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# Mood Disorders and Cardiovascular Disease

Jennifer L. Gordon, Kim L. Lavoie,  
André Arsenault, Blaine Ditto and Simon L. Bacon  
*McGill University, Université du Québec à Montréal,  
Montreal Heart Institute, Concordia University,  
Montreal Behavioural Medicine Centre  
Canada*

## 1. Introduction

### 1.1 Cardiovascular disease (CVD)

Cardiovascular disease (CVD) accounts for 29% of global deaths, making it the leading cause of mortality worldwide. In 2004, 17.1 million people died from CVD and this number is expected to increase to 23.6 million by 2030 (World Health Organization, 2007). The most important mechanism contributing to the development and progression of CVD is atherosclerosis, the process by which fatty plaques accumulate on the inner walls of arteries, leading to their narrowing and loss of elasticity. This process is thought to generally begin with damage to the vascular endothelium, which is a layer of cells lining the vascular wall. The endothelium plays a critical role in many important functions, such as the dilation and constriction of blood vessels and arteries, thrombus (blood clot) formation, and inflammation (Quyyumi, 2003). When damage to the endothelium occurs, low-density-lipoproteins (LDL's), commonly known as "bad" cholesterol, permeate the endothelial lining, allowing them to enter the inner layer of the arteries. An inflammatory response, the immune system's attempt to promote self-repair, is triggered. As part of this inflammatory response, macrophages, whose function is to ingest and decompose pathogens found in the body, engulf these LDL particles and form what are called "foam cells". The accumulation of foam cells in the arterial wall form a "fatty streak", a yellowish slightly raised area that is the precursor to atherosclerotic plaques. If the endothelium continues to be damaged, triggering an escalation of the inflammatory response, a fibrous cap eventually covers the lesion, forming a hard plaque. The arterial wall calcifies and hardens. The formation of the plaque and the hardening of the artery cause obstruction of blood flow. If a plaque cap is unstable and becomes damaged, a thrombus can form, increasing the risk of a myocardial infarction (heart attack) or stroke (Stanner, 2005), which occur when blood flow to the heart or brain are completely obstructed. Given that endothelial damage and inflammation are so critical to the atherosclerotic process, factors that damage the endothelium or promote the inflammatory response indirectly contribute to atherosclerosis and therefore CVD.

### 1.2 Risk factors for CVD

A variety of factors have been shown to contribute to the development of CVD. Hypertension, for example, is thought to contribute to CVD by impairing endothelial

function. It is believed to do so by decreasing the endothelium's production of an important substance called nitric oxide (Panza et al., 1993). Nitric oxide plays an important role in promoting vasodilation and inhibiting inflammation and platelet aggregation and is key in maintaining good endothelial function and therefore preventing CVD.

Insulin resistance, a condition where normal levels of insulin are inadequate to trigger glucose absorption by liver, muscle and fat cells, has also been shown to contribute to endothelial dysfunction (Laine et al., 1998; Steinberg et al., 1996) and is also thought to do so by impairing nitric oxide production (Petrie et al., 1996). Insulin resistance, and the hyperglycemia (elevated blood sugar) which often accompanies it, is also believed to promote inflammation and fatty streak formation in a variety of complex mechanisms (Nigro et al., 2006; Reusch & Draznin, 2007).

Dyslipidemia, characterized by high LDL and triglyceride levels, also contributes to CVD by damaging the endothelium and by being directly involved in the formation of foam cells (Maggi et al., 1994). Having low levels of HDL (high density lipoprotein or "good" cholesterol) is also detrimental since HDL protects against atherosclerosis. In fact, research suggests that increasing HDL levels may be a therapeutic method to reversing plaque accumulation (Lee & Choudhury, 2007), partly through its beneficial effect on endothelial function (O'Connell & Genest, 2001).

Several psychological variables have also been found to contribute to CVD development. For example, the famous INTERHEART study found that psychosocial factors represented the third most important risk factor for myocardial infarction, with only smoking and high cholesterol being associated with more risk (Yusuf et al., 2004). Numerous studies have since confirmed that several psychosocial factors, including depression, anxiety, hostility, lack of social support, and chronic life stress (Rozanski et al., 1999), play an important role in contributing to CVD. However, depression is arguably the most important of these factors.

### 1.3 Depression and CVD

Depressed individuals exhibit many of the risk factors that contribute to atherosclerosis, including hypertension (Davidson et al., 2000; Jonas et al., 1997; Rabkin et al., 1983) and insulin resistance (Everson-Rose et al., 2004; Timonen et al., 2005). Unsurprising then, both depressive symptoms (Sherwood et al., 2005) and diagnosed major depression (Rajagopalan et al., 2001) are associated with endothelial dysfunction as well as vascular inflammation (Joynt et al., 2003). As mentioned above, this increased incidence of CVD risk factors in depressed individuals translates to increased risk of CVD. One meta-analysis of prospective studies examining the development of CVD in initially healthy individuals found that major depression was associated with a 2.5-fold increased risk of developing CVD compared to non-depressed individuals (Van der Kooy et al., 2007). Another meta-analysis found that clinical depression in CVD patients was also associated with a 2- to 2.5-fold increased risk of all-cause mortality compared to those without depression (van Melle et al., 2004).

Although it is clear that depression is associated with many CVD risk factors and that it predicts the development of CVD, the mechanisms behind this association are unclear. Two main pathways have been proposed (Joynt et al., 2003): the first assumes that depression is linked to CVD and its risk factors through an imbalance or dysregulation in the

physiological systems involved in the stress response: the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. The second proposes that depressed patients' tendency to engage in poor health behaviours, such as smoking and over-eating, is responsible for their unhealthy cardiovascular profiles. In this chapter, we will examine the evidence supporting each of these potential pathways (see Fig. I).

## **2. Physiological pathways**

### **2.1 The autonomic nervous system (ANS) and sympathoadrenal (SA) system**

#### **2.1.1 The ANS, SA system, and CVD**

One of the most important physiological systems involved in the stress response is the ANS. There are two branches that work together to form the ANS. On the one hand, the parasympathetic nervous system (PNS) releases the neurotransmitter acetylcholine to promote a resting state, decreasing heart rate and blood pressure. On the other hand, the sympathetic nervous system (SNS) releases the neurotransmitter adrenaline to prepare the body for action during times of stress or alertness by increasing heart rate, blood pressure, and the heart's contractile force (D. S. Goldstein, 2006). The SNS branch of the ANS also promotes the release of adrenaline and noradrenaline in the form of hormones through the sympathoadrenal (SA) system. Though both the neurotransmitter and hormonal forms of adrenaline have similar functions, the hormonal form has a more systemic effect on the body.

While the SNS plays an important role in preparing the body to react to danger, chronic activation of the SNS can have negative consequences for the cardiovascular system. Many indicators of dominance of the SNS over the PNS have been shown to predict future cardiac mortality. For example, reduced heart rate variability (variation in the amount of time between heart beats), an indicator of increased SNS relative to PNS activity, predicts myocardial infarction and cardiac mortality (La Rovere et al., 1998; Nolan et al., 1998; Tsuji et al., 1994). Impaired heart rate recovery (i.e. drop in heart rate) after exercise (Cole et al., 2000; Farrell et al., 1992; Mora et al., 2003; Morshedi-Meibodi et al., 2002; Nishime et al., 2000) as well as reduced baroreflex sensitivity, the ANS' ability to alter heart rate in response to changes in blood pressure, two known indicators of sympathetic dominance, have similarly been found to predict cardiac outcomes (Farrell et al., 1992; La Rovere et al., 1998). SNS hyperactivity is likely related to cardiac mortality by causing instability in the heart's electrical system, causing the heart to beat abnormally (arrhythmias), which can cause sudden cardiac death (Coker et al., 1984). In addition, sympathetic dominance likely increases one's risk of CVD through disruption of the SA system.

The SA system, as mentioned above, is also greatly involved in the body's stress response. When the hormonal forms of adrenaline and noradrenaline are released into the bloodstream, some of their main effects on the cardiovascular system include altering heart rate and the heart's contractile force, as well as promoting the release of stored sugar into the blood stream. Adrenaline and noradrenaline also impact the cardiovascular system by stimulating the HPA axis, whose effects are described below.

As is the case with the neurotransmitter form of adrenaline, chronically high levels of plasma adrenaline and noradrenaline can contribute to the development of many of the

CVD risk factors observed in depressed patients. For example, chronically high levels of adrenaline and noradrenaline can induce hypertension by increasing blood flow (Esler, 2000) and promote the development of insulin resistance by preventing muscle cells from absorbing the insulin that is in the blood stream, (Lembo et al., 1993; Mancia et al., 2007). Plasma adrenaline and noradrenaline can also cause blood platelets to aggregate, an essential step in the formation of a thrombus (Anfossi & Trovati, 1996).

### 2.1.2 ANS and depression

Much research supports the hypothesis that an imbalance in the ANS, and subsequently the SA system, is a mechanism linking depression to CVD. For example, numerous studies have found both clinical depression (Carney et al., 2001) and self-reported depressive symptoms (Guinjoan et al., 2007) to be associated with poorer heart rate variability, indicating SNS dominance. Depressed mood has also been shown to be associated with markers of decreased parasympathetic cardiac control in reaction to laboratory stressors (Hughes & Stoney, 2000). Depression has also been associated with elevated resting heart rate (Dawson et al., 1977; Lahmeyer & Bellur, 1987), poor heart rate recovery after exercise (Gordon et al., 2011), reduced baroreflex cardiac control (Watkins & Grossman, 1999) and increased systolic blood pressure during exercise (Pelletier et al., 2009), once again, indicating sympathetic dominance. Finally, depression is associated with electrical instability of the heart (Nahshoni et al., 2000; Yeragani et al., 2000), likely a consequence of ANS dysfunction, increasing the risk of arrhythmias (Carney et al., 1993).

Depressed individuals have also been found to exhibit signs of a hyperactive SA system. For example, we have long known that depressed patients exhibit higher plasma noradrenaline levels, thought to parallel SA activity, compared to non-depressed controls (Esler et al., 1982; Lake et al., 1982; Roy et al., 1988; Veith et al., 1984; Wyatt et al., 1971). One study had 60 healthy women complete the Beck Depression Inventory (BDI) and compared the catecholamine levels of the 15 women with highest scores to the 15 with the lowest scores in response to a public speaking task. The “depressed” women were found to have higher plasma noradrenaline levels (in addition to greater blood pressure and several measures of sympathetic activation) during the task compared to the “non-depressed” group (Light et al., 1998). Another study examined BDI scores and physiological recovery to a stress-inducing public speaking task in non-depressed women. It found that although all participants exhibited high plasma adrenaline levels immediately after the stressor, only the women with scores in the high-normal range had high adrenaline levels 45 minutes post-stressor (Gold et al., 2004). In contrast, participants with low BDI scores had similar adrenaline levels to non-stressed controls within 30 minutes of the stressor. These analyses adjusting for perceived stress during the task, reducing the possibility that the more “depressed” participants simply found the task more psychologically stressful. Collectively, these studies suggest that depressive symptoms, even when in the sub-clinical range, are associated with enhanced SA system activation, both in general and in response to stressful tasks. Furthermore, the latter study suggests that this physiological response does not result simply from depressed people feeling more psychologically distressed in response to stressful tasks than non-depressed people. Instead, depressive symptoms appear to be associated with an imbalance in ANS cardiac control.



## 2.2 The HPA axis

### 2.2.1 The HPA axis and CVD

The HPA axis, through its release of hormones called glucocorticoids, the most important of which is cortisol in humans, also plays a pivotal role in the body's stress response, though its effects are delayed but longer-lasting than the ANS'. As with adrenaline, increased cortisol release is helpful during stress but is thought to contribute to the development of CVD when chronically activated (G. E. Miller et al., 2002). This is most apparent in patients with Cushing's Syndrome, a disorder characterized by the hypersecretion of cortisol, who are at four times the risk of developing CVD compared to the general population (Arnaldi et al., 2004; Mancini et al., 2004; Whitworth et al., 2000). Even people with sub-clinical Cushing's Syndrome (Tauchmanova et al., 2002) and people who have been cured from this disorder for five years (Colao et al., 1999) are at an increased risk of developing CVD. Cortisol exposure while awake (Dekker et al., 2008) and decline in cortisol levels throughout the day (Matthews et al., 2006) are also independently associated with atherosclerosis. A recent study has also shown that urinary cortisol levels predict cardiac mortality – in fact those in the highest tertile of urinary cortisol exhibit a 5-fold increased risk in CV death (Vogelzangs et al., 2010).

Elevated cortisol levels are thought to increase one's risk of developing CVD through several mechanisms. For example, chronically elevated levels of cortisol can lead to the development of hypertension, which has long been known to be a consequence of Cushing's Syndrome (Whitworth et al., 2000). Many placebo-controlled studies have confirmed that a dose-response relationship exists between cortisol and blood pressure in healthy individuals as well (Whitworth et al., 1989; Whitworth et al., 1984; Williamson et al., 1996). Cortisol's hypertension-inducing effect can be partially explained by its tendency to increase both salt and water retention (Panarelli et al., 1998) and to constrict the blood vessels by inhibiting its production of nitric oxide, a substance that dilates the blood vessels (Kelly et al., 1998). High cortisol levels can also contribute to insulin resistance by impairing insulin-dependent glucose uptake and enhancing glucose production in the pancreas (Andrews & Walker, 1999; Reynolds & Walker, 2003).

Cortisol levels are associated with the development of endothelial dysfunction in both clinical and sub-clinical cases of Cushing's Syndrome (Baykan et al., 2007; Colao et al., 1999). Studies blocking the production of cortisol have discovered that it is also responsible for the endothelial dysfunction observed in healthy participants in response to acute stress, for example, a public speaking task (Broadley et al., 2005). Though this effect may be partially due to cortisol's effect on blood pressure and insulin resistance, it is also thought to induce endothelial dysfunction by inducing cell apoptosis, a series of biochemical events that cause endothelium cell death (Vogt & Schmid-Schonbein, 2001) and decreasing the endothelium's production of nitric oxide (Johns et al., 2001).

Elevated cortisol levels also causes the accumulation of abdominal obesity, a well-known risk factor for CVD (Hubert et al., 1983). The effect of cortisol on fat deposition is not only clear in Cushing's Syndrome patients, studies also show cortisol levels to be associated with abdominal obesity in healthy people (Fraser et al., 1999). Research suggests this may help explain the association between excess cortisol and high cholesterol and triglyceride levels (Walker et al., 2000).

### 2.2.2 The HPA axis and depression

There is a great deal of research suggesting that depressed individuals have a hyperactive HPA axis. Numerous studies have found that depressed patients exhibit abnormally high cortisol and corticotropin releasing factor levels, another byproduct of the HPA axis (Plotsky et al., 1998). Depressed coronary artery disease patients have also been found to exhibit lower cortisol levels in the morning and higher levels in the evening (i.e. “flatter” cortisol rhythms) compared to both non-depressed coronary artery disease patients and depressed patients without coronary artery disease (Bhattacharyya et al., 2008). That depressed individuals fail to show glucocorticoid suppression in response to the dexamethasone suppression test demonstrates that the abnormally high cortisol levels seen in depressed patients could be due to a dysfunctional feedback system (Carroll et al., 1968; Schatzberg et al., 1984).

Depressed people have also been found to exhibit abnormal cortisol responses to psychological stressors. A meta-analysis of seven laboratory studies (Burke et al., 2005) found that depressed people exhibit much higher post-stress recovery cortisol levels compared to non-depressed controls. Another study examining cortisol responses to daily stressors (Peeters et al., 2003) found that depressed individuals exhibited no change in cortisol levels in response to the stressors. Similarly, a study examining cortisol responses to orthopedic surgery found that while chronically depressed patients had significantly higher cortisol levels than non-depressed controls before the surgery, their cortisol levels failed to increase in response to the stress as did the non-depressed patients’ (Kudoh et al., 2000).

Abnormalities in the HPA axis are also believed to be involved in the vascular inflammation observed in depressed patients. Although depressed patients are believed to have abnormally high levels of circulating glucocorticoids, which have anti-inflammatory properties, their glucocorticoid immune receptors are thought to be desensitized, perhaps because of their chronic over-exposure to cortisol, and therefore less responsive to the anti-inflammatory actions of circulating glucocorticoids (Cooney & Dinan, 1996).

In summary, there are several physiological pathways by which depression may confer risk for CVD. However, evidence suggests that health behaviours may also be important in explaining the relationship between depression and CVD. These health behaviours will be discussed in the following section.

## 3. Behavioural pathways

Depressed individuals tend to engage in several poor health behaviours known to contribute to CVD, which may explain their increased risk of developing CVD. In this chapter, we will discuss four behaviours in relation to depression: excess calorie consumption (i.e., obesity), physical inactivity, smoking, and excess alcohol consumption, all of which are important risk factors for CVD. In fact, in the INTERHEART study, including nearly 30 000 participants, these four health behaviours were found to explain 75% of the population attributable risk (PAR) for myocardial infarction (Yusuf et al., 2004).

### 3.1 Smoking

#### 3.1.1 Smoking and CVD

Smoking is arguably the most important and well-established risk factor for CVD (Yusuf et al., 2004), with the number of pack years (# of packs smoked/ day X # years of smoking) a person has smoked being consistently associated with the level of severity of atherosclerotic development (Herbert, 1975; Ramsdale et al., 1985; Wang et al., 1994). Smoking is thought to contribute to atherosclerotic development via several pathways. One pathway is by damaging the endothelium. Numerous studies have confirmed that smokers have significantly impaired endothelial function compared to non-smokers (Barua et al., 2001; Esen et al., 2004; Kiowski et al., 1994; Zeiher et al., 1995) and that this dysfunction can last up to three months after a smoker quits (Celermajer et al., 1993). Smoking is thought to have this impact on the endothelium through two main mechanisms: by increasing oxidative stress, which deactivates nitric oxide (Puranik & Celermajer, 2003) and by causing direct endothelial cell damage (Bernhard et al., 2003; Hoshino et al., 2005).

Smoking also contributes to the inflammatory response involved in CVD development. Cigarette smoking has been associated with elevated levels of several markers of inflammation (Bermudez et al., 2002; Mendall et al., 1997; Tappia et al., 1995; Tracy et al., 1997). Cigarette smoke extract has also been found to double the rate at which macrophages are created and engulf LDL's to form foam cells (Shen et al., 1996).

Smoking may also contribute to atherosclerosis by altering one's lipid profile. Studies have found smokers to have higher levels of LDL and triglycerides and lower levels of HDL compared to non-smokers (Craig et al., 1989). Several studies have confirmed that cigarette smoke extract increases the oxidation of LDL cholesterol, a step that allows the LDL to cross the endothelial layer (Frei et al., 1991; Heitzer et al., 1999; Pech-Amsellem et al., 1996; Yokode et al., 1988).

Smoking also increases thrombosis (blood clotting) through several mechanisms, including increasing platelet aggregation (Blache, 1995; Fusegawa et al., 1999; Rival et al., 1987), altering the release of antithrombotic and prothrombotic factors by endothelial cells (Kannel et al., 1987; Sambola et al., 2003; Smith et al., 1997) as well as altering fibrinolysis, the process by which blood clots are broken down (Barua et al., 2002; Newby et al., 1999; Pretorius et al., 2002). In having such an effect on thrombosis, smoking greatly increases the chances that atherosclerosis will lead to a myocardial infarction (Ambrose & Barua, 2004).

#### 3.1.2 Smoking and depression

There is a strong association between depression and smoking. Several studies have found that depression in adolescence is associated with a greater risk of smoking initiation (Lam et al., 2005; Weiss et al., 2005), and that this risk increases with increasing depression severity (Escobedo et al., 1998). Several studies find that depressed patients are also less successful at quitting smoking compared to non-depressed patients (Burgess et al., 2002; Ginsberg et al., 1995), but that their ability to quit is improved with cognitive behaviour therapy (S. M. Hall et al., 1994). It is therefore unsurprising that cross-sectional studies find a strong link between depression and smoking (Almeida & Pfaff, 2005; Escobedo et al., 1996). Given that smoking is such an important contributor to CVD and that depressed patients are more



likely to smoke than non-depressed individuals, smoking may explain why depressed patients are at an increased risk for CVD.

## 3.2 Obesity

### 3.2.1 Obesity and CVD

Obesity, defined as a body mass index (BMI) of 30 kg/m<sup>2</sup> or larger (Soodini & Hamdy, 2004), or a waist circumference greater or equal to 88 cm for women and 102 cm for men (Grundy, 2006), is a well-known risk factor for CVD. Obese individuals have been found to have increased mortality rates (Ajani et al., 2004; Hu et al., 2004; Widlansky et al., 2004) and are 2.4 times more likely to develop CVD compared to normal weight individuals (Lawlor & Leon, 2005). This is unsurprising given the long list of CVD risk factors associated with obesity, including hypertension, insulin resistance, dyslipidemia, and endothelial dysfunction (Smoak et al., 1987). Although obesity is influenced by several factors, studies have found caloric consumption to be the most important predictor of weight loss or gain and caloric restriction to be the most successful means of inducing weight loss (Blumenthal et al., 2000; Brownell, 1999; Elfhag & Rossner, 2005; Jakicic et al., 2003; Petersen & Harper, 2004). In this chapter, “obesity” will therefore be considered a proxy of long-term excess caloric consumption although it is not a behaviour per say.

The increase in CVD risk factors in obese individuals is believed to be a consequence of adipose tissue's release of signaling proteins called adipokines (Gordon et al., 2008). For example, most adipokines (e.g., leptin, resistin) are known to induce endothelial dysfunction by decreasing nitric oxide availability, leading to endothelial cell death (Beltowski et al., 2004; Bouloumie et al., 1999; Clapp et al., 2004; Meldrum, 1998; Mercurio & Manning, 1999). In addition, several adipokines, promote the inflammatory response that contributes to atherosclerosis (Lee & Pratley, 2007). Exceptionally, one beneficial adipokine, adiponectin, which promotes the production of nitric oxide, is downregulated in obese individuals (Avogaro & de Kreutzenberg, 2005; Chen et al., 2003).

Adipokines may also contribute to CVD through their tendency to induce hypertension. One adipokine called leptin, for example, is thought to induce hypertension by promoting sympathetic activation (Hall et al., 2001). Another adipokine called interleukin (IL)-6, may also contribute to the development of hypertension through its stimulation of the HPA axis (Yudkin et al., 2000). Finally, Angiotensin-II, another adipokine, contributes to hypertension by constricting the blood vessels (Brasier et al., 2002).

Several adipokines also contribute to insulin resistance. For example, one study found that the acute administration of the adipokine resistin induces glucose intolerance. The same study also found an improvement in blood glucose levels and insulin sensitivity when obese mice were given an anti-resistin antibody (Steppan et al., 2001). Adipokines also contribute to obesity-induced insulin resistance by inhibiting insulin's signal to fat and muscle cells to absorb glucose (Senn et al., 2002; Uysal et al., 1997). Finally, adiponectin, down-regulated in obese individuals, is known to reduce the risk of insulin resistance (Yamauchi et al., 2001). Obesity may also contribute to CVD through its association with high LDL cholesterol levels (Denke et al., 1993; Morrison et al., 1999), although the mechanism behind this association is not completely understood.

### 3.2.2 Obesity and depression

Studies have consistently found depression to be associated with obesity. For example, one found that in a nationally representative sample, overweight and obese women and overweight (but not obese) men were more likely to report depressive mood compared to participants with a healthy weight (Heo et al., 2006). Another study comparing clinically depressed individuals to controls with no history of psychiatric illness also found that the depressed individuals had a significantly greater average BMI compared to controls (V. M. Miller & Vanhoutte, 1988). Several longitudinal studies aimed at determining whether the onset of depression precedes or follows the onset of obesity also found that depressive symptoms predict obesity later in life. For example, one such study measured depressed mood ratings and BMI in adolescents and found that, after controlling for baseline BMI and other confounding variables (e.g. self-esteem and physical activity levels), 'depressed' adolescents (measured using the Center for Epidemiologic Studies Depression Scale (CES-D scale)) were twice as likely to be obese at one-year follow-up compared to non-depressed adolescents (Goodman & Whitaker, 2002). Another found similar results, with depressed younger adolescents being more than twice as likely to become obese towards the end of adolescence (Richardson et al., 2003). Childhood depression has also been found to be predictive of adult obesity after adjusting for childhood BMI (Pine et al., 2001). However, a recent meta-analysis of longitudinal studies suggests that obesity also predicts the onset of depression, suggesting a bi-directional relationship (Luppino et al., 2010).

Given that obesity is closely associated with depression and is such a well-known contributor to CVD, it represents a plausible mechanism explaining the relationship between depression and CVD. For these same reasons, physical inactivity may also potentially explain the link between depression and CVD.

## 3.3 Physical inactivity

### 3.3.1 Physical inactivity and CVD

It has long been known that maintaining an active lifestyle is beneficial for CV health. However, perhaps less commonly known is that although regular exercise is beneficial partly through its calorie-burning effects, its benefits on the cardiovascular system extend beyond this. In fact, increased physical activity has been associated with lower CVD risk independent of body weight (Haapanen-Niemi et al., 2000).

Much of this benefit is believed to be due to exercise's effect on the endothelium. Many studies have found increased physical activity to be associated with better endothelial function (Kingwell et al., 1996; Rinder et al., 2000; Rywik et al., 1999). Intervention studies have supported the idea that increased physical activity predicts improvements in endothelial function, even without weight loss (Clarkson et al., 1999). It is thought to do so mainly through exercise's tendency to increase nitric oxide availability. Through an increase in blood flow, exercise stimulates the increased production of nitric oxide by activating sensors located on the endothelium that are meant to detect blood flow and cause the endothelium to release nitric oxide to dilate the arteries when blood flow is high (Garcia-Cardena et al., 1998; Schwartz & Lechene, 1992). Furthermore, exercise produces antioxidant factors (Fukai et al., 2000), which prevent the oxidation and destruction of nitric oxide.

Physical activity may also protect against atherosclerosis through its anti-inflammatory effect. Numerous cross-sectional studies have found increased physical activity to be associated with lower levels of inflammatory markers (Church et al., 2002; Ford, 2002; Reuben et al., 2003; Wannamethee et al., 2002). Furthermore, while only a few studies have examined the effect of an exercise intervention on inflammation, these have found a significant reduction in inflammatory markers after exercise training (Mattusch et al., 2000; J. K. Smith et al., 1999; Tisi et al., 1997). Most recently, one study found inflammation to be the most important mechanism linking physical activity and CVD, accounting for 59% of the inverse association (Mora et al., 2007). However, it is important to note that while this study considered many potential mechanisms linking physical activity and inflammation, it did not measure endothelial function. The extent to which the relationship between exercise and inflammation is explained by exercise's beneficial effect on the endothelium is therefore unknown.

In addition to directly benefiting the endothelium, physical activity also likely reduces the risk of CVD through its effects on other CVD risk factors. For example, randomized controlled trials suggest that three to five 30-60 minute bouts of physical activity per week result in a clinically significant reduction in blood pressure (Arroll & Beaglehole, 1992; Fagard, 2001). In the short-term, physical activity is thought to reduce blood pressure by dilating the arteries and in the long-term, it reduces SNS activity and results in a fitter, stronger heart that is able to more easily pump blood into the body. Physical activity is also known to reduce the risk of developing insulin resistance as it promotes glucose uptake by muscle cells (for energy) and makes them more sensitive to insulin: even a single exercise session is sufficient to improve insulin sensitivity for 1-2 days (Thompson et al., 2001). One study found that an exercise intervention could prevent the development of type II diabetes in a group of insulin resistant middle-aged men and women (Tuomilehto et al., 2001). Increased physical activity also increases HDL cholesterol as well as lowers LDL cholesterol and triglyceride levels (Thompson et al., 2001).

### 3.3.2 Physical inactivity and depression

Research suggests that depressed individuals are less active than the general population. Cross-sectional studies have found self-reported physical activity levels to be inversely related to levels of depressive symptoms in adolescents (Piko & Keresztes, 2006), fibromyalgia patients (Oliver & Cronan, 2002), as well as in the general adult population (De Moor et al., 2006; Galper et al., 2006). One study of 4493 CVD-free elderly ( $\geq 65$  years) men and women found a negative association between depressive symptoms and number of blocks walked in the last week (Ariyo et al., 2000). Another study of 6247 elderly men and women initially free of disability corroborates this finding: participants high in depressive symptoms reported more physical disability and less mobility every year during the six-year follow-up compared to those with low depressive symptoms (Penninx et al., 1999). A recent study by the same research group found that individuals suffering from a mood disorder spend significantly more time in front of the computer and television (de Wit et al., 2011), both of which are negatively correlated to physical activity.

Although there is much evidence suggesting that exercise can decrease depressive symptoms (Brosse et al., 2002), it is likely that a bi-directional relationship exists between depression and physical activity. This is supported by studies such as the one conducted by

Penninx et al. (1999), finding that depression often precedes physical inactivity. Given the benefits of physical activity on CV health and given that depressed patients tend to be relatively inactive, physical inactivity represents a plausible mechanism linking depression and CVD.

### **3.4 Alcohol consumption**

#### **3.4.1 Alcohol consumption and CVD**

The contribution of alcohol consumption to CVD is not as straightforward as the other three health behaviours discussed above. This is because researchers have found that while larger quantities of alcohol can damage the cardiovascular system, smaller quantities may actually be beneficial (Fuchs et al., 1995; Gaziano et al., 2000; Keil et al., 1997; Murray et al., 2002). These beneficial effects of small quantities of alcohol are likely due to its tendency to improve endothelial function by increasing the production of nitric oxide (Davda et al., 1993; Hendrickson et al., 1999) as well as increasing HDL levels (Watts et al., 1996) though this evidence is still considered somewhat controversial.

In larger quantities, though, the negative cardiovascular effects of alcohol outweigh the beneficial effects. Consuming the equivalent of four alcoholic beverages or more in one sitting is enough to induce endothelial dysfunction (Bau et al., 2005). Many studies have confirmed that chronic alcohol abuse is associated with important impairments in endothelial function (Di Gennaro et al., 2007; Maiorano et al., 1999; Zilkens et al., 2003). This effect is thought to be due to the increased oxidative stress produced by excessive amounts of alcohol, causing endothelial cell apoptosis (Croft et al., 1996; Soardo et al., 2005; Spyridopoulos et al., 2001; Sun & Mayhan, 2001). Large quantities of alcohol may also impair the production of nitric oxide (Persson & Gustafsson, 1992).

Excess alcohol consumption may also contribute to atherosclerosis through inflammation. Several studies have found that while moderate alcohol consumption is associated with lower levels of several inflammatory markers, consumption of large amounts of alcohol is associated with increased levels of these markers (Imhof et al., 2001; Imhof et al., 2004).

It is well-established that alcohol consumption contributes to the development of hypertension (Beilin, 1995; Beilin & Puddey, 2006; McFadden et al., 2005), regardless of beverage type (Zilkens et al., 2005). A meta-analysis of randomized controlled trials examining the effect of alcohol reduction on blood pressure found that a reduction in alcohol intake is consistently associated with a significant drop in blood pressure, and that a dose-response relationship can be seen such that the greater the drop in alcohol consumption, the greater the drop in blood pressure observed (Xin et al., 2001).

#### **3.4.2 Alcohol consumption and depression**

Depression is associated with heavier alcohol consumption. Epidemiological studies have consistently found major depression and alcohol dependence to be highly co-morbid (B. I. Goldstein & Levitt, 2006; Grant, 1995; Kessler et al., 1997). One study found that 32.3% of Canadian adults who had had a depressive episode in the last year were alcohol-dependent while only 9.5% of non-depressed adults were alcohol-dependent (Lukassen & Beaudet, 2005). Similarly, one prospective study found that among 1383 women at risk for heavy

alcohol use, those with a history of a depressive disorder were 2.6 times more likely to be heavy alcohol users one year later compared to those with no history of a depressive disorder (Dixit & Crum, 2000). Another large study of 22 954 adults from four different countries also found an odds ratio between 2 and 5 depending on the country when examining the comorbidity of alcoholism within the past 12 months with lifetime depressive disorders (Swendsen et al., 1998). Increased alcohol consumption may therefore contribute to depressed patients’ risk for developing CVD.

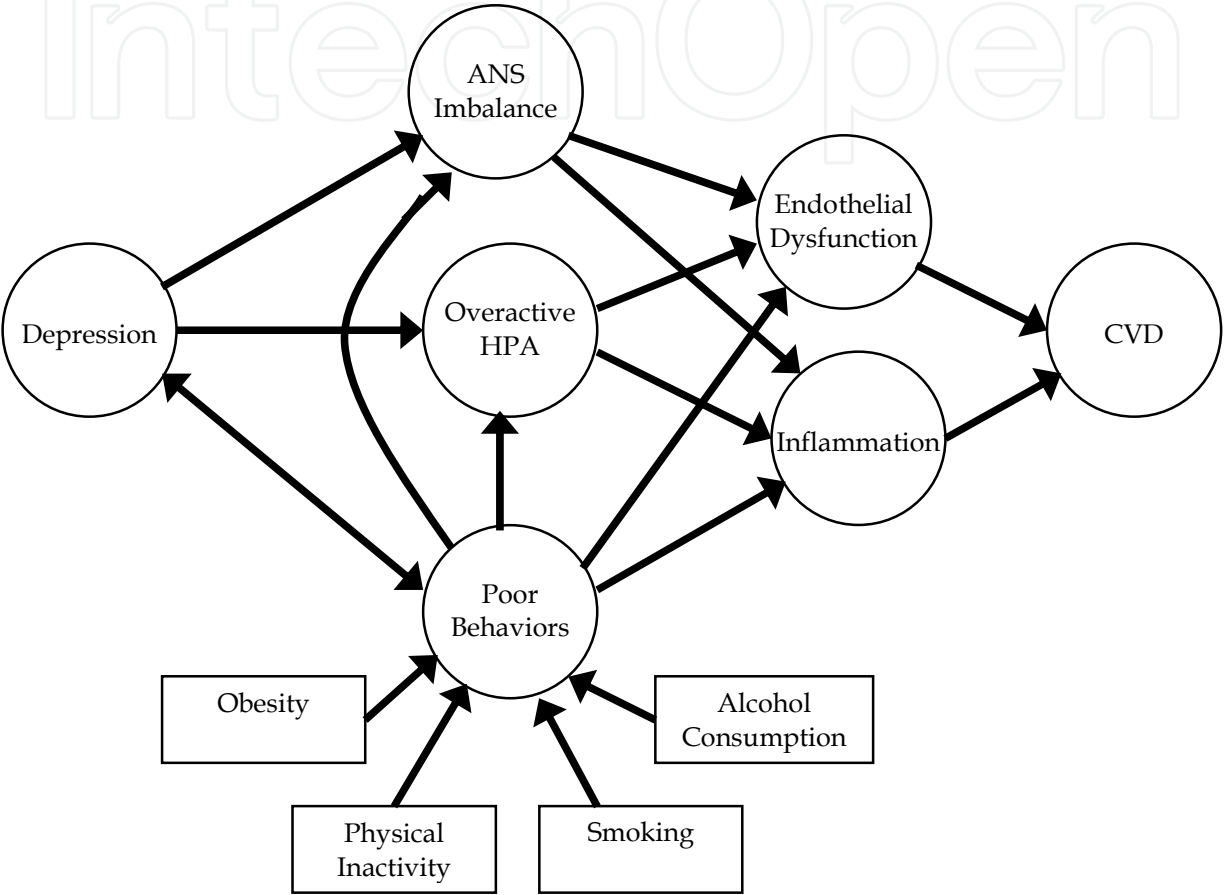


Fig. 1. Proposed model explaining how depression contributes to CVD

4. Conclusion

While our understanding of the mechanisms involved in linking depression to CVD has expanded greatly in the last decade, our knowledge of the relative importance of these mechanisms remains limited. To date there have been only two studies that have aimed to determine their relative importance. The first study of 1017 coronary heart disease patients found that smoking, medication non-adherence and physical inactivity accounted for 48% of the effect of depressive symptoms on the risk of CV events in the following 6 years. Physical inactivity accounted for the largest proportion of the variance (31.7%) (Whooley et al., 2008). A second similar study in 6576 healthy participants also found that smoking, physical inactivity and alcohol consumption accounted for 65% of the variance in the association between psychological distress and CVD (Hamer et al., 2008). However, since this study measured psychological distress and not depressive symptoms, one



should be cautious in generalising its findings to depression. Nonetheless, these studies seem to suggest that health behaviours account for at least half of the relationship between psychological variables and CVD. However, further research is required to replicate these findings.

To date, there have been a small number of studies attempting to improve the CV prognosis of depressed post-myocardial infarction patients through depression treatment. The largest study to date (Berkman et al., 2003), called the ENRICHD trial, included 2481 patients who had recently suffered a myocardial infarction and were either depressed or reported low levels of social support. Half of the participants received usual care by their physician while the other half received individual cognitive behavioural therapy lasting a maximum of 6 months. Following individual therapy, if necessary, participants could also receive 12 weeks of group therapy and up to 12 months of antidepressant treatment. The intervention was successful in reducing depressive symptoms, though results were somewhat modest: while depressed patients having received therapy experienced an overall decrease of 8.6 points on the Beck Depression Inventory, their usual care counterparts experienced a 5.8-point decrease. However, despite the improvement in depressive symptoms, this did not translate to an improvement in their CV prognosis: patients in the intervention group did not differ from the usual care group in subsequent CV events or mortality.

A second study, the CREATE trial (Lesperance et al., 2007), examined the efficacy of citalopram and interpersonal psychotherapy (IPT) among 284 coronary artery disease patients diagnosed with depression. Participants were randomised to four interventions: 1) IPT plus clinical management and citalopram; 2) IPT plus clinical management and placebo pill; 3) clinical management only and citalopram; 4) clinical management and placebo pill. It was found that while IPT was not more successful than clinical management alone in treating depression, citalopram was successful in reducing depressive symptoms with the citalopram group exhibiting a 14.7-point decrease on the BDI-II and the placebo group exhibiting a 11.1-point decrease. Yet, despite the improvement in depressive symptoms, the four groups did not differ in CV outcomes following treatment.

These and other studies (Frasure-Smith et al., 1997; Glassman et al., 2002) suggest that even when interventions successfully decrease depressive symptoms in cardiac patients, this does not translate to improved prognosis. This, despite research finding that antidepressants have been found to result in modest improvements in ANS balance (Khaykin et al., 1998; McFarlane et al., 2001). Though there has been much speculation as to why this is (Joynt & O'Connor, 2005; Sheps et al., 2003), further research is needed to uncover the answer. One potential explanation may relate to poor health behaviours persevering despite improvements in depressive symptoms. Based on the studies by Whooley et al. (2008) and Hamer et al. (2008), health behaviours appear to account for a significant proportion of the relationship between depression and CVD outcomes. However, treating depression may not automatically translate to immediate improvements in health behaviours. Obesity, smoking, excessive alcohol consumption, and physical inactivity, which depressed individuals are particularly prone to developing, are not particularly easy behaviours to alter. It is therefore possible that in addition to psychotherapy targeted at depressive symptoms, depressed patients may also require interventions specifically targeted at improving their health behaviours in order to exhibit noticeable improvements in their CV health. Considering the bi-directionality of the

relationship between depression and obesity (Luppino et al., 2010) and depression and physical activity (Penninx et al., 1999), targeting health behaviours directly may also lead to improvements in depressive symptoms.

Future intervention studies may therefore be improved by assessing health behaviours and implementing interventions specifically aimed at altering health behaviours, such as motivational interviewing (W. R. Miller & Rollnick, 2002). Assessing participants' ANS and HPA axis functioning throughout interventions may also be useful in identifying the critical components of a successful intervention and the toxic components of depression that we should target. Until this research is conducted, clinicians treating depressed individuals at high risk for CVD might consider routinely integrating interventions targeting health behaviour change into their practice.

## 5. Glossary

**Adrenaline and noradrenaline:** substances called catecholamines released by the sympathetic nervous system (as neurotransmitters) and the sympathoadrenal system (as hormones) to induce the fight-or-flight response; both forms have similar cardiovascular effects but as hormones, their effects are more systemic and longer-lasting

**Apoptosis:** process by which cells die

**Autonomic nervous system (ANS):** biological system key in orchestrating the body's response to stress; is composed of two opposing branches – the sympathetic nervous system and the parasympathetic nervous system

**Cortisol:** steroid hormone and type of glucocorticoid released into the blood by the hypothalamic-pituitary-adrenal axis in response to stress

**Endothelium:** a single layer of cells lining the interior of the blood vessels; is involved in many important aspects of cardiovascular health, including vessel dilation and constriction, inflammation and blood clot formation

**High-density lipoproteins (HDL):** commonly known as “good” cholesterol, protects against atherosclerosis by removing LDL cholesterol from the bloodstream

**Hypothalamic-pituitary-adrenal (HPA) axis:** circuit involving the hypothalamus, pituitary gland and adrenal gland resulting in the release of hormones called glucocorticoids into the bloodstream, the most important of which is cortisol in humans; is involved in the stress response

**Low-density lipoproteins (LDL):** commonly known as “bad” cholesterol, contributing to atherosclerosis

**Myocardial infarction:** technical term for “heart attack”; occurs when a blood clot completely obstructs blood flow to the heart and heart cells die as a result

**Nitric oxide:** substance produced by the endothelium that is key in maintaining its health

**Parasympathetic nervous system (PNS):** branch of the autonomic nervous system that promotes a resting state through the release of acetylcholine; its activation reduces heart rate and blood pressure

Stroke: occurs when a blood clot completely obstructs blood flow to the brain and brain cells die as a result

Sympathetic nervous system (SNS): branch of the autonomic nervous system that induces the fight-or-flight response in response to stress through the release of adrenaline and noradrenaline; its activation raises heart rate and blood pressure

Thrombus: technical term for “blood clot”

## 6. References

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## **Clinical, Research and Treatment Approaches to Affective Disorders**

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The causes, development and outcomes of disorders are determined by the relationship of psychological, social and cultural factors with biochemistry and physiology. Biochemistry and physiology are not disconnected and different from the rest of our experiences and life events. This system is based on current studies that report that the brain and its cognitive processes show a fantastic synchronization. Written by the foremost experts on Affective Disorders worldwide, this book is characterized by its innovative, refreshing, and highly sensitive perspective on current knowledge of diagnostic, neurobiology, early life stress and treatment of Mood Disorders. The authors share a deep understanding of unique challenges and difficulties involved in Affective Disorders, and have achieved a balance among clinical, research and new treatment approaches to Affective Disorders. The chapters are written in a comprehensive, easily readable, and highly accessible style, stimulating readers, clinicians and researchers.

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Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821



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