-mediated hyperaemia is calculated as the ratio between post obstructive and baseline pulse wave amplitude, corrected to systemic changes measured in the contralateral, non-obstructed arm. An example of an EndoPAT reading from an adolescent subject is presented in Figure 9.



In the current study, the algorithm proposed by the manufacturer was used to calculate the reactive hyperaemia index (RHI), based on the equation:

$$RHI = [(a/b)/(c/d)] \times \text{baseline correction factor}$$

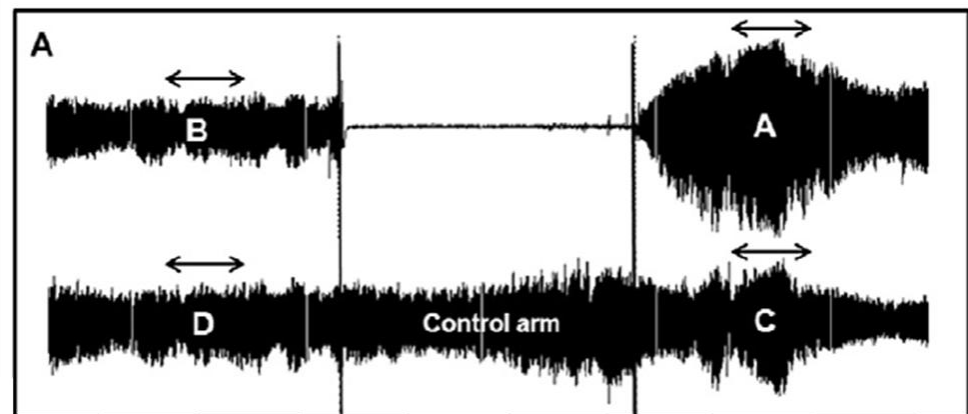
Whereby;

a: Mean PAT amplitude between 90 s–150 s post occlusion of the occluded arm

b: Mean PAT amplitude from the baseline period of the occluded arm

c: Mean PAT amplitude between 90 s–150 s post occlusion of the control arm

d: Mean PAT amplitude from the baseline period of the control arm



*Adapted from Bruyndonckx et al. (2013)*

*Figure 9.* Example of a PAT recording from an adolescent subject, showing the raw pulse wave amplitudes, where A is the Mean PAT amplitude between 90s and 150s post-occlusion of the occluded arm; B is the Mean PAT amplitude from the baseline period of the occluded arm; C is the Mean PAT amplitude between 90s and 150s post-occlusion of the control arm; and D is the Mean PAT amplitude from the baseline period of the control arm.

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EndoPAT has demonstrated reliability and validity as a measure of endothelial function among paediatric populations based on the available but scant literature (Muller et al., 2013; Selamet Tierney et al., 2009). EndoPAT measures have also been used in accurately identifying the early stages of atherosclerosis (Bonetti et al., 2004).

### **Covariate Measures**

**Pubertal development.** The self-report Tanner stages of pubic hair, breast development, and date of menarche were employed (Tanner, 1962) using diagrams based on those previously described (Duke, Litt, & Gross, 1980). In grade 2 and grade 4, the self-assessment took place at home with guidance from parents and in grade 6 the self-assessment was completed at the Canberra Hospital under the supervision of an experienced teacher. Assessment of pubertal maturation allowed for adjustment based on biological maturation rather than age.

Pubertal maturation is thought to be a predictor of the reactive hyperaemia (Radtke et al., 2012), and increases in EndoPAT assessed reactive hyperaemia with pubertal advancement have been demonstrated, which is thought to be related to an increase in sex hormones (Bhangoo, Sinha, Rosenbaum, Shelov, & Ten, 2011). The effects of pubertal maturation on measures of insulin sensitivity (Diabetes Control and Complications Trial Research Group, 1994), adiposity (Garnett et al., 2004) and mental health factors (Whittle et al., 2012) have also been demonstrated. With this knowledge, pubertal maturation was assessed in the current thesis to allow for the adjustment of this potentially confounding variable in succeeding studies.

**Height and weight.** Height and weight measurements were collected at the school. Height was measured by a portable stadiometer to the nearest 0.001 m and body mass by portable electronic scales to the nearest 0.05 kg. To assist comparisons of this study's sample with other studies, body mass index was calculated

(notwithstanding the problems associated with measures of BMI in longitudinal studies of developing children; Telford et al., 2008) using the equation:

$$\text{Weight (kg)} / \text{Height (m)}^2$$

## **Ethics**

Ethics approval for studies in the current doctoral thesis was obtained from the Human Research Ethics Committee (HREC) of the Australian National University, ACT Health Department and the ACT Department of Education. Ethics approval for the entire LOOK Study was also obtained from the Ethics Committee of the Australian Sports Commission. All parents gave informed and written consent for their children to participate in the LOOK study, as well as the psychological component specifically. The children also gave written consent for the psychological component, a condition required by the HREC of the Australian National University.

## **Statistics**

The following is an overview of the general data modelling framework developed to quantify relationships between nominated response variables and candidate explanatory variables for the current study's clustered, longitudinal data. Due to the sampling design, data in the current research is multi-level, and the response variables (representing cardiovascular risk measures e.g. physical fitness, insulin resistance, arterial stiffness, and endothelial function) vary at three levels; between-school, between-child (within a school), and within-child. The same applies to the candidate explanatory variables representing psychological stress and depression. Other candidate explanatory variables, such as the measure of SES vary only at the school level.

A particular strength of the current longitudinal study is that our multi-level data allows for the segregation of inferences pertaining to regression relationships at

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different levels. We can estimate the difference in cardiovascular risk measures across schools within suburbs, which differ by one unit in SES or in the mean of any given explanatory variable (e.g. psychosocial stress or depression), and distinguish these estimates from effects of explanatory variables on cardiovascular measures for individuals. Further we can estimate effect sizes for the expected change in the response over time per unit change in any explanatory variable for a given individual.

It follows that we do not have to make the strong assumption that the between-child (cross-sectional) and within-child (longitudinal) relationships are the same, as is the case with cross-sectional studies. The within-child regression coefficient is estimated by comparing individual responses at different times assuming the given explanatory variable changes with time. For most responses there is considerable variability across individuals due to unmeasured genetic, environmental and lifestyle characteristics. These tend to persist over time and their influence is cancelled in the estimation of the within-child relationship, however, they obscure the estimation of the between-child relationships. In other words, for a given individual we are able to make inferences relating to a response by modifying the value of a given covariate. This is distinct (and possibly stronger) than inferences we can make by predicting, for a selected individual from a cohort of individuals, the response on the basis of the value of the covariate.

To distinguish these effects and to take account of the dependence structure of the data, the statistical model utilised in all but one of the empirical studies undertaken in the current Ph.D. thesis has the following form, with psychosocial stress as an example of the explanatory variable:

Cardiovascular Risk Measure (e.g. arterial stiffness) = constant + Group effect + SES effect +  $\text{Stress}_s$  + school random effect + Sex effect + Sex.Group interaction +  $\text{Stress}_c$  + child random effect + Year effect + Sex.Year effect + Group.Year effect +  $\text{Stress}_w$  + possible interactions between fixed effects + within-child random error

Whereby  $\text{Stress}_s$  denotes the vector of arterial stiffness means for each school, which varies only at the school level;  $\text{Stress}_c$  is the vector of differences between each child arterial stiffness mean and the school mean, which varies only at the child level; and  $\text{Stress}_w$  is the vector of differences between repeat observations and the relevant child arterial stiffness mean, which varies only at the observation level.  $\text{Stress}_w$  +  $\text{Stress}_c$  +  $\text{Stress}_s$  represent the totality of components of the original vector of Stress. The statistical models used in investigations undertaken separately for each sex (rather than combining data from boys and girls in the same investigation) do not include the sex effect or any sex interaction effect. As previously mentioned, the potential for any effect of the intervention used in LOOK on candidate relationships reported in this thesis were adjusted for in this model, denoted by the term Group in the above model.

After adjusting for all design variables and other key explanatory variables it was assumed that the correlation between observations within-a-child do not depend on the number of years between observations. In general, we found no empirical evidence to suggest that the default 'uniform' correlation model was inappropriate. Similar models to the one above apply when Stress is replaced by the other explanatory variable Depression. Our mean or fixed effect model can be readily extended and interpreted within this framework.

The model outlined here fits within the general framework of general linear mixed models (Galwey, 2014). Restricted maximum likelihood is used to estimate variance components and weighted least squares for estimating fixed effects. Statistical significance of effects was assessed by calculating adjusted Wald statistics.

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General model checking procedures were routinely used to identify aberrant data and to check the model assumptions. Data transformation of explanatory variables, insulin resistance and cardiorespiratory fitness were used to satisfy distributional and linearity assumptions required for validity of subsequent statistical analysis and these procedures are explained throughout the individual empirical chapters.

### **Research Hypotheses**

The aim of this thesis was to investigate the influence of two psychological factors, namely the experience of psychosocial stress and depressive symptoms, on a set of established risk factors for CVD among a cohort of apparently healthy children and following them through to adolescence. This research was developed based on developmental theory, which informs how the studies were developed and the order in which the empirical findings are presented; beginning with investigations into primordial and lifestyle factors during childhood and adolescence, and subsequently examining the potential effects of early psychological distress on more direct and prognostically significant measures of cardiovascular health during adolescence. The specific hypotheses to be tested in the current work are presented in the following sections, along with a corresponding Table (see Tables 5 to 8) that summarises the measurements utilised to assess each hypothesis and the data sample available for each year based on the measures included in that study.

**Study 1 Hypotheses (Chapter 6)**

1. Psychosocial stress and depressive symptoms in children are related to primordial risk factors for CVD, including lower levels of physical activity and fitness.
2. Children who increase in psychosocial stress and depressive symptoms during the transition from childhood to adolescence will develop a less favourable profile of primordial risk factors, including lower levels of physical activity and fitness.

Table 5.

*Measurements and Number of Observations for Study 1*

	Measurements	Girls	Boys
Grade 2 (2005)	Psychosocial stress		
	Depression	394	397
	Physical activity		
	Fitness		
Grade 6 (2009)	Psychosocial stress		
	Depression	255	265
	Physical activity		
	Fitness		
Grade 10 (2013)	Psychosocial stress		
	Depression	136	122
	Physical activity		
	Fitness		

**Study 2 Hypotheses (Chapter 7)**

3. Psychosocial stress and depressive symptoms in children are related to metabolic risk factors for CVD, including greater fatness and insulin resistance.
4. Children who increase in psychosocial stress and depressive symptoms during the transition from childhood to adolescence will develop a less favourable profile of metabolic risk factors, including greater fatness and insulin resistance.

Table 6.

*Measurements and Number of Observations for Study 2*

	Measurements	Girls	Boys
Grade 2 (2005)	Psychosocial stress		
	Depression	365	382
	%Body fat		
	HOMA-IR		
Grade 6 (2009)	Psychosocial stress		
	Depression	255	234
	%Body fat		
	HOMA-IR		
Grade 10 (2013)	Psychosocial stress		
	Depression	132	115
	%Body fat		
	HOMA-IR		



**Study 3 Hypotheses (Chapter 8)**

5. Psychosocial stress and depressive symptoms in adolescents are related to arterial health, including greater arterial stiffness and blood pressure.
6. Adolescents who increase in psychosocial stress and depressive symptoms during the transition from late-childhood to adolescence will have poorer vascular health, including greater arterial stiffness and increased blood pressure.

Table 7

*Measurements and Number of Observations for Study 3*

	Measurements	Girls	Boys
Grade 6 (2009)	Psychosocial stress		
	Depression		
	PWV	255	266
	Blood Pressure		
Grade 10 (2013)	Psychosocial stress		
	Depression		
	PWV	136	122
	Blood Pressure		

**Study 4 Hypotheses (Chapter 9);**

7. Psychosocial stress and depressive symptoms in childhood and adolescence are related to poorer vascular health during adolescence, including greater endothelial dysfunction.
8. Adolescents who increase in psychosocial stress and depressive symptoms during the transition from childhood to adolescence will have poorer vascular health in adolescence, including greater endothelial dysfunction.

Table 8

*Measurements and Number of Observations for Study 4*

	Measurements	Girls	Boys
Grade 2 (2005)	Psychosocial stress	114	94
	Depression		
Grade 3 (2006)	Psychosocial stress	114	94
	Depression		
Grade 6 (2009)	Psychosocial stress	114	94
	Depression		
Grade 10 (2013)	Psychosocial stress	114	94
	Depression		
	Endothelial Function		

*Note:* Longitudinal analyses were limited to participants who has an assessment of endothelial function in grade 10.

## Chapter Conclusions

The research presented in the current Ph.D. thesis forms part of the longitudinal LOOK Study. The research stemming from this thesis focuses on a specific few areas of the overall LOOK study, in order to investigate the influence of psychosocial stress and depressive symptoms on cardiovascular health. This investigation therefore draws data from LOOK research areas of psychology, physical activity and fitness, metabolic health and cardiovascular health. Whilst these areas are the focus of the current research, the breadth of areas assessed as part of the LOOK study enables the current author to draw inferences regarding findings resulting from the current investigations, based on a larger context of further supplementary and relevant findings arising from other areas of LOOK. This is a strength of the LOOK study, as it promotes a broader understanding and overview of the interrelated factors across disciplines, which likely contribute to a child's health and wellbeing.

Instruments utilised in the current study, along with the potential methodological limitations of these assessments, have been introduced. These considerations form an important aspect of the current work, particularly when interpreting outcomes. Similarly, it is useful to hold in mind the characteristics of participants involved in the ensuing studies when considering the findings reported. For the most part, the children in the current study are healthy community-dwelling youth, living in a city of relatively high SES compared to the rest of Australia, with ample open spaces and facilities for sport and recreation. The methods outlined in this chapter form the research design for the succeeding empirical chapters, which begins in the next chapter with Study 1.

## **CHAPTER 6**

# **PSYCHOLOGICAL DISTRESS LEADS TO REDUCED PHYSICAL ACTIVITY AND FITNESS IN CHILDREN: THE AUSTRALIAN LOOK LONGITUDINAL STUDY**

### **Publication:**

Olive, L. S., Telford, R. M., Byrne, D. G., Abhayaratna, W. P., & Telford, R. D. (2016). Psychological distress leads to reduced physical activity and fitness in children: The Australian longitudinal LOOK study. *Journal of Behavioral Medicine*, (epub ahead of print).

### **Context Statement**

This chapter presents the first of the four empirical studies undertaken in the current Ph.D. thesis. In this study, we test Hypotheses 1 and 2 to determine whether the primordial risk factors of physical inactivity and low cardiorespiratory fitness are influenced by psychosocial stress and depression. Participants are followed from childhood into adolescence over a timeframe spanning 8 years. The following study, therefore, investigates one potential behavioural pathway that may link psychological distress in youth to an increased risk of CVD development, but also provides some insight into physiological factors (i.e. cardiorespiratory fitness) that may influence the plausible biological mechanisms outlined in Chapter 4.

### **Abstract**

**Background:** Stress and depression can affect an individual's level of physical activity and fitness, which may place them at risk of developing cardiovascular disease.

**Aim:** This study investigates the longitudinal effects of stress and depression on physical activity and cardiorespiratory fitness among youth.

**Methods:** Seven-hundred and ninety-one children, initially aged eight years, from the LOOK study completed a modified version of the Children's Depression Inventory, the Children's Stress Questionnaire, and objective physical activity and cardiorespiratory fitness assessments. Follow-up assessments occurred on three occasions, every four years.

**Results:** Depressive symptoms had a direct effect (longitudinal) on the cardiorespiratory fitness of girls, with a similar trend for boys. In cross-sectional analyses, a child who identified with more symptoms of depression and stress was likely to be less fit and less physically active, which in girls extended to less moderate-to-vigorous physical activity.

**Conclusion:** Our findings, that both physical activity and fitness are impacted by depression and stress may contribute to strategies directed towards achieving enhanced physical activity and reductions in obesity.

### Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, with an estimated 17.5 million deaths each year (WHO, 2012). The role of psychological factors in the aetiology and progression of CVD has been increasingly recognised and there is now an extensive literature, including several prospective studies, as well as many systematic reviews and meta-analyses, which have shown that individuals experiencing depression and chronic or traumatic psychosocial stress have an increased risk of developing new CVD (Frasure-Smith & Lespérance, 2006; Hemingway & Marmot, 1999; Nicholson et al., 2006; Van der Kooy et al., 2007), as well as a poorer prognosis and increased risk of future mortality for individuals with established CVD (Barth et al., 2004; Lichtman et al., 2014; Meijer et al., 2011). Several plausible pathways exist, which may explain the link between psychosocial factors and CVD, including the effect of stress and depression on cardiovascular function via the hypothalamic–pituitary–adrenal axis (HPA-axis) and sympathetic nervous system (Grippe & Johnson, 2009). Another potential pathway may be through unfavourable behavioural changes associated with psychopathology, such as physical inactivity and poor cardiorespiratory fitness (CRF), these being well accepted risk factors for CVD.

Both psychosocial stress and depression have been associated with low levels of physical activity (Jerstad et al., 2010; Mouchacca et al., 2013; Rottenberg et al., 2014) and reduced cardiorespiratory fitness (Gerber et al., 2013; Hollenberg, Haight, & Tagger, 2003; Shomaker et al., 2012). Much of the evidence regarding these links has been based on studies conducted among adults. However, with knowledge that the processes leading to CVD originate in childhood (Berenson et al., 1998; Juonala et al., 2010), coupled with the well documented incidence of both childhood obesity and sedentary lifestyle among youth, understanding when in the life course psychological factors first exert their influence on CVD risk factors may inform prevention efforts undertaken with children, with the aim of improving current and future cardiovascular health.

Although research into the link between physical activity, fitness and aspects of mental health is not new, the literature has predominantly focused on the positive effect of physical activity and increased fitness on a range of mental health outcomes, including both stress and depression. However, few studies have considered the reciprocal relationship even though there is sufficient reason to believe that these relationships also occur in the opposite direction (Roshanaei-Moghaddam, Katon, & Russo, 2009; Rottenberg et al., 2014). For example, a systematic review of the adult literature investigating the effect of depression on physical activity concluded that depression was associated with subsequent low levels of physical activity (Roshanaei-Moghaddam et al., 2009). Among the paediatric literature, Rottenberg et al. (2014) found lower physical activity levels among adolescents with child-onset clinical depression compared to never-depressed siblings and age-matched controls. However, the Rottenberg et al. (2014) study did rely on self-report assessments of physical activity, generally considered a problematic procedure, even in healthy children (Prince et al., 2008; Rowlands, Ingledew, & Eston, 2000).

Key features of clinically diagnosed Major Depressive Disorder (MDD) include anhedonia, decreased energy, tiredness and fatigue, with even the smallest tasks seeming to require substantial effort. Subclinical levels of depressive symptoms are likely to have similar effects, to a lesser degree of disturbance (Allan, Johnston, Johnston, & Mant, 2007; Ziegelstein et al., 2000). Therefore, it is not difficult to see how these symptoms may lead to important behavioural changes, including the loss of interest in, or pleasure from physical activity participation (Jerstad et al., 2010), and subsequently, decreased fitness. Cognitive bias or attributional styles common to depression may also play a role in limiting an individual's motivation or self-efficacy relating to exercise (Rudolph, Hammen, & Burge, 1997; Suija, Pechter, Kalda, Tähepõld, Maaros, & Maaros, 2009).

In addition, there has been little discussion as to whether mental health factors have a differential effect on physical activity of varying intensities. Taken from a

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motivational perspective, vigorous forms of physical activity often require more intense levels of either actual or perceived motivational effort compared to lighter forms (Biddle & Mutrie, 2008). Therefore, vigorous activity may be more likely affected by a depressed or stressed state than lower intensity physical activity. Given the benefits of higher intensity exercise to body fat control and fitness (Tremblay et al., 1990; Williams, 2001), alerting health professionals to the likely effects of stress and depression on the quality of a paediatric client's physical activity may prove useful, especially when treating youth identified at risk for CVD. To date, no investigations have focused on the effects of mental health factors, such as the presence of depressive symptoms and perceived stress, on participation in varying intensities of physical activity.

What is clearly needed here are well designed longitudinal studies that explore the relationships between depression, psychosocial stress and multiple risk factors for CVD to allow some conceptual approximation to possible causalities. It is common to examine the potential influence of one mental health construct on one CVD risk factor, despite knowledge that these risk factors tend to cluster together, and that this clustering increases the relative risk for CVD (Berenson et al., 1998). Therefore, the present study sought to determine whether depression or psychosocial stress, experienced during the transitional period of childhood into adolescence, had a detrimental effect on physical activity and CRF, both being well-established risk factors for CVD. This study seeks to overcome some of the limitations of previous investigations by using objective measures of physical activity and fitness rather than relying on self-report measures, which are thought to be unreliable among younger populations (Prince et al., 2008; Rowlands et al., 2000); and extending cross-sectional studies by implementing a longitudinal design spanning eight years of child-adolescent development. The strength of a longitudinal design, in comparison with cross-sectional observations, is the increased confidence we draw in our inferences. Longitudinal, repeat observations on the same child share genetic, family and environmental influences, and so remove or reduce the effects of these potential confounders.



Additionally, with the introduction of accelerometer measurements during the final two follow-up assessments, this study also investigates the effect of stress and depression on moderate-to-vigorous physical activity (MVPA) and light physical activity (LPA), between grade 6 and grade 10. It is hypothesised that children with higher levels of stress and depressive symptoms will show a change in their distribution of daily physical activity over time, with more active time being spent in LPA and less time spent in MVPA.

## **Method**

### **Participants**

Participants were from the Lifestyle of our Kids (LOOK) study, which commenced in 2005 with a cohort of 853 initially grade 2 children aged 7 to 9 years. Of the 853 children recruited, we obtained data which satisfied our inclusion criteria for 791 children (397 boys *M* age = 8.18; 394 girls *M* age = 8.13). Follow-up data for this study were collected in grade 6 (266 boys, 255 girls) and grade 10 (122 boys, 136 girls), longitudinal data making use of a child whose measurements were obtained on two or more occasions. The sample size for longitudinal analyses varied between models (dependents on the variables included in each model), but ranged from 676 to 707 children.

### **Attrition**

For the most part, attrition of participants was due to school closures in the ACT and relocation of students to non-LOOK schools (*N* = 146). In addition, 15 of the 853 children who initially provided consent to participate in the LOOK study withdrew over the course of the study. Further attrition was explained by child absences on the day of testing. However, children who missed one or more assessments in a particular year remained in the study and were included in analyses with the statistical model adjusting

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for missing values. Analyses of baseline data, comparing children who withdrew from the study prior to any longitudinal assessment to those who remained in the study, indicated that children leaving the study were more stressed ( $p = .002$ ) and depressed ( $p = .013$ ) than those remaining in the study. No further significant differences on physical activity or fitness were observed. Therefore, the potential effects of attrition should be considered when interpreting the outcomes of this study.

### Measures

**Depression.** All children were given a modified (19 item) form of the Children's Depression Inventory (CDI; Kovacs, 1992), with a forced-choice (symptom present or absent response format). The original CDI has demonstrated validity and reliability (Kovacs, 1992) in assessing clinical and sub-clinical depression in preadolescent groups. The remaining items in our modified version reflect a range of depressive symptoms relevant to a diagnosis of major depressive disorder, including both affective (e.g. negative mood and anhedonia) and somatic (e.g. lack of energy, aches and pains) symptoms. These remaining items could therefore be considered to reflect depressed mood but not clinical depression, with the modified scale resulting in a full scale score of depression that ranged from 19 to 38, with higher scores indicating greater severity of depressive symptoms.

**Psychosocial stress.** The Children's Stress Questionnaire (CSQ) was used to assess psychosocial stress among our cohort (Byrne et al., 2011). The CSQ is a 50-item inventory assessing stressor exposure and the impact of self-reported stressor experience over the past 12-months. Children are asked to rate how stressful they found each event on a 5-point Likert scale (1 = *'This did not happen to me'*, 2 = *'It happened but it didn't matter to me'*, 3 = *'It made me a bit upset'*, 4 = *'It made quite upset'*, 5 = *'It made me very upset'*), resulting in the entire inventory score spanning 50

to 250, with higher scores indicating greater stress. The CSQ has been shown to be a valid and reliable measure of psychological stress among children as young as 8 years, and has also been shown to correlate with depression 12 months later at age 9 years, as well as with anxiety 24 months later at age 10 years (Byrne et al., 2011).

### **Physical activity**

**Pedometers.** To measure physical activity, children wore New Lifestyle pedometers (Lee's Summit, MO, USA) on their hip for seven consecutive days. Measurements collected on the first day were excluded as they did not form a full day and also to account for the potential influence of the novelty of wearing a pedometer. A physical activity index was calculated using Best Linear Unbiased Predictor (BLUPS; Robinson, 1991), which was chosen to maximise the use of data and due to its desirable statistical properties. Pedometers were used for the entire duration of the LOOK study. However, with advancements in technology and affordability, accelerometers were introduced in the final years of primary school.

**Accelerometers.** In the current study, accelerometers (Actigraph GT1M, Pensacola, FL, USA) were introduced in addition to pedometer assessments, to assess intensity in addition to volume of physical activity. With accelerometer data in the current study being confined to grade 6 and grade 10, and pedometers employed for the entirety of the study. Accelerometers were positioned on a belt around the waist in line with the right knee. The first day of data were discarded to minimise any potential reactivity. Daily accelerometer counts were used as a measure of volume of physical activity and cut off points for LPA were defined as 101 to 2,296 counts per minute and MVPA classified as greater than 2,297 counts per minute based on published recommendations (Evenson et al., 2008; Trost et al., 2011). An epoch length of 60 seconds was used and days of accelerometer data were included if there were 10 or more hours of activity. In the absence of any established non-wear time criteria for

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children in the extant literature (Cain et al., 2013), the current study deemed an hour assessment to be invalid if there were more than 30 zero counts in a row (30 minutes of non-wear time). Accelerometer data were collected on both weekdays and weekends, and at least three days data comprising at least two weekdays and one weekend day, were required for inclusion in the analyses. Actigraph accelerometers have been validated for use in both children and adolescents (Mattocks et al., 2007). Accelerometer data were analysed without the low frequency extension function using Meterplus software, Version 4.2 (San Diego State University, USA).

**Cardiorespiratory fitness.** Cardiorespiratory fitness was assessed using the 20-meter multistage shuttle test (MSST). The MSST has been well-established as a reliable field-test among children (Tomkinson et al., 2003). The assessment of CRF in this study offers a complimentary assessment to physical activity, providing a more “overall” indication of a child's activity level whilst taking into account the child's inherited predispositions for CRF (i.e. the ability of the child's circulatory and respiratory system to supply oxygen to the working muscles). Compared to pedometer and accelerometer assessed physical activity, which provide a measure of physical activity behaviour (but are inherently flawed due to being influenced by the idiosyncrasies of the particular days physical activity is measured), a measure of CRF may provide a more stable, indirect physiological index of activity levels.

**Socioeconomic status.** The Australian Bureau of Statistics Socioeconomic Indexes for Areas (SEIFA) was used as a measure of SES (Australian Bureau of Statistics, 2009). As previously described, this index represents different aspects of relative socioeconomic disadvantage and/or advantage in a geographic area including economic and social resources, education and occupation, as measured by the government Census. Schools participating in the LOOK study were all a part of the Australian Capital Territory and were relatively homogeneous in terms of SES. The

average SES index of the suburbs in our study ( $M = 1085$ ,  $SD = 40$ , range 982 to 1160) was higher than the average index of all towns and cities throughout Australia ( $M = 980$ ,  $SD = 84$ , range 598 to 1251).

### **Procedure**

Data for this study were collected over three time periods, with baseline data collection occurring in 2005 when participants were in grade 2 and follow-up data collected 4 years (2009, grade 6) and 8 years later (2013, grade 10). Measures of psychosocial stress, depressive symptoms, physical activity and CRF were collected at all three time points. Accelerometer assessments were collected in grade 6 and grade 10. Psychological data were collected in whole class groups of between 20 and 30 children by a psychologist who could answer children's questions regarding item meanings, and many classes were supervised as well by a class teacher. Measures of stress and depression were presented to children via a PowerPoint presentation and participants made response choices on individual hand-held key-pads, which were then relayed back to a lap-top computer using KEEpad interactive software and devices. The response device presented facial images (representing a corresponding idiographic scale) on individual key-pads, color-coded to match the response colour presented on the PowerPoint slide, in order to facilitate self-reports of stress and depression. All items were simultaneously read to participants as they were presented so as to take account of varying levels of reading ability across classes. Anchors of time, pertaining to memorable experiences, such as Christmas, birthdays and school holidays were provided to facilitate accuracy in recall of the timing of stressful events. Measures of physical activity and CRF were collected in a separate session by an exercise scientist, with the same researcher collecting all physical data from grade 2 through to grade 10. Similarly, physical fitness testing took place in whole class groups where the MSST was administered in the school's gymnasium and pedometers and accelerometers were handed out with instructions on how they should be worn.

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Ethics approval for the study was obtained from the ACT Department of Education, the Human Research Ethics Committee (HREC) of the Australian National University, and the Ethics Committee of the Australian Sports Commission (for the entire LOOK Study). All parents gave informed and written consent for their children to participate in the LOOK study, as well as the psychological component specifically. The children also gave written consent, a condition required by the HREC of the Australian National University.

### **Statistical Analysis**

The statistical model used in the current study has been presented in previous LOOK study publications (Olive, Byrne, Cunningham, & Telford, 2012; Telford et al., 2012) and in Chapter 5 on Research Design. A further discussion can also be found in Van De Pol and Wright (2009). The statistical model reported here fits within the general framework of general linear mixed models (Galwey, 2014) and was developed to account for the dependence structure that is a result of the current studies longitudinal and sampling design. The mixed model used in the current study allows for analyses of regression relationships between the response variable (e.g. physical activity or fitness) and candidate explanatory variables (stress and depression) at two levels; within-child (longitudinal) and between-children (cross-sectional), whilst accounting for nesting of children in schools. The ability to separate these effects is a strength of the current study and a particular strength of longitudinal studies, in that it is not necessary to make the strong assumption that the between-child and within-child relationship are the same, as is the case with cross-sectional studies.

Analyses were conducted in R version 3.1.1 (R Core Team, 2012). The mixed model used in the current study acknowledges that children, within the same school (noting that children were selected into the study as school groups rather than individuals) are subjected to shared experiences, which may result in their reported physical activity or fitness being more homogeneous than those of a random sample of

children drawn across schools. Equally, at the within-child level, it recognises that repeat observations on the same child share the same genetic, family and environmental influences, so it is expected that repeat observations within a child will be more homogeneous than observations between children. In order for our proposed statistical model to reflect the sampling design we must specify and account for this dependence structure. For this reason, the variables between-child (within a school) and within-child should be considered as random effects in our model.

Our statistical model estimates effect sizes for the expected change in the response variable (e.g. physical activity) over time per unit change in the explanatory variable (e.g. depression), using repeated measures obtained from children. Restricted maximum likelihood was used to estimate variance components and weighted least squares for estimating fixed effects. Statistical significance of effects was assessed by calculating adjusted Wald statistics (Kenward & Roger, 1997). The response variable CRF was scaled by square root to better meet linearity assumptions and a physical activity index was calculated using Best Linear Unbiased Predictor (BLUPS; Robinson, 1991) as previously described (Telford, Cunningham, & Telford, 2009b). General model checking procedures were routinely used to identify aberrant data and to check the model assumptions.

## **Results**

A summary of participant characteristics based on raw scores can be seen in Table 9. Significant differences between boys and girls levels of physical activity and fitness (Sallis, 1993) have been documented in the literature and were also observed among our cohort. For this reason, analyses into the effects of psychosocial stress and depressive symptoms on physical activity and fitness were conducted separately for each sex. All models made adjustments for SES.

### **Stress and Depression**

On average, approximately 40% of girls and 42% of boys reported elevated depressive symptoms in grade 2 (greater than or equal to 26 on the modified CDI, which is proportionate to the original CDI's suggested cut-off of 20; Kovacs, 1992). This declined to 22% and 20% for girls and boys respectively during grade 6 and increased again during grade 10, with 64% of girls and 51% of boys reporting elevated depression scores. It should be noted that this characterisation of symptoms is not a precise clinical indicator of depression but rather provides some description of depression in the current sample and therefore should be interpreted with some caution. On average, the frequencies with which children in the sample affirmed that they had experienced any particular stressor over the one year sampling period ranged from 70% for common hassles to 20% for specific and potentially traumatic events. Significant changes in stress and depression over time were observed for both boys and girls (all  $p < 0.05$ ). This change was characteristic of a decline in both stress and depression between grade 2 and grade 6, followed by a significant increase in depression for both boys and girls and a significant increase in stress for girls but not boys between grade 6 and grade 10. Although on average, boys and girls showed similar trajectories of stress and depression during the primary school years, significant differences were observed between the genders by grade 10, where girls reported significantly greater stress and depression. In addition, boys had lower stress at baseline compared to girls but there was no significant difference at the first follow-up four years later. This is consistent with previous literature, where emerging psychopathology during adolescence is more often reported among girls compared to boys (Petersen, Sarigiani, & Kennedy, 1991).

### **Physical Activity and Cardiorespiratory Fitness**

Significant changes in physical activity and CRF over time were also observed for both boys and girls. Among girls, physical activity declined at each year of



measurement that was included in the current study. On average, girls in the current study took 9471 steps in grade 2 (age 8 years), 8398 steps in grade 6 (age 12 years) and 8306 steps in grade 10 (age 16 years), which is below recommendations of 11,000 steps per day (Tudor-Locke et al., 2011). Additionally, there was a significant decline in MVPA ( $p < .001$ ) and LPA ( $p < .001$ ) among girls from age 12 to 16 years. On average, girls increased in fitness over the duration of the study, which equated to an average increase of 2.2 levels on the 20m MSST between grade 2 and grade 6, with a smaller average increase of 0.2 levels between grade 6 and grade 10.

A slightly different picture emerged for boys, who were consistently and significantly more active than girls at each assessment time point. However, similar to girls, boys were also measured with a consistent decline in physical activity across the measurement years included in the current study. On average, boys took 11,662 steps in grade 2 (age 8 years), 9926 steps in grade 6 (age 12 years) and 9672 steps in grade 10 (age 16 years), which is below recommendations of 13,000 steps per day for boys (Tudor-Locke et al., 2011). Boys were also measured with a significant decline in MVPA ( $p = .001$ ) and LPA ( $p < .001$ ) and a consistent and significant increase in fitness over the duration of the study, which equated to an average increase of 2.3 levels on the MSST between each year of measurement.

### **Effects of Depression and Stress on Cardiorespiratory Fitness**

Longitudinal analyses, based on repeated measures of the same child and therefore limiting the confounding effect of genetic and environmental factors, indicated that depression had a significant and negative effect on CRF for girls ( $\beta = -0.008$ ,  $p = .034$ ). Put in more practical terms, if a typical 16 years old girl had increased her CDI depression score by 10% (and 54% of girls increased by at least this amount between grades 6 and 10) then we could expect her CRF to have decreased by 3% (95% CI 0.4 to 6%). There was evidence of a similar trend among boys, although this did not reach statistical significance ( $\beta = -0.009$ ,  $p = .071$ ). No significant longitudinal effects of stress

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on CRF were found for either boys ( $\beta = -0.001, p = .138$ ) or girls ( $\beta = -0.001, p = .138$ ). Although this study focuses on longitudinal relationships, it is of interest that significant cross-sectional relationships were found between CRF and depression (boys  $\beta = -0.027, p < .001$ ; girls  $\beta = -0.013, p < .001$ ) and stress (boys  $\beta = -0.003, p = .009$ ; girls  $\beta = -0.002, p = .035$ ). A summary of effects is provided in Table 10.

### **Effects of Depression and Stress on Physical Activity**

No evidence for a longitudinal effect of depression (boys:  $\beta = 0.093, p = .363$ ; girls:  $\beta = 0.063, p = .557$ ) or stress (boys:  $\beta = 0.003, p = .795$ ; girls:  $\beta = -0.012, p = .601$ ) on physical activity was found among the current cohort. Cross-sectionally (between-child effect), physical activity was significantly related to both stress (boys  $\beta = -0.071, p = .009$ ; girls  $\beta = -0.040, p = .035$ ) and depression (boys  $\beta = -0.508, p = .001$ ; girls  $\beta = -0.222, p = .035$ ) for both boys and girls. These cross-sectional relationships indicated that on average, children who took fewer pedometer assessed steps per day also had higher levels of self-reported stress and depression. A summary of these effects can be seen in Table 10. In addition to pedometer assessed physical activity accelerometer assessments were also carried out in grade 6 and grade 10, allowing investigations into physical activity intensity. In line with previously cited work (Biddle & Mutrie, 2008), the current study focused on two activity intensities - MVPA and LPA. Longitudinal analyses did not reveal any evidence for an effect of stress or depression on MVPA or LPA for either boys or girls (see Table 11 for a summary). At the cross-sectional level, among girls, MVPA was significantly and negatively related to stress ( $\beta = -0.114, p = .042$ ) and depression ( $\beta = -0.883, p = .008$ ), where girls who spent less time in MVPA also had greater levels of stress and depressive symptoms. Similar relationships were not found among boys. No significant effect of either stress or depression was found for LPA.

Table 9

*Means and Standard Deviations (in brackets) for Boys and Girls in Grade 2, Grade 6 and Grade 10 for Physical and Psychological Variables*

	Boys			Girls		
	Grade 2	Grade 6	Grade 10	Grade 2	Grade 6	Grade 10
PA BLUPS	107.99(11.09) <sup>†</sup> •	99.63(11.38) <sup>†</sup>	98.35(12.07) <sup>†</sup>	97.29(10.06) <sup>†</sup> •	91.41(9.20) <sup>†</sup>	91.33(9.61) <sup>†</sup>
MVPA	NA	47.99(22.93) <sup>†</sup> •	26.99(14.10) <sup>†</sup>	NA	34.45(17.33) <sup>†</sup> •	20.52(10.50) <sup>†</sup>
Light	NA	329.98(55.55)•	274.12(71.86)	NA	332.88(52.18)•	257.36(71.94)
CRF	4.15(1.46) <sup>†</sup> •	6.39(2.14) <sup>†</sup> •	9.01(2.71) <sup>†</sup>	3.48(1.77) <sup>†</sup> •	5.48(1.77) <sup>†</sup> •	5.86(1.93) <sup>†</sup>
Stress	94.86(22.90) <sup>†</sup> •	80.54(21.41)	81.26(17.46) <sup>†</sup>	96.82(21.52) <sup>†</sup> •	83.80(19.77)•	86.08(18.19) <sup>†</sup>
Depression	25.11(4.26)•	22.45(3.24)•	23.10(4.18) <sup>†</sup>	25.12(4.39)•	23.04(3.14)•	27.28(4.39) <sup>†</sup>

*Note:* PA BLUPS is the physical activity index, approximately equal to the square root of average daily steps per day (pedometer assessed); MVPA moderate-to-vigorous physical activity, Light is light activity, both assessed with accelerometers at two time-points (grade 6 and grade 10); CRF is cardiorespiratory fitness, the number of stages reached in the multistage run; Stress is the child's CSQ score; Depression is the child's CDI score; <sup>†</sup> denotes significant sex effects; • denotes significant change over time when compared with the subsequent year

Table 10

*Model Estimates ( $\beta$ ) with 95% Confidence Intervals (in Brackets) for Within-child and Between-child Relationships of Physical Activity and Fitness with Key Explanatory Variables Stress and Depression*

	Physical Activity		$\sqrt{\text{Fitness}}$	
	Boys	Girls	Boys	Girls
	$\beta$ (SE)	$\beta$ (SE)	$\beta$ (SE)	$\beta$ (SE)
Stress <sub>w</sub>	0.003 (-0.032, 0.038)	-0.012 (-0.048, 0.024)	-0.001 (-0.003, 0.001)	-0.001(-0.002, 0.001)
Stress <sub>b</sub>	-0.071 (-0.123, -0.019)**	-0.040 (-0.085, 0.005)*	-0.003(-0.005, -0.001)***	-0.002(-0.003, -0.001)**
Depression <sub>w</sub>	0.093 (-0.126, 0.311)	0.063 (-0.154, 0.279)	-0.009(-0.018, 0.001)	-0.008(-0.015, -0.001)*
Depression <sub>b</sub>	-0.508 (-0.810, -0.206)**	-0.222 (-0.467, 0.023)*	-0.027(-0.037, -0.017)***	-0.013(-0.021, -0.004)***

\*  $p < .05$ , \*\*  $p < .01$ , \*\*\*  $p < .001$ ; Physical activity is BLUPS; Fitness is square root of cardiorespiratory fitness, the number of stages reached in the multistage

Table 11

*Model Estimates ( $\beta$ ) with 95% Confidence Intervals (in Brackets) for Within-child and Between-child Relationships of Accelerometer Assessed Moderate-to-Vigorous and Light Activity with Key Explanatory Variables Stress and Depression*

	MVPA		LPA	
	Boys	Girls	Boys	Girls
	$\beta$ (SE)	$\beta$ (SE)	$\beta$ (SE)	$\beta$ (SE)
Stress <sub>w</sub>	0.469 (-0.481, 1.419)	0.391 (-0.135, 0.917)	0.646 (-2.109, 3.401)	-1.276 (-3.442, 0.890)
Stress <sub>b</sub>	-0.724 (-1.694, 0.247)	-0.883 (-1.523, -0.244)*	0.672 (-2.389, 3.733)	-1.063 (-4.048, 1.922)
Depression <sub>w</sub>	0.077 (-0.045, 0.199)	-0.061 (-0.133, 0.010)	0.322 (-0.046, 0.689)	-0.138 (-0.462, 0.187)
Depression <sub>b</sub>	0.007 (-0.181, 0.195)	-0.114 (-0.226, -0.002)**	0.345 (-0.257, 0.947)	0.013 (-0.522, 0.549)

\*  $p < .05$ , \*\*  $p < .01$ ; MVPA is moderate-to-vigorous activity; Light is light activity both assessed with accelerometers at two time-points (grade 6 and grade 10)

### Discussion

In this prospective cohort study, we found new evidence indicating that a change in depressive symptoms has a direct effect (i.e. within-child) on the CRF of girls, whereby it is expected that on average, a 10% increase in a girls CDI depression score would result in approximately a 3% decrease in her CRF (as assessed by the MSST); and we also found a trend for the direct effect of depression on CRF among boys. At the cross-sectional level, this study further demonstrates that within the transitional period of childhood to adolescence, a child identified with more symptoms of depression is likely to be less physically active and less fit. Likewise, a child identified as being more stressed has lower levels of fitness and physical activity, which in girls extended to less MVPA. Taken together, these findings provide support for the premise that both stress and depression have an unfavourable effect on the physical activity and fitness profiles of youth between the ages of 8 to 17 years.

As indicated earlier, few studies have investigated the effects of mental health factors on physical health outcomes, especially in children. Although no prospective studies among children have been published, there are previous cross-sectional studies, undertaken in other sections of the population, which support our longitudinal findings that a child who has an increase in depressive symptoms from childhood to adolescence will have a reduction in fitness. Firstly, in a cohort of obese adolescents those reporting elevated depressive symptoms were less fit than those without elevated symptoms (Shomaker et al., 2012); and secondly, in a study of older adults, depression was associated with impaired fitness (Hollenberg et al., 2003).

Any explanation of this study's longitudinal findings, of a direct effect of depression on CRF among girls, needs to take into consideration the way in which CRF was assessed. The MSST is a running test of maximal effort and therefore has a number of aspects that may limit performance, which reach beyond the physiological capacity of the child. For example, in addition to performance being limited by the child's physiology in terms of cardiovascular fitness and local muscular endurance,

performance on the test is also dependent on a number of psychological factors, including motivation to do well and by the child's ability to tolerate discomfort. Depression is known to affect motivation and self-efficacy (Bandura, 1991; Bandura, 1997a). This may be due to somatic symptoms of lethargy and psychomotor retardation (American Psychiatric Association, 2013), but also due to cognitive biases that are common to a depressed mood state (Rudolph et al., 1997). This may include a decreased ability for the child to experience enjoyment and a sense of achievement or a lack of self-belief in their ability to complete a maximal performance test. We can also hypothesise that a child characterised by greater stress and depressive symptoms may seek to minimise any further trauma, this time induced by cardiorespiratory and local muscular fatigue, which accompanies any maximal running test. Furthermore, we may refer to the Central Governor theory intended to explain fatigue and tiredness (Noakes, 2007), which proposes that the central nervous system limits stressful muscular activity as a mechanism of self-preservation. We hypothesise that psychological disturbances might increase the level of sensitivity of any such underlying unconscious limitation to strenuous physical activity. We can also view these potential contributors to performance in the fitness test from a cognitive behavioural framework (Beck, 1967, 2002). A child with symptoms of depression or stress may not have sufficient belief in their own abilities to tolerate discomfort associated with a maximal effort test, or may approach the test with an expectation of failure, which would likely limit their performance (Rudolph et al., 1997).

Our longitudinal findings on CRF were corroborated by the significant effect of both depression and stress on pedometer assessed physical activity in our between-child analyses, and further, by accelerometer data among girls. This is consistent with findings from Rottenberg et al. (2014), who reported that clinically depressed adolescents had lower levels of physical activity compared to their never-depressed siblings and control counterparts. With regards to the current findings, there is no obvious reason as to why girls, but not boys, with higher levels of stress and

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depression accumulate less MVPA. However, it could be hypothesised that this is the result of sociocultural factors that have reinforced girls to be more vigilant to threats-to-self in their physical environment, including the potential for negative comments about their physical abilities or how their body looks. Support for this hypothesis is provided by Vu, Murrie, Gonzalez, and Jobe (2006), who reported that taunting, name calling, and teasing from boys, but also other girls, were prominent reasons why girls did not participate in more physical activity. Alternatively, we might speculate that this difference be hormonally based, in that the more pronounced increase in muscle mass and reduction in percent body fat typical of boys in the early adolescent period, a strong contributor to fitness, may over-ride or mask any psychological effect.

Cardiorespiratory fitness provides an objective, surrogate measure of physical activity exposure (Stofan, DiPietro, Davis, Kohl, & Blair, 1998) and in addition to the expected age related increase in CRF among developing children, we would expect to see increased fitness among children who were more active at a sufficient intensity. This was certainly the case in the current cohort, where post-hoc analyses indicated that children who were more physically active were also fitter. Our accelerometer data provide some evidence that psychological disturbance experienced among children and young people may have the greatest impact on activities of higher intensity. This may offer a new avenue in addressing the global problem of physical inactivity and low fitness among children and young people. Our data suggest that strategies might include improving mental health symptoms, particularly in those who are identified with early signs of concern. Arming children with the tools to identify and cope with negative emotional states, such as feelings of depression and stress, may not only serve to improve psychological wellbeing but may also influence a child's readiness and willingness to participate in physical activity. The advantages of so doing may have magnified benefits, given that any increase in physical activity and fitness may subsequently stimulate a positive feedback loop and in turn improve psychological wellbeing. In accordance with our discussion of how depression might affect a child's



performance in the fitness test, we can again refer to social cognitive theory (Bandura, Pastorelli, Barbaranelli, & Caprara, 1999). Children with high depressive symptoms may have low self-efficacy and unfavourable beliefs in their ability to successfully participate in physical activity (Bandura, 1997b), which in turn may limit their physical activity participation.

Further to a psychological explanation, and perhaps even associated with the Central Governor Theory of fatigue alluded to previously, depression may affect physical fitness more directly by modifying central neural pathways. Several studies have suggested that depression is the result of chronic hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA-axis) and the locus coeruleus-noradrenalin system (Gold, 2015; Gold & Chrousos, 1999). Due to the fact that these systems are responsible for behavioural and neuroendocrine responses, chronic hyperactivity may result in autonomic adaptations, with possible down regulation of adrenergic receptors, which could influence cardiorespiratory performance. Disturbances to the HPA-axis and noradrenalin systems are also thought to play a role in the pathogenesis of CVD (Pereira, Cerqueira, Palha, & Sousa, 2013).

Finally, in looking to provide a better understanding of the relationships between psychology and physicality, and having considered the method of measuring fitness, we also need to consider the currently available instruments with which we measure the psychological characteristics of children and adolescents. That we found no evidence of any direct (longitudinal) effect of stress on physical activity and fitness does not lead to any inference that such an effect is non-existent. It may be that the measure used was not sensitive enough to detect changes within a child; or that the stressors experienced by children in our cohort were not of sufficient intensity or were not experienced for a sufficient duration to produce the psychological or neurobiological changes that may be involved in the link between stress and reduced CRF and physical activity. The latter appeared to be the case among children in the current cohort, where reductions in stress were seen between grade 2 and grade 6, followed

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by a subsequent increase from grade 6 to grade 10. Based on repeated measures of individual child profiles in the current study, trajectories of stress and depression, for the most part, did not show a consistent pattern of change over the full duration of the study (e.g. increases at each time point or decreases at each time point). Additionally, the young age of our participants at baseline may have meant children had difficulty accurately recalling stressful events in the measured time-frame of one year. Although efforts were made to increase accuracy of recall by providing context through memorable reference points, such as school holidays and birthdays, this cannot be ruled out. It also remains that some children might use physical activity as a means of coping with stress, and therefore we would expect that during periods of stress that physical activity and potentially, fitness would increase. This may be one reason as to why we did not uncover evidence at the within-child level.

However, that just one longitudinal relationship showed significance in the current study was not surprising. Longitudinal relationships have proven difficult to detect in the current cohort, even when investigating those between physical activity, fitness and precisely measured blood lipids (Telford et al., 2009b). Underlying this are several factors: the relative homogeneity of data within an individual in comparison to those between individuals; the potentially confounding effects of growth and development among youth; and measurement instruments in physical activity, fitness, stress and depression, each of which has limitations in precision and reliability.

### **Strengths and Limitations**

This study has a number of strengths, which extend previous studies. The longitudinal design, spanning eight years and covering the important transition from childhood to adolescence is unique to the current study. Another strong aspect of the study was its employment of objective measures of physical activity and fitness, thereby avoiding typically unreliable self-reporting in children (Rowlands et al., 2000). On the other hand, even these objective assessments must also be considered as

limited in their validity and we have alluded to this in our discussion. For example, pedometer-assessed physical activity is limited in its capacity to capture activities such as swimming and cycling, which may have resulted in under-reporting of total activity in the current cohort. However, prior work has indicated that despite these limitations, pedometers provide a good overall assessment of physical activity, with pedometer assessed physical activity being strongly associated with direct observation of activity in a free-living environment (McNamara, Hudson, & Taylor, 2010). Another strong aspect was the multi-disciplinary approach of the overall LOOK study, as a number of assessments beyond the variables of focus in the current study assisted our interpretation of effects. For example, although not the focus of the current paper, assessments of body image and self-esteem for physical abilities allowed us to further investigate psychological factors contributing to these associations.

A limitation of the current study was the use of self-report measures of psychosocial stress and depression, particularly the need to employ a modified version of the CDI. Future studies would benefit from employing more objective measures of stress and utilising structured interviews, which can also distinguish children who meet a clinical diagnosis for depression from those who do not. This level of assessment would also provide a more detailed description of the pattern of presenting symptoms (e.g. dominated by somatic or affective symptoms; characteristic of increases or decreases in appetite/sleep etc.), and whether a child is entering a depressive episode, remitting, or remaining the same. This level of detail will allow for more meaningful investigations into the interplay between mental health states and components of physical health. However, this approach is not always feasible due to time constraints and resources, as was the case in the current study.

### **Conclusion**

In conclusion, with our repeated measure design limiting the confounding effect of genetic and environmental factors, we report evidence that depression directly

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effects fitness in girls, with a trend for a similar effect among boys. In addition, children under more stress were less active and less fit. These findings may contribute to strategies directed towards achieving reductions in obesity and enhanced physical activity.

### **Chapter Conclusions**

The findings reported in this chapter provide support for Hypothesis 1, that psychosocial stress and depressive symptoms in children are related to primordial risk factors for CVD, including lower levels of physical activity and fitness; and partial support for Hypothesis 2, that children who increase in depressive symptoms during the transition from childhood to adolescence will develop a less favourable profile of primordial risk factors, including lower fitness.

The significance of these relationships among younger populations is perhaps best illustrated by research that implicates physical inactivity and low fitness as a risk factor for CVD and further, by emerging findings that physical activity patterns track from childhood into adulthood. In terms of the former, increased fitness has been shown to be a protective factor in the risk for CVD related mortality, even in the presence of other established CVD risk factors. For example, it has been shown that among fit individuals, who also had any combination of elevated blood pressure, elevated cholesterol level or smoking, had lower mortality rates compared to low-fit individual with none of these further risk factors (Blair et al., 1996). Similarly, unfit lean men have been shown to have a greater risk of all-cause and CVD-related mortality than both fit-and-lean men, and fit-but-obese men (Lee, Blair, & Jackson, 1999).

Adding to the importance of the findings reported here is the evidence that physical activity may track from childhood into adulthood (Malina, 2001; Telama et al., 2014). Facilitating the establishment of health-promoting behaviours, such as health promoting physical activity during childhood is vital for an individual's development and future health. Given the evidence that health behaviours, including physical activity

participation, may be more amenable to change earlier in life, as the foundations of behaviour are being laid (Allison, Adlaf, Ialomiteanu, & Rehm, 1999; Catalano et al., 2004; Epstein et al., 1995; Milligan et al., 1997), addressing aspects of psychological health, which negatively influence a child's prospects of developing such health behaviours may be an important focus for intervention. Improvement in depressive symptomology and physical fitness profiles in youth are likely to have further positive consequences for health, including further benefits to metabolic health.

Insulin resistance and excess body fatness, both characteristics of poor metabolic health, are well-established risk factor for CVD. Adequate levels of physical activity and fitness relate closely to improved insulin resistance and fatness, thus providing an avenue through which psychosocial stress and depression may affect the risk for CVD. More recently, evidence has emerged which implicates symptoms of stress and depression more directly in associations with both insulin resistance and fatness. In the following chapter, the findings from Study 2, which investigates the impact of psychosocial stress and depression on insulin resistance and fatness among children of our cohort, are reported.

## **CHAPTER 7**

# **PSYCHOSOCIAL-STRESS AND DEPRESSION IN YOUTH EFFECTS BODY FATNESS AND INSULIN RESISTANCE: THE LOOK LONGITUDINAL STUDY**

### **Publication**

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### **Context Statement**

Building on evidence emerging from Study 1, investigating the influence of psychosocial stress and depressive symptomology on behavioural CVD risk factors, including physical activity and subsequent cardiorespiratory fitness, in this chapter we continue our investigations into the influence of psychological factors on primordial risk factors. This time the focus is on the influence of symptoms of psychosocial stress and depression on a set metabolic health indicators, namely insulin resistance and percent body fat. Obesity and insulin resistance are established risk factors for CVD and are also closely related in themselves, with obesity and overweight being a strong predictor of insulin resistance. Emerging evidence has implicated depression and stress more directly with levels of insulin resistance and body fatness. In the following study, we test Hypothesis 3 and 4, and examine whether insulin resistance and percent body fat are influenced by symptoms of psychosocial stress and depression, following our cohort over 8 years of child-adolescent development.

**Abstract**

**Background:** Depression and psychosocial stress have been linked to increases in insulin resistance in adults, however, less is known about these relationships in paediatric populations. Depression has also been shown to influence obesity, a known risk factor for insulin resistance and subsequent Type 2 diabetes. With the increasing rates of obesity among paediatric populations, understanding the effect of psychological influences on both body fatness and insulin resistance (independent of adiposity) in children may inform adjunct approaches in preventive medicine.

**Aim:** This study examined the longitudinal and cross-sectional effect of both psychosocial stress and depressive symptoms on insulin resistance and percent body fat in a cohort of Australian children, following them as they transitioned from childhood into adolescence.

**Methods:** Participants were 791 initially grade 2 children (aged 7 to 8 years; 394 girls), selected from the community. Psychosocial stress was assessed using the Children's Stress Questionnaire, whilst depressive symptoms were assessed using the Children's Depression Inventory. Fasting blood samples for serum insulin and plasma glucose were collected to estimate the homeostasis model assessment-insulin resistance (HOMA-IR). Measures were taken of height and weight, from which BMI was calculated. Other measures included percent body fat (dual energy x-ray absorptiometry); and covariate assessments measures included physical activity, which was assessed using pedometers; and pubertal maturation, which was assessed using Tanner's stages of maturation.

**Results:** Boys who reported more symptoms of depression had higher insulin resistance, irrespective of adiposity ( $\beta = 0.012$ ,  $p = .016$ ); and longitudinally, we found a trend for boys who developed more depressive symptoms to develop higher insulin resistance ( $\beta = 0.011$ ,  $p = .073$ ). These findings did not extend to girls. Furthermore, boys with higher depressive symptoms had higher percent body fat ( $\beta = 0.193$ ,  $p =$

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.011), and longitudinally, boys whose depressive symptoms increased became fatter ( $\beta = 0.127, p = .046$ ). Girls with higher stress were also fatter ( $\beta = 0.033, p = .020$ ).

**Conclusions:** We provide strong evidence that even early symptoms of depression are a risk factor for increased insulin resistance, independent of adiposity. In addition, our evidence that depression leads to overweight and obesity in a dose-response manner provides further reason to suggest early attention to children with depression, even in pre-clinical stages, may reduce the risk for chronic disease in later life.



## Introduction

Increased insulin resistance is a physiological precursor of Type 2 diabetes (Martin et al., 1992; Taylor, 2012), which in turn has been unequivocally linked to increased risk for CVD (Howard et al., 1996; Laakso & Kuusisto, 2014). Similarly, depression and psychosocial stress have been associated with both insulin resistance (Kan et al., 2013; Räikkönen, Keltikangas-Järvinen, Adlercreutz, & Hautanen, 1996) and increased risk of developing Type 2 diabetes in adults (Anderson, Freedland, Clouse, & Lustman, 2001; Heraclides, Chandola, Witte, & Brunner, 2009; Knol et al., 2006; Mezuk, Eaton, Albrecht, & Golden, 2008). Meta-analytic examinations undertaken with adults have shown that depression in non-diabetic populations increases the risk of developing diabetes by 37-60% (Kan et al., 2013; Knol et al., 2006; Mezuk et al., 2008); with further evidence indicating that diabetics who go on to experience depression also have a poorer prognosis and increased risk of mortality (van Dooren et al., 2013). Also among adults, stressful life events, daily hassles and work stress have been associated with both insulin resistance and Type 2 diabetes (Fang, Boden, Siu, & Tseng, 2015; Heraclides et al., 2009). While the adult evidence for a causal link between psychological factors, metabolic factors and CVD risk is compelling, it is not fully reflected in a much smaller volume of evidence coming from studies of children and adolescents. However, the persuasive nature of the evidence from adult populations likely points to similar pathways between earlier psychological disturbance and metabolic risk in children and adolescents.

Based on a framework that draws from the adult empirical data there is a clear need for investigations among younger populations, which use strong methodology and longitudinal designs. From the existing paediatric literature, a positive association between low mood and depression with insulin resistance has been reported (Jeffery, Hyland, Hosking, & Wilkin, 2014; Shomaker et al., 2011; Shomaker et al., 2010). However, the majority of these studies have been cross-sectional, with only one longitudinal study published to date. Shomaker et al. (2011), in their prospective study,

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provided evidence that earlier depression was associated with higher insulin resistance among children aged 5 to 13 years, although, this study's design precluded investigations of any effect of change in depression on change in insulin resistance. From reviewing the literature, there is a clear need for studies that utilise a within-subjects design (i.e. studies based on repeat observations of the same child). It is expected that the associations derived from repeat observations within a child, which share the same genetic, family and environmental influences lend themselves to a higher level of inference than cross-sectional observations. No longitudinal studies investigating the effect of psychosocial stress on insulin resistance in children or adolescents have been published. However, there is cross-sectional evidence of an association between the homeostatic model of insulin resistance (HOMA-IR) and a range of potentially stressful experiences in adolescents, including high levels of internalised racism (Chambers et al., 2004) and low SES status (Goodman, Daniels, & Dolan, 2007).

One potential pathway that might link depression and psychosocial stress to insulin resistance is via behavioural and lifestyle changes associated with poor mental health, including low physical activity and poor diet, both factors that influence body fat accumulation and impaired blood glucose control (Telford, et al., 2009c; Telford, et al., 2012). Moreover, psychosocial stress and depression may have a more direct effect on increased fatness via direct physiological pathways (Rosmond & Bjorntorp, 2000); this in itself providing a link between psychological characteristics and insulin resistance. Increased body fat and potentially specific distribution of fat, such as intra-abdominal (visceral) fat, are known to increase insulin resistance and the risk for Type 2 diabetes in adults (Goran, Ball, & Cruz, 2003; Venables & Jeukendrup, 2009). Among children and adolescents, fatness has been associated with greater insulin resistance (Freedman et al., 1987; Gutin et al., 1994) and greater insulin resistance has been documented among obese youth compared to their non-obese counterparts (Legido et al., 1989). This was the case for children of the LOOK study, at least during late

childhood between the ages of 8 and 12 years, where it was observed that a one unit increase in percent body fat resulted in a 2.2% and 1.6% increase in homeostasis model of insulin resistance (HOMA-IR) for boys and girls respectively (Telford et al., 2012).

Although the mechanisms explaining the link between psychosocial stress, depression and increased adiposity and insulin resistance are complex and likely to be multifactorial, pertinent to this discussion is that obesity related cytokine inflammatory responses have been associated with disruption of insulin sensitivity and pancreatic  $\beta$ -cell function, and contribute to the development of Type 2 diabetes (Stuart & Baune, 2012; Wang, Guan, & Yang, 2010). In addition to the potential pathway mediated by adiposity, depression and stress-related disorders are thought to directly affect cell-mediated cytokine production via hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA-axis; Bao, Meynen, & Swaab, 2008) and sympathetic nervous system (SNS; Barton et al., 2007). Moreover, psychosocial stress related stimulation of the HPA-axis and SNS has been shown to result in the secretion of hormones including glucocorticoids (cortisol in humans), adrenaline, and neuropeptide Y, placing stress on blood glucose control (see Stuart & Baune, 2012). Therefore, it appears that plausible biological mechanisms exist that can potentially explain the link between psychological factors and insulin resistance, and that this is likely mediated via the stress response.

In light of this evidence, the aim of the present study was to investigate whether insulin resistance and percent body fat are negatively influenced by symptoms of psychosocial stress and depression in healthy children as they move into adolescence. This may help to inform us of the potential benefits of early (or primordial) psychologically based interventions targeting the prevention of metabolic dysfunction. We hypothesised that greater insulin resistance will be observed among children reporting more psychosocial stress and higher levels of depressive symptoms. With obesity a known risk factor for Type 2 diabetes, we also investigated the effect of stress and depression on body composition. We hypothesised that children with greater

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percent body fat will also self-report more symptoms of psychosocial stress and depression, raising the possibility, at least in part, of an adiposity mediated effect of stress or depression on insulin resistance in youth.

### **Method**

#### **Participants**

A summary of participant characteristics can be seen in Table 12. Children were all participants of the LOOK longitudinal study cohort (Telford et al., 2009a). Participant numbers, based on blood collections collected at each year of measurement were 747, 490 and 247 in grade 2, grade 6 and grade 10 respectively. A similar number of participants also completed psychological, percent body fat, physical activity and puberty assessments. All data were used to quantify cross-sectional (between-child) relationships for IR and psychological factors. For longitudinal relationships (within-child), the general linear mixed model adjusts for any missed measurements and so maximizes use of existing data. Children were recruited into the study via the participating school principal and parents. Initially, 30 outer suburban schools, selected for their relative homogeneity to each other and in relation to the Australian average in terms of SES were approached to participate, of which 29 schools agreed. From the 890 grade 2 children enrolled in these schools, 853 children with parental consent agreed to participate. A more detailed description of the methodology of sampling and procedure can be found in Telford et al. (2009a).

#### **Attrition**

Fifteen children withdrew from the study. The remaining missed assessments were due to either absence from school on the day of assessment, relocation to a school outside the jurisdiction, technical difficulties with blood collections or inadequate compliance with test procedures, including failure to fast and an inability to make another appointment. Children who missed an assessment in a particular year

remained in the study and were included in the analysis, with the statistical model adjusting for missing values. Despite the fact that attrition was unlikely to affect relationships (in contrast with an intervention study) we compared the characteristics at baseline of those children who later left the study. These analyses revealed that children remaining in the study had significantly healthier psychological profiles (e.g. were less stressed,  $p = .002$ ; and less depressed,  $p = .013$ ) and were thinner ( $p = .044$ ) than children leaving the study (or not participating in a given year). No further differences were observed. The potential effects of attrition need to be considered when interpreting the outcomes of the current study.

## Measures

**Psychosocial stress.** Psychosocial stress was assessed using the Children's Stress Questionnaire (CSQ; Byrne et al., 2011). The CSQ is a 50-item self-report questionnaire that assesses the self-reported impact of a range of stressor experiences relevant to children occurring over the past 12-months. Children are asked to report their stressor experience on a 5-point likert scale, ranging from 1 = *'This did not happen to me'*, 2 = *'It happened but it didn't matter to me'*, 3 = *'It made me a bit upset'*, 4 = *'It made quite upset'*, 5 = *'It made me very upset'*. Response items are then summed to form the CSQ Full scale, resulting in a full scale spanning 50 to 250, with higher scores indicating greater psychosocial stress. The CSQ has been shown to have good internal and test-retest reliability (Cronbach's alpha greater than 0.9 at each year of measurement) and both construct and predictive validity (Byrne et al., 2011).

**Depressive symptoms.** Depression was assessed using a modified version of the Children's Depression Inventory (CDI; Kovacs, 1982, 1992), the validity and reliability of which has been tested and reported elsewhere (Byrne et al., 2011; Olive, Telford, Byrne, Abhayaratna, & Telford, 2016). Modification to this scale was required to gain approval from the Jurisdiction's Department of Education. The full scale of this

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modified version comprised 19 items, with response choices limited to two (symptom present or absent). This resulted in full scale score of depression that ranged from 19 to 38, with higher scores indicating greater severity of depressive symptoms.

**Blood collection and the homeostasis model of insulin resistance.** Morning fasting blood samples were collected at participating schools by trained phlebotomists experienced with children. Breakfast was provided to children subsequent to blood collection. Serum samples were mixed and allowed to clot for up to 30 min before centrifugation. Blood was not taken from a child where there was doubt as to whether they had fasted or refrained from vigorous exercise; instead a new appointment was made. Samples were centrifuged on site for 10 min at 2850 rpm (Spintron GT-25P; Spintron Pty Ltd., Australia) and then either immediately frozen in ice and stored at -80°C for subsequent analysis or taken to the pathology laboratories at Canberra Hospital for immediate analysis. Care was taken to maximize consistency of laboratory handling of samples. All samples were subject to the same procedures, which were carried out according to instrument manufacturers' standards, and biochemical analysis was performed within acceptable limits of internal quality control. Insulin concentration was measured using microparticle enzyme immunoassay on the AXSYM (Abbott laboratories). The homeostatic model of IR (HOMA-IR) was our surrogate of insulin resistance, where;

$$HOMA-IR = [fasting\ insulin\ (mU/L) \times fasting\ glucose\ (mmol/L)]/22.5$$

This measure has been validated for use with children (Gungor et al., 2004; Huang et al., 2002) and has shown to be of acceptable reliability (Keskin, Kurtoglu, Kendirci, Atabek, & Yazici, 2005). Whilst insulin sensitivity may be a more appropriate term in asymptomatic children, HOMA-IR can be compared with previous publications in children (Jeffery et al., 2007; Metcalf et al., 2008; Srinivasan et al., 2006).

Table 12.

*Means (and Standard Deviations in Brackets) for Participant Characteristics Based on Raw Data*

	Boys			Girls		
	Grade 2	Grade 6	Grade 10	Grade 2	Grade 6	Grade 10
	N=382	N=234	N=115	N=382	N=234	N=115
HOMA-IR	0.90 (0.30, 2.09)	1.75 (0.80, 4.70)	1.70 (0.88, 5.44)	1.00 (0.40, 2.60)	2.60 (1.20, 6.73)	2.22 (1.10, 4.14)
Glucose (mmol/L)	4.74 (0.53)	5.34 (0.39)	5.20 (0.49)	4.67 (0.66)	5.33 (0.72)	5.10 (0.37)
Insulin (IU/L)	4.52 (3.37)	9.10 (6.09)	9.17 (5.28)	5.31 (4.67)	12.49 (4.67)	9.93 (4.20)
Stress	94.86 (22.90)	80.54 (21.41)	81.26 (17.46)	96.82 (21.52)	83.80 (19.77)	86.08 (18.19)
Depression	25.11 (4.26)	22.45 (3.24)	23.10 (4.18)	25.12 (4.39)	23.04(3.14)	27.28 (4.39)
%Body Fat	22.70 (5.86)	24.44 (7.20)	17.46 (7.13)	27.99 (6.35)	27.65 (6.36)	31.29 (6.08)
PA BLUPS	107.99 (11.09)	98.04 (11.38)	98.35 (12.07)	97.29 (10.06)	91.41 (9.20)	91.33 (9.61)
Puberty	NA	5.08 (1.75)	8.66 (1.24)	NA	5.44 (1.58)	8.56 (1.21)
BMI (kg/m <sup>2</sup> )	16.75 (2.47)	19.22 (3.07)	22.84 (3.07)	16.87 (2.45)	19.36 (3.06)	23.13 (3.71)

*Note.* HOMA-IR reported as median and 5<sup>th</sup> and 95<sup>th</sup> percentile; PA BLUPS is the physical activity index, approximately equal to the square root of average daily steps per day (pedometer assessed); Stress is the child's CSQ score; Depression is the child's CDI score; Puberty is Tanner Stage; BMI is body mass index.

**Percent body fat.** Percent body fat was assessed using dual energy x-ray absorptiometry (Hologic Discovery QDR Series; Hologic Inc., Bedford, MA). All scans were performed with children wearing light clothing and total body scans were analysed using QDR Hologic Software Version 12.4.7 to generate total lean tissue mass and fat mass from which percent body fat was calculated.

### **Physical activity**

Physical activity was measured using New Lifestyle pedometers (Lee's Summit, MO, USA), which record the number of steps taken per day. The validity of New Lifestyle pedometers detection mechanism has been previously demonstrated in children (Beets et al., 2005). Children wore pedometers on their hip (in line with their left patella) for seven consecutive days. A physical activity index was calculated using best linear unbiased predictor (BLUPS; Robinson, 1991) or "shrunken mean". The BLUPS index is calculated for a given individual by providing a weighted combination of the population mean and the mean for that individual. The BLUPS method was chosen for its desirable statistical properties. The details of its calculation have been previously described (see Telford et al., 2009b).

**Height and weight.** Height was measured by a portable stadiometer to the nearest 0.01 m and body weight by portable electronic scales to the nearest 0.05 kg. Assessments were conducted in private with individual children in either a hospital or school setting.

**Pubertal status.** The effects of pubertal maturation on measures of insulin sensitivity (Diabetes Control and Complications Trial Research Group, 1994), adiposity (Garnett et al., 2004) and mental health factors (Whittle et al., 2012) have been demonstrated. Therefore, pubertal maturation was assessed in the current study using the self-report Tanner stages of pubic hair, breast development, and date of menarche



(Tanner, 1962) using diagrams based on those previously described (Duke et al., 1980). In grade 2, the self-assessment took place at home with guidance from parents and in grade 6 and grade 10 the self-assessment was completed in a hospital setting under the supervision of an experienced teacher.

**Socioeconomic status.** The Australian Bureau of Statistics (ABS) Socioeconomic Indexes for Areas (SEIFA) was used as a measure of SES (ABS, 2009) as previously described.

### **Procedure**

Assessments for the present study were collected at three time points. Baseline assessments occurred in 2005 when children were in grade 2 (7 to 9 years), with follow-up assessments occurring four- and eight-years later in grade 6 (11 to 13 years) and grade 10 (15 to 17 years) respectively. Psychological data was collected at participating schools in class groups. Self-report measures of stress and depression were administered by a psychologist and were presented to children via a PowerPoint presentation using TurningPoint software. Children responded using hand-held keypads utilising KEEpad interactive software, which was relayed back via wireless connection and saved on a laptop. Each individual item was read out to children and the psychologist was able to answer any queries the children may have had regarding the meaning of questionnaire items. During the administration, time anchors, such as birthdays and major school holidays were utilised to assist children with recall and to reduce the likelihood of recall bias relating to under reporting of symptoms due to failure to recall, or from over-reporting symptoms occurring outside the measurement period. Morning fasting blood samples were collected at school by nursing staff as outlined previously. Physical activity and fitness assessments were conducted in whole class groups by the same exercise scientist across each year of measurement. For the most part, measures of psychological health, physical activity and fitness, and blood

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samples were collected on different days within a two-month window, all occurring within the same season (summer).

### **Statistical Analysis**

General linear mixed models (Galwey, 2014) were used to assess candidate relationships in the current study. The current mixed model was developed to account for the dependence structure that is a result of the current studies sampling design. This model has been previously presented in Olive et al. (2016). The mixed model used in the present study allows for analyses of regression relationships between the response variable (e.g. insulin resistance) and candidate explanatory variables (e.g. stress and depression) at both the within-child (longitudinal) and between-children (cross-sectional) level.

Our model, in adjusting for the effect school (cluster effect) acknowledges that children within the same school are subjected to shared experiences, which may result in their reported psychological or metabolic measures being more homogeneous than those of a random sample of children drawn across schools. In order for our proposed statistical model to reflect the sampling design we must specify and account for this dependence structure. Therefore, the variables between-child (within a school) and within-child are considered as random effects in our model. Final models were adjusted for percent body fat (where percent body fat was not the response variable), physical activity, puberty and SES.

Our statistical model estimates effect sizes for the expected change in the response variable (e.g. insulin resistance) over time per unit change in the explanatory variable (e.g. depression), using repeated measures obtained from the same child. Restricted maximum likelihood is used to estimate variance components and weighted least squares for estimating fixed effects. Statistical significance of effects was assessed by calculating adjusted Wald statistics (Kenward & Roger, 1997). HOMA-IR was scaled by natural logarithm to better meet linearity assumptions and a physical

activity index was calculated as previously described (Telford et al., 2009b). General model checking procedures were routinely used to identify aberrant data and to check the model assumptions. Analyses were conducted separately for boys and girls and this approach has been supported in the literature (Kurtoglu et al., 2010).

## Results

A summary of participant characteristics, based on raw scores can be seen in Table 12. Participant levels of stress and depression have been previously reported (Olive et al., 2016; and in Chapter 6) but to provide the reader with an idea of the mental health status of the current cohort, a brief summary is provided. Mental health trajectories in the current cohort were characterised by a decline in stress and depression for both boys and girls between grade 2 and grade 6, followed by a significant increase in depression for both boys and girls and a significant increase in stress for girls only between grade 6 and grade 10. With the exception of stress at baseline, where girls were significantly more stressed than boys ( $p = .009$ ), no further sex differences in stress or depression were found at age 8 or 12 years. However, by age 16 years, girls had significantly greater stress ( $p = .030$ ) and depression ( $p = .028$ ), which is consistent with previous literature (Nolen-Hoeksema, 2001).

To provide an idea of the physical health of the current cohort, by age 16 years, 13.6% of girls and 15.7% of boys had evidence of an elevated HOMA-IR of greater than three, the suggested cut-point for risk of metabolic syndrome (Tresaco et al., 2005). While suggested cut-points for HOMA-IR among paediatric populations have varied across samples (ranging from 2.5 to 4), a cut-point of three was chosen as characteristics of the sample used in Tresaco et al. (2005) more closely reflected the current sample compared to other studies (Aradillas-García et al., 2012; Madeira et al., 2008; Singh, Garg, Tandon, & Marwaha, 2013). This reflects a decrease from previous reports of the same cohort based on data from children at age 12 years (23% of boys and 31% of girls; Telford et al., 2012). The median HOMA-IR values were greater in

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girls than boys at ages 8, 12, and 16 years respectively. In addition, girls had significantly greater percent body fat than boys at each measurement period (all  $p < .001$ ). While boys showed a small but significant increase between 8 and 12 years ( $p < .001$ ), followed by a significant decrease between 12 and 16 years ( $p < .001$ ); girls were measured with a non-significant increase in percent body fat between 8 and 12 years, and a significant increase during the transition into adolescence between the ages of 12 and 16 years ( $p < .001$ ). However, it should be noted that as previously reported in Telford, Cunningham, and Abhayaratna (2014) a plateau period was evident among this cohort between ages 10 and 12 years, with no significant change in percent body fat being observed at this time. These findings were divergent to BMI measures taken from the same children at this time, where a linear increase in BMI was observed (see Telford et al., 2014).

Notwithstanding the limitations associated with BMI in longitudinal studies with children (Telford et al., 2014), the body composition of children in the current cohort were classified according to their body mass index (BMI) to assist a comparison with other studies. Among LOOK participants included in the current study by the end of grade 2 (8-years) approximately 20% of girls and 24% of boys were classified as overweight or obese; in grade 6 (12 years) this increased to 24% of girls and 25% of boy; and by grade 10 (age 16 years) 10% of girls and 7% of boys were classified as being in this category. In terms of pubertal maturations, by age 16 years, a greater proportion of girls were assessed as being further along in pubertal maturation with 27.2% of girls and 25.4% of boys self-reporting they were in stage 5 of the Tanner stages of pubertal maturation.

### **Effect of Depression and Stress on HOMA-IR**

Longitudinal analyses, based on repeated measures of the same child provided evidence of a trend that increases in depressive symptoms were associated with increases in HOMA-IR for boys, although this did not reach statistical significance ( $\beta =$

0.011,  $p = .073$ ). We found no evidence for a similar effect among girls ( $\beta = -0.008$ ,  $p = .429$ ), however, we would expect that the decrease in HOMA-IR observed among girls between age 12 and 16 years would tend to offset any relationship between depression and HOMA-IR. Similarly, we found no evidence for a longitudinal effect of stress on HOMA-IR for either boys ( $\beta = -0.001$ ,  $p = .394$ ) or girls ( $\beta = <0.001$ ,  $p = .791$ ). While this study focuses on longitudinal effects, it is still of interest that cross-sectional (between-child) relationships between HOMA-IR and depression were evident among boys only ( $\beta = 0.012$ ,  $p = .016$ ). Associations between HOMA-IR and psychosocial stress were not significant at the cross-sectional level for either boys ( $\beta = 0.002$ ,  $p = .081$ ) or girls ( $\beta = 0.001$ ,  $p = .149$ ). A summary of these effects can be seen in Table 13.

Table 13

*Table of Effects ( $\beta$ ) and Standard Error (in brackets) for Within-child and Between-child Relationships of HOMA-IR with Key Explanatory Variables Stress and Depression*

	Boys		Girls	
	$\beta$ (SE)	$p$	$\beta$ (SE)	$p$
Depression <sub>w</sub>	0.011 (0.008)	.073	-0.008 (0.007)	.429
Depression <sub>b</sub>	0.012 (0.007)	.016	-0.002 (0.006)	.803
Stress <sub>w</sub>	<-0.001 (0.003)	.394	<0.001 (0.001)	.791
Stress <sub>b</sub>	0.002 (0.003)	.081	0.001 (0.001)	.149

*Note.* <sub>w</sub> - within-child (longitudinal effect); <sub>b</sub> - between-child (cross-sectional effect)

**Effects of Depression and Stress on Percent Body Fat**

A significant longitudinal effect of depression on percent body fat was found among boys, whereby boys with greater depressive symptoms also had higher percent body fat ( $\beta = 0.127$ ,  $p = .046$ ). No evidence for a similar effect was found among girls ( $\beta = 0.048$ ,  $p = .412$ ), nor did we find any longitudinal effect of stress on percent body fat for either boys ( $\beta = -0.014$ ,  $p = .116$ ) or girls ( $\beta = 0.006$ ,  $p = .504$ ). Between-child analyses revealed a significant effect of depression on percent body fat for boys ( $\beta = 0.193$ ,  $p = .011$ ) and a significant effect of stress ( $\beta = 0.033$ ,  $p = .020$ ) on percent body fat for girls, such that children with greater stress and depression also had higher percent body fat. A summary of these effects can be seen in Table 14.

Table 14

*Table of Effects ( $\beta$ ) and Standard Error (in brackets) for Within-child and Between-child Relationships of Percent Body Fat with Key Explanatory Variables Stress and Depression*

	Boys		Girls	
	$\beta$ (SE)	$p$	$\beta$ (SE)	$p$
Depression <sub>w</sub>	0.127 (0.060)	.046	0.048 (0.049)	.412
Depression <sub>b</sub>	0.193 (0.089)	.011	0.083 (0.087)	.201
Stress <sub>w</sub>	-0.014 (0.010)	.116	0.006 (0.009)	.504
Stress <sub>b</sub>	0.021 (0.016)	.123	0.033 (0.016)	.020

<sub>w</sub> - within-child (longitudinal effect); <sub>b</sub> - between-child (cross-sectional effect)

## Discussion

The current study shows that apparently healthy boys who report more symptoms of depression have higher insulin resistance. In other words, there is a statistically significant 'dose-response' relationship, whereby higher depressive symptoms are associated with higher insulin resistance. When we consider this finding along with the longitudinal trend whereby boys displaying increased depressive symptoms develop higher insulin resistance, together with the above outlined physiological mechanistic links between stress, depression and insulin resistance, the case that early depressive symptoms in boys may be the cause of this metabolic dysfunction is strengthened. Moreover, these relationships between depressive symptoms and insulin resistance emerge after adjustment for percent body fat, a well-established contributor to higher insulin resistance (Zhang, Hu, Zhang, & Zhou, 2015). This independence of psychological association leads to even more support for the premise that early attention to depression per se in childhood and adolescence may reduce insulin resistance and ongoing metabolic dysfunction.

Two other avenues of support emerge for an effect of depression on metabolic dysfunction. Firstly, we found cross-sectional evidence that boys with higher depressive symptoms had higher percent body fat, and that boys whose depressive symptoms increased became fatter. It is well established that overweight or obese children are prone to higher insulin resistance (Telford et al., 2012) and obesity is a well-established risk factor for Type 2 diabetes (Bell, Kivimaki, & Hamer, 2014; Eckel et al., 2011; Goran et al., 2003). Our evidence that depression leads to overweight and obesity in a dose-response manner provides further reason to suggest early treatment in the onset of depression may well be an important aspect of a preventive medical role in chronic disease.

Secondly, in an earlier study (presented in Chapter 6; Olive et al., 2016) we showed that the lower the fitness and physical activity of children and adolescents the higher their depression, independent of adiposity. Physical inactivity, like obesity, has

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been shown to be associated with insulin resistance (Telford et al., 2009c; Telford et al., 2012) thereby providing another pathway that implicates depression in the onset of metabolic dysfunction and chronic disease.

So, given (a) that a boy with depressive symptoms is more likely to be insulin resistant irrespective of adiposity; (b) that a depressed child is more likely to be fatter and less physically active (both of these being risk factors for insulin resistance), and (c) the general relationship between depression and stress (another potential risk for insulin resistance), there is a bank of evidence that even early symptoms of depression are a risk factor for increased insulin resistance.

This opens up potentially important preventive medical considerations. Our data suggest that identification and treatment of early non-clinical or clinically diagnosed depression may reduce early onset insulin resistance. In turn, given that metabolic diseases may have their roots in childhood (Ehtisham, Barrett, & Shaw, 2000), early attention to children with depression, even in pre-clinical stages, may reduce the risk for chronic disease in later life. Evidence-based psychological interventions that are effective in reducing depressive symptoms, such as cognitive behavioural therapy (Butler, Chapman, Forman, & Beck, 2006; Harrington, Whittaker, Shoebridge, & Campbell, 1998), may prove useful in this context; and in light of the findings reported in Chapter 6, physical activity interventions, of a type that positively effect mood, may also prove beneficial in treating depressive symptoms in children. To date, no such intervention has been investigated among younger populations but the current findings lend support for psychological interventions that target depressive symptoms among children and adolescents as a preventative measure, or indeed in treating metabolic disorders during youth. Furthermore, these findings may provide possible avenues of exploration among the adult populations and go some way to explaining why not all patients with obesity and/or inadequate physical activity patterns develop Type 2 diabetes.



The findings reported here are supported by previous work among youth, where depression was associated with greater insulin resistance in both longitudinal (Shomaker et al., 2011) and cross-sectional investigations (Jeffery et al., 2014; Shomaker et al., 2010), and with adult data, where depressive symptoms were related to increased risk for developing Type 2 diabetes (Mezuk et al., 2008; Mezuk, Heh, Prom-Wormley, Kendler, & Pedersen, 2015). In contrast to prior studies, where participants were selected for being overweight or obese, participants in the current study were apparently healthy children drawn from the community, allowing the current findings to be generalised to the broader population.

Furthermore, our findings linking depressive symptoms in a boy, with his adiposity, is also supported by prior longitudinal studies among adolescents. For example, Stice et al. (2005) reported that among adolescents of healthy weight, baseline depression was associated with a four-fold increased risk for obesity four years later. Similar effects did not extend to girls in our cohort, which is in contrast to what has been previously reported (Goodman & Whitaker, 2002). There is no obvious reason as to why these relationships did not extend to girls, given adjustments were made for puberty and physical activity. One potential explanation may relate to a possible response bias resulting from gender differences in self-reports of depression (Sigmon et al., 2005), which may have emerged as children moved into adolescence. And while there has been a focus on girls in the literature investigating the link between increased fatness and aspects of poor mental health (Lawler & Nixon, 2011; Olive et al., 2012), the findings reported here linking depression and percent body fat lend support to the premise that males possibly face similar pressure to meet an ideal body type that may relate to negative mood states, which is less often reported in the literature.

It is also worth noting that despite commonly held beliefs that depression and childhood obesity are related, few longitudinal studies have been able to demonstrate this association among younger populations. In contrast to the adolescent literature,

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the majority of longitudinal studies among children report that depressive symptoms do not predict later BMI change, body fat or obesity status (for a review see Incedon, Wake, & Hay, 2011). The weaker findings reported among children compared to adolescents may be indicative of the age at which this relationship first arises. Alternatively, this may reflect methodological limitations, with much of the childhood literature being confounded by low methodological quality, including the use of non-validated assessments and in some instances, relying on self-reported height and weight when calculating BMI (Incedon et al., 2011). Further to these limitations, while BMI may provide a reasonable means of classifying fatness, it is problematic and misleading when used in longitudinal analyses with growing children (Telford et al., 2014).

The current study extends prior research among children and adolescents by utilising a longitudinal design spanning eight years, with multiple follow-up assessments spanning both child and adolescent development. A strength of the work reported here was the use of an objective assessment of body fat and therefore not having to rely on BMI as a surrogate measure of adiposity, which can be problematic in longitudinal studies among growing children (Telford & Cunningham, 2008). Another strong aspect was the statistical adjustment for a number of potentially confounding covariates, which became evident as part of the larger multidisciplinary LOOK study, including pubertal stage, the absence of which has been identified as a weakness in prior studies (Incedon et al., 2011).

On the other hand, a number of limitations exist including the rate of attrition from baseline. Our analyses of those who left the study compared to those who remained reveal significant differences in the response variable, percent body fat, indicating that children leaving the study had greater percent body fat at baseline than those remaining in the study. Children who remained in the study were also less stressed and less depressed at baseline. Any influence of this difference in participants is likely to result in an under reporting of the effects investigated in this study, with the

potential for stronger relationship occurring among children with greater symptoms of psychological distress and greater percent body fat. The reliance on self-report measures to assess both psychosocial stress and depressive symptoms may also be seen as a limitation; without additional measures of physiologically based stress responses, our assessments are limited in their ability to identify clinically relevant levels of psychopathology, which may be related to risk for later chronic disease (Badimon et al., 2012; Dekker et al., 2000; Turner et al., 2005). However, self-reported assessments of psychosocial stress are a common practice in field work and the current study was not focussed on assessing clinical depression per se but rather on early symptoms, within a preventive medicine framework in a sample of apparently healthy youth. A final limitation was that, although we investigated a community-dwelling sample of apparently healthy and predominantly white children, the findings may not be generalizable to youth of different nationality with differing SES and ethnicity.

### **Conclusion**

In summary, the current study provides evidence that apparently healthy boys, who report more symptoms of depression, have higher insulin resistance, together with some evidence that when they show an increase in depressive symptoms their insulin resistance is increased. In addition, boys whose depressive symptoms increased were more likely to become fatter. Taken together, along with the fact that there are likely plausible biological mechanisms that may link psychological risk factors with insulin resistance, the case that early depressive symptoms in boys may be the cause of this metabolic dysfunction is strengthened. The evidence presented here points to the potential efficacy of a novel approach to the prevention of metabolic and chronic diseases; one which focuses on the treatment of early onset depression and depressive symptoms in children and adolescents.

### **Chapter Conclusions**

Based on the findings from the first two empirical studies, there is an emerging story that symptoms of psychosocial stress and depression, experienced earlier in the life course may negatively influence the risk for later CVD. The findings reported in this chapter provide strong evidence for this line of thinking, given the direct link between insulin resistance and percent body fat with pre-clinical depressive symptoms. The current investigation now moves to adolescence, where we seek to articulate the potential impact of psychological factors on more direct measures of cardiovascular function, introducing a set of intermediary risk markers for CVD. Specifically, the following chapter investigates the impact of psychosocial stress and depressive symptoms on arterial function, namely arterial stiffness and blood pressure.

## CHAPTER 8

# THE EFFECT OF PSYCHOSOCIAL STRESS AND DEPRESSIVE SYMPTOMS ON BLOOD PRESSURE AND ARTERIAL STIFFNESS THROUGH ADOLESCENCE: THE LOOK LONGITUDINAL STUDY

### Publication

Olive, L. S., Telford, D. T., Byrne, D. G., & Abhayaratna, W. P. (under review) Psychosocial stress, depression and arterial function through adolescence: The LOOK longitudinal study. Submitted to *The American Journal of Hypertension* (February 2016).

### Context Statement

Given the findings arising from the first two empirical chapters, suggesting that primordial risk factors for CVD are influenced by depressive symptoms, we sought to extend the scope of this work by determining whether these relationships were also evident among more direct and prognostically significant measures of cardiovascular health. A measure of arterial stiffness was, therefore, introduced based on evidence of its predictive capacity for determining CVD risk (Ben-Shlomo et al., 2014; Willum Hansen et al., 2006), and its appropriateness for use in our young sample, with changes in arterial function, including increased stiffening, being previously documented in youth (Hudson, Rapala, Khan, Williams, & Viner, 2015). Measures of blood pressure are also investigated in the current study to contribute to our understanding of the effects of psychosocial stress and depressive symptoms on arterial function during adolescence.

Assessments of arterial stiffness and blood pressure took place at the final two measurement periods of the LOOK Study, in grade 6 and grade 10, our cohort better

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described as adolescents rather than children. Moreover, given the level of attrition in LOOK over the later years, the investigations reported in this chapter are conducted on the combined sample, rather than split by gender, with the aim of increasing statistical power. Consequently, it is important to adjust for sex in our statistical models, given the differences that have emerged so far on a number of physiological and psychological aspects between boys and girls of our cohort; but also in terms of differences in arterial stiffness between the sexes, with females generally displaying greater arterial stiffness (Ahimastos, Formosa, Dart, & Kingwell, 2003; Rossi, Frances, Kingwell, & Ahimastos, 2011).

**Abstract**

**Background:** Among adults, psychosocial stress and depression are associated with greater arterial stiffness, and with high blood pressure and hypertension. Very few reports exist which examine these relationships in younger populations, particularly those using longitudinal designs.

**Aim:** The purpose of the present study was to evaluate the effect of psychosocial stress and depression on blood pressure and arterial stiffness in a prospective cohort study of Australian boys and girls followed through to adolescence.

**Method:** Participants were initially 486 (239 girls; *M* age = 11.6 years) healthy children. The Children's Depression Inventory was used to assess depressive symptoms and psychosocial stress was measured via the Children's Stress Questionnaire. Central pulse wave velocity, a measure of arterial stiffness, was assessed using applanation tonometry, as was mean arterial pressure; with further assessments of supine brachial blood pressure and percent body fat (dual x-ray absorptiometry). All measures were repeated four years later in grade 10, at age 16 years.

**Results:** We found no cross-sectional or longitudinal evidence that children self-reporting higher levels of psychosocial stress and depressive symptoms had greater arterial stiffness. However, children who reported an increase in depressive symptoms had an increase in diastolic blood pressure ( $\beta = 0.161$ ,  $p = .030$ ) and mean arterial pressure ( $\beta = 0.182$ ,  $p = .016$ ). An effect was also found for pulse pressure, where higher pulse pressure was found in children with lower psychosocial stress at grade 2 ( $\beta = -0.109$ ,  $p = .020$ ), and in children self-reporting a decrease in stress between grade 6 and grade 10 ( $\beta = -0.182$ ,  $p = .003$ ).

**Conclusion:** Findings from the current study contribute to the scant paediatric literature but only provide limited support for any influence of psychological factors on blood pressure. Depressive symptoms in apparently healthy adolescents may exert some influence on later risk for cardiovascular disease via increases in diastolic blood

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pressure and mean arterial pressure, but these effects were small. The negative relationship found between pulse pressure and psychosocial stress may reflect, in part, the higher diastolic pressure in children undergoing more psychosocial stress, but does indicate the difficulty in interpreting these relationships in children.



## Introduction

Depression and psychosocial stress have been identified as important risk factors for cardiovascular disease (CVD; Khayyam-Nekouei, Neshatdoost, Yousefy, Sadeghi, & Manshaee, 2013; Rosengren et al., 2004; Steptoe & Kivimaki, 2012), and there is now evidence to suggest that these associations exist even at low levels of psychological disturbance (Ariyo et al., 2000). Moreover, it is increasingly recognised that CVD has its origins in childhood (Berenson et al., 1992; Wissler et al., 1998). Similarly, both children and adolescents can experience a range of psychosocial stressors (Kessler, 1997; Kraag et al., 2006); with some going on to develop clinical depression (Birmaher et al., 1996; Ries Merikangas & He, 2014) or at least depressive symptoms (Hood et al., 2006; Roberts, Rosario, Slopen, Calzo, & Austin, 2013). Owing to the fact that psychological distress is thought to influence CVD risk, both directly via associated physiological changes (Baune et al., 2012; H. Chen, Yiu, & Tse, 2011; Dao et al., 2010; Frasure-Smith & Lespérance, 2010; Grippo & Johnson, 2009), and indirectly through invoking health compromising behaviours (e.g. physical inactivity, poor dietary habits and smoking; Bonnet et al., 2005; Jacka et al., 2014; Kinnunen et al., 2006; Rottenberg et al., 2014; Weinberger et al., 2013), early psychological based strategies may help prevent the development of CVD.

On considering the evidence linking psychosocial stress, depression and CVD, it is unlikely that the influence of psychological factors on CVD risk occurs only on reaching adulthood. While there is solid evidence indicating that depression and psychosocial stress are linked to both the aetiology and prognosis for CVD in adults (Frasure-Smith & Lespérance, 2006; Leung et al., 2012; Nicholson et al., 2006; O'Brien et al., 2014; Rosengren et al., 2004; Van der Kooy et al., 2007), there is currently little evidence of this (aetiological) relationship among young populations, where it is theorised that a similar relationship exists. Although it is not possible to assess these relationships in terms of disease end-points, which are rarely present among children and adolescents, investigations into the relationship between physiological and

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prognostically significant measures of cardiovascular health and pre-clinical psychological stress and depression have been reported (Chen et al., 2012; Dietz & Matthews, 2011; Lambiase et al., 2012; Low et al., 2009; Roemmich et al., 2011). Advancements in non-invasive methods for assessing cardiovascular function have facilitated research in this area with younger populations, and one area that has attracted attention has been the assessment of arterial stiffness.

In adults, pulse wave velocity (PWV), a measure of arterial stiffness, has proven to be a good predictor of major cardiovascular events, (Ben-Shlomo et al., 2014; Mattace-Raso et al., 2006; Vlachopoulos et al., 2010) and all-cause mortality (Laurent et al., 2001) independent of traditional cardiovascular risk factors. Moreover, associations between PWV and psychological disturbance have also been reported in the literature (Dietz et al., 2011; Logan et al., 2012; Tiemeier, Breteler, van Popele, Hofman, & Witteman, 2003). For example, carotid-femoral PWV (considered to be the “gold standard” measure of regional arterial stiffness; Laurent et al., 2006; Van Bortel et al., 2012) has been associated with both acute psychological stress (Vlachopoulos et al., 2010; Vlachopoulos et al., 2006) and chronic life stress (Bomhof-Roordink et al., 2015). Contradictory findings have also been reported in the context of work stress (Nomura, Nakao, Karita, Nishikitani, & Yano, 2005), where greater arterial stiffness was associated with lower levels of work place stress (job strain). However, in that study a measure of brachial PWV was utilised, a procedure thought to be problematic due to the introduction of systematic errors relating to the amplitude of the pressure wave, which is higher in peripheral than central arteries (Laurent et al., 2006; Sakuragi & Abhayaratna, 2010). Similarly, increased arterial stiffness has been linked with the experience of clinical depression, including DSM-IV diagnosed major and minor depression (American Psychiatric Association, 2000) and dysthymia (Oulis et al., 2010; Satoh, Fujii, & Tsutsui, 2015; Seldenrijk et al., 2011); and with depressive symptoms among adults, including the elderly (Tiemeier et al., 2003).

Given the evidence that exists among adults linking arterial stiffness with depression and to some degree psychosocial stress, research in children and adolescents is beginning to adopt a similar focus. Adolescence is a period of transition, marked by stress for many, and the emergence of psychopathology, including depressive presentations, is distinctly increased compared to childhood (Lawrence et al., 2015; Sawyer et al., 2001). Moreover, the systematic plasticity that is characteristic of youth growth and development may render the adolescent brain and cardiovascular system even more susceptible to underlying psychophysiological disruption, which in turn, may link psychosocial stress and depression to risk of CVD, and further, to CVD in adulthood.

In addition, the beginnings of arterial stiffness have been shown to occur in younger populations (Núñez et al., 2010), making it an appropriate indicator of vascular health at this early age. While it is acknowledged that arterial stiffness is not the only cardiovascular risk marker that may be important in terms of predicting cardiovascular health, decreased arterial compliance is considered one of the earliest detectable manifestations of adverse structural and functional changes within the vascular wall (Cavalcante, Lima, Redheuil, & Al-Mallah, 2011; O'Rourke & Mancia, 1999). In addition, previous evidence has indicated that greater arterial stiffness is evident among youth displaying higher levels of depressive symptoms and chronic stress (Dietz & Matthews, 2011; Su et al., 2014). Dietz and Matthews (2011) found a significant association between depressive symptoms and arterial stiffness among a sample of healthy adolescent boys and girls after adjustments for a number of important sociodemographic, clinical, and psychological confounders. Sub-analyses in this study, which separated adolescents based on depression severity (moderate vs. severe) indicated that more severe depressive symptoms were associated with higher PWV (where higher PWV is indicative of greater arterial stiffness) compared to moderate symptoms. This is suggestive of a dose-response relationship between impaired arterial function and depression, as documented in adults (Seldenrijk et al.,

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2011). Similarly, Su et al. (2014) found that in healthy adolescents and young adults, those exposed to a moderate or severe level of adverse events (chronic stressors) during the first 18 years of life had higher PWV compared to those not exposed.

Clinically high blood pressure is also an important CVD risk factor, and one that has received much attention in studies investigating the role of psychological factors in the risk for CVD development. Studies among adults have suggested that chronic exposure to stress increases current and prospective blood pressure (Carroll et al., 2001; Chida & Steptoe, 2010; Gasperin, Netuveli, Dias-da-Costa, & Pattussi, 2009); and depression is positively associated with hypertension (Adamis & Ball, 2000; Nakagawara, Witzke, & Matussek, 1987; Scalco, Scalco, Azul, & Lotufo Neto, 2005) and its incidence (Davidson, Jonas, Dixon, & Markovitz, 2000; Jonas, Franks, & Ingram, 1997; Meng, Chen, Yang, Zheng, & Hui, 2012). However, the evidence has been inconclusive, with reports of either positive, negative, or borderline relationships (Delaney et al., 2010; Everson, Kaplan, Goldberg, & Salonen, 2000; Hildrum, Romild, & Holmen, 2011; Jonas et al., 1997; Meyer, Armenian, Eaton, & Ford, 2004; Patten et al., 2009; Phillips, 2011; Shinn, Poston, Kimball, St Jeor, & Foreyt, 2001; Vogt, Pope, Mullooly, & Hollis, 1994; Yan et al., 2003). Fewer studies have examined the prospective effects of psychosocial stress relating chronic day-to-day “hassles” (representing the way in which individuals respond to daily stressors in their normal lives) on current and future blood pressure. Moreover, literature into the prospective effects of both psychosocial stress and depression on blood pressure among younger populations is sparse.

Most of the paediatric literature has focused on assessing the effects of acute-mental stressors introduced in laboratory settings and cardiovascular reactivity. It has been reported that systolic blood pressure (SBP) and diastolic blood pressure (DBP) increase on exposure to controlled mental stress (Roemmich et al., 2011; Roemmich et al., 2009); and that the reported increase in SBP reactivity has been associated with greater carotid intima-media thickness (CIMT), a pre-clinical marker of CVD (Lambiase

et al., 2012; Roemmich et al., 2011; Roemmich et al., 2009). While these studies have the benefit of more controlled laboratory conditions, they are limited in their ecological validity, and have, for the most part, been cross-sectional in design. Given the chronic nature of CVD, it is theorised that to have a significant clinical impact on cardiovascular function and subsequent CVD development, psychological exposures would also need to be chronic in nature.

One study that did investigate chronic life stress among youth reported that higher DBP was found amongst adolescents self-reporting greater chronic stress (assessed via the Life Events Questionnaire for Adolescence); and increases in chronic stress were predictive of an increase in cardiovascular reactivity in both SBP and DBP (Low et al., 2009). Only one study has investigated the prospective association between blood pressure and depression among youth (Hammerton, Harold, Thapar, & Thapar, 2013). Here, it was found that lower SBP was predictive of future new-onset depressive disorder. Interestingly, this effect was not apparent in investigations involving adolescents from the general population, where a weak positive association was reported between blood pressure and future depressive disorder; nor did the authors find any evidence to suggest that a depressive disorder at baseline was predictive of future blood pressure (Hammerton et al., 2013). The latter study suggests that the direction of effect for blood pressure on depression may be influenced by the individual's level of risk for developing depression, suggestive of a genetic influence. Adolescents in that study were deemed at risk if their parents had a diagnosable depressive disorder, indicating there might be a shared genetic or environmental component contributing to both low blood pressure and depression. More prospective evidence is required among younger populations and across populations of varying risk, to determine whether these findings can be replicated.

Investigations of the influence of psychological factors on arterial function and blood pressure among youth are important for progressing our understanding of the earliest stages of CVD and the possible contribution of psychological distress. The

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paucity of studies investigating the effects of psychosocial stress and depression on arterial function among children and adolescents opens up a new and productive area of research, which may lead to novel preventive strategies in youth. Moreover, the conflicting findings in the blood pressure literature calls for further studies utilising robust and prospective designs to increase our understanding of the direction of these relationships. Despite the complexities of research in rapidly developing and apparently healthy young bodies, one advantage of working with children and adolescents is the absence of the treatments that accompany adults with CVD, especially those pharmacological, which are potentially confounding and require careful control.

The aim of the current study was to explore the prospective relationship between psychosocial stress and depression with arterial function, namely arterial stiffness, and blood pressure. It is hypothesised that children who increase in stress and depressive symptoms between grade 6 and grade 10 will also show an increase in arterial stiffness (e.g. increased PWV) and blood pressure. Similarly, it is hypothesised that at the cross-sectional level children displaying greater arterial stiffness (e.g. higher PWV) and higher blood pressure will also be measured with greater levels of psychosocial stress and depressive symptoms at both grade 6 and grade 10.

### **Method**

#### **Participants**

Participants were recruited from 29 primary schools in the outer suburbs of the Australian Capital Territory (ACT) to form the cohort of the LOOK Study. This resulted in 853 grade 2 children being recruited. Data reported on in the current study are from the two most recent measurement periods of LOOK collected in 2009 and 2013, which reflects the period of transition from grade 6 in primary school to grade 10 in high school. At grade 6, the sample consisted of 520 children (265 boys, 255 girls; *M* age = 11.6 years).

## Attrition

The natural attrition from a longitudinal study such as this is not uncommon, but it is pertinent to report that the primary reason for attrition between intake and follow-up was movement of families out of location, school closures or absences from school on the day of testing. In addition, 15 of the initial 853 children who provided consent to participate, withdrew from the study. Analyses investigating differences in key variables between children who left the study and those making up the current sample indicated no significant differences in baseline PWV or blood pressures measures between the two groups. However, children who left the study and non-participants (e.g. children absent on testing days) were significantly more stressed at baseline than children remaining in the study ( $p = .011$ ). The potential effect of attrition on psychosocial stress should be considered when interpreting the findings of this study.

## Measures

**Children's Stress Questionnaire.** Psychosocial stress was assessed using the Children's Stress Questionnaire (CSQ: Byrne et al., 2011), which is a 50-item self-report questionnaire. The CSQ assesses the occurrence and impact of a range of stressor experiences relevant to children and is an extension of the well validated and reliable Adolescent Stress Questionnaire (ASQ: Byrne et al., 2007; McKay, Percy, & Byrne, 2014). The validity and reliability of the CSQ has previously been shown and a more detailed explanation of the development of the CSQ can be found in Byrne et al., (2011). Response options for each item are scored on a 5-point Likert scale ranging from 1 = *'This did not happen to me'*, 2 = *'It happened but it didn't matter to me'*, 3 = *'It made me a bit upset'*, 4 = *'It made quite upset'*, 5 = *'It made me very upset'*. This resulted in a full scale score ranging from 50 to 250 with higher scores on the CSQ indicate greater levels of stressor experience.

**Children's Depression Inventory.** Depression was assessed in the LOOK study using a modified version of the Children's Depression Inventory (CDI: Kovacs, 1982, 1992). Response options were limited to a forced-choice (symptom present or absent) response format and items indicating conspicuous clinical depression (persistent crying, suicidal ideation and worthlessness) were removed from the CDI in order to gain ethics approval among the initially young population of LOOK. The original CDI has demonstrated validity and reliability in assessing clinical and sub-clinical depression in 12 to 16 year olds (Kovacs, 1992). Our modified version has also been shown to have sound validity and reliability (see Olive et al., 2016). This resulted in a full scale ranging from 19 to 38, whereby higher scores indicate greater depressive symptoms.

**Pulse wave velocity.** Carotid-femoral PWV, the gold standard measure of arterial stiffness, was assessed non-invasively using the SphygmoCor system (AtCor Medical, Sydney, Australia). Electrocardiogram-gated carotid and femoral waveforms were recorded using applanation tonometry. Carotid-femoral path length was measured as the difference between the surface distances joining, (1) the suprasternal notch, the umbilicus and the femoral pulse, and (2) the suprasternal notch and the carotid pulse. Carotid-femoral transit time was estimated in 8 to 10 sequential femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. Pulse wave velocity was calculated as the carotid-femoral path length divided by the carotid-femoral transit time, whereby higher PWV is indicative of greater arterial stiffness. This method is considered to be the gold standard in arterial stiffness measurement (Laurent et al., 2006; Van Bortel et al., 2012). In addition, mean arterial pressure (MAP) was obtained from the pressure waveform and pulse pressure was obtained from pulse wave analysis of radial applanation tonometry, using transfer function (SphygmoCor Windows software).



**Blood pressure.** Supine brachial blood pressure was determined using an automated oscillometric Omron 7051T. The average of two measurements made at one minute intervals was recorded for both SBP and DBP. Blood pressure measurements were taken in a quiet room, where children rested in the supine position for five minutes prior to measurement. A measure of pulse pressure was calculated by subtracting DBP from SBP (Franklin, Khan, Wong, Larson, & Levy, 1999).

#### **Covariate measures**

**Percent body fat.** Body composition was measured using dual x-ray absorptiometry (DXA, Hologic Discovery QDR Series, Hologic Inc., Bedford, MA, USA) and QDR Hologic Software Version 12.4:7 was used to generate fat mass and percent body fat calculation.

**Height.** Height was measured by a portable stadiometer to the nearest 0.01m. Height measurements were collected at the school in a quiet area away from other participants.

**Socioeconomic status.** The ABS Socioeconomic Indexes for Areas (SEIFA) was used as a measure of SES (ABS, 2009), as previously described. Schools participating in the current study were relatively homogeneous in terms of SES. The average SES index of the suburbs in the current study ( $M = 1085$ ,  $SD = 40$ , range 982 to 1160) was higher than the average index of all towns and cities throughout Australia ( $M = 980$ ,  $SD = 84$ , range 598 to 1251).

#### **Statistics**

In the current study, we chose to analyse change in the cardiovascular health measures from grade 6 to grade 10 as the response variables, thus eliminating statistical complication arising from dependencies associated with the repeated-

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measures nature of these data. However, we included 'school' as a random factor to allow for the possibility of a school (cluster) effect on changes in cardiovascular health outcomes. This effect was not found to influence the reported relationships and did not improve the model fit, and was therefore removed from the final working model. General linear modelling was used to quantify and assess the effects of change in psychosocial stress and depression on change in carotid-femoral PWV and blood pressure measures. Our models included adjustment for any effect of variation in the initial (grade 6) measurements on these differences. Other concomitant variables such as gender, age, SES, MAP, height and percentage of body fat were considered and assessed as possible confounders for PWV measures. The statistical software used to analyse our data was R version 3.1.1 (R Core Team, 2012).

### Results

With a focus on the transition from childhood into adolescence, firstly we investigated the effect of psychosocial stress and depression on PWV. Measures were taken in grade 6 (11 to 13 years), and grade 10 (15 to 17 years). Four hundred and eighty-six children (247 boys and 239 girls) completed valid assessments of all measures in grade 6, with 211 children (101 boys and 110 girls) completing all measures at follow-up four years later.

#### Participant Characteristics

A summary of participant characteristics can be seen in Table 15. There were changes in psychological health during the developmental period spanning grade 6 to grade 10. A significant increase in depressive symptoms for both boys and girls (73.7% of boys,  $p < .001$ ; and 77.9% of girls,  $p < .001$ ); and a significant increase in psychosocial stress for girls (59.1% of girls,  $p = .019$ ) and a non-significant increase for boys (56.4% of boys,  $p = .912$ ), were evident, with some children experiencing symptoms that might be considered troubling, if not clinically significant. However, this

was not the case for all children, with a proportion of participants having reductions in both depression (20.2% of boys and 15.9% of girls) and stress (41.6% of boys, 35.7% of girls). No significant gender differences were observed between boys and girls for either psychosocial stress or depressive symptoms, with the exception of the pattern of change over time in depression (time x gender interaction;  $p = .048$ ), which indicated that girls had a steeper increase in depressive symptoms between grade 6 and grade 10 compared to boys.

Similar to psychological measures, increases in carotid-femoral PWV were observed for the majority of boys (78.6%) and girls (73.2%), however, these increases were not significant (both  $p > 0.1$ ). Similarly, no significant differences were observed between boys and girls PWV ( $p > 0.2$ ). A non-significant increase in MAP was observed for both boys and girls (both  $p > 0.4$ ). In terms of blood pressure measures, significant increases in blood pressure (SBP, DBP, and pulse pressure) were observed for boys (all  $p < 0.01$ ), however, the increases seen in girls were not significant (all  $p > .05$ ). Boys had a significantly greater increase in SBP ( $p < .001$ ) and pulse pressure ( $p < .001$ ); and a significantly greater decrease in DBP compared to girls over time ( $p = .006$ ).

Similar to psychological measures, increases in carotid-femoral PWV were observed for the majority of boys (78.6%) and girls (73.2%), however, these increases were not significant (both  $p > 0.1$ ). Similarly, no significant differences were observed between boys and girls carotid-femoral PWV ( $p > 0.2$ ). A non-significant increase in MAP was observed for both boys and girls (both  $p > 0.4$ ). In terms of blood pressure measures, significant increases in blood pressure (SBP, DBP, and pulse pressure) were observed for boys (all  $p < 0.01$ ), however, the increases seen in girls were not significant (all  $p > .05$ ). Boys had a significantly greater increase in SBP ( $p < .001$ ) and pulse pressure ( $p < .001$ ); and a significantly greater decrease in DBP compared to girls over time ( $p = .006$ ).

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Table 15.

*Participant Characteristics (Means and Standard Deviation in Brackets) Categorised by Gender and Grade*

	Boys		Girls	
	Grade 6 (N = 293)	Grade 10 (N = 123)	Grade 6 (N = 276)	Grade 10 (N = 146)
Age, years	12.6 (0.36)	15.6 (0.24)	13.9 (0.55)	15.5 (0.53)
Depression*	22.84 (3.30)	26.24 (4.17)	22.92 (2.98)	27.39 (4.39)
Stress**	80.57 (21.64)	81.62 (17.04)	83.20 (17.76)	85.84 (17.89)
PWV, m/sec	5.0 (2.0)	5.2 (0.7)	5.0 (1.8)	4.9 (0.6)
MAP, mmHg	78 (8)	78 (7)	80 (8)	79 (7)
Brachial SP, mmHg	116 (12)	127 (9)	116 (11)	117 (8)
Brachial DP, mmHg	62 (7)	60 (7)	64 (7)	63 (6)
Brachial PP, mmHg	53 (10)	67 (8)	52 (9)	54 (7)
% Body Fat	24.9 (7.3)	18.4 (7.3)	28.2 (6.4)	31.4 (5.9)
Height, cm	153.61 (7.68)	175.72 (7.11)	153.98 (6.85)	164.18 (6.34)

\*Depression - depressive symptoms reported on Children's Depression Inventory;

\*\*Stress - Children's Stress Questionnaire

**Effect of depression and stress on Carotid-Femoral Pulse Wave Velocity and Mean Arterial Pressure**

During the transition from late-childhood to adolescence, our longitudinal data did not reveal any significant effects that children who self-reported increases in psychosocial stress ( $\beta = -0.005$ ,  $p = .954$ ) or depression ( $\beta = 0.118$ ,  $p = .161$ ) also had higher carotid-femoral PWV. Further analysis, at the cross-sectional level also revealed no significant effect of either psychosocial stress or depression on carotid-femoral PWV among our cohort at either grade 6 (baseline: stress  $\beta = 0.041$ ,  $p = .367$ ; depression  $\beta = 0.039$ ,  $p = .390$ ) or grade 10 (four-year follow-up: stress  $\beta = -0.085$ ,  $p = .184$ ;

depression  $\beta = -0.019$ ,  $p = .776$ ). A summary of these findings are presented in Table 16.

**Post-hoc analyses.** To further test the robustness of our models, it was of interest to determine whether any relationship between psychological factors and carotid-femoral PWV existed in children who displayed riskier profiles, both in terms of (a) higher levels of PWV and (b) a greater number of symptoms of psychosocial stress or depression, and whether this differed from relationships found among the whole cohort.

Therefore, post-hoc analyses were undertaken, firstly, to investigate the candidate relationships among participants scoring in the top 15th percentile on carotid-femoral PWV (greater than or equal to 6 m/sec). This cut-off was guided by the empirical literature and by the pattern of relationships in the current cohort, which were inspected via scatter plots. These are depicted in Figures 10 and 11 for the association between carotid-femoral PWV and depression in grade 6 and grade 10 respectively; and in Figures 12 and 13 for the association between carotid-femoral PWV and psychosocial stress in grade 6 and grade 10 respectively. These analyses did not provide evidence of a significant relationship between carotid-femoral PWV with psychosocial stress or depression among children scoring in to top 15th percentile for PWV (all  $p > .100$ ). A summary of these findings can be seen in Table 17.

Similarly, investigations among children scoring in the top 25th percentile (again, chosen for its clinical relevance with the psychological measures) for either psychosocial stress or depression were performed. Pulse wave velocity was not significantly related to either psychosocial stress or depression in these children, in either cross-sectional or longitudinal analyses (all  $p > .100$ ). A summary of these findings are summarised in Table 18.

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Table 16.

*Table of Effects for Depressive Symptoms and Psychosocial Stress with Carotid-Femoral Pulse Wave Velocity (cf PWV) and Mean Arterial Pressure (MAP)*

Variable	$\beta$	SE	$p$
<u>cf PWV</u>			
Depression Grade 6	.024	.027	.390
Depression Grade 10	-.003	.010	.776
Change Depression	.047	.034	.161
Stress Grade 6	.004	.004	.367
Stress Grade 10	-.003	.002	.184
Change Stress	.000	.008	.954
<u>MAP</u>			
Depression Grade 6	.098	.119	.413
Depression Grade 10	.044	.105	.674
Change Depression	.300	.123	.016
Stress Grade 6	.012	.018	.520
Stress Grade 10	-.005	.025	.851
Change Stress	.021	.027	.445

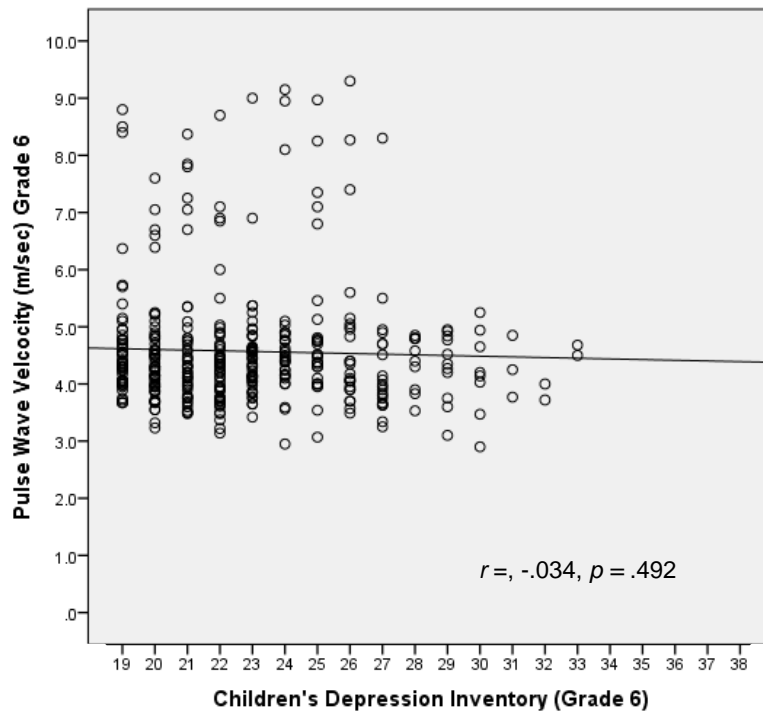


Figure 10. Scatterplot showing the association between carotid-femoral pulse wave velocity and depressive symptoms (Children's Depression Inventory) at grade 6.

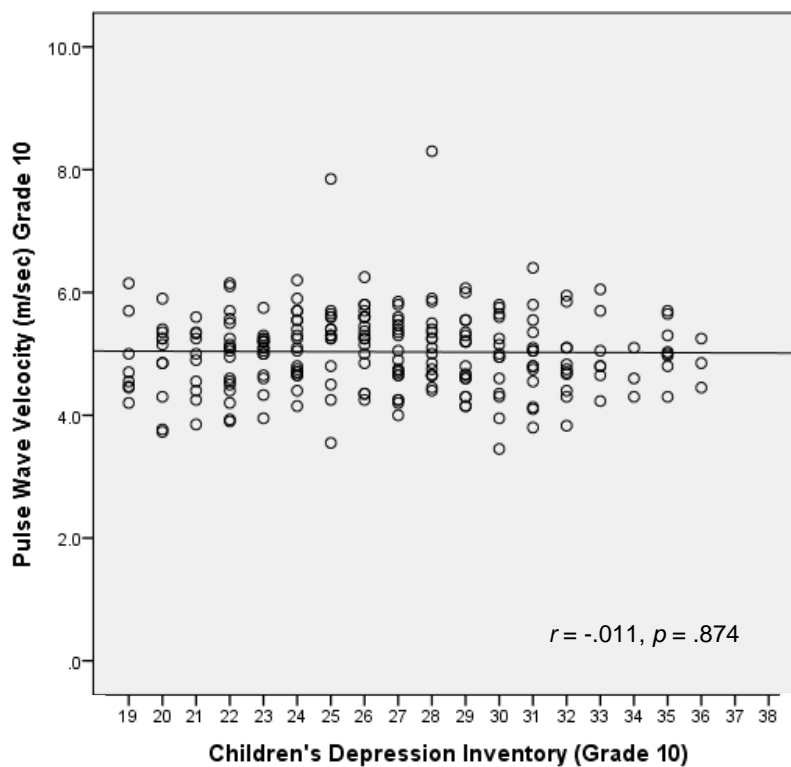


Figure 11. Scatterplot showing the association between carotid-femoral pulse wave velocity and depressive symptoms (Children's Depression Inventory) at grade 10.

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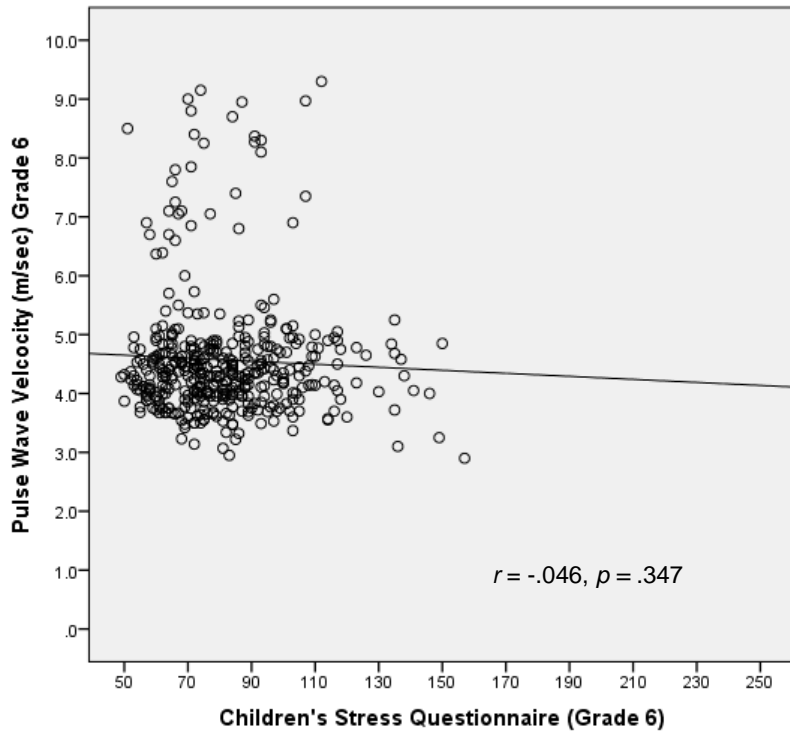


Figure 12. Scatterplot showing the association between carotid-femoral pulse wave velocity and psychosocial stress (Children's Stress Questionnaire) at grade 6.

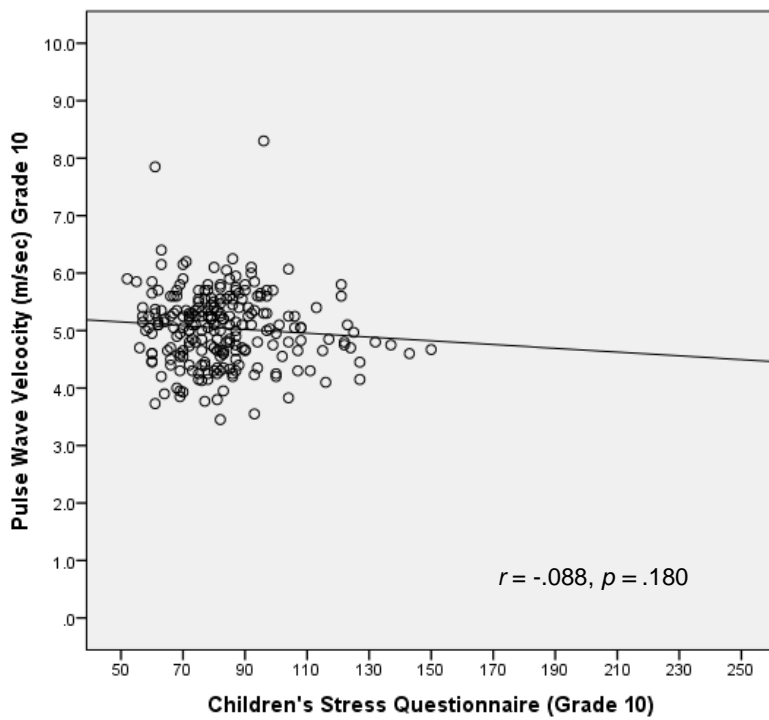


Figure 13. Scatterplot showing the association between carotid-femoral pulse wave velocity and psychosocial stress (Children's Stress Questionnaire) at grade 10.



Table 17.

*Sensitivity Analyses for Effects of Depressive Symptoms and Psychosocial Stress on Carotid-Femoral Pulse Wave Velocity in Children with High PWV*

Variable	$\beta$	SE	<i>p</i>
Depression Grade 6	.090	.058	.129
Depression Grade 10	-.001	.038	.985
Change Depression	.017	.030	.572
Stress Grade 6	.008	.008	.371
Stress Grade 10	.018	.013	.210
Change Stress	-.018	.023	.450

*Note.* High PWV = scores greater than or equal to 6 m/sec

Table 18.

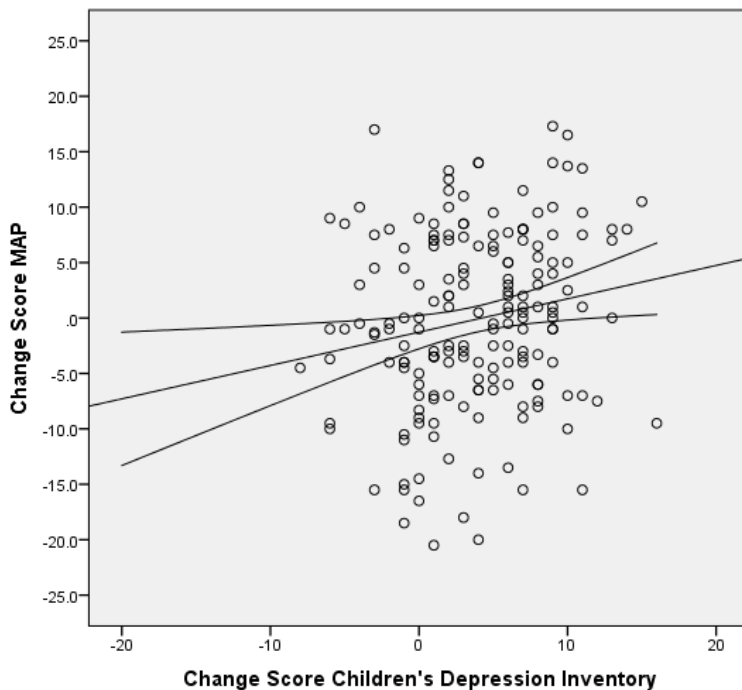
*Sensitivity Analyses for Effects of High Depressive Symptoms and Psychosocial Stress on Carotid-Femoral Pulse Wave Velocity*

Variable	$\beta$	SE	<i>p</i>
Depression Grade 6	.000	.050	.994
Depression Grade 10	.001	.012	.916
Change Depression	.058	.048	.230
Stress Grade 6	.014	.014	.321
Stress Grade 10	.000	.006	.958
Change Stress	.020	.015	.167

*Note.* Analyses include only children scoring in the top 25<sup>th</sup> percentile for depressive symptoms (CDI) and psychosocial stress (CSQ)

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Investigations into MAP revealed that children who increased in depressive symptoms also increased in MAP ( $\beta = 0.182, p = .016$ ) and this relationship can be seen in Figure 14. No longitudinal effect of psychosocial stress on MAP was found ( $\beta = 0.057, p = .445$ ); nor was there any evidence at the cross-sectional level to indicate that MAP was significantly related to either psychosocial stress (grade 6:  $\beta = 0.030, p = .520$ ; grade 10:  $\beta = -0.012, p = .851$ ) or depressive symptoms (grade 6:  $\beta = 0.038, p = .413$ ; grade 10:  $\beta = 0.028, p = .674$ ). A summary of these findings can be seen in Table 16.



*Figure 14.* Effect and 95% confidence for change in Children's Depression Inventory on change in mean arterial pressure (MAP) between grade 6 and grade 10.

### **Effect of depression and stress on Blood Pressure**

Our longitudinal data provided no evidence to indicate that children self-reporting increases in either psychosocial stress ( $\beta = -0.088, p = .199$ ) or depressive symptoms ( $\beta = 0.096, p = .166$ ) also had higher SBP. However, it was observed that a

child reporting an increase in symptoms of depression had higher DBP ( $\beta = 0.161$ ,  $p = .030$ ; (Figure 15); and there was a similar trend for children reporting an increase in psychosocial stress to have higher DBP ( $\beta = 0.129$ ,  $p = .079$ ). Investigations into psychological effects on pulse pressure revealed that children reporting a decrease in psychosocial stress had lower pulse pressure ( $\beta = -0.182$ ,  $p = .003$ ; Figure 16). Similar effects were found in cross-sectional analyses at grade 6, whereby children with higher pulse pressure also reported lower levels of psychosocial stress ( $\beta = -0.109$ ,  $p = .020$ ). A summary of relationships between pulse pressure and symptoms of psychosocial stress and depression can be seen in Table 19. No significant cross-sectional associations were found for either SBP or DBP with symptoms of psychosocial stress or depression at either grade 6 or grade 10. A summary of both longitudinal and cross-sectional effects relating to SBP and DBP is provided in Table 20.

Table 1.

*The Relationship between Pulse Pressure with Depression and Psychosocial Stress*

	$\beta$	SE	$p$
Depression Grade 6	-.093	.139	.503
Depression Grade 10	-.177	.120	.141
Change Depression	-.014	.152	.925
Stress Grade 6	-.050	.021	.020
Stress Grade 10	-.049	.028	.086
Change Stress	-.096	.032	.003

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Table 20

*Table of Effects for Depressive Symptoms and Psychosocial Stress with Systolic (SBP) and Diastolic (DBP) Blood Pressure*

Variable	$\beta$	SE	<i>p</i>
<u>SBP</u>			
Depression Grade 6	.013	.172	.938
Depression Grade 10	-.133	.134	.324
Change Depression	.148	.178	.166
Stress Grade 6	-.028	.027	.288
Stress Grade 10	-.047	.032	.142
Change Stress	-.050	.039	.199
<u>DBP</u>			
Depression Grade 6	.104	.104	.315
Depression Grade 10	.054	.099	.589
Change Depression	.254	.117	.030
Stress Grade 6	.020	.016	.202
Stress Grade 10	.004	.024	.876
Change Stress	.045	.026	.079

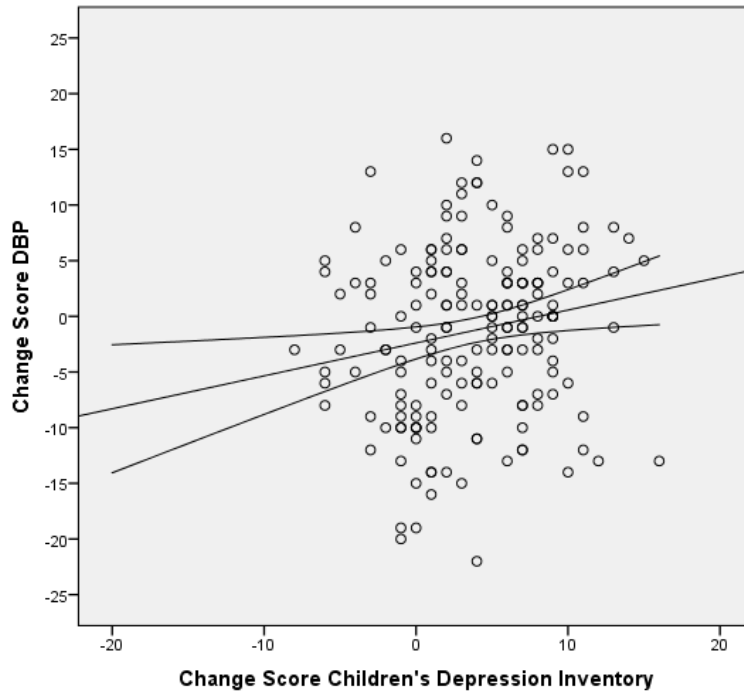


Figure 15. Effect and 95% confidence interval for change in Children's Depression Inventory Full Scale score on change in diastolic blood pressure (DBP) between grade 6 and grade 10.

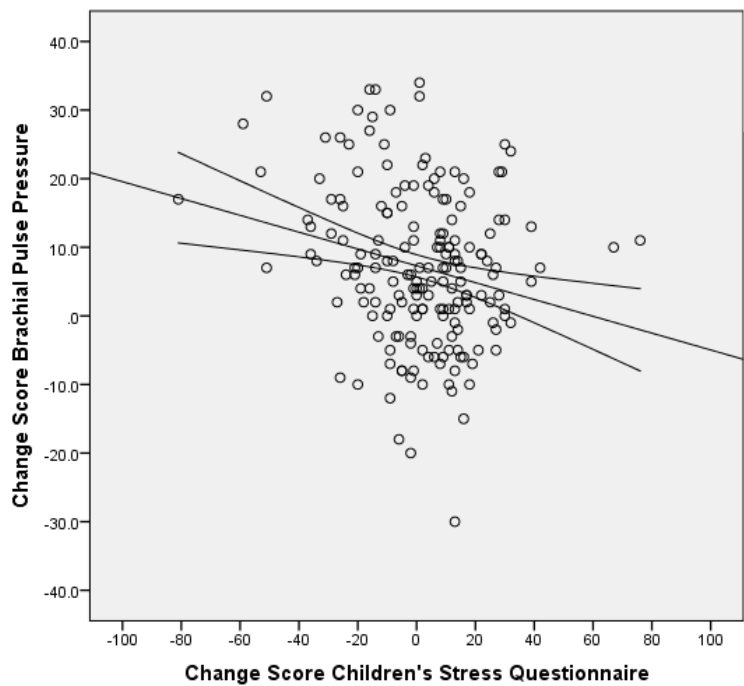


Figure 16. Effect and 95% confidence for change in Children's Stress Questionnaire on change in pulse pressure between grade 6 and grade 10.

### Discussion

This study investigated the effects of symptoms of psychosocial stress and depression on arterial stiffness and blood pressure in apparently healthy community-dwelling children, who were followed through to adolescence. Our data provide evidence that DBP and MAP increased in children who developed more symptoms of depression. Furthermore, children with greater psychosocial stress in grade 6 had lower pulse pressure, and those whose psychosocial stress decreased were also measured with increased pulse pressure. There was no evidence of any effect of psychosocial stress or depressive symptoms on arterial stiffness (aortic stiffness) in either cross-sectional or longitudinal investigations.

This study is the first (to our knowledge) to investigate the potential influence of psychosocial stress and depressive symptomology on current and future blood pressure among adolescents. Our finding that adolescents self-reporting an increase in depressive symptoms also had higher MAP and DBP (longitudinal) provides preliminary evidence that changes in blood pressure are affected by depressive symptomology, even those of a pre-clinical level. Whilst these effects might be considered modest, they are supported by adult data showing that depression increases the risk of high blood pressure (Patten et al., 2009), and in younger adults, that depression is predictive of later hypertension (Davidson et al., 2000; Rutledge & Hogan, 2002). Such findings are consistent with reports that DBP is more sensitive to psychosocial stress than SBP (Mann et al., 2015), and are further supported by prior findings among younger populations, indicating that DBP may be a better means of risk assessment in younger subjects, due to its relationship with central pressure. In younger populations, DBP has been shown to be a more accurate surrogate of central systolic and pulse pressure. Although the reasons explaining this difference in younger populations compared to older subjects is not entirely clear, it has been hypothesised that that “an age dependant differences in the amplification of the pressure wave form as it moves from the aorta to the brachial artery may be responsible” (Wilkinson,

Franklin, Hall, Tyrrell, & Cockcroft, 2001, p.1463). In support of this hypothesis, Wilkinson et al. (2001) found that pressure amplification is reduced as peripheral diastolic pressure increases in subjects less than 50 years of age and that this is due to increased early wave reflection. Such findings go some way in explaining the paradoxical effects between DBP, SBP and PP with psychosocial stress and depression reported in the current study.

In further support of our findings linking depression with DBP, the link between depressive symptoms and high blood pressure is biologically plausible. One potential pathway being via dysregulation of the autonomic nervous system (Bajko et al., 2012; d'Audiffret et al., 2010; Scalco et al., 2005), which may occur in both depression (Dao et al., 2010; Kemp et al., 2010) and in hypertension (Feber, Ruzicka, Geier, & Litwin, 2014; Julius, 1991; Mancia & Grassi, 2014). Specifically, autonomic dysfunction involving alterations of adrenergic pathways, in influencing both endothelial tone and cardiac output will tend to elevate blood pressure (Bajko et al., 2012; d'Audiffret et al., 2010; Dwight & Stoudemire, 1997; Ford et al., 1998; Malan, Hamer, Frasure-Smith, Steyn, & Malan, 2014; Siever & Davis, 1985). However, it still remains that the effects found in the current study were small, although within the context of this study in growing children and instruments which cannot be claimed to be of the highest order of reliability; it is likely that our small, but significant effects are real.

Our finding that pulse pressure was significantly lower among adolescents reporting higher psychosocial stress and among those reporting an increase in psychosocial stress was surprising and did not support our hypothesis. It appeared that the reduction in pulse pressure was brought about mainly by the increase in DBP, unaccompanied by a proportionally higher increase in SBP. Perhaps the nature of our study might partly explain our conflicting, and perhaps counter-intuitive, finding relating to lower pulse pressure.

Firstly, our cohort is young healthy and growing, and increased SBP is a feature of the development of this group as they become older. In this context, unlike in

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adulthood where increased SBP may be a precursor of cardiovascular dysfunction, increases in SBP may simply be a characteristic of a developing cardiovascular system. Secondly, while several previous studies have investigated the effect of controlled mental stressors on cardiovascular reactivity, few have investigated these effects in response to stress arising from day-to-day hassles. Our finding that children reporting increasing levels of psychosocial stress also had reductions in pulse pressure may, in part, be explained by the nature of the stressors our adolescents experienced. For example, when stressors are weak, habituation may occur, with prior evidence indicating that repeated exposure to a mild stimulus may lead to a gradual decrease in plasma catecholamine responses, which in turn affect hemodynamic reactivity and hence define blood pressure (McCarty & Pacak, 2007). Alternatively, there is also evidence that after many repeated exposures to negative stressor experiences, the body and brain become exhausted and activation of defence systems (e.g. adaptive stress response) cease to occur (Fuchs & Flügge, 2011; McEwen, 2005); a process that might be hypothesized to be associated with a decrease in SBP and pulse pressure. This habituation hypothesis is interesting, although it sits contradictory to the increase we found in DBP. In any case, caution is needed when interpreting our findings, especially when psychosocial stress was only assessed at two time points in the current study with a four-year follow-up; our data not assessing the duration of the reported stressors or the exposure to further stressors in the time between these measurements.

Our lack of evidence for any effect of psychological factors on PWV is divergent from previous reports of positive associations between arterial stiffness and stress (Logan et al., 2012; Vlachopoulos et al., 2006) and depression in adults (Bomhof-Roordink et al., 2015; Tiemeier et al., 2003), and with depression in older adolescents (Dietz & Matthews, 2011). There are a number of plausible reasons for the contradictions. Most notably, the participants in the current study were younger than in the prior investigations, which involved 13-29 year-olds (Dietz & Matthews, 2011; Su et



al., 2014), and with older adults (Tiemeier et al., 2003). Arterial stiffness increases with age, (Lee & Oh, 2010), although there was little evidence of any increase within the age range of our cohort. The younger age of our participants (12 to 16 years) may also have contributed to a greater uniformity and lower incidence of any cardiovascular dysfunction than participants in the above-cited studies, which would tend to offset the findings of any relationships between the psychology and cardiovascular health of our participants. The younger age of our cohort and lower degree of cognitive development, may have also affected the level of understanding and ability to report on changes in psychological state, especially in grade 6. Finally, although our LOOK study data provided evidence of increasing symptoms of psychosocial stress and depression as children moved into adolescence, the level of symptoms experienced for the majority of participants fell in what could be characterised as a 'psychologically healthy' range. It may be that both stressor exposure and the level of depressive symptoms experienced by our cohort were, in general, not severe enough to have a direct impact on cardiovascular function.

### **Conclusion**

In the current study, we found evidence that children increasing in depressive symptoms during the transition from late-childhood to adolescence exhibit increases in DBP, but that children increasing in psychosocial stress develop lower pulse pressure. Interpretation of these apparently conflicting results requires further investigation. Our findings contribute to the scant paediatric literature but thus far did not uncover a direct effect of psychosocial stress or depression on arterial stiffness in a relatively young cohort of apparently healthy children and adolescents. However, in addition to the effects of depression and stress on blood pressure reported in the current study, our findings of relationships between depression and other well-established risk factors for CVD, namely obesity and low fitness in previous investigations, do suggest that psychological health may play a role in the early stages of CVD. It is only through

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continuing longitudinal studies, such as the LOOK study, that the clinical significance of early signs of stress and depression in children will be revealed.

### **Chapter Conclusions**

Psychological factors, including both stress and depression have been identified as reliable risk markers of future CVD. Understanding how and when in the life course the effects of psychological factors on cardiovascular function occur is important for informing primordial prevention efforts. While there appears to be plausible biological pathways that link psychosocial stress and depression with vascular function, these relationships were, for the most part, undetected in our sample of adolescents. Even so, the current study contributes to the literature as the first investigation on the effects of psychosocial stress and depression on arterial stiffness in children and younger adolescents, using the most robust methodology currently available for large cohort analyses. This study lays the basis for follow-up work into these associations, taking a life course perspective.

Given the uncertainties in our findings, including the inconsistency of reported effects of psychosocial stress and depressive symptoms on blood pressure assessments, we sought to expand the investigation by measuring endothelial function. Endothelial dysfunction is thought to be one of the earliest indications of cardiovascular dysfunction, even in apparently healthy populations, and youth. The following chapter reports on the influence of symptoms of psychosocial stress and depression, on endothelial function in our cohort of young healthy children and adolescents.

## **CHAPTER 9**

# **EFFECTS OF CHILDHOOD DEPRESSION AND STRESS ON ENDOTHELIAL FUNCTION IN ADOLESCENCE: FINDINGS FROM THE LOOK LONGITUDINAL STUDY**

### **Publication**

Olive, L. S., Byrne, D. G., Abhayaratna, W. P., & Telford, D. T. (under review). Effects of childhood stress and depression on endothelial function: The LOOK longitudinal study. Submitted to *International Journal of Behavioral Medicine* (February 2016).

### **Context Statement**

Endothelial dysfunction is thought to be one of the earliest indicators of cardiovascular dysfunction. Despite not having found a relationship between psychosocial stress or depression with our measures of arterial function (e.g. arterial stiffness and blood pressure), given the earlier findings indicating a significant influence of psychosocial stress and depressive symptoms on fitness, physical activity, fatness and insulin resistance, all factors which may affect healthy endothelial function, we sought to extend our investigations to include what may be considered one of the earliest prognostically significant markers of CVD, endothelial function.

As outlined in Chapter 4, endothelial dysfunction is thought to be a mechanism that may link psychological distress to CVD. Currently, very little published evidence exists that investigates these relationships in younger populations, with only one prospective study being identified in the literature. A measure of endothelial function was introduced to the LOOK study during the adolescent phase in grade 10. Therefore, the analytical approach taken in the following study differs from those previously reported, owing to the fact that only one measure of endothelial function was available. As a result, the prospective relationships investigated in the current study include

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longitudinal data, collected over childhood and adolescence for both psychosocial stress and depressive symptoms only. In the following study we investigate our final hypotheses, to determine whether psychosocial stress and depressive symptoms in childhood and adolescence are related to poorer vascular health in adolescents, including greater endothelial dysfunction; and whether adolescents who increase in psychosocial stress and depressive symptoms during the transition from childhood to adolescence will have greater endothelial dysfunction during adolescence.

### Abstract

**Background:** Associations between stress, depression and endothelial function have been reported in adults but we know little about these relationships in younger populations.

**Aim:** The aim of the current study was to examine the effects of psychosocial stress and depressive symptoms measured serially during childhood and adolescence on endothelial function measured in adolescence.

**Method:** Participants were 203 grade 2 children (111 girls; *M* age = 7.6 years) from the LOOK longitudinal study, who were followed through to adolescence (16 years). Self-reported psychosocial stress and depression were assessed using the Children's Stress Questionnaire and the Children's Depression Inventory respectively; endothelial function was assessed using EndoPAT 2000 system; and adjustments for potential confounders were made for fitness, assessed with the 20-metre multi-stage shuttle test; pubertal development, assessed using Tanner stages of maturation; and socioeconomic status.

**Results:** Our data did not provide evidence to suggest that endothelial dysfunction in adolescence would be greater in children who became more stressed and depressed during the transition from childhood into adolescence. Similarly, no significant effect of stress or depression on endothelial function was found in cross-sectional investigations at age 16 years, or in the predictive capacity of the psychological measures during childhood on endothelial function at late adolescence.

**Conclusions:** Our data revealed no evidence that psychosocial stress or depression symptoms had an effect on endothelial function in healthy 16 year-old boys and girls. Furthermore, psychological stress and depression measured during the previous 8 years in these adolescents was not able to predict variation in their endothelial function during adolescence.

### Introduction

Chronic life stress and depression have been identified as significant risk factors for the development and prognosis of cardiovascular disease (CVD; Frasere-Smith & Lespérance, 2006; Glozier et al., 2013; Hare, et al., 2014). Despite historical beliefs that childhood is a relatively untroubled time, there is evidence that children experience stressors both in the form of ongoing daily hassles (Byrne et al., 2011; Jewett, 1997) and stressful life events (Kraag et al., 2006), and a proportion of children will experience either clinical or subclinical levels of depression, with estimates for the prevalence of diagnosable depressive disorders in children and adolescents ranging from 3% to 6% (Jane Costello et al., 2006; Merikangas et al., 2010a; Sawyer et al., 2001). Similarly, although CVD generally manifests in adulthood, the pathological processes leading to CVD begin much earlier (Berenson & Srivivasan, 2005). Advances in non-invasive assessments of vascular function, a predictor of CVD (Fathi & Marwick, 2001), have opened up research possibilities with younger populations to examine the effect of psychological disturbance on vascular function and future CVD risk.

Although the precise mechanisms that may underlie relationships between psychological characteristics and risk of CVD are not well understood, several plausible hypotheses have been proposed. For example, there is evidence that both psychosocial stress and depression can induce physiological changes, including dysregulation of the autonomic nervous system and HPA-axis (Allen & Patterson, 1995; Grippo & Johnson, 2002; Pereira et al., 2013) and behavioural changes, such changes in physical activity participation, diet and smoking behaviour (Kassel, Stroud, & Paronis, 2003; Kiecolt-Glaser et al., 2014; Sabiston et al., 2013), all of which promote the development and progression of CVD (Grippo & Johnson, 2009), which gives weight to the premise that early psychological factors may influence subsequent cardiovascular health.

Endothelial dysfunction is one potential mechanism that may link early stress and depression with increased risk for CVD (Cooper et al., 2011; Toda & Nakanishi-Toda, 2011). The vascular endothelium plays a crucial role in maintaining vascular homeostasis and regulates several physiological functions, including vascular tone and vasomotor function. Endothelial dysfunction, which has been described as – “*an imbalance between the vasodilating and vasoconstricting milieu for the endothelium*” (Deanfield et al., 2005, p. 7) - is implicated in inflammation, platelet aggregation and thrombosis (Demirtas et al., 2014).

Among the adult literature, a number of observational studies and case-control trials have shown significant negative effects of depression on endothelial function at both clinical and subclinical levels (Broadley et al., 2002; Garcia et al., 2011; Lavoie et al., 2010; Sherwood et al., 2005; van Sloten et al., 2014; Wagner, Tennen, Mansoor, & Abbott, 2006). A systematic review of studies investigating the impact of depression on endothelial function among healthy adults and patients with known CVD or elevated risk for CVD reported a small-to-moderate effect size ( $r = 0.19$ , 95% CI 0.08-0.29) based on findings from 12 studies (Cooper et al., 2011). The effect size increased when only examining patients with CVD or known risk factors ( $r = 0.29$ ).

Of the few published studies undertaken with children and adolescents, findings have also demonstrated the adverse impact of depressive symptoms on endothelial function (Osika et al., 2011; Tomfohr et al., 2008; Tomfohr et al., 2011; Waloszek et al., 2015). One of the earliest investigations found that among adolescent girls aged 15 to 19 years, depressive symptoms were associated with impaired endothelial function (derived from an EndoPAT measure of reactive hyperaemia peripheral arterial tonometry) in a cross-sectional analysis after adjustments for age, race and contraception use (Tomfohr et al., 2008). This association was found despite reports of only mild levels of depressive symptoms by participants. Consistent with earlier findings, in the follow-up study with the same cohort of adolescent girls, it was found that impairment in endothelial function was more evident during periods of greater

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depressive symptomology (Tomfohr et al., 2011). However, predictive evidence was not forthcoming in this study, earlier depressive symptoms being unrelated to endothelial function six months later. Other cross-sectional investigations among adolescents have also associated depressive symptoms with impaired endothelial function in healthy (Waloszek et al., 2015) and clinic-based populations, but only in girls (Osika et al., 2011).

Similar to depression, brief episodes of psychosocial stress have been shown to effect endothelial dysfunction in a number of experimental and observational studies among adults (Ghiadoni et al., 2000; Gottdiener et al., 2003; Spieker et al., 2002; Takase et al., 2004). A recent review of the literature concluded that acute experiences of mental stress impaired endothelial function, although this finding was not consistent across all studies (Poitras & Pyke, 2013). Most research in this area has been undertaken with adults. One of the few studies that investigated adolescents reported that boys showed a greater vasoconstrictive response to a mental stressor, followed by a less vasodilatory response, and took longer to return to baseline levels compared to girls, indicative of a less healthy response (Chen et al., 2012). The practical significance of these findings is highlighted by a recent meta-analysis, which reports that greater cardiovascular reactivity to, and slower recovery from acute mental stress predicts adverse future cardiovascular health (Chida & Steptoe, 2010). Similarly, in young medical students, in whom a high frequency of stress, smoking, physical inactivity, and unhealthy nutritional habits were evident; the main contributors to endothelial dysfunction were stress and smoking (Mancaş et al., 2008).

Given the lack of prospective studies among younger populations, the aim of the current study was to investigate the impact of psychosocial stress and depressive symptoms on endothelial function among the Lifestyle of our Kids (LOOK) study cohort, following participants from childhood into adolescence. It is hypothesised that higher levels of stress and depression will be associated with endothelial dysfunction after adjusting for potential confounding variables.



## Method

### Participants

Participants were recruited from 29 primary schools in the Australian Capital Territory (ACT) to form the cohort of the Lifestyle of our Kids (LOOK) Study. An assessment of endothelial function was added to the testing schedule for LOOK during the most recent measurement period, which occurred in 2013. The number of observations in the current study varied with each measurement period, with 791, 750, 520 and 258 psychological assessments (e.g. depression and stress) taken in grade 2, grade 3, grade 6 and grade 10 respectively, with a similar number for endothelial function in grade 10 ( $N = 203$ ).

### Attrition

The natural attrition from a longitudinal study such as this is not uncommon, but it is pertinent to report the primary reasons for attrition between intake and follow-up. In the present study, 15 children withdrew from the LOOK study altogether. The remaining missed assessments were due to either migration of families out of the study Territory, absence from school on the day of testing, and lack of availability on weekends to attend the endothelial assessment. In contrast with an interventional study, attrition is unlikely to affect a study of relationships. Regardless, a comparison of data from children who remained in the study with those who left revealed that children leaving the study reported more symptoms of psychosocial stress ( $p = .002$ ) and depression ( $p = .013$ ) compared to children remaining in the study. Further analyses were undertaken to determine whether differences in cardiovascular risk profiles, based on other measurements undertaken in the LOOK study, including systolic blood pressure, blood lipids, insulin resistance and percent body fat, were evident at baseline between children leaving the study and those remaining. We found no evidence of any difference (all  $p > 0.05$ ), which suggests that attrition in the current study was unlikely to have resulted in any bias in our assessment of endothelial function. However, the

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potential effects of attrition relating to difference in psychological characteristics should be considered when interpreting the findings reported here.

### **Measures**

This study reports on data collected in grade 2, grade 3, grade 6 and grade 10, with all measures collected at each time-point with the exception of endothelial function, which was introduced into the LOOK study in grade 10.

**Psychological assessments.** Measures of stress and depression were collected at school in class groups. Items were presented to children via a PowerPoint presentation and participants made response choices on individual hand-held key-pads, which was relayed back to a lap-top computer using KEEpad interactive software and devices (LUL Technology). The response device presented facial images representing a corresponding idiographic scale on individual key-pads, colour-coded to match the response colour presented on the PowerPoint slide in order to facilitate self-reports of stress and depression. All items were simultaneously read to participants as they were presented to take account of varying levels of reading ability across classes.

***Children's Depression Inventory.*** Depression was measured using the Children's Depression Inventory (CDI; Kovacs, 1992). The CDI has demonstrated validity and reliability in assessing depression in pre-adolescent and adolescent groups (Kovacs, 1982, 1992; Masip, Amador-Campos, Gómez-Benito, & Gándara, 2010; Myers & Winters, 2002). Modification to the original scale was necessary to gain acceptance for use in primary schools by a number of school principals and from the jurisdiction's Education Department and Ethics Committee and these modifications have been described in detail in Byrne et al. (2011). The modified CDI comprised 19 items, with response choices limited to two (symptom present or absent). This resulted

in full scale score of depression that ranged from 19 to 38, with higher scores indicating greater severity of depressive symptoms

**Children's Stress Questionnaire.** Stress was measured using the Children's Stress Questionnaire (CSQ; Byrne et al., 2011), which was developed for the LOOK study and based largely on the widely used Adolescent Stress Questionnaire (ASQ; Byrne et al., 2007), a validated and reliable measure of psychological stress in adolescence (Byrne et al., 2011). The CSQ is 50-item self-report inventory assessing the degree of self-reported impact of stressor experience over the past year. Children are asked to rate how stressful they found each event on a 5-point Likert scale (1 = *'This did not happen to me'*, 2 = *'It happened but it didn't matter to me'*, 3 = *'It made me a bit upset'*, 4 = *'It made quite upset'*, 5 = *'It made me very upset'*). This resulted in the entire inventory score spanning 50 to 250, with higher scores indicating greater stress.

**Endothelial function.** Endothelial function was assessed non-invasively by trained technicians using the EndoPAT 2000 (Itamar). The EndoPAT device captures a beat to beat plethysmographic recording of the finger arterial pulse wave amplitude with pneumatic probes. A peripheral arterial tonometry (PAT) probe is attached to the index finger of each hand, one forming the test finger and the other the control. The EndoPAT examination involves three phases: (1) the baseline phase, which is recorded for 5 minutes, (2) the occlusion phase, where a blood pressure cuff is inflated to supra-systolic pressure for 5 minutes on the test arm, and (3) the reactive hyperaemia phase, which occurs after the cuff is released and the signal is recorded for 5 minutes. In a healthy individual, pulse amplitude will increase rapidly after cuff deflation, allowing increase blood flow and therefore the delivery of oxygen and removal of metabolic products. This is known as reactive hyperaemia, which is thought to be a vital response after a period of ischemia. An attenuated response after cuff deflation is an indication of impaired endothelial function. Data obtained from the

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control finger is used to adjust for systemic effects during the computerised algorithm calculation. In the current study, a standardized algorithm proposed by the manufacturer was used to calculate the reactive hyperaemia index (RHI; Bruyndonckx et al., 2013). EndoPAT has demonstrated reliability and validity as a measure of endothelial function, including preliminary evidence for its use in paediatric populations (Muller et al., 2013; Selamet Tierney et al., 2009). EndoPAT measures have also been used in accurately identifying the early stages of atherosclerosis (Bonetti et al., 2004).

**Cardiorespiratory fitness.** The 20-metre multi-stage shuttle test (MSST) was used as a measure of cardiorespiratory fitness (CRF) and has been well-established as a reliable field-test of fitness among children (Tomkinson et al., 2003). The MSST requires maximal effort and therefore performance may be influenced by participant motivation, but it is a practical and commonly used method to measure CRF in a large sample. Measures of fitness were collected in a separate session at the school by an exercise scientist across each data collection time-point.

**Pubertal maturation.** Pubertal maturation is thought to be a predictor of endothelial function (Radtko et al., 2012), and increases in EndoPAT assessed RHI with pubertal advancement have been demonstrated (Bhangoo et al., 2011). With this knowledge, pubertal development was assessed in the current study to allow for the adjustment of this potentially confounding variable. The self-report Tanner stages of pubic hair, breast development, and date of menarche were employed (Tanner, 1962) using diagrams based on those previously described (Duke et al., 1980). The self-assessment was completed at a hospital paediatric unit under the supervision of an experienced teacher. Assessment of pubertal maturation meant that adjustments based on biological maturation could be made rather than relying on age.

**Socioeconomic status.** The Australian Bureau of Statistics (ABS) Socio-economic indexes for areas (SEIFA; ABS, 2009), was used as a measure of socioeconomic status (SES), as previously described.

### **Ethics**

This study was approved by the ACT Health Department Research Ethics Committee, and from the Human Research Ethics Committee of the Australian National University, the ACT Department of Education, and the Human Research Ethics Committee of Australian Institute of Sport. Parental consent was obtained for all measures in this study, and children understood that their participation was entirely voluntary and that they could withdraw at any time. The children also provided written consent for psychological measures, a condition requested by the Human Research Ethics Committee of the Australian National University.

### **Statistical Analysis**

Hierarchical linear regression was used to assess the prospective effect of psychosocial stress and depression at each time point on endothelial function at age 16 years. In addition, general linear modelling was used to quantify and assess the effects of change in psychosocial stress and depression between grade 2 (7 to 9 years) and grade 10 (16 to 17 years) on endothelial function in grade 10. Children who missed an assessment in a particular year remained in the study and were included in the analysis, with the statistical model adjusting for missing values, provided they were assessed for endothelial function.

Our models adjusted for the potential confounding effects of gender, SES, CRF, puberty and school (as the “cluster” unit with varying teachers and school climate). In preliminary models, SBP was also included as a covariate, however, the inclusion of which did not improve the model fit nor did it change the outcome of results. Therefore, the simpler statistical model, which excluded SBP, was used as the final model.

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General model checking procedures were routinely used to identify aberrant data and to check the model assumptions. Statistical computation was undertaken using the statistical package R version 3.1.1 (R Core Team, 2012).

### Results

#### Characteristics of Participants

At the commencement of the LOOK study, approximately 90% of children had one or both parents of Caucasian descent, 7% of Asian descent, 1% was indigenous Australian or Polynesian, and 2% were unknown. Table 21 shows unadjusted characteristics of the participants at each year of measurement.

**Endothelial function.** The average EndoPAT score for the current sample was in the healthy range. ( $M = 2.21$ ,  $SD = 0.62$ ). Reference values for EndoPAT RHI from the manufacturer suggest an index of 1.67 and below as indicating endothelial dysfunction (Itamar-Medical, 2015). However, this index is based on adult data, the clinical significance of which is yet to be determined in younger populations. Therefore, caution is required when using this reference value for interpreting scores with the current sample. With this in mind, 21% of our cohort recorded RHI scores of 1.67 or below (adult reference values indicating endothelial dysfunction); a further 19% of participants recorded RHI scores between 1.67 and 2.00 (borderline endothelial dysfunction; Bruyndonckx et al., 2013); the remaining 60.1% of participants recording scores indicative of healthy endothelial function by the adult-based reference ranges.

Table 21.

*Unadjusted Means (Standard Deviations in Brackets) for Measured Characteristics of Boys (M; N = 92) and Girls (F; N = 111) Included in Our Study at Grade 2, Grade 3, Grade 6, and Grade 10*

		Grade 2	Grade 3	Grade 6	Grade 10
		<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
EndoPAT	<i>F</i>	Not assessed	Not assessed	Not assessed	2.12 (0.56)
	<i>M</i>	Not assessed	Not assessed	Not assessed	2.20 (0.59)
Psychosocial Stress	<i>F</i>	93.48 (20.28)	94.31 (23.91)	83.90 (19.13)	87.87 (18.31)
	<i>M</i>	91.93 (23.50)	90.30 (23.75)	80.53 (22.68)	82.84 (20.06)
Depression	<i>F</i>	24.90 (3.88)	24.67 (4.63)	22.75 (2.90)	27.56 (4.72)
	<i>M</i>	24.98 (4.39)	24.16 (4.26)	22.98 (3.03)	25.91 (4.38)
<sup>a</sup> Tanner Stage	<i>F</i>	Not assessed	Not assessed	2.60 (0.78)	4.33 (0.60)
	<i>M</i>	Not assessed	Not assessed	2.50 (0.87)	4.32 (0.67)
<sup>b</sup> CRF	<i>F</i>	3.47 (1.08)	3.88 (1.28)	5.48 (1.77)	5.86 (1.93)
	<i>M</i>	4.15 (1.46)	4.89 (1.83)	6.39 (2.14)	9.01 (2.71)

<sup>a</sup>Tanner stage = self-assessed pubertal stage ranking; <sup>b</sup>CRF = cardiorespiratory fitness, the number of stages completed in the multistage run

**Depression and psychosocial stress.** There was an overall increase in depressive symptoms over time, averaging 0.24 points in the CDI per year ( $p < 0.001$ ). This change was characteristic of a decrease in depressive symptoms from grade 2 through to grade 6, followed by a significant increase from grade 6 to grade 10 ( $p < 0.001$ ). In contrast, children reported an average decrease in psychosocial stress over time of 0.77 points on the CSQ per year ( $p = 0.015$ ) although there was an increase in stress between grade 6 and grade 10, this was not statistically significant. Individual changes in symptoms of depression and psychosocial stress across each year of

## CHAPTER 9

measurement are presented graphically for each child in Figure 17 and Figure 18 respectively.

**Fitness and pubertal development.** Overall, fitness increased over time ( $p < 0.001$ ). Self-assessments of pubertal maturation at grade 10, the year the EndoPAT assessment took place, indicated that 30% of boys and 32% of girls were self-assessed as being in Tanner stage 5; 50% of boys and 48% of girls were in stage 4; 15.9% of boys and 20% of girls were in stage 3, and 4.5% of boys and no girls were self-assessed as being in Tanner stage 2. When exploring the potential effects of puberty and fitness on endothelial function among our cohort, both separately for boys and girls and combined, we found no significant effect of puberty (boys  $p = 0.366$ ; girls  $p = 0.309$ ) or fitness (boys  $p = 0.897$ ; girls  $p = 0.346$ ) on endothelial function at grade 10. However, when utilising data from all years of measurement, there was some evidence for a positive effect of fitness on endothelial function for girls ( $p = 0.058$ ), but this benefit did not extend to boys.

### **Effect of Psychosocial Stress and Depressive Symptoms on Endothelial Function**

A series of hierarchical linear models assessed the effect of both psychosocial stress and depression on endothelial function at each year of measurement. Firstly, we assessed the effect of self-reported depression and stress at each year of measurement (entering all years of data in the same model, with separate models for depression and stress) on endothelial function at grade 10. Although all relationships occurred in the hypothesised direction, there were no significant effects of depression (see Table 22) or psychosocial stress (see Table 23) on endothelial function, either prospectively or concurrently at 16 years (all  $p > 0.05$ ). This remained unchanged when adjusting for the potentially confounding effects of cardiorespiratory fitness and pubertal status. Secondly, we assessed whether changes in depression and



psychosocial stress between grade 2 and grade 10 were associated with endothelial dysfunction at grade 10, but no evidence emerged to support our study hypothesis, that children who became more stressed and depressed would also have poorer endothelial function in adolescence. A summary of these findings is presented in Table 24.

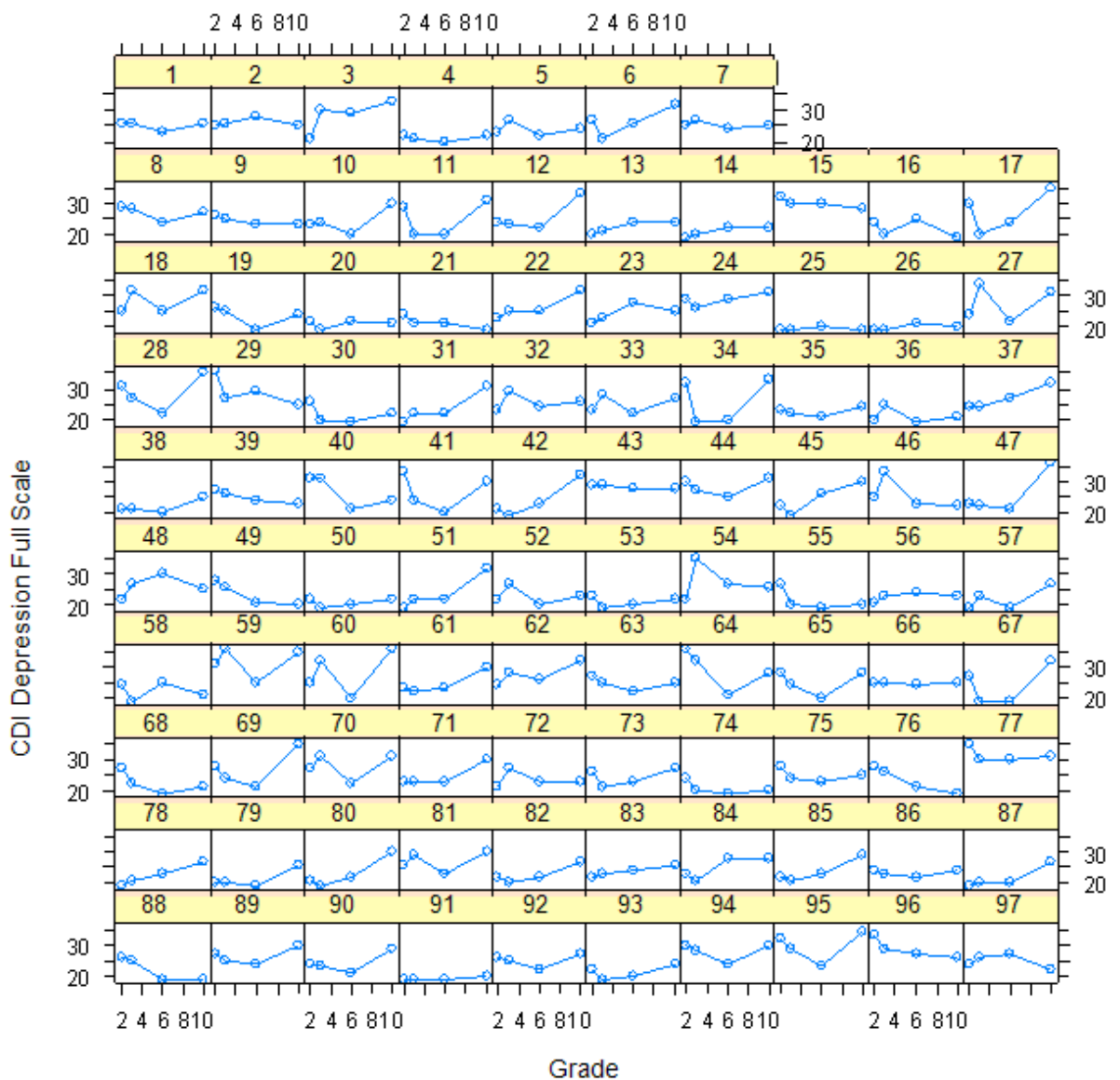


Figure 17. Depressive symptom trajectories based on Children's Depression Inventory full scale score for children of the LOOK study measured in grade 2, 3, 6 and 10.

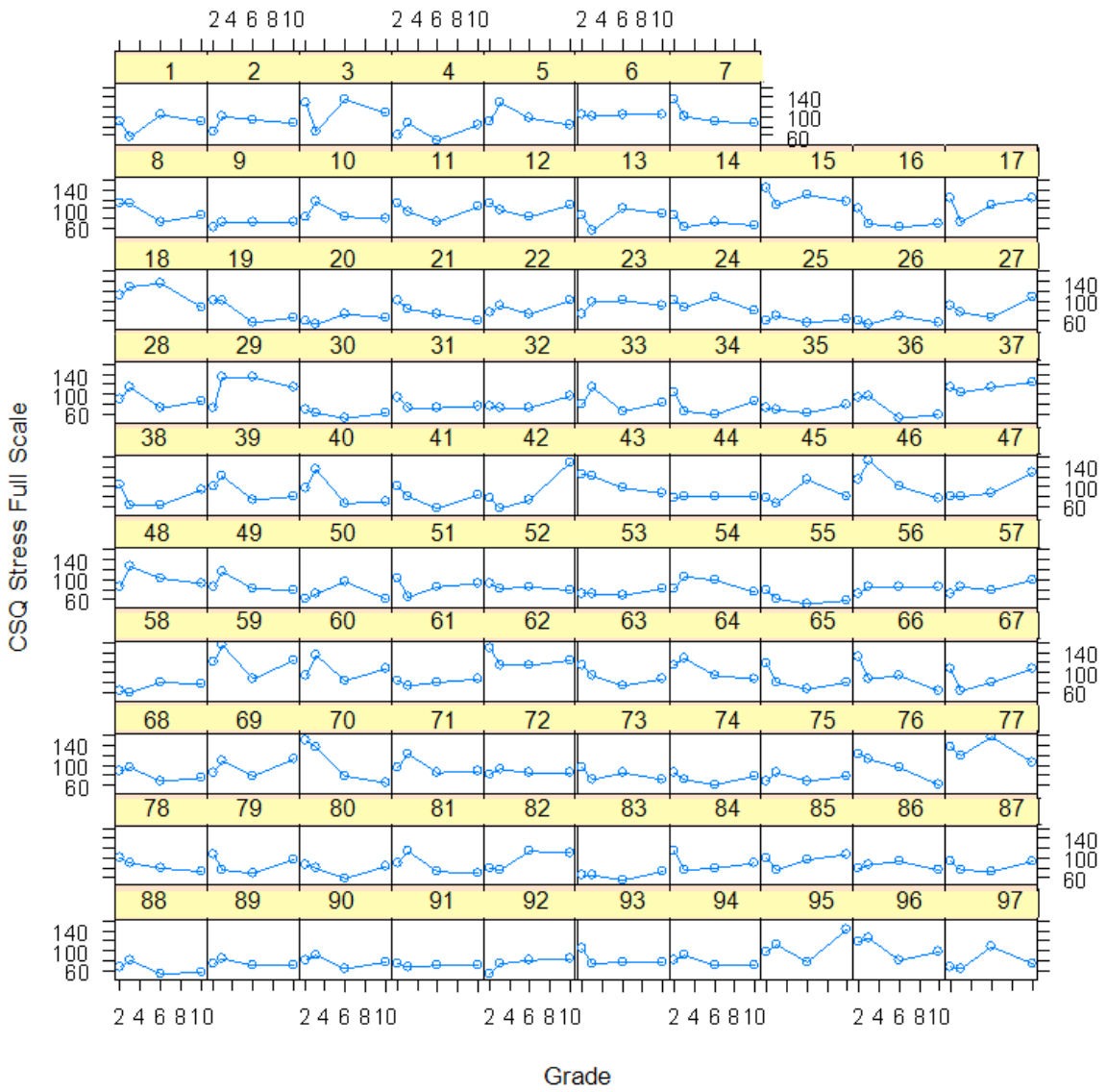


Figure 18. Psychosocial stress trajectories based on Children’s Stress Questionnaire full scale score for children of the LOOK study measured in grade 2, 3, 6 and 10.

Table 22

*Summary of Hierarchical Regression Analysis for Depressive Symptoms Predicting Endothelial Function at Age 16 years*

	<i>B</i>	<i>SE B</i>	$\beta$	<i>p</i>
<i>Step 1</i>				
Sex	0.079	0.128	0.064	.537
CRF	0.023	0.023	0.105	.314
<i>Step 2</i>				
Sex	0.077	0.130	0.062	.555
CRF	0.020	0.024	0.091	.414
Depression Grade 2	0.000	0.014	0.003	.973
Depression Grade 3	-0.004	0.014	-0.027	.794
Depression Grade 6	-0.018	0.019	-0.090	.351
Depression Grade 10	-0.001	0.013	-0.010	.919

$R^2 = 0.008$  for Step 1;  $\Delta R^2 = -0.26$  for step 2 ( $p > 0.05$ )

Table 23

*Summary of Hierarchical Regression Analysis for Psychosocial Stress Predicting Endothelial Function at Age 16 years*

	<i>B</i>	<i>SE B</i>	$\beta$	<i>p</i>
<i>Step 1</i>				
Sex	0.079	0.128	0.064	.537
CRF	0.023	0.023	0.105	.314
<i>Step 2</i>				
Sex	0.086	0.129	0.070	.506
CRF	0.024	0.024	0.108	.316
Stress Grade 2	-0.001	0.003	-0.054	.596
Stress Grade 3	-0.001	0.003	-0.02	.853
Stress Grade 6	-0.003	0.003	-0.095	.358
Stress Grade 10	0.003	0.003	0.080	.417

$R^2 = .008$  for Step 1;  $\Delta R^2 = -.21$  for step 2 ( $p > 0.05$ )

Table 24

*Longitudinal Effects of Psychosocial Stress and Depressive Symptoms Predicting Endothelial Function at Age 16 years*

	<i>B</i>	<i>SE B</i>	$\beta$	<i>p</i>
Change Depression 05-13	0.001	0.009	0.012	.883
Change Stress 05-13	0.002	0.002	0.073	.344

*Note: Analyses adjusted for sex*

### Discussion

This prospective cohort study did not provide evidence that early symptoms of psychological stress or depression were associated with endothelial dysfunction during the transitional period of childhood into adolescence; nor did we uncover any evidence to indicate a prospective or concurrent effect of psychosocial stress and depressive symptoms on endothelial dysfunction. Our data, therefore, do not support the hypothesis that endothelial function is influenced by early symptoms of stress and depression in healthy children and adolescents.

Our lack of evidence for an effect of depression or stress on endothelial function is not consistent with previous studies carried out in adolescents. For example, depression was found to co-vary with endothelial function in a cohort of adolescent females assessed during clinic visits, such that endothelial function declined during periods when depressive symptoms were greater than usual (Tomfohr et al., 2011). Similarly, a significant relationship between depressive symptoms and poor endothelial function among a healthy cohort of 14 year-old boys and girls was found in a Swedish study (Osika et al., 2011). On the other hand, consistent with the current study, earlier longitudinal investigations failed to find evidence that prior depression was predictive of endothelial dysfunction beyond current levels of depressive symptoms (Tomfohr et al.,

2011). In seeking to explain these contrasting outcomes, differences in the design of the studies in question may be relevant.

Firstly, in contrast to studies with clinic-based study populations (Tomfohr et al., 2011; Waloszek et al., 2015) children from the LOOK study were healthy community-dwelling children, not selected on the basis of any psychological disorder. Indeed, blood screening and echocardiographic assessment carried out during the LOOK study (Sakuragi et al., 2009; Telford et al., 2015), together with documentation from the parents of their child's wellbeing and ability to participate in vigorous physical activity were good assurances that children were in good physical and mental health.

Secondly, children of the LOOK study were much younger at initial assessment (7 to 8 years) and the first follow-up (8 to 9 years) than in previous studies, where participant mean age ranged from 14 years (Osika et al., 2011) to as old as 19 years (Tomfohr et al., 2011) in studies investigating depression; and from 10 to 17 years in the study assessing response to stress (Chen et al., 2012). Older children will have greater cognitive capacity for interpreting self-report items, so we can expect a more accurate response. Furthermore, older children will have been exposed to more life experiences that potentially impact upon stress and depression, which may in turn expose relationships not apparent in their earlier years. Certainly within the age range of our cohort, depressive symptoms increased with age and endothelial function is known to decline as adolescents approach adulthood (Lakatta & Levy, 2003).

Thirdly, there were differences in self-report measures of depression across the studies, with the Centre for Epidemiologic Studies Depression Scale or one of the various Beck inventories, including the Beck Depression Inventory (Tomfohr et al., 2011) & the Beck Youth Inventory (Osika et al., 2011) being used in prior studies. Disparities in measurement instruments not only make it difficult to compare studies but they may also contribute to differences in findings, possibly through variation in the way children interpret the questions.

Although our study is unable to provide evidence to support the hypothesis that endothelial function can be influenced by psychosocial stress and depression, several plausible biological pathways have been proposed to explain these links. Depression and psychosocial stress have been associated with dysregulation in the autonomic nervous system and neuro-endocrine hypothalamic-pituitary-adrenal axis (Gold et al., 1988; Goldston & Baillie, 2008; Selye, 1950), and the dysregulation of these systems have been linked to endothelial dysfunction (Broadley et al., 2005; Harris & Matthews, 2004). In addition, depression may act as a chronic stressor that contributes to endothelial dysfunction through abnormalities in cellular adhesion, migration, and proliferation (Strike & Steptoe, 2004). Oxidative damage has also been implicated in this relationship (Higashi, Maruhashi, Noma, & Kihara, 2014), with depression being associated with biomarkers of oxidative damage, which in turn reduce the bioavailability of nitric oxide, blunting normal vasodilatory response (Landmesser, Hornig, & Drexler, 2004; Pennathur & Heinecke, 2007). It is likely that the factors described here and others associated with depression and stress combine to disrupt homeostatic mechanisms in the endothelium,

A strength of this study was its incorporation of the longitudinal assessments of psychosocial stress and depression, which facilitate greater inferential power on previous studies relying on cross-sectional data analyses. Further strengths of the current study include the sample size of the cohort, and the collaboration between experienced psychology, physiology and cardiology staff. The current findings must also be interpreted in light of its limitations. Firstly, psychosocial stress and depression were assessed using self-report measures. Although it was not viable to conduct clinical interviews with each individual child in this large-scale longitudinal study due to limited resources, it is possible that children may have had difficulty interpreting questionnaire items, particularly during the earlier stages when they were only 7 years. This may also explain the variation across years in child symptoms trajectories for stress and depression. Although steps were taken to ensure participant understanding,

such as reading each item out loud, providing relatable and age-appropriate examples and giving participants the opportunity to ask questions regarding item meaning, this possibility cannot be dismissed. It is also possible that a child's interpretation of the items changed with age, with a tendency to over-report at a younger age compared to at an older age, a feature previously demonstrated in youth (Worchel, Nolan, & Willson, 1987). On the other hand, there was good internal reliability (CDI Cronbach's Alpha range = .77- .86; CSQ Cronbach's Alpha range = .90 to .93) and test-re-test reliability in the current study for both the CSQ ( $r = .316$  to  $.495$ ) and the CDI ( $r = .205$  to  $.420$ ). It may also be the case that participants experienced stressful events not listed on the inventory and therefore were not reflected in their overall CSQ score, which could affect the predicted relationships with endothelial function.

Additionally, stress was measured within a psychological framework, assessing individual appraisals of a series of stressors. While any such measurements were outside the scope of this study, without a physiological measure of the stress response we cannot comment on whether our appraisals of stress in a child lead to a stress-response, the most likely mediator between psychosocial stress and vascular function (Grippe & Johnson, 2009). Finally, our measures of endothelial function must also be considered in terms of its limited application in youth. While EndoPAT has emerged as a promising tool for investigating endothelial function among adults, this method is still relatively new to paediatric investigations and current methods of endothelial function in children may be developed with more sensitivity (Bruyndonckx et al., 2013).

### **Conclusion**

In conclusion, our data revealed no evidence of an effect of psychosocial stress or depression on endothelial function in healthy 16 year-old boys and girls. Furthermore, psychological stress and depression measured during the previous eight years in these 16 year-old adolescents was not able to predict variation in their endothelial function.



### **Chapter Conclusion**

Similar to our investigation on arterial stiffness, the current study failed to find an association between psychosocial stress and depression and endothelial function. Based on this evidence, it may be concluded that the strongest influence of psychosocial stress and depression on CVD risk among children and adolescents, is operating through primordial risk factors, rather than on more direct intermediary risk markers at this young age. In the following and final chapter, we summarise the major findings arising from this Ph.D. thesis and provide a discussion on future directions for this field, including the identification of areas for further research and the clinical implications of the current findings.

## **CHAPTER 10**

### **GENERAL DISCUSSION**

#### **Review of Thesis Aims and Objective**

Cardiovascular disease is a leading cause of morbidity and mortality worldwide. Cardiovascular medicine has increasingly recognised the childhood origins of adult CVD, and accordingly, primordial prevention strategies in children are becoming more common place (Lloyd-Jones et al., 2010). This is perhaps most evident in terms of intervention efforts aimed at the prevention and treatment of CVD risk factors including, childhood obesity (Dietz & Gortmaker, 2001; Freedman et al., 1999; Sothorn, 2004; Steinberger & Daniels, 2003; Story, 1999) and physical inactivity (Quirk, Blake, Tennyson, Randell, & Glazebrook, 2014; van Sluijs, McMinn, & Griffin, 2007). Given emerging recognition that psychological distress can influence CVD risk, both directly, via inducing physiological change (Baune et al., 2012; Frasere-Smith & Lespérance, 2010; Grippo & Johnson, 2009) and indirectly, by influencing the adoption of health risk behaviours (Jacka et al., 2014; Rottenberg et al., 2014; Weinberger et al., 2013), primordial prevention strategies may benefit from considering the role of psychological distress in CVD development over the life course. However, despite substantial evidence in adults, where the association between depression, stress and increased CVD risk has been extensively documented, less is known about the impact of pre-clinical symptoms of psychosocial stress and depression experienced earlier in the life course on CVD risk. This then raises the question; how do earlier experiences of psychosocial stress and depression effect CVD risk factors in youth?

The research reported in this thesis set out to answer this question by investigating the potential influence of two relevant psychological constructs, namely the experience of psychosocial stress and depressive symptoms, on a set of established risk factors and prognostically significant markers of CVD among a cohort

of apparently healthy children. This was achieved by following the same cohort of children for almost a decade (and so into adolescence), documenting simultaneously multiple elements of CVD risk, whilst capturing a profile of psychological distress. Investigations on the impact of psychosocial stress and depression were undertaken in accordance with a developmental framework, beginning with investigations of primordial risk factors that were likely to occur early in the life course and then moving to more direct intermediary markers of risk for CVD development as children aged and transitioned into adolescence. Across four empirical studies, the current research investigated the impact of psychosocial stress and depressive symptomology on (1) behavioural risk factors, namely physical activity and cardiorespiratory fitness, (2) metabolic risk factors, including percent body fat and insulin resistance, and (3) prognostically significant intermediary markers of CVD, those being arterial stiffness, blood pressure and endothelial function. In this chapter, the key findings relating to each of these three areas are summarised, followed by a discussion on how these studies contribute to our current understanding of how psychological distress influences CVD risk in youth. Finally, targets for future research are identified and the practical implications of this research for the practicing psychologist are presented.

### **Summary of Findings: Contributions to the Literature and Implications**

#### **Primordial Risk Factors**

**Behavioural risk factors and symptoms of psychosocial stress and depression.** Firstly, it was demonstrated that the experience of pre-clinical levels of psychosocial stress and depressive symptoms negatively impact on a range of primordial risk factors for CVD. Specifically, in this thesis evidence was reported (Chapter 6) to suggest that a child, who becomes more depressed during the transition from childhood into adolescence, will have lower cardiorespiratory fitness. This finding was clearly articulated in girls with evidence for a similar trend among boys. Further

evidence was provided in this study, which demonstrated that both boys and girls identified with more symptoms of depression, and as being more stressed, were more likely to be less physically activate and less fit. Interestingly, in girls, feeling more stressed also impacted negatively on their physical activity intensity, where they were less likely to engage in health promoting moderate-to-vigorous physical activity (MVPA).

The models utilised in this thesis contribute to our understanding of the effects of physical activity and fitness on pre-clinical levels of psychological distress (e.g. psychosocial stress and depression symptoms) in children as they enter adolescence, making use of longitudinal data, which were previously lacking among this age group. Here, it is worth noting that, to date, the literature in this area has predominately focussed on the reciprocal relationship between physical activity and fitness on psychological health, and how aspects of mental health are positively influenced by physical activity participation and increased fitness. While these investigations are important, the findings reported in this thesis suggest the opposite is also true, lending support for a bidirectional relationship between psychosocial stress and depression with physical activity and fitness. Although the research presented in this thesis is not able to elucidate the direction of causality given the observational nature of this study, what the current findings do highlight is the importance of addressing mental health symptoms when attempting to improve the physical activity and fitness levels of youth.

The practical impactions of this work, therefore lies in the ability to inform interventions efforts, by offering new avenues to address the global problem of physical inactivity, and by association, obesity in youth via strategies that aim to alleviate mental health symptoms and specifically those relating to depression. Interventions that arm children with the necessary skills to identify, regulate, and cope with difficult emotions, including experiences of stress and depressed mood, may not only improve their psychological wellbeing, but potentially increase their willingness and motivation to engage in physical activity, and therefore their physical activity levels. The clinical

significance of any such improvements in youth in terms of their cardiovascular health, is demonstrated by prior work indicating that increases in physical activity, even of a moderate level, lead to decreased progression of subclinical atherosclerotic vascular changes (e.g. endothelial dysfunction and aortic intima media thickness) in healthy adolescence (Pahkala et al., 2011). Therefore, these findings should be of interest to paediatric psychologists and exercise physiologists, teachers and medical practitioners alike as a novel means of improving physical health among children at risk. Improvements in a child's profile of psychological distress and therefore, the potential improvement in their physical activity and fitness levels, may have further benefits to their health, including metabolic health, which was the focus in Study 2.

**Metabolic risk factors and symptoms of psychosocial stress and depression.** In addition to the significant influence on behavioural risk factors for CVD (e.g. physical activity and fitness), research arising from Study 2 (Chapter 7) implicates a further role for psychological distress on the metabolic health of children and adolescents. Insulin resistance, a key determinant of metabolic syndrome (Meigs et al., 1997; Ruige et al., 1998), is an important risk factor for Type 2 diabetes (Weyer, Bogardus, Mott, & Pratley, 1999) and CVD (Gotoh et al., 2012; Ruige et al., 1998). In Chapter 7, a strong case was presented that early depressive symptoms in boys may be causally related to metabolic dysfunction. Whilst this was not tested directly in the current work, and strong claims of causality are not permitted from these observational studies, it does however remain that a convincing line of evidence has presented itself for further investigation.

This line of thinking is based on a series of findings arising from the current research and that of others; beginning with the discovery of a dose-response relationship between insulin resistance and depressive symptoms in boys of our cohort, whereby boys who had higher levels of insulin resistance also reported more symptoms of depression. This was coupled with a longitudinal trend whereby boys who

displayed an increase in depressive symptoms developed higher insulin resistance. Moreover, these relationships emerged after adjustment for percent body fat, a well-established contributor to higher insulin resistance (Zhang et al., 2015).

Two further avenues of support for an effect of depression on metabolic dysfunction emerged with findings that boys who increased in depressive symptoms also became fatter; given the knowledge that obesity is well-established as a risk factor for Type 2 diabetes (Bell et al., 2014) and that obese children are prone to higher insulin resistance (Telford et al., 2012). Secondly, in Study 1 of this project, it was found that the lower the physical activity and fitness of a child the higher their depression, again this relationship occurring independent of percent body fat. Given the association between physical activity and insulin resistance (Telford et al., 2009b; Telford et al., 2012), this thereby provides another pathway implicating depression in the onset of metabolic dysfunction. With the series of findings presented here, along with the contribution of previous researchers, which provides evidence of plausible physiological mechanistic links between stress, depression and insulin resistance, the bank of evidence that even early symptoms of depression are a risk for increased insulin resistance is strengthened.

This opens up potentially important preventative medical considerations. Our data suggest that identification and treatment of early non-clinical or clinically diagnosed depression may reduce early onset insulin resistance. In turn, given that metabolic diseases may have their roots in childhood (Ehtisham et al., 2000), early attention to children with depression, even in the early pre-clinical stages, may reduce the risk for chronic disease in later life. To date, no such intervention has been investigated among younger populations but the current findings lend support for psychological interventions that target depressive symptoms among children and adolescents, as a preventative measure, or indeed in treating metabolic disorders during youth. Furthermore, these findings may provide possible avenues of exploration among adult populations and go some way to explaining why not all those with obesity

and or inadequate physical activity patterns develop Type 2 diabetes. Clinical trials to evaluate the potential benefit of psychological interventions among individuals with or at risk of metabolic dysfunction may prove fruitful.

Given the findings emerging from the first two studies, and owing to the fact that both physical inactivity and insulin resistance are well established risk factors for CVD, there appeared to be a growing case that psychosocial stress, and perhaps more likely given the earlier findings, symptoms of depression, may be related to cardiovascular function among children in our cohort. This was the focus of the final two investigations (Study 3 in Chapter 8 and Study 4 in Chapter 9).

**Intermediary risk markers and symptoms of psychosocial stress and depression.** Our group studied two prognostically significant measures of arterial function to determine whether symptoms of depression and psychosocial stress influenced cardiovascular function more directly during adolescence. While other researchers have demonstrated a significant impact of depression and depressive symptoms (and to some degree psychosocial stress) on endothelial function and arterial stiffness among youth (Dietz & Matthews, 2011; Su et al., 2014; Tomfohr et al., 2011; Waloszek et al., 2015), we failed to uncover any evidence to suggest that either psychosocial stress or depression had an impact on arterial stiffness or endothelial function in our cohort. However, given the significant relationships we found between psychological and both behavioural and metabolic risk factors for CVD, together with our previously published findings in this cohort linking (a) percent body fat and blood levels of LDL-cholesterol (Telford et al., 2015), and (b) physical activity and percent body fat with both insulin resistance (Telford et al., 2012) and arterial stiffness (Sakuragi et al., 2009), there is considerable support for the hypothesis that psychosocial stress and depression in childhood and adolescence may increase arterial stiffness and the risk of developing CVD later in life.

It is also worth noting that lack evidence for a relationship between psychosocial stress and depression with either arterial stiffness or endothelial function is in contrast to previously published literature in youth (Dietz & Matthews, 2011; Osika et al., 2011; Su et al., 2014; Tomfohr et al., 2008; Tomfohr et al., 2011; Waloszek et al., 2015). Although the evidence base among younger populations is sparse, with few studies with which to compare the current findings, this disparity with published work is perhaps not entirely unexpected, given the fact that the current sample was relatively young and selected on the bases of their good health. Given previous reports of significant relationships between psychological distress and pre-clinical markers of CVD, coupled with our findings of the negative impact of depressive symptoms and psychosocial stress on both behavioural and metabolic risk factors for CVD, further investigations among younger, apparently healthy populations appear warranted.

Our additional investigations on the influence of psychosocial stress and depression on blood pressure revealed inconsistent findings, similar to previous reports in both adults and younger populations (Chida & Steptoe, 2010; Hammerton et al., 2013). In the current work it was observed that children who became more depressed also had increases in diastolic blood pressure and mean arterial pressure; and that those becoming more stressed had a reduction in pulse pressure. However, these conflicting effects were small and may have been influenced by several factors.

The most obvious relates to our measurement of psychosocial stress, which may not have captured the type of stress most relevant to physiological change in the vasculature (e.g. stress of a sufficiently chronic nature). Furthermore, our work (Study 3, reported in Chapter 8) suggested that psychological factors may be operating through blood pressure rather than affecting arterial stiffness more directly. These observations may help inform future studies among children and adolescents to set up investigations more specifically geared toward capturing effects of psychological distress on arterial function; for example, choosing instruments that adequately capture stress of a chronic nature. Our observations also highlight the importance of



experimentally controlling or statistically adjusting for blood pressure when investigating relationships between vascular changes (such as arterial stiffening) and psychological distress.

To summarise the overall findings reported in this thesis, the relationships between psychological variables and the set of risk factors and risk markers for CVD that were investigated in the current work are presented in Figure 19. In this figure, the significant relationships reported in prior examinations of the LOOK data to date, based on the same cohort of children are also outlined to provide a more comprehensive picture of the interrelated pathways of association. At this point it is also acknowledged, that a progression in the literature away from unidimensional models of the stress-health research and the shift towards a more dynamic relationship of potential bi-directional causality is evident (Cohen et al., 2007; Hammen, 2005; Lazarus, 1999), and although the relationships between the variables described in Figure 19 may be uni- or bi-directional, and so provide evidence for corresponding causality, it is important to remind ourselves that the observational nature of our data do not permit confident inferences of causality.

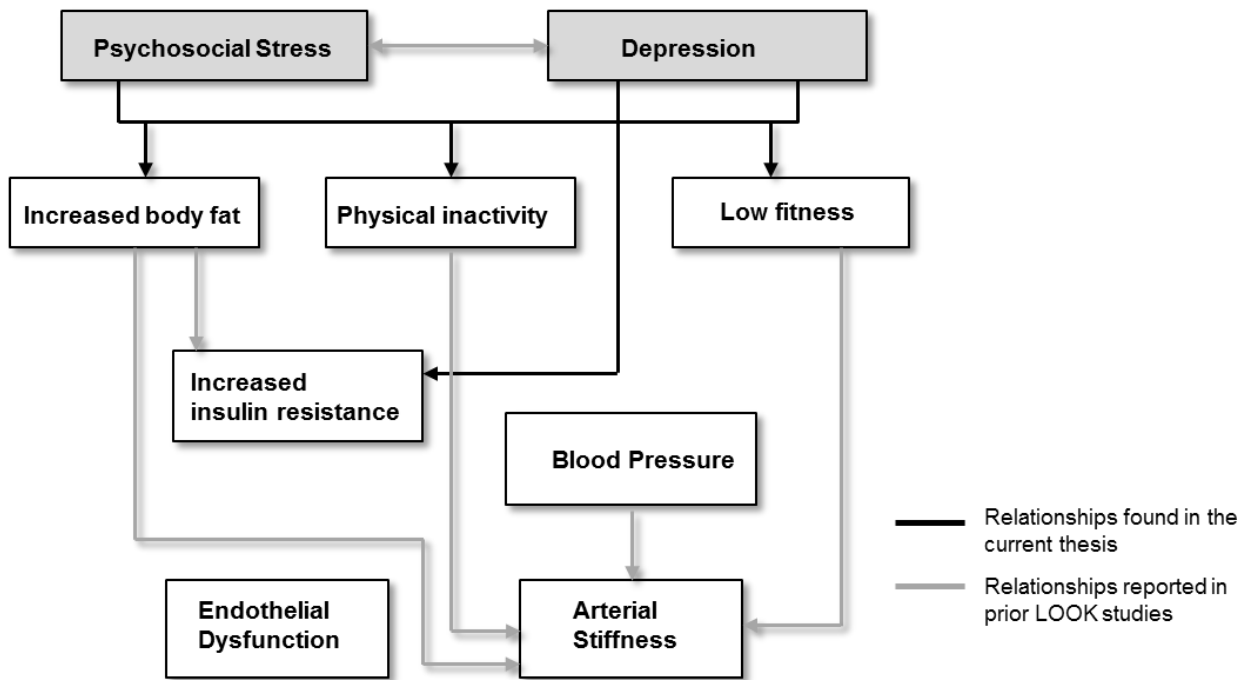


Figure 19. Schematic representation of the relationships between psychosocial stress and depression with CVD risk factors and prognostic markers.

What is apparent from Figure 19 is that the variables investigated form part of a potentially bi-directional interactive network. Any absence of pathway links between variables is not necessarily due to any absence of association but an absence of published research. A salient feature of Figure 19, however, is that psychological factors may influence cardiovascular function at the tissue level, via their effects of physical health attributes (e.g. physical activity, fitness, fatness). As previously suggested, whether this mediated effect is sustained as children age, and whether risk factors in childhood are true representatives of disease in adulthood is yet to be determined. As further investigations emerge based on the LOOK data and in other longitudinal studies already in place around the world, and as risk inevitably presents as disease in many of our participants, we will be in a better position to determine this.

### **Future Directions**

The findings arising from the work reported in the current thesis have contributed to the bank of knowledge as to how early experiences of psychological stress and depressive symptoms affect a set of established behavioural and metabolic risk factors for CVD. This research points to a number of future directions that may advance the field of behavioural medicine concerning the interplay between psychology and cardiology. It also raises a number of further questions, which are addressed in following section.

### **Further Investigations in Youth**

Reflections from the current research regarding the nature of our cohort may assist those conducting further research in this area. Participants of the LOOK study, which formed the cohort used in the current work, were recruited from outer suburban primary schools in the ACT. As previously indicated, participating schools were relatively homogeneous in terms of SES. In addition, the average SES index of the suburbs in our study was approximately 10% higher than the average index of all towns and cities throughout Australia. This lack of variation in SES among our participants, who for the most part could be classified as Caucasian and Middle Class, may have had some bearing on the outcomes reported in this thesis. The strongest and most consistent evidence for a relationship between psychosocial experiences in childhood and adverse cardiovascular outcomes has been found for chronic and severe exposures, such as childhood adversity (e.g. sexual and physical abuse, neglect; Dong et al., 2004; Korkeila et al., 2010). Children in our cohort may not have been exposed to psychological adversities of a magnitude that has previously been suggested to result in the physiological changes that are thought to provide a link between psychological distress and cardiovascular dysfunction; and therefore, early pathogenesis for CVD may not have been initiated. As previously stated throughout the chapters of this thesis, it is unlikely that the experience of a single stressor at this early

age will have a significant effect on CVD development. More likely, it is the ongoing exposure to stressors, which result in an unhealthy chronic stress response, and therefore, subsequent tissue and organ dysfunction.

Despite the absence of any effect of psychosocial stress on arterial function, our work provided evidence that depression (even of a pre-clinical level) may increase established behavioural and metabolic risk factors for CVD. Future investigations may benefit from focussing on adolescent populations, where psychological disturbances are likely to emerge more strongly, allowing sufficient time for any effect of the exposures to take place. Future studies may also benefit from investigating participants drawn from a more heterogeneous population in terms of their SES status.

### **Measurement Instruments in Paediatric Populations**

An ongoing question that arose throughout this project was that relating to the measurement instruments available to assess the constructs under investigation, and whether these instruments were sufficiently sensitive to capture changes in either the psychological or physiological variables. The problematic nature of stress measurement has been long debated in the literature. In the current work, attempts were made to clearly articulate how stress was operationalised and assessed, based on contemporary stress theory. However, the operationalization of stress within a 'process' framework in the current project was not without its limitations. To truly capture the multivariate processes that define stress, involving inputs, outputs, and the mediating activities of appraisal and coping (Lazarus, 1990), the measurement of stress may benefit from abandoning a simple input-output analysis and instead attempt to more fully capture the fluid process. Within a process framework, the measurement of stress may involve a series of measures that assess each level of the stress process (e.g. key inputs including stressor exposures and antecedents, including person variables and beliefs that may guide appraisals; mediating processes like appraisals and coping generated by stressor exposure; and markers of the response, both

biological and behavioural). This type of assessment also calls for a more complex analytic approach, for example utilising systems biology or network analyses. Because stress measurement of this kind involves a larger investment of participant and researcher time, along with complex data modelling, it may not always be feasible, particularly in large scale projects like LOOK.

Staying with this line of questioning relating to stress measurement, there is a need to develop methods of assessing the stress response in large cohort studies, which would have been valuable in the current series of studies. While it is possible to obtain a more reliable estimate of stress response markers, such as systemic sympathetic activity, by employing arterialised venous sampling (Barton, et al., 2007; Linares et al., 1987; Veith et al., 1994), this method is not usually viable in large-scale studies or among paediatric populations. Therefore, like self-report assessments of stressor exposure and appraisals, measurement of the stress response is met with its own difficulties, owing largely to the complexities involved with isolating the stimulus to which a response is being made (be that a stressor appraised as threatening, or something unrelated like physical activity).

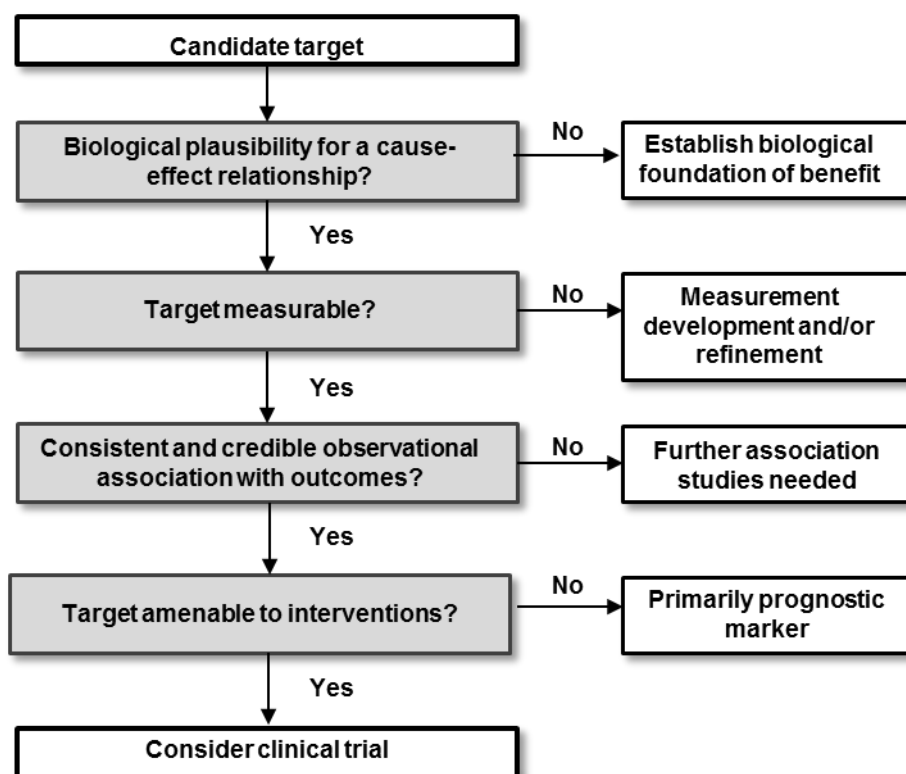
Similar methodological considerations arise when considering the currently available instruments to assess arterial function in children. While both the assessments of arterial stiffness (pulse wave velocity) and endothelial function (EndoPAT) used in the current study have showed promising results as a prognostic marker in adults, less is known of their validity and reliability in children. It remains that current methods of arterial stiffness and endothelial function in children may require refinement (Bruyndonckx et al., 2013; Sakuragi & Abhayaratna, 2010). One example of this might be the development of a separate set of algorithms for EndoPAT assessments that may more accurately capture endothelial function in children (Bruyndonckx et al., 2013). Similarly, our assessments of physical activity and fitness have their own limitations. For example, pedometer assessed physical activity is limited to an assessment of steps and therefore does not capture activities such as swimming,

cycling, or more stationary physical activity like yoga. In addition, the 20-meter multistage shuttle test used to assess cardiorespiratory fitness requires maximal effort and therefore performance may be influenced by participant motivation. In summary, while the instruments used in the current work have all been scientifically “validated”, it does remain that a number of limitations are evident in terms of their specificity and reliability.

### **Future Research**

The current research provides support for considering the psychological health of a child in terms of early risk of developing CVD and has shown us that children with early signs of depression and stress may be at increased risk for the development of CVD. But knowing the evidence constitutes just the first part of the picture – the second part begs the critical question of how that evidence may be translated into practice. Here I attempt to do that.

At the outset of this discussion, I acknowledge that in order to translate the findings of the current research into potential therapies or intervention programs with clinical benefit for youth, a better understanding of the pathophysiology establishing the foundation of the benefit is necessary. However, our data, together with previously published research linking psychological distress and metabolic health, provide a stronger basis for further research that may identify any causal relationship and the effectiveness of any corresponding intervention. It has been proposed that for a novel intervention to be considered for clinical trials, it should fulfil the requirements outlined in Figure 20. In applying these criteria to the current work, a number of targets for future research are identified.



*Adapted from Marti et al. (2012)*

*Figure 20.* Proposed schema for evaluation of candidate targets for clinical trials.

Firstly, what becomes evident when applying these criteria is a need to more clearly establish the biological foundations or mechanisms that could plausibly link psychosocial stress and depression to CVD. While this is a complex task, without knowledge of the underlying pathways and mechanisms, the credibility of any identified associations between psychological factors and cardiovascular health is jeopardised, which may limit possibilities for novel intervention. Moreover, effective treatment of stress-related disorders (particularly in the context of a CVD prevention model) that so intimately intertwines psychology and physiology demand the psychologist's attention and some understanding of physiology (and pathophysiology), to successfully treat excessive stress arousal and its pathological consequences (in a psychological context). Secondly, there is a need to develop and refine the currently available measurement instruments, which has been discussed in more detail in the previous

section. This measurement development is particularly important for assessments relating to stress and in assessments of intermediary CVD risk markers in children. Thirdly, a consistent association between psychological distress and measures of cardiovascular function among younger populations is yet to be established, partially due to the paucity of published research in this area, highlighting the need for further studies among youth. Future studies will need to be prospective in their design and be able to adequately capture the psychological constructs in more detail and with more precision. A focus on chronic stress and severe trauma may prove to be a fruitful line of investigation, as would the inclusion of clinical interviews in the assessment of depression. Finally, a better understanding of whether aspects of cardiovascular function in youth are amenable to intervention is yet to be elucidated both in terms of psychological interventions, but also in relation to other primordial prevention programs, where the research that is able to test such effects is yet to materialise. What is clear from these reflections is the need for much more research in youth to justify a clinical trial into the efficacy of psychological intervention.

### **Implications for the Practising Psychologist**

It could also be argued on the grounds of the findings arising from the current work (e.g. significant influence of psychosocial stress and depressive symptoms on primordial risk factors) that existing primordial interventions, such as those aimed at increasing physical activity and fitness or reducing overweight and obesity, may benefit from a greater consideration of mental health factors, so justifying the involvement of a psychologist in any multidisciplinary program aimed at improving CVD risk. This would be particularly important among children considered to be at risk of developing depression.

The psychologist is well placed to contribute to primordial prevention programs, and it is not uncommon to see the application of psychological theory in the program development of many primordial prevention programs and interventions. For example,



behaviour change theories such as the Health Belief Model (Becker, 1979; Becker, Maiman, Kirscht, Haefner, & Drachman, 1977; Becker & Rosenstock, 1984) and the Theory of Planned Behaviour (Ajzen & Madden, 1986; Ajzen & Fishbein, 1980) are well known by several fields of health professionals and commonly utilised in health promotion and intervention development (Hardeman et al., 2002; McEachan, Conner, Taylor, & Lawton, 2011), as is the Stages of Change model (DiClemente et al., 1991; Prochaska & DiClemente, 1984; Prochaska, DiClemente & Norcross, 1992); Social Cognitive Theory (Bandura, 1991; Bandura, 1997a), and the Social Ecological Model (McLeroy, Bibeau, Steckler, & Glanz, 1988; Sallis, Owen, & Fisher, 2008). More recently, the adoption of Motivational Interviewing (Miller & Rollnick, 2013) theory and strategies have been considered in physical activity and weight management interventions with promising results (Brodie & Inoue, 2005; Hardcastle, Taylor, Bailey, Harley, & Hagger, 2013; Harland et al., 1999). While the application of health promotion and behaviour change theory is important and arguably a key feature in the success of such programs (Glanz & Bishop, 2010), what is evident from the findings emerging from the current thesis is the need for greater awareness and consideration of mental health in the development and delivering these programs.

From a cognitive behavioural perspective (Beck, 1970, 1976; Beck, Ruch, Shaw, & Emery, 1979), it is supposed that efforts to resolve mental health issues can produce positive change in a child's cognitive style, behavioural response, and subsequent emotional experience (James, James, Cowdrey, Soler, & Choke, 2013; Stasiak, Hatcher, Frampton, & Merry, 2014). This in turn, may positively affect health behaviours and therefore, improve primordial CVD risk factor profiles in youth (Lustman, Griffith, Freedland, Kissel, & Clouse, 1998; Wing, Phelan, & Tate, 2002). In addition, by instilling the skills to more successfully navigate difficult emotional experiences and improve a child's ability to process and regulate negative emotions that inevitably will arise, it is hypothesised that the threshold at which a stressor (be that arising from the environment or from within the child via memories, emotional or

cognitive triggers) may elicit a chronic, unhealthy stress response, and therefore the physiological changes likely associated with CVD risk (d'Audiffret et al., 2010; Grippo & Johnson, 2009; Huffman et al., 2013; Rozanski et al., 1999), will be reduced or occur less frequently (Everly & Lating, 2012). While this line of causation is yet to be determined, the findings of a significant relationship between psychosocial stress, depressive symptoms and physical fitness, fatness and insulin resistance reported in the current thesis provide support and justification for further research that is able to investigate causality.

In addition to providing intervention and psychotherapies, the involvement of a psychologist in the development of primordial prevention programs may provide further benefits through the provision of specialist education to health workers from other professions and teachers, on the warning signs that may be relevant to look for in depressive presentations, and in providing psychoeducation on a course of action these professionals could take with children considered to be at risk.

### **Concluding Comments**

The research reported in this thesis has investigated the impact of two psychological risk factors, namely psychosocial stress and depression, on a set of established behavioural and metabolic risk factors for CVD, and with more direct prognostic intermediary markers of arterial function. Our findings of direct relationships between depression and other well-established risk factors for CVD, namely obesity, low fitness, and greater insulin resistance, during childhood and adolescence suggest that psychological health may play a role in the early stages of CVD. On the other hand, no evidence emerged of any effect of psychosocial stress or depression on our measures of arterial function, considered to be a more direct and compelling indicator of early cardiovascular risk. It is through continuing longitudinal studies such as the LOOK study, and others around the world, that the clinical significance of early signs of stress and depression in children will be better understood.

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