# Association Between Exercise And Depression In Adults With A Non-Communicable Chronic Disease

Mélanie Béland

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By: Mélanie Béland

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Signed by the final examining committee:

_____ Chair
Dr. Gilles Peslherbe

_____ External Examiner
Dr. Wolfgang Linden

_____ External to Program
Dr. Angela Alberga

_____ Examiner
Dr. Theresa Bianco

_____ Examiner
Dr. Mark Ellenbogen

_____ Thesis Supervisor
Dr. Simon Bacon

Approved by _____
Dr. Karen Li, Graduate Program Director

Thursday, March 15, 2018

_____
Dr. André Roy, Dean
Faculty of Arts and Science

## ABSTRACT

**Association Between Exercise And Depression In Adults With A Non-Communicable Chronic Disease**

**Mélanie Béland, Ph.D.**
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People living with a non-communicable chronic disease (NCD) are about twice as likely as the general population to suffer from depression. This comorbid condition is associated with several negative consequences, such as worse prognosis and higher risks of mortality. Recent research has examined the beneficial effect of exercise on depressive symptoms and have reported positive results, similar to pharmacotherapy and psychological intervention. However, to date, no study has examined the effect of aerobic exercise on reducing depressive symptoms in NCDs. Moreover, a handful of studies have looked at the association between exercise and depressive symptoms in the asthma population. In order to address these gaps, this thesis systematically reviewed previous literature in the area of aerobic exercise and depressive symptoms in patients with NCDs and explored the association between leisure-time physical activity and depressive symptoms in adults with asthma.

The first study was a systematic review which aimed at assessing the beneficial effects of aerobic exercise on depressive symptoms in a NCD population. A total of 24 studies were included in the meta-analysis. The results revealed a moderate effect of aerobic exercise interventions on depressive symptoms in NCDs in comparison to usual care.

The second study was a cross-sectional study assessing the association between leisure-time physical activity (LTPA) and depressive symptoms in adults with asthma. A total of 953 participants from two asthma cohorts were included. Results revealed that engaging in any LTPA was associated with lower depressive symptoms. Moreover, there was a strong association between engaging in vigorous LTPA and lower depressive symptoms in participants with high

levels of depressive symptoms. However, these relationships were no longer meaningful once they were adjusted for inhaled corticosteroid dose and asthma control.

In summary, the research has demonstrated that people with depressive symptoms and a NCD benefit from engaging in aerobic exercise, even at low levels. Given the results of this thesis, practitioners, such as clinical psychologists, may be instrumental in promoting aerobic exercise to clients who depressive symptoms comorbid with a NCD. Further research is needed to better understand the relationship in NCDs, most notable in respiratory diseases and type 2 diabetes.

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## CONTRIBUTION OF AUTHORS

The following thesis is comprised of two manuscripts.

**CHAPTER 2: Aerobic Exercise Alleviates Depressive Symptoms In Patients With a Major Non-Communicable Chronic Disease: A Systematic Review and Meta-analysis**

**Authors:**

Mélanie Béland: Conceptualization of study, performed updated systematic review screening and data extraction, analyzed the data, wrote the manuscript.

Kim L. Lavoie: Helped with conceptualization of experiment, assisted with the writing of the manuscript.

Samantha Briand: Performed the systematic review screening and data extraction

Una White: Performed the systematic review screening and data extraction

Claudia Gemme: Performed updated systematic review screening and data extraction

Simon L. Bacon: Conceptualized and designed the experiment, conceptualized the data analysis, assisted with the writing of the manuscript.

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**CHAPTER 3: Associations between leisure time physical activity and depressive symptoms in patients with asthma**

**Authors:**

Mélanie Béland: Conceptualization of study, analyzed the data, wrote the manuscript.

Simon L. Bacon: Conceptualized and designed the experiment, conceptualized the data analysis, assisted with the writing of the manuscript.

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## LIST OF ABBREVIATIONS AND ACRONYMS

12M-PAR: 12-month physical activity recall interview

ACQ: Asthma Control Questionnaire

AE : Aerobic exercise

AQLQ: Asthma Quality of Life Questionnaire

ASES: Asthma Self-Efficacy Scale

BDI-II: Beck Depression Inventory, revised

BA: Behavioural activation

BMI: body mass index

CI: confidence interval

CVD: Cardiovascular disease

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

ES: Effect size

FEV1: forced expiratory volume in one second

GSLTPAQ: Godin-Shephard Leisure-Time Physical Activity Questionnaire

HADS : Hospital Anxiety and Depressio Scale

HSCM: Hôpital du Sacré-Coeur de Montréal

ICS: Inhaled corticosteroids

LTPA: Leisure-time physical activity

MET: Metabolic Equivalent

NCD: Non-communicable chronic disease

PA: Physical activity

RCT: Randomized Controlled Trial

PRIME-MD: Primary Care Evaluation of Mental Disorders

SMD: Standard mean difference

T2D: Type 2 diabetes

UC: Usual care

# CHAPTER 1
# INTRODUCTION

## Non-communicable chronic diseases

Non-communicable chronic diseases (NCDs) such as cardiovascular diseases, type 2 diabetes, cancer and respiratory diseases are rapidly increasing worldwide. NCDs are defined as "diseases or conditions that occur in, or are known to affect, individuals over an extensive period of time and for which there are no known causative agents that are transmitted from one affected individual to another" (Daar et al., 2007). In Canada, the prevalence of NCDs have been steadily climbing. For instance, the prevalence of asthma is about 10.8% (Statistics Canada, 2014a), while diabetes is about 10.1% (Statistics Canada, 2014b), cardiovascular diseases (CVDs) is about 10.4%, but about 18% in those aged 65 years and older (Public Health Agency of Canada, 2016), chronic obstructive pulmonary disorder about 9.6% (Public Health Agency of Canada, 2011), and cancer about 7.6% (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017). The global disease profile is changing at a fast pace, with deaths and disabilities from NCDs exceeding those from infectious diseases and nutritional deficiencies (World Health Organization, 2014a). NCDs account for about 70% of global deaths and 47% of the global burden of disease (World Health Organization, 2014a). In Canada, NCDs account for about 88% of deaths, with the four major NCDs accounting for 67% of them (i.e., cancer=30%, CVDs=27%, respiratory diseases=7%, diabetes=3%) (World Health Organization, 2014a).

Two important characteristics of NCDs include their chronic / insidious nature and the long-term disability resulting from it. Another important characteristic of NCDs is that they are generally preventable. Indeed, common risk factors such as smoking, poor diet, high alcohol consumption, and physical inactivity can be prevented (Daar et al., 2007). It has been estimated that about 40% of cancer and about 80% of type 2 diabetes and premature cardiovascular morbidity could be prevented or delayed through the practice of healthy habits, such as healthy diet, nonsmoking, moderate alcohol consumption and regular physical activity (Mozaffarian et al., 2016; Willett et al., 2006). Identifying ways to improve management of the diseases, and quality of life in people living with a NCD is important in order to reduce the substantial economic and humanistic burden on society and patients.

*Cardiovascular diseases*

Cardiovascular disease (CVD) is an overarching term which includes any disease affecting the heart or blood vessels (i.e. myocardial infarction, stroke, coronary artery disease, hypertension and atherosclerosis), and is a major cause of morbidity and mortality worldwide (Mendis, Puska, & Norrving, 2011). In Canada alone, CVD accounts for about 25% of all deaths (Statistics Canada, 2014c). It is the most expensive chronic disease in Canada, costing more than $20.9 billion each year in terms of physician services, hospital costs, cardiac rehabilitation, medication, lost wages, and reduced productivity (Bond, Stonebridge, & Theriault, 2010). CVD has a complex etiology that involves both modifiable and non-modifiable factors. Modifiable risk factors include stress, high-fat diet, obesity, smoking, and physical inactivity, while non-modifiable risk factors include sex, age, ethnicity, family history of CVD, (Deaton et al., 2011; Mozaffarian et al., 2016; Rozanski, Blumenthal, & Kaplan, 1999). It is suggested that up to 80% of early CVDs can be prevented by adopting healthy behaviours (Ford et al., 2009; Mozaffarian et al., 2016).

*Cancer*

Cancer is a disease of the cells characterized by uncontrolled cell proliferation (Tortora & Derrickson, 2008). Uncontrolled cell reproduction leads to the development of a tumor or neoplasm. Symptoms related to cancer may vary depending of the type and stage of cancer; however, a typical physical effect of cancer is pain. Pain is often caused by a tumour pressing on normal tissue or nerves and afflicts up to 94% of cancer patients (Bedard et al., 2013; Melzack, Wall, & Ty, 1982). Cancer is the leading cause of death in Canada, with the highest rates of mortality attributed to lung and colorectal cancer in both women and men whilst, specific to sex, breast cancer has the highest rate of mortality in women and prostate cancer is the leading cause of cancer-related deaths for men (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017; World Health Organization, 2014b). Moreover, approximately 40% of Canadians will receive a diagnosis of cancer during their lifetime (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017). Previous studies have suggested that between 41% and 95% of cancers are caused by health behaviours and lifestyle, such as smoking, obesity and physical inactivity (Anand et al., 2008; Grundy et al., 2017).

*Diabetes (type 2)*

Type 2 diabetes (T2D) is a metabolic disorder characterized by insulin resistance, small production of insulin, and high blood sugar and accounts for approximately 90% of all diagnosed cases of diabetes worldwide (World Health Organization, 2013). Typical symptoms include frequent urination, thirst, increased appetite, and weight loss. Symptoms may also include fatigue, blurred vision, and sores that do not heal. T2D is a progressive disease and symptoms may be slow to appear (World Health Organization, 2013). As a result, T2D can take years to be diagnosed. If not treated properly, it can lead to further complications, such as kidney failure and CVDs, and even death (World Health Organization, 2013). The main cause of mortality in T2D is CVD, which accounts for up to 80% of deaths in persons with T2D (Sowers, Epstein, & Frohlich, 2001). The main risk factors of T2D include obesity and physical inactivity (World Health Organization, 2013). In fact, physical activity is considered a critical factor that can aid in delaying or preventing development of the disease (Narayan, Boyle, Thompson, Sorensen, & Williamson, 2003; Williams, 2001).

*Respiratory diseases*

*COPD.* Chronic obstructive pulmonary disease (COPD) is an irreversible, progressive illness and is characterized by expiratory airflow obstruction, increasing abnormal shortness of breath, and respiratory tract infections (O'Donnell et al., 2008). COPD is not curable and gradually deprives individuals of their health, limits their daily activities and reduces their quality of life (Canadian Thoracic Society, n.d.). Since the illness is progressive, it can often go undiagnosed for many years (Antó, Vermeire, Vestbo, & Sunyer, 2001). While COPD may not have a cure, it is preventable. Indeed, the most important risk factor is smoking, which accounts for 80% to 90% of COPD cases in North America (Health Canada, 2013; U.S. Department of Health and Human Services, 1984). Additionally, about 80% of COPD deaths in Canada are due to smoking tobacco (Rehm et al., 2006).

Given there is no cure for COPD, the emphasis in healthcare has been to minimize or prevent exacerbation (Scullion & Holmes, 2011; Vijayasaratha & Stockley, 2008). Optimal COPD management is multi-faceted and typically includes early diagnosis, pharmacotherapy (e.g.

inhaled corticosteroids), as well as behaviour changes (e.g., smoking cessation, increase in levels of physical activity) (Celli et al., 2004). COPD is the fourth leading cause of mortality in Canada and is currently a leading cause of hospitalization (Canadian Institute for Health Information, 2008; Canadian Thoracic Society, 2010). Additionally, approximately 50% of COPD patients have a lifetime hospital readmission for exacerbation (Almagro et al., 2002). In Canada, COPD has the highest 1-year hospital readmission rate of all NCDs (Canadian Thoracic Society, 2010). Uncontrolled COPD exacerbation results in direct and indirect economic and social burdens due to the use of healthcare resources and the cost of disability, decreased productivity, and premature mortality (Dang-Tan, Ismaila, Zhang, Zarotsky, & Bernauer, 2015).

*Asthma.* Asthma is the most common NCD affecting children and the 4$^{th}$ most common NCD affecting adults, after cardiovascular diseases, cancer, and type 2 diabetes (World Health Organization, 2017c). Asthma is defined as a chronic respiratory disease and is marked by reversible and intermittent airway obstruction, inflammation, as well as airway hyperresponsiveness to a variety of stimuli, such as allergens, cold air, smoke, obesity, airway irritants (e.g., smoking), and exercise. Asthma exacerbations are commonly characterized by difficulty breathing, wheezing, recurrent cough, and tightness in the chest. If left untreated, asthma can be fatal.

While asthma is not often preventable, it is possible to reduce the symptomatology and disease outcomes, such as worst asthma control and death by avoiding stimuli and by appropriate treatment options. A wide range of pharmacological treatments exist to help control the symptoms of asthma, such as inhaled corticosteroids (long-term controller medication). Despite the availability of these treatments, asthma remains poorly controlled with up to 53% of Canadian asthma patients having a suboptimal control of their asthma (Global Initiative for Asthma, 2017; Subbarao, Mandhane, & Sears, 2009). About 75% of Canadians living with asthma report having an asthma attack and having been affected in their daily activities by asthma symptoms in the past 12 months (Canadian Lung Association, 2016). Poor control leads to greater health care service utilization, overuse of bronchodilators, worse quality of life, decreased work productivity, and greater functional impairments (FitzGerald, Boulet, Mclvor, Zimmerman, & Chapman, 2006). These suggest that there may be other factors besides

pharmacological treatment that may influence asthma control.

**Depression**

Depression is a serious public health problem and is known to cause severe disability. It presents with a range of affective, cognitive, and somatic symptoms including sad or depressed mood, loss of enjoyment in activities that were once normally enjoyed, feelings of guilt, worthlessness or hopelessness, difficulties with concentration, reduced energy, changes in appetite and sleep, and withdrawal from normal activities (American Psychiatric Association, 2010). A diagnosis of major depressive disorder (MDD) is made when at least five of these aforementioned symptoms have been present during a 2-week period, with at least one of the symptoms being depressed mood, or loss of interest or pleasure, and consists of a change from previous functioning.

According to the World Health Organization, depression is the leading cause of disability worldwide and is expected to be the second leading cause of disease burden by 2020, preceded only by cardiovascular diseases (World Health Organization, 2017a). In Canada, it is estimated that the point prevalence of depression is about 5%, while the lifetime prevalence is 11.3% (Pearson, Janz, & Ali, 2013; Vollmer et al., 1999; Williams, Wagner, Kannan, & Bolge, 2009).

Sub-clinical levels of depression have been shown to be associated with increased mortality rate and is a major cause of disability (Cuijpers & Smit, 2002; The National Institute for Health Care Excellence, 2009). Validated tools, like the Beck Depression Inventory (BDI) and the Hospital Anxiety and Depression Scale (HADS) are essential for measuring depressive symptoms along a continuum. While these scales do not accurately predict major depressive disorder, they are nonetheless useful in quantifying the extent of depressive symptoms (Maj, 2011). For the purpose of the thesis, I will refer to depression as sub-clinical symptoms, unless specified otherwise.

Identifying biological and cognitive, and behavioural processes underlying depression—and the links among them—that can be targeted by intervention is a global health priority. Below, I am describing some of the most studied mechanisms of depression.

*Biological theories*

One of the most promising research areas in depression involves inflammation. Substantial evidence has implicated inflammation in the etiology of depression (e.g., Alesci et al., 2005; Miller & Raison, 2016; Raedler, 2011; Raison, Capuron, & Miller, 2006). Inflammation is a key component of the immune system's ability to clear infection and repair injured tissue. Characterized by redness, heat, pain, and swelling, inflammation results from the release of pro-inflammatory cytokines from immune cells. Cytokines can additionally communicate with the brain via various routes and result in emotional, cognitive, and behavioural changes collectively termed "sickness behaviours" (Dantzer, Connor, Freund, Johnson, & Kelley, 2008). These sickness behaviours, including fatigue, loss of appetite, and social withdrawal, are considered an adaptive response intended to reduce the spread of infection and promote healing. However, when inflammation persists, as when the inflammatory response is maintained by ongoing psychosocial stress rather than physical injury, prolonged inflammatory signaling can have detrimental effects, such as the development of cancer, arthritis, and clinical depression (Miller, Maletic, & Raison, 2009; Slavich & Irwin, 2014).

Meta-analyses have concluded that individuals living with depression typically tend to exhibit higher levels of the pro-inflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), as well as inflammatory markers including IL-1 receptor antagonist (IL-1ra; a marker of IL-1 activity) and C-reactive protein (CRP), compared to non-depressed individuals (Hiles, Baker, de Malmanche, & Attia, 2012; Howren, Lamkin, & Suls, 2009). However, these results are likely driven by a subpopulation of depressed individuals with elevated inflammation (Raison & Miller, 2011). Raison and Miller (2011) have suggested that elevated inflammatory markers are seen in approximately one third of individuals with depression. Moreover, inflammation is not specific to depression and can also be found in other psychiatric conditions (e.g., posttraumatic stress disorder, schizophrenia), as well as in many NCDs (e.g., asthma, cancer, CVD, type 2 diabetes) (Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Pearson et al., 2003; Pradhan, Manson, Rifai, Buring, & Ridker, 2001; Spitzer et al., 2010). While evidence has implicated inflammation in the development of depression, inflammation shows limited sensitivity and specificity as a driver of depression, and its influence on fundamental processes in depression remain unclear.

Genetic variations have also been linked to increased risk of depressive episodes (Gibb, Beevers, & McGeary, 2013; Disner, Beevers, Haigh, & Beck, 2012). Variants of the serotonin transporter gene, brain derived neurotrophic factor, and dopamine receptors are three genetic factors that have been most often associated with vulnerability to depression and likely interact as cumulative risk factors (Gibb et al., 2013).

*Cognitive theory*

Beck's cognitive theory of depression – arguably the most influential cognitive theory – is based on Beck's research on depression and asserts that negative cognitive schemas are central to the development and maintenance of depression (Beck, 1976). Negative cognitive schemas are longstanding mental structures stemming from negative early life experiences that shape individuals' interpretations of their experiences. When activated by negative events later in life, these schemas lead to negative outcome expectancies, which then lead to depression. Beck identified three negative cognitive schemas related to depression: negative views of the self, the world, and the future. Beck labeled the tendency to attribute negative outcomes to internal global, and stable factors the *negative cognitive triad* (Beck, 1976). Studies have repeatedly shown an association between negative cognitive triad and depression and is viewed as a vulnerability factor (Abela et al., 2011; Braet, Wante, Van Beveren, & Theuwis, 2015; Gunter, 2008; Husky, Mazure, Maciejewski, & Swendsen, 2007).

Another cognitive model, the hopelessness theory of depression, posits that people with negative cognitions tend to overgeneralize their perceptions of helplessness in unavoidable aversive situations or new situations, referred to as stressful life events, despite the possibility of escape (Abramson, Metalsky, & Alloy, 1989). Individuals who blame themselves for uncontrollable events are more likely to be chronically depressed than those who blame external cause. The hopelessness theory of depression has received empirical support over the last three decades (Abramson et al., 1989; Abramson et al., 1999; Haeffel & Hames, 2014; Liu, Kleiman, Nestor, & Cheek, 2015). Moreover, there is strong evidence in the literature that negative life events, such as the loss of a family member or a new medical diagnosis, play a large role in the etiology of depression (Brown & Harris, 1978; Brown, Harris, & Peto, 1973; Hammen, 2006).

*Behavioural model*

According to the behavioural model, depression assumes that insufficient engagement in rewarding activities leads to a decreased engagement in activities, which limits opportunities for future rewarding interactions and leads to depressed mood (Lewinsohn & Graf, 1973). From a behavioural standpoint, depressive symptoms present as depressed behaviours. Antecedent and consequent events maintain depressed behaviours, affective experiences, and responses (Polenick & Flora, 2013). For example, a change in activity level due to injury may lead to feeling disappointed and worthless about being unable to help build a grandchild's playhouse, which may result in negative self-critical remarks. Restricted daily activity has been proposed as a common pathway leading to depression, regardless of risk factors (Fiske, Wetherell, & Gatz, 2009).

Overall, biological, cognitive, and behavioural processes increase vulnerability to depression and play an interactive role in the development and maintenance of depression (Kendler, 2008; Kendler, 2011).

**NCDs and depression**

The incidence and prevalence of depression is higher in people living with a NCD compared to the general population (Pirl, Greer, Temel, Yeap, & Gilman, 2009). Depression can have a major impact on their disease course and health outcomes. It has been associated with worse prognosis (Egede, 2007; Strine, Mokdad, Balluz, Gonzalez, et al., 2008), disease complications (Katon & Sullivan, 1990), and higher rates of mortality (Katon, Lin, & Kroenke, 2007; Lin et al., 2010). Depression has also been associated with worse adherence (including exercise regimens) (DiMatteo, Lepper, & Croghan, 2000; Grenard et al., 2011). The following subsection highlights how depression affects some NCDs more specifically. It should be noted that I will not go in details about whether depression or chronic disease comes first, but rather, I will focus on their association.

*Cardiovascular diseases*

The prevalence of depression in people with cardiovascular diseases (CVD) is estimated between

10-27% and has been associated with both increased incidence and worse outcomes of CVD, independent of traditional CVD risk factors, such as smoking and high blood pressure (Lett et al., 2004; Lichtman et al., 2008). Evidence from the literature suggests that poor health behaviours, in particular physical inactivity, are largely responsible for the additional risk of CVD associated with depression (de Voogd et al., 2009; Gimeno-Santos et al., 2014).

*Cancer*

The depression rate varies depending of the type of cancer, but overall, between 20% and 50% of patients experience depression (Brummett et al., 2003; Spoletini et al., 2008; Win et al., 2011). Regardless of the cancer site, depression negatively impacts quality of life (Massie, 2004; Philip, Merluzzi, Zhang, & Heitzmann, 2013) and medical adherence (Möller, 2008; Singh et al., 2005). Depression has also been associated with increased recurrence rates of cancer and higher risk of mortality (Pinquart & Duberstein, 2010) and suicide (Miller, Mogun, Azrael, Hempstead, & Solomon, 2008).

*Diabetes (type 2)*

Depression in diabetes is estimated to range between 17 and 30% (Jehn et al., 2006; Pasquini & Biondi, 2007) and is associated with micro- (e.g., nephropathy) and macro-vascular (e.g., hypertension) complications, insulin resistance, and mortality (Ali, Stone, Peters, Davies, & Khunti, 2006; Semenkovich, Brown, Svrakic, & Lustman, 2015). Additionally, the presence of comorbid depression in diabetes has been associated with a decrease in health-related quality of life (de Groot, Anderson, Freedland, Clouse, & Lustman, 2001; Williams et al., 2011) and poor diabetes self-care, including poor diet, medical adherence, and physical inactivity (Egede & Hernandez-Tejada, 2013; Schmitz et al., 2014).

*Respiratory diseases*

*COPD.* The prevalence of depression in people living with COPD is about 40% (Hynninen, Breitve, Wiborg, Pallesen, & Nordhus, 2005; Schane, Woodruff, Dinno, Covinsky, & Walter, 2008; Yohannes, Willgoss, Baldwin, & Connolly, 2010). The co-morbidity is associated with a decrease in treatment adherence (DiMatteo, Haskard, & Williams, 2007) and worse quality of life. It is also associated with a higher risk of exacerbation (Laurin et al., 2009) and mortality

(Omachi et al., 2009).

*Asthma.* Depression is estimated to be as high as 35% in asthma patients (Mead, Theadom, Byron, & Dupont, 2007). It has been associated with worse asthma control (Ahmedani, Peterson, Wells, & Williams, 2013; Barth, Schumacher, & Herrmann-Lingen, 2004; Lavoie et al., 2005), quality of life (Lavoie et al., 2006; Ouellet et al., 2012), and increased number of exacerbations (Urrutia et al., 2012). High levels of depressive symptoms have also been associated with unhealthy behaviours, such as smoking, poor diet, and physical inactivity (Strine, Mokdad, Balluz, Berry, & Gonzalez, 2007).

**Physical activity and exercise**

Physical activity is defined as any bodily movements that involves large muscle groups and requires more energy than resting (World Health Organization, 2018). Examples include occupational tasks (e.g., house chores, working) but also planned leisure time physical activities (LTPA) (e.g., yoga, running). These planned LTPA are called exercise, which is a subcategory of physical activity (World Health Organization, 2018). Exercise is defined as activities that are "planned, structured, and repetitive and has as a final or an intermediate objective of improvement or maintenance of physical fitness" (Caspersen, Powell, & Christenson, 1985). Aerobic exercises are activities which increase pulmonary and cardiovascular system activity (e.g. cycling, running) and involve large muscle groups (Lin et al., 2004). Anaerobic exercises, also known as resistance exercises, are activities in which muscular strength is used in working against a resistive load and during which the body's demand for oxygen exceeds the oxygen supply available and therefore relies on energy sources available in muscles (e.g. weight lifting) (Caspersen et al., 1985; Garber et al., 2011).

Physical activity has many benefits in the general population, such as improved cardiovascular and cardiorespiratory capacity, quality of life, maintenance of healthy weight (Caspersen et al., 1985; Garber et al., 2011), as well as prevention of NCDs (Haskell et al., 2007). It has also been associated with increase of positive mood and well-being (Warburton, Nicol, & Bredin, 2006). For example, people who exercise regularly exhibit less depressive symptoms and anxiety than people who are not physically active (Reed & Buck, 2009).

Despite the effects of physical activity, only about 18% of adults in Canada attain the recommended amount of physical activity and more than half of Canadian adults do not engage in physical activity at all (Statistics Canada, 2017). According to the Canadian Society for Exercise Physiology (Canadian Society for Exercise Physiology, 2011), to achieve cardiorespiratory fitness, adults should engage in a minimum of 150-minutes of moderate-intensity planned aerobic exercise, or 75 minutes of vigorous-intensity, in bouts of at least 10 minutes for optimal health. Additionally, adults should also resistance train twice a week. Aerobic exercise is considered to be of moderate intensity if an individual attains 55 to 69% of their maximum heart rate (MHR) (Norton, Norton, & Sadgrove, 2010). MHR can be estimated by subtracting the participants' age from 220 (Canadian Society for Exercise Physiology, 2011). A vigorous intensity exercise achieves 70 to 89% of one's MHR.

**NCDs and physical activity**

Exercise has been found to be beneficial in various NCDs, such as cardiovascular diseases, cancer, and chronic obstructive pulmonary disorder (COPD) (De Moor, Beem, Stubbe, Boomsma, & De Geus, 2006; Lane, Jackson, & Terry, 2005). As such, it is often prescribed as a first line of treatment in people living with a NCD (Bacon et al., 2015; Carson et al., 2013).

*Cardiovascular diseases*

As noted earlier, physical inactivity is a major risk factor in CVD. It is responsible for 12.2% of the global burden of CVD, independent of other CVD risk factors (e.g., hypertension, smoking) (Yusuf et al., 2004). A recent study in the United States described the prevalence of physical activity in adults with CVD and found that about 55% of the participants reported being moderately active, while only 28% met the physical activity guidelines (Evenson, Butler, & Rosamond, 2014). Exercise has been shown to improve CVD risk factors, such as triglycerides, high-density lipoprotein (HDL), and waist circumference, as well as reducing risk of mortality and morbidity due to CVD (Mozaffarian et al., 2016; Yu, Yarnell, Sweetnam, & Murray, 2003). It has also been shown to increase quality of life and reduce depressive symptoms (Blumenthal, Sherwood, et al., 2012; Tu et al., 2014).

*Cancer*

In Canada, about 21% of cancer survivors are physically active (Courneya, Katzmarzyk, & Bacon, 2008). Physical activity guidelines specific to cancer patients stipulate that cancer survivors should avoid physical inactivity and that physical activity is safe both during and following treatment (Schmitz et al., 2010). A growing body of evidence suggest a clear benefit of exercise during and after adjuvant treatment for preventing or managing the impact of a variety of adverse effects of cancer (e.g., fatigue, weight gain, decreased functional capacity) (Speck, Courneya, Mâsse, Duval, & Schmitz, 2010) and may improve survival and decrease the risk for recurrence (Loprinzi, Cardinal, Winters-Stone, Smit, & Loprinzi, 2012). Moreover, regular exercise has been shown to have a positive effect on psychological outcomes, such as depression, in cancer patients and survivors (Craft, Vaniterson, Helenowski, Rademaker, & Courneya, 2012).

*Diabetes (type 2)*

People living with T2D show significantly low levels of physical activity (Morrato, Hill, Wyatt, Ghushchyan, & Sullivan, 2007). In Canada, 65% to 71.9% of adults with T2D do not meet the physical activity guidelines (Plotnikoff et al., 2006). However, there is strong evidence for the use of physical activity as a management tool within diabetes care (Plotnikoff, Costigan, Karunamuni, & Lubans, 2013). Physical activity has been shown to significantly improve glycemic control, cholesterol, and diabetes-related complications, such as diabetic retinopathy and kidney failure care (Balducci et al., 2012; Liubaoerjijin, Terada, Fletcher, & Boulé, 2016; Umpierre et al., 2011). Moreover, moderate increases in levels of exercise have been shown to reduce HbA1c and improve insulin sensitivity, improve quality of life, and reduce risks of depression (Chudyk & Petrella, 2011; Colberg & Grieco, 2009). As such, exercise is considered a cornerstone in diabetes care.

*Respiratory diseases*

*COPD.* Patients with COPD are less physical active compared to healthy people (Vorrink, Kort, Troosters, & Lammers, 2011). Levels of physical activity decreases over time, as the disease progresses (Waschki et al., 2015). Low levels of physical activity have been associated with increased risk of exacerbations (Moy, Teylan, Weston, Gagnon, & Garshick, 2013), hospital

admissions, and mortality (Waschki et al., 2011). It is also associated with increased risk of depression and decrease in quality of life (Gimeno-Santos et al., 2014). Thus, improving physical activity levels has become a major concern in COPD, with pulmonary rehabilitation (PR) being the cornerstone of COPD management (McCarthy et al., 2015). PR, which encompass exercise training, along with patient education and self-management training, is effective in reducing dyspnea, improving quality of life, and increase functional capacity (McCarthy et al., 2015).

*Asthma.* Asthma patients are at risk of exacerbation, also known as exercise-induced bronchoconstriction (EIB), whenever they exercise, if proper precautions have not been taken (i.e. use of bronchodilator 30 minutes prior activity) (American Academy of Allergy, 2017). The dyspnea experienced during exercise, or the fear of experiencing it due to past experiences or stories from others, may keep adults with asthma from participating in sports or any types of physical activities (Hung et al., 2005; Warburton et al., 2006). As such, asthma patients tend to be less active and physically fit compared to healthy population, with up to 50% who don't exercise (Avallone & McLeish, 2013; Disabella, Sherman, & DiNubile, 1998). Exercise has been consistently found to be safe for asthma patients, both in children and adults (Clark & Cochrane, 1988; Disabella et al., 1998; Emtner, Herala, & Stålenheim, 1996; Wright, Lavoie, Jacob, Rizk, & Bacon, 2010). Moreover, exercise is beneficial for asthma patients. It has been proven to be efficacious in reducing inhaled corticosteroid dose and dyspnea related to exercise, as well as improve quality of life and asthma control (Bacon et al., 2015; Carson et al., 2013; Wanrooij, Willeboordse, Dompeling, & van de Kant, 2014).

**Depression and exercise**

Significant evidence in the general population indicate that exercise has a beneficial effect on depression and subclinical levels of depression (Colberg et al., 2010; Lennon, Carey, Gaffney, Stephenson, & Blake, 2008; Schmitz et al., 2010). It would also seem to provide a protective effect against developing depression (Byrne & Byrne, 1993; G. Cooney, Dwan, & Mead, 2014). Studies have also shown that exercise provides similar benefits to antidepressant medication and cognitive-behavioural therapy, both the current gold standard treatments for treating depression, with reported reductions of between 67% and 75% of depressive symptoms (Carek, Laibstain, &

Carek, 2011; Mössner et al., 2007). This may be especially important for the 30% of patients that reportedly do not respond positively to prescribed pharmacotherapy (Cooney et al., 2014; Daley et al., 2007). Moreover, antidepressants have been shown to cause several adverse effects including loss of appetite and sleep problems, which can be alleviated with exercise (Ferguson, 2001). For example, exercise contributes to the reduction in time taken to fall asleep, thus improving sleep time (Yang, Ho, Chen, & Chien, 2012). Exercising can also reduce fatigue, a common somatic depressive symptom, which is often not improved by the use of medication (Cornelissen & Smart, 2013). Therefore, exercise can be considered as an alternative treatment for depression in healthy individuals to the standard treatment options.

*Potential mechanisms explaining the exercise-depression relationship*

While there have been consistent findings linking exercise and depression, the mechanisms linking them together remain unclear. Several psychological (e.g., self-efficacy hypothesis, distraction hypothesis, mastery hypothesis, social interaction hypothesis) and physiological (e.g., inflammation hypothesis, monoamine hypothesis) mechanisms have been proposed; however, research to date has not extensively examined them.

*Self-efficacy hypothesis.* Self-efficacy, or the level of confidence that one feels they possess to meet the challenge at hand, has been proposed as a psychological mechanism by which exercise may help reduce symptoms of depression (Bandura, 1997). Self-efficacy refers to the belief that one possesses the skills to complete a task as well as the confidence that the task can be completed with the desired outcome obtained (Bandura, 1997).

According to Bandura (1997), depressed people often have a low sense of efficacy to cope with their depressive symptoms, which often leads to negative self-evaluations, negative ruminations, and faulty styles of thinking. Not being able to stop or restructure negative thoughts has been associated with higher levels of depression (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Kavanagh & Wilson, 1989). Self-efficacy is known to be important to the initiation and maintenance of health behaviours, including exercise (McAuley, 1992; Williams et al. 2008). Conversely, exercise may provide an effective opportunity to enhance self-efficacy based on its ability to provide a meaningful mastery experience, which is thought to be the best factor

influencing the development of self-efficacy (Bandura, 1997). Learning how to monitor exercise behaviours, set short and long-term exercise goals, and utilize social support through positive support from the exercise specialist and significant others can all contribute to feelings of mastery.

Research examining the relationship between self-efficacy and exercise has mainly focused on the enhancement of physical self-efficacy and efficacy to regulate exercise behaviours (McAuley, 1992; McAuley, Lox, & Duncan, 1993). Individual with high self-efficacy for exercise are more likely to exercise. However, the relationship between self-efficacy and exercise in depressed patients has not been studied extensively and findings have been ambiguous (Bodin, & Martinsen, 2004; Singh, Clements, & Fiatarone, 1997; Singh et al., 2005). Several intervention studies have found that being involved in an exercise program was associated with enhanced feelings of self-efficacy, which, in turn, were associated with a reduction of depression severity (Annesi, 2004; Craft, 2005; Gary, 2006). Thus, it is hypothesized that the antidepressant properties of exercise may be related to enhanced feelings of self-efficacy.

*Distraction hypothesis*. It has been suggested that exercise serves as a distraction from worries, anxiety, and depressing thoughts (Leith, 1994; Nolen-Hoeksema, Morrow, & Fredrickson, 1993; Paluska & Schwenk, 2000). Distraction refers to a response style in which an individual uses distracting activities (e.g., a hobby, work) in an attempt to focus on something other than the depressed mood (Greist, Klein, Eischens, Gurman, & Morgan, 1979; Nolen-Hoeksema et al., 1993).

Distraction has been shown to positively influence the management of depression and reduce symptoms of depression compared to more self-focused or introspective activities (e.g., journal keeping) (Just & Alloy, 1997). Research comparing distraction with rumination, which involves the tendency to passively and repeatedly focus on one's negative feelings and the consequences of those feelings, has shown that individuals who ruminate generally have more severe and longer lasting episodes of depression than those who use distraction as a response style (Just & Alloy, 1997; Morrow & Nolen-Hoeksema, 1990; Nolen-Hoeksema, et al., 1993). Results are less

conclusive when exercise is compared to other types of distraction, such as relaxation and social contact. For example, exercise has been shown to be more effective than education but similar to relaxation in reducing depressive symptoms (Cooney et al., 2013).

Overall, exercise appears to be an effective distracting activity. When exercising, people are often focused on training goals or paying attention to physiological changes such as their breathing, heart rate, or sore muscles (Leith, 1994). Furthermore, exercise offers the opportunity for positive reinforcement as exercise goals are met and daily workouts become less painful and tiring. Therefore, the antidepressant effects of exercise may result from the ability of exercise to provide periodic distraction from negative thoughts and feelings of depression.

*Mastery hypothesis.* A recent study found a bidirectional association between depressive symptoms and sense of mastery (Assari & Lankarani, 2017). Furthermore, Bandura (1990) has suggested that mastery experiences can be critical to preventing and overcoming depression. According to the mastery hypothesis, the mere fact of exercising can make individuals feel like they have achieved something, which in turn can contribute in reducing depressive symptoms. As an individual who exercise gains mastery of physical skills, they may take this feeling of control into everyday life (LePore, 1997). While mastery has been proposed as a possible mechanism explaining the association between exercise and depression, it does not appear to have been studied and thus the exact role of mastery has not been yet clearly established.

*Social interaction hypothesis.* Social support has a consistent, positive relationship with exercise across many diverse populations (Allender, Cowburn, & Foster, 2006; Van der Horst, Paw, Twisk, & Van Mechelen, 2007; Wendel-Vos, Droomers, Kremers, Brug, & Van Lenthe, 2007). According to the social interaction theory (Gosselin & Taylor, 1999), social relationships and mutual support between those who participate in exercise can act as a buffer against mental health problems. The social support gained by exercising in a social environment may enhance the effects of exercise and contribute to a greater reduction in the symptoms of depression (Gosselin & Taylor, 1999). Indeed, social support has been linked to both reductions in depression levels and participation in exercise (Gosselin & Taylor, 1999) as well as improved overall psychological health (Sarason, Sarason, & Gurung, 1997).

To date, few studies have examined the role of social context in the association between exercise and depressive symptoms. Results from these studies have been mixed (Biddle & Mutrie, 2001; Plante et al., 2003). Moreover, most exercise intervention studies have not controlled or adjusted for social contact and some studies have allowed more social contact in experimental groups than in control groups (O'Neal, Dunn, & Martinsen, 2000). To date, studies have been limited to a single exercise session intervention or did not have a control group.

*Inflammation hypothesis.* Individuals with depression have elevated concentrations of pro-inflammatory biomarkers, specifically C-reactive protein, IL-6 and IL-1b, and TNF-α (Eyre, Papps, & Baune, 2013; Howren et al., 2009). Exercise has been shown to reduce these biomarkers (Glynn, McFarlin, & Markofski, 2007; Hamer et al., 2012; Pedersen et al., 2003). Moreover, individuals who exercise regularly tend to have lower levels of inflammatory markers compared to individuals who do not exercise (King, Carek, Mainous, & Pearson, 2003; McFarlin et al., 2006). Given that regular physical exercise induces anti-inflammatory effects, it might contribute to explain the positive effects of exercise in the treatment of depression.

*Monoamine hypothesis.* The monoamine hypothesis proposes that exercise enhances the brain's aminergenic synaptic transmission (i.e., serotonin, noradrenaline, and dopamine) which affect arousal and attention (Faulkner & Carless, 2003). Exercise modifies one or more of the major brain monoamines (e.g., serotonin, dopamine, and norepinephrine). These chemicals are markedly reduced in depressed patients. Exercise may reduce depression by increasing the levels and transmission capabilities of these chemicals. Previous studies have reported positive effect of exercise on the serotonergic system (Chaouloff, 1997; Heijnen, Hommel, Kibele, & Colzato, 2015; Lin & Kuo, 2013) and have hypothesized that exercise might improve the efficiency of the monoamine system response in depressive patients (Blake, 2012). It should be noted that depression is not always explained by monoamine deficiency, which might explain why current antidepressants, most of which target monoamines, may not always be effective in treating depression (Blake, 2012).

Overall, literature suggests that a combination of biopsychosocial factors may explain the

association between exercise and depression. However, it is not clear yet whether the aforementioned mechanisms have an additive effect or whether there may be variations according to the depression severity, individual personality and other unknown variables that have yet been explored.

*Exercise as a treatment for depression*

Recently, several guidelines for the treatment of depression have added exercise as an intervention option (American Psychiatric, 2010; The National Institute for Health Care Excellence, 2009). While the APA does not provide a great deal of detail on how to use this approach, the NICE guidelines recommend that exercise programs be delivered in groups with support from a competent practitioner and should consist of three 45-60 minutes sessions per week for an average of 12 weeks (The National Institute for Health Care Excellence, 2009). It should be noted that this recommendation is addressed to patients with persistent sub threshold depressive symptoms or mild to moderate depression and that the guide does not recommend specifically a type of exercise (e.g. aerobic vs anaerobic) given lack of evidence on the topic.

**Exercise for depression in NCDs**

In NCDs, the role of exercise on depressive symptoms has been examined in retrospective (e.g., Courneya and Freidenreich, 1997), cross-sectional (e.g. Haedtke et al., 2017) and prospective studies (Daley, 2008). Additionally, intervention studies have shown promising effect of exercise on depressive symptoms in several types of NCDs (Segar et al., 1998). However, it is not clear how specific types of exercises are efficacious. For example, in a systematic review, Coventry and colleagues (2013) assessed the efficacy of complex psychological and lifestyle interventions in reducing depressive symptoms in people with COPD and found that multi-component exercise training produced significant reduction in depression (standardized mean difference [SMD] -0.47; confidence interval [CI] -0.66 to -0.28) (Coventry et al., 2013). However, the authors did not define the term ‘multi-component’ and did not look at look at aerobic and anaerobic exercises separately. A similar trend was noted in various systematic reviews across NCDs. Given that aerobic exercise is a major component in the physical activity recommendations for optimal health and that there seems to be a lack of unifying research on the relationship between aerobic exercise and depressive symptoms in people living with a NCD, it is important to look at the

association to get a better picture.

In asthma population, a handful of studies have looked at the association between exercise and depressive symptoms. A recent cross-sectional study found that lower aerobic capacity, as determined by a treadmill test, was associated with high level of depressive symptoms (J. C. Brown et al., 2012; Coventry & Hind, 2007; Tu et al., 2014). Conversely, few studies have examined the effect of an aerobic exercise intervention on depressive symptoms in adults with moderate and severe asthma. A recent study by Turner and colleagues (2011) examined the role of exercise on depressive symptoms in older adults with asthma and found that exercise appears to provide benefits and to reduce depressive symptoms in asthma (Turner, Eastwood, Cook, & Jenkins, 2011). Similar outcomes were noted in two other studies (Güell et al., 2006; Mendes et al., 2013).

**Knowledge gaps in the literature**

While much research has contributed and supported the link between exercise and depression, there are several knowledge gaps that still exist in the literature. First, to my knowledge, there has been no systematic reviews that examined specifically the role of aerobic exercise on depressive symptoms in NCDs. One systematic review looked at the effect of exercise training on depressive symptoms in chronic illnesses, in which they performed sub-analyses for aerobic exercise (Herring, Puetz, O'Connor, & Dishman, 2012). However, the authors used a broad definition of the term 'chronic illness', thus including conditions that are risk factors rather than chronic diseases (e.g., obesity) and psychological comorbidity to depression (e.g. anxiety). Additionally, no studies in diabetes were included. Given this, there is a need to examine the role of aerobic exercise training on depressive symptoms in people living with NCDs, specifically cardiovascular diseases, cancer, diabetes Type 2, and respiratory diseases.

Second, most intervention studies on depression in NCDs focus on multi-component interventions (e.g., cardiac rehabilitation), rather than exercise alone. As such, it is harder to assess the specific role of exercise on depressive symptoms.

Third, a limited number of studies have examined the association between exercise and

depressive symptoms in asthma and T2D populations. Moreover, the relation between exercise and depressive symptoms has not been assessed in a large cohort. For the purpose of my thesis, and for practicality (e.g., access to asthma databases), I have decided to focus on asthma population for my second paper. I believe studying the association in large cohorts of adults with asthma can help strengthen the previous findings.

Fourth, no previous studies on the relationship between exercise and depressive symptoms in adults with asthma have been conducted in North America. Given that almost 1 Canadian out of 10 suffer from asthma, there is a need to study the association between exercise and depression in the Canadian context.

**Significance of research**

Understanding how depression impacts level of aerobic exercise in people living with a NCD may be particularly important for optimal disease treatment and management. For example, by illustrating that aerobic exercise is indeed able to reduce depression in asthma patients, clinicians may be more likely to encourage patients to start or continue exercising, for both physical, but also psychological, benefits.

**Goal of thesis**

The **overarching aim** of this thesis is to **examine the relationship between exercise and depression in people with a non-communicable chronic disease, with a particularly emphasis on asthma**.

In a first step, I sought to get a wider perspective on the association between exercise and depression, in order to better understand how depression may benefit from an exercise intervention. Thus, I conducted a meta-analysis for my first paper, including the four major categories of NCDs; cardiovascular diseases, cancer, diabetes type 2 and respiratory diseases. The main goal was to **assess the effect of aerobic exercise on depressive symptoms among adults living with a NCD**.

Following the results of the meta-analysis, I sought to **understand more specifically the association between leisure-time physical activity (LTPA) and depressive symptoms in asthma patients**. This resulted in my second paper. Specifically, it was hypothesized that people who engage in LTPA would report lower depressive symptoms. Exploratory goals sought to look at the relationship between the LTPA prescription (e.g., intensity, frequency, duration) and seasonal patterns, and depressive symptoms.

# CHAPTER 2

Aerobic Exercise Alleviates Depressive Symptoms In Patients With a Major Non-Communicable Chronic Disease: A Systematic Review and Meta-analysis

**Abstract**

**Objective:** To assess whether aerobic exercise was superior to usual care in alleviating depressive symptoms in patients living with a major non-communicable disease.
Data sources: Data were obtained from online databases (PubMed, PsycINFO and SPORTDiscus), as well as from reference lists. The search and collection of eligible studies was conducted up to October 18th, 2018 (PROSPERO registration number CRD42017069089).

**Study selection:** We included interventions that compared aerobic exercise to usual care in adults who reported depressive symptoms (i.e., not necessarily the clinical diagnosis of depression) and were living with a major noncommunicable disease.

**Results:** Twenty-four studies were included in the meta-analysis (4,111 patients). Aerobic exercise alleviated depressive symptoms better than did usual care (SMD = 0.50; 95% confidence interval (CI), 0.25 to 0.76; grading of recommendations assessment, development and evaluation (GRADE): low quality). Aerobic exercise was particularly effective in alleviating depressive symptoms in cardiac patients (SMD = 0.67; 95% CI 0.35 to 0.99).

**Conclusion:** Aerobic exercise alleviated depressive symptoms in patients living with a major non-communicable disease, particularly in cardiac populations. Whether aerobic exercise treats clinically diagnosed depression was outside the scope of this study.

## Introduction

Depression is a serious public health problem and is a major cause of disability (Cuijpers & Smit, 2002). Depression presents with a range of affective (e.g., sadness), cognitive (e.g., feelings of guilt), and somatic (e.g., loss of appetite) symptoms (American Psychiatric Association, 2010). A diagnosis of major depressive disorder (MDD) is made when at least five symptoms have been present during a 2-week period, with at least one of the symptoms being depressed mood, or loss of interest or pleasure. In addition to diagnosed depressive disorder, it is possible to assess the range of depressive symptoms individuals present with. This is normally done using standard validated questionnaires, with elevated levels of symptoms indicative, but not conclusive, of potential diagnosable depressive disorder. Depression and depressive symptoms are both associated with decreased levels of health-related quality of life, increased use of health services and increased mortality rate (Cuijpers & Smit, 2002; The National Institute for Health and Care Excellence, 2010).

Patient with major non-communicable chronic diseases (NCDs), e.g., cardiovascular diseases (CVDs), cancers, respiratory diseases (i.e., chronic obstructive pulmonary disease, COPD), and type 2 diabetes (T2D), have depression rates two- to three-fold higher than the general population (Katon, 2011; Lavoie et al., 2005; Nan et al., 2012; Strine, Mokdad, Balluz, Berry, & Gonzalez, 2008). Depression also predicts future development of NCDs (Katon, 2011; Mezuk, Eaton, Albrecht, & Golden, 2008). For example, depression is associated with the development of CVD in healthy adults (Van der Kooy et al., 2007; Wulsin & Singal, 2003), all-cause mortality (Barth, Schumacher, & Herrmann-Lingen, 2004; Blumenthal et al., 2003; Cuijpers & Smit, 2002; Whang et al., 2009), worse asthma control among patients with asthma (Lavoie et al., 2005), and a higher risk of reinfarction among cardiac patients (Fenton & Stover, 2006). Therefore, treating depression and subclinical depression in those living with a NCD is of clinical importance.

Exercise alleviates depressive symptoms and is comparable to cognitive behavioural therapy and antidepressants in populations without a major NCD (Cooney et al., 2013). When disease-specific precautions are taken, exercise is safe in people living with a NCD (Burr, Davidson, Shephard, & Eves, 2012; Colberg et al., 2010; Lavie, Milani, Marks, & de Gruiter, 2001; Stefani,

Galanti, & Klika, 2017). Systematic reviews have shown that multiple types of exercise, e.g., aerobic, resistance, and mixed, alleviate depressive symptoms in populations with cancer (Brown et al., 2012; Craft, Vaniterson, Helenowski, Rademaker, & Courneya, 2012), COPD (Coventry & Hind, 2007) and CVDs (Clark et al., 2010; Tu et al., 2014); results are less clear in patients with diabetes (van der Heijden, van Dooren, Pop, & Pouwer, 2013).

Notable limitations in existing systematic reviews of exercise for depression in patients with NCDs include: analyzing different types of exercise together (e.g., resistance, aerobic, mixed), rather than each individual type of exercise (specifically aerobic) (Brown et al., 2012; Craft et al., 2012; van der Heijden et al., 2013); and not exploring the levels of exercise intensity. In short, we reviewed aerobic exercise as a stand-alone intervention for depressive symptoms in NCD.

**Methods**

Our systematic review and meta-analysis was conducted according to the Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & The Prisma, 2009); the PROSPERO registration number is CRD42017069089.

*Study selection*

Studies that compared aerobic exercise to usual care were included. Aerobic exercise was defined as sustained activity using large muscle groups, which increase pulmonary and cardiovascular system activity (e.g. cycling, running) (World Health Organization, 2017a). Studies using other forms of exercise (e.g. resistance training, yoga) were excluded. Usual care was defined as the receipt of standard clinical care specific to the patient's disease. Studies were excluded if participants in the comparison group performed any form of exercise (e.g. aerobic, resistance) or were explicitly encouraged to exercise. Studies in which the comparison group received any active depression treatments (e.g. pharmacotherapy, psychotherapy) or placebo pharmacotherapy were also excluded. Studies where the comparison group received a non-exercise and/or non-depression treatment (e.g. relaxation, education) were included only if the same treatment was also present in the intervention group. Finally, studies where the main intervention combined aerobic exercise with another exercise modality (e.g., aerobic exercise

and resistance training) or active non-exercise treatment were also excluded (e.g., aerobic exercise and rehabilitation).

Consistent with other aerobic exercise systematic reviews (Baillet et al., 2010; Kelley, Kelley, & Vu Tran, 2001; McDonnell, Smith, & Mackintosh, 2011; O Brien, Nixon, Tynan, & Glazier, 2004) and American College of Sports Medicine recommendations (American College of Sports Medicine, 1998), the aerobic exercise intervention in the studies needed to occur at least twice a week at a minimum of moderate intensity (> 50% of maximum heart rate or 3 Metabolic Equivalents (METs)) and last for at least 4 weeks. The studies could be randomized (RCTs) or non-randomized, but must have included only adults aged 18 years or older living with a major NCD. Using the WHO definition (World Health Organization, 2017b), the included NCDs were: cardiovascular diseases, respiratory diseases, cancer and T2D. Studies also needed to measure depression using a clinical assessment tool or depressive symptoms using a validated self-report questionnaire. These measurements need to occur both pre- and post-intervention.

*Literature search*

The literature search was conducted using the PubMed, PsycINFO and SPORTDiscus electronic databases. Other sources, such as references from previous reviews or relevant papers, were also searched for additional records. Studies were identified using standardized search terms, including ‘depression’, ‘exercise’, ‘cancer’, ‘type 2 diabetes’, ‘cardiovascular disease’, and ‘respiratory disease’ (see supplementary file 1 for a detailed list). Studies published up to October 18$^{nd}$, 2018 in French or English and collecting data from human samples were considered. Conference abstracts, dissertations, theses, and articles published in non-peer-reviewed journals were not included for review. The search and screening phases were conducted independently by at least two investigators. Any discrepancies were resolved by a third investigator.

*Data extraction*

A data extraction form was developed specifically for the purpose of the current systematic review. Variables of interest included: depression scores, frequency, intensity, and duration of aerobic exercise training, and types of NCDs. Data extraction was performed for study

characteristics (e.g., study eligibility criteria, study methodology), participant characteristics (e.g., sex, age), and the variables of interest. Studies that met all criteria were put forward for data extraction by at least two independent investigators. The corresponding authors of the selected studies were contacted when the required data was not reported.

*Quality assessment*

Quality assessment was made independently by at least two investigators using the Downs and Black checklist (Downs & Black, 1998). This widely used checklist (Ganga et al., 2017; Laframboise & deGraauw, 2011; Lanting, Johnson, Baker, Caterson, & Chuter, 2017; Warburton, Charlesworth, Ivey, Nettlefold, & Bredin, 2010), which has high internal consistency and good test-retest (r=.88) and inter-rater (r=.75) reliability (Downs & Black, 1998) was chosen because it has been developed for use with both randomized and non-randomized studies (Deeks et al., 2003). It provides an overall score for the quality of each study, ranging from 0 to 32, with a higher score reflecting better quality. However, for the current study, the item on power was modified; authors were given 1 point if they had conducted a statistical power calculation and 0 if there were no power calculations. The maximum score was therefore changed to 28. Quality scores were categorized using the following ranges: excellent(26–28); good(20–25); fair(15–19); and poor (≤14)(Hooper, Jutai, Strong, & Russell-Minda, 2008).

Additionally, the quality of evidence was determined using the Grading of Recommendations Assessment, Development and Evaluation system (GRADE)(Balshem et al., 2011). The overall quality of evidence, categorized as “high,” “moderate,” “low,” or “very low,” was assessed using five criteria: risk of bias, inconsistency (i.e., unexplained heterogeneity in the direction of effect), indirectness (i.e., differences between the population, intervention and/or outcomes reported in included studies and those of interest), imprecision (i.e., wide confidence intervals leading to uncertainty about the true magnitude of effect), and other (e.g., publication bias).

*Assessment of publication bias*

We performed Begg and Mazumdar’s test and Eggers’s test of the intercept in order to quantify the publication bias captured by funnel plots and test its significance (Peters et al., 2010). A substantial publication bias signifies that the meta-analysis will likely overestimate the ES. Duval and Tweedie’s trim and fill, which yields an estimate of the effect size after adjusting for

publication bias, was also used (Duval & Tweedie, 2000). Finally, a fail-safe N, which represents the number of studies of null effect that would need to be included in the analysis to reduce the significance of observed effects to $p>0.05$, was calculated (Rosenberg, 2005). All of these were conducted only on the primary meta-analysis (i.e., aerobic exercise vs usual care).

*Heterogeneity*

Heterogeneity among studies was assessed using Cochran's Q. There was heterogeneity when $p<0.05$. Additionally, the Higgins $I^2$ test was also assessed (Higgins & Green, 2011; Higgins & Thompson, 2002), which provides a measure of degree of inconsistency with: 0-40% = minimal heterogeneity; 30-60% = moderate heterogeneity; 50-90% = substantial heterogeneity; and 75-100% = considerable heterogeneity.

*Data analysis*

Data were analyzed using Comprehensive Meta-Analysis software (CMA) and GRADEPro GDT (Biostat, 2015; Evidence Prime, 2015). Standardized mean differences (SMDs) with 95% confidence intervals (CI) were calculated for aerobic exercise vs. comparison group, using depressive symptom scores pre- and post-intervention. If means were not reported (n=2), we estimated them from a figure shown in the article (Payne, Held, Thorpe, & Shaw, 2008; Segar et al., 1998). When standard deviations were not reported (n=6)(Blumenthal, Babyak, et al., 2012; Gonçalves et al., 2008; Isaksen, Munk, Giske, & Larsen, 2016; Payne et al., 2008; Segar et al., 1998; Stern, Gorman, & Kaslow, 1983), we estimated them based on the largest study of the same NCD which also used the same measure of depressive symptoms. This technique was previously used by Herring and colleagues (Herring, Puetz, O'Connor, & Dishman, 2012). The SMDs were categorized as follows: SMDs of 0.2-0.5 = small effect, SMDs of 0.5-0.8 = moderate effect and SMDs $\geq$ 0.8 = large effect (Cohen, 1988). We expected a high level of heterogeneity between studies; therefore, the random effects model, using the DerSimonian and Laird method, was used. Positive SMDs reflects an advantage of aerobic exercise interventions compared to usual care.

Subgroup analyses were performed to assess the efficacy of different components of the aerobic exercise interventions on depressive symptoms. The moderators were chosen in accordance with

the FITT principle (frequency, intensity, type, time); more specifically, the moderators included exercise training frequency (2 to 3 times/week vs 4 to 5 times/week), duration of training sessions (less than 30 minutes vs 30 to 60 minutes vs over 60 minutes), and length of intervention (less than 12 weeks vs 12 weeks and more). Additionally, type of NCD (cardiac, lung, cancer, T2D) was also included as a moderator. Finally, we undertook meta-regression analyses to assess the effects of the aforementioned moderators.

## Results

### *Study selection*

The initial search yielded 12,541 studies after duplicates were removed. A total of 32 articles met all inclusion criteria and were included in the qualitative analysis, 24 of which were included in the quantitative meta-analysis (figure 1).

### *Study characteristics*

*Participant characteristics.* Included studies had a total of 4,111 participants (Asbury et al., 2008; Asbury et al., 2012; Blumenthal, Babyak, et al., 2012; Blumenthal et al., 2005b; Cadmus et al., 2009; Chen, Tsai, Wu, Lin, & Lin, 2015; Chrysohoou et al., 2014; Courneya et al., 2003; Courneya et al., 2007; Courneya et al., 2009; Dodd et al., 2010; Ergun, Eyigor, Karaca, Kisim, & Uslu, 2013; Gary, Dunbar, Higgins, Musselman, & Smith, 2010; Gayle, Spitler, Karper, Jaeger, & Rice, 1988; Gokal et al., 2015; Gonçalves et al., 2008; Güell et al., 2006; Isaksen et al., 2016; Kitzman, Brubaker, Morgan, Stewart, & Little, 2010; Koukouvou et al., 2004; Kulcu, Kurtais, Tur, Gülec, & Seckin, 2007; Lennon, Carey, Gaffney, Stephenson, & Blake, 2008; Mendes, Gonçalves, et al., 2010; Monga et al., 2007; Payne et al., 2008; Roviaro, Holmes, & Holmsten, 1984; Sardar, Boghrabadi, Sohrabi, Aminzadeh, & Jalalian, 2014; Segar et al., 1998; Smith et al., 2007; Stern et al., 1983; Topcuoglu, Gokkaya, Ucan, & Karakuş, 2015; Van Den Berg-Emons, Balk, Bussmann, & Stam, 2004). Of these, 2,003 participants were in the comparison group (49%), while 2,108 were in the aerobic exercise group (51%). Patient characteristics and trial designs are described in table 1. Seven studies assessed the effect of aerobic exercise on depressive symptoms in women only (Asbury et al., 2008; Cadmus et al., 2009; Courneya et al., 2007; Dodd et al., 2010; Gokal et al., 2015; Payne et al., 2008; Segar et al., 1998), whereas four studies included men only (Güell et al., 2006; Monga et al., 2007; Roviaro et al., 1984; Sardar et

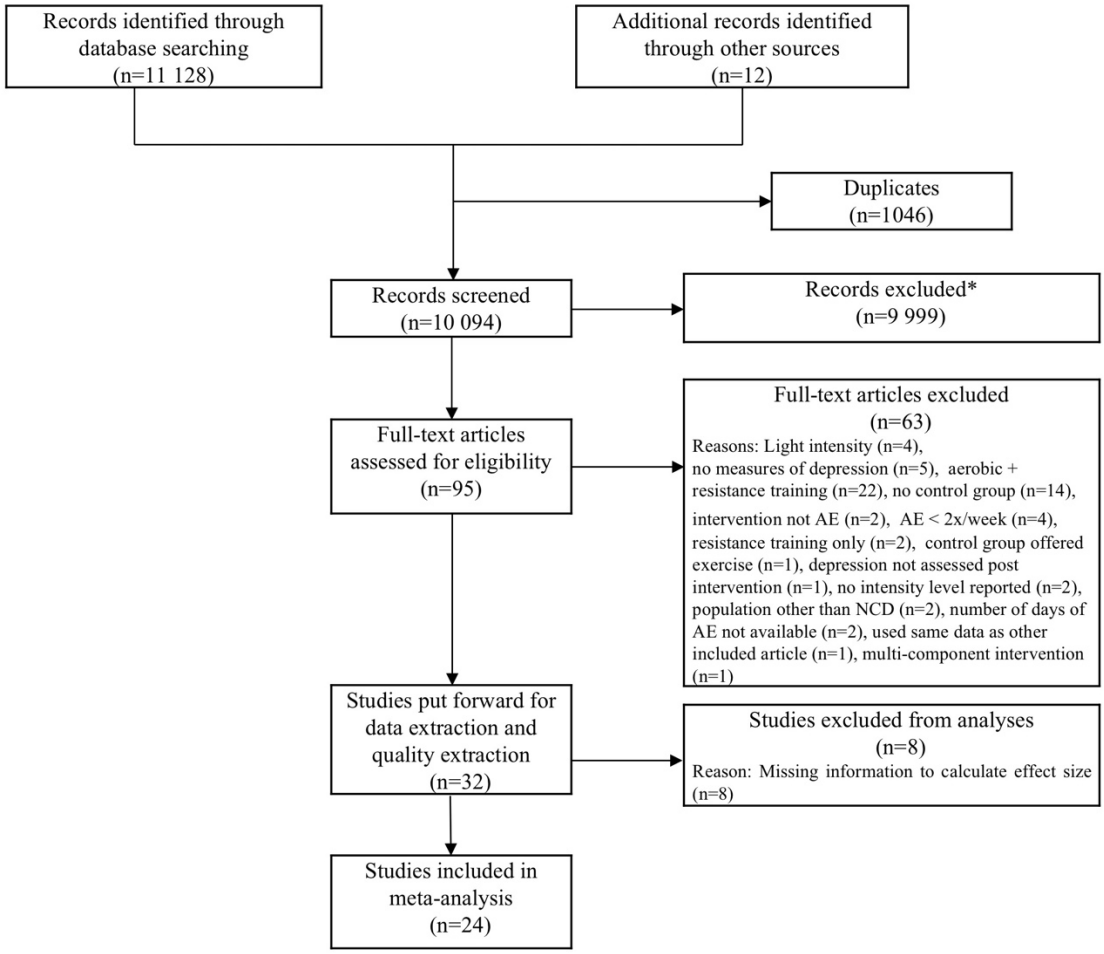
al., 2014). Participants' mean age ranged from 34 to 70 years (mean=56.9; median=58.5) with sample sizes ranging from 15 to 2,322 participants (41% women).

*Intervention characteristics.* The intervention length ranged from 4 to 24 weeks (mean=12.7, median=12). Exercise training frequency varied between 2 and 5 sessions per week (mean=3.1, median=3), each session lasted between 20 and 80 minutes (mean=42.3, median=32.5), with an average of 126 minutes of aerobic exercise per week. The average training intensity was moderate. Twenty studies included aerobic exercise that was supervised and centre-based while eight trials were conducted at home; the remainder of the trials (n = 3) were initially centre-based and then patients transitioned to doing home-based exercise. One trial did not provide this information (Sardar et al., 2014). Follow-ups ranged from none to two years, with only four studies reporting follow-up results, ranging from 2 to 24 months post intervention (Asbury et al., 2012; Blumenthal, Babyak, et al., 2012; Isaksen et al., 2016; Roviaro et al., 1984). Finally, only 12 studies (39%) reported whether there was the presence of adverse effects during the intervention (Asbury et al., 2008; Asbury et al., 2012; Cadmus et al., 2009; Chen et al., 2015; Courneya et al., 2007; Courneya et al., 2009; Dodd et al., 2010; Ergun et al., 2013; Gary et al., 2010; Kitzman et al., 2010; Koukouvou et al., 2004; Kulcu et al., 2007). Of those, only one study reported minor negative adverse effects, such as arm and knee discomfort t(Dodd et al., 2010).

*Effects of aerobic exercise intervention*

Eight studies did not provide complete raw data of outcome measures (Asbury et al., 2012; Dodd et al., 2010; Gayle et al., 1988; Lennon et al., 2008; Mendes, Gonçalves, et al., 2010; Roviaro et al., 1984; Smith et al., 2007; Topcuoglu et al., 2015). These authors were contacted by e-mail. Only two replied, and none were able to provide the necessary additional information to allow for the calculation of an ES. Therefore, 24 studies were included in the meta-analysis. Of those, eleven studies included participants with cardiovascular diseases (Asbury et al., 2008; Blumenthal, Babyak, et al., 2012; Blumenthal et al., 2005a; Chrysohoou et al., 2014; Gary et al., 2010; Isaksen et al., 2016; Kitzman et al., 2010; Koukouvou et al., 2004; Kulcu et al., 2007; Stern et al., 1983; Van Den Berg-Emons et al., 2004), ten included participants with

Figure 2.1. Flow chart of study inclusion




*Reasons for exclusion: not an intervention study (n=3 192), age restriction (n=488), cross-sectional studies (n=2 226), design and psychometric studies (n=116), exercise other than aerobic (n=192), gender and sex studies (n=102), language restriction (n=411), animal studies (n=467), intervention not exercise (n=621), irrelevant study population (n=1 456), prevalence studies (n=188), studies on QoL (n=255), review papers (n=195), intervention not measuring depression (n=49), no reference group (n=26), intervention less than 4 weeks (n=15)

Cancer (Cadmus et al., 2009; Chen et al., 2015; Courneya et al., 2003; Courneya et al., 2007; Courneya et al., 2009; Ergun et al., 2013; Gokal et al., 2015; Monga et al., 2007; Payne et al., 2008; Segar et al., 1998), two studies included participants with respiratory diseases (Gonçalves et al., 2008; Güell et al., 2006) and one study included participants with T2D (Sardar et al., 2014).

*Intervention vs usual care.* The pooled SMD for all trials was 0.50 (95% CIs, 0.25 to 0.76; figure 2), indicating a statistically significant ($p$<.001) moderate effect in favor of the intervention, such that aerobic exercise alleviated depressive symptoms relative to comparison. However, this association showed substantial heterogeneity ($Q_{23}$=185.4, $p$<.001; $I^2$=87.6%).

*Subgroup-analyses*

*Training frequency.* A small effect was found for studies that required training two to three times a week (SMD=0.46; 95%CIs=0.17-0.76), but heterogeneity was found to be substantial ($Q_{17}$=153., $p$<.001; $I^2$=88.9%). There was a larger effect size for aerobic exercise training four to five times a week (SMD=0.64; 95%CIs=0.12-1.16); $Q_5$=17.5, $p$=.004; $I^2$=71.4%), though, this was not statistical different from two to three times/week ($p$=.526). Additionally, exploratory post hoc analyses were performed to assess a difference in levels of depressive symptoms between studies who met the physical activity recommendations (i.e., minimum 150 minutes of aerobic exercise weekly) and those who did not (i.e., less than 150 minutes). There was no statistical difference ($p$=.979) between the studies who met recommendations (SMD=0.48; 95%CIs=0.21-0.75) and those who did not (SMD=0.49; 95%CIs=0.14-0.84).

*Duration of training sessions.* A small effect was found for studies that prescribed 30 minutes or less of aerobic exercise (SMD=0.48; 95%CIs=0.09-0.86; $Q_{12}$=135.6, $p$<.001; $I^2$=91.2%), while a moderate effect was found for studies with training sessions lasting 31-60 minutes (SMD=0.51; 95%CIs=0.06-0.62; $Q_4$=13.1, $p$=.011; $I^2$=69.5%) and 60+ minutes per session (SMD=0.50; 95%CIs=0.21-0.81; $Q_6$=7.2, $p$=.207; $I^2$=30.5%). Meta-regression analysis did not find duration of training sessions to influence the overall effect size ($p$=.983).

*Length of intervention.* A moderate effect was found for both interventions that lasted less than 12 weeks (SMD=0.50; 95%CIs=0.10-0.90; $Q_5$=10.3, $p$=.068; $I^2$=51.3%) and 12 weeks or longer (SMD=0.50; 95%CIs=0.20-0.80; $Q_{16}$=163.8, $p$<.001; $I^2$=89.8%). Meta-regression analysis showed no significant effect of length of intervention ($p$=.956).

*Type of NCD.* A moderate effect was found in favor of exercise (SMD=0.67; 95%CIs=0.35-0.99) in cardiac patients. However, there was substantial heterogeneity ($Q_{10}$=60.2, $p$<.001; $I^2$=81.7%). There was a small intervention effect in cancer studies (SMD=0.22, 95%CIs=0.07-0.37; $Q_9$=6.4, $p$=.603; $I^2$=0.0%). A large, non-statistically significant, effect was found in respiratory diseases (SMD=0.98; 95%CIs=-0.01-1.96; $Q_1$=2.9, $p$=.088; $I^2$=65.6%). Finally, only one included study was conducted in patients with T2D, which did not yield significant results (SMD=0.11; 95%CIs=-0.43-0.65).

*Publication bias and quality of assessment*

Figure 3 represents a funnel plot of SMDs and standard error for all studies. The Egger regression ($p$<.001) suggested high publication bias. Duval and Tweedie's trim and fill procedure suggested that four studies were missing on the right of the mean effect, resulting in an imputed effect size of 0.60 (95%CIs=0.38-0.82). Finally, the fail-safe analyses revealed that 998 intervention studies with null findings would need to have been added to the 24 studies included in the meta-analysis to render the results non-significant.

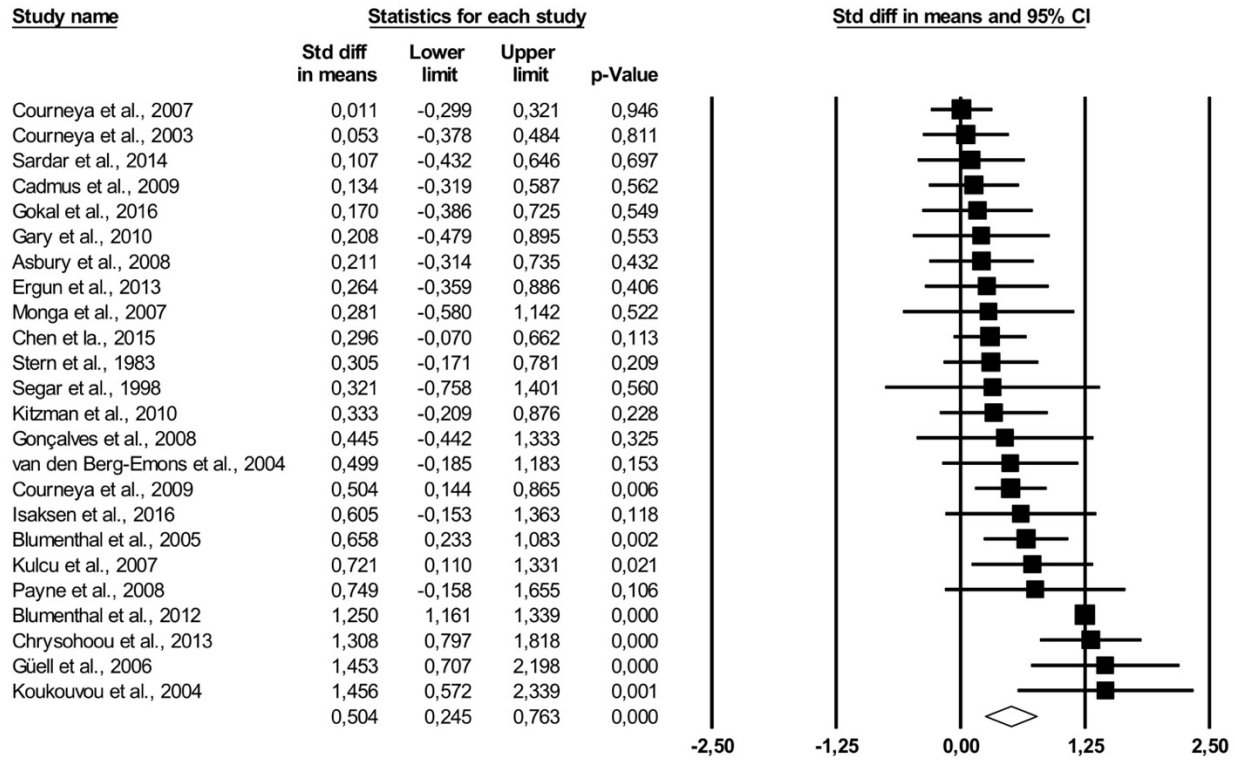
The quality assessment scores ranged between 10 and 23 (mean=16.1; median=16: see Table 1). Overall, the quality of the studies was fair, with 18/24 studies rating 15 and over (75%). Six studies were rated as poor, mainly due to poor external validity and selection bias. When excluding poor quality studies, the overall effect size slightly increased (SMD=0.54; 95%CIs=0.25-0.84; $Q_{17}$=149.91, $p$<0.001; $I^2$=88.66%); however, meta-regression analyses revealed that study quality did not seem to account for significant variations in the overall effect of aerobic exercise on depressive symptoms ($p$=.729). Thus, the six studies with poor quality were not excluded from the analyses. The overall GRADE rating applied to this evidence indicated low quality. The quality of evidence was downgraded because of inconsistency, which

Table 2.1. Main characteristics of studies included in the systematic

| Study | N[a] | Exercise Intervention | Duration (days/week) | Duration (weeks) | Session length (min.) | Type of NCD | Depression assessment | RCT | D&B | Included in meta-analysis ? |
|---|---|---|---|---|---|---|---|---|---|---|
| Asbury et al., 2008 | 64 | Mix | 2 | 8 | 80 | Cardiac (Chest pain) | HADS | Yes | 11 | Yes |
| Asbury et al., 2012 | 42 | Mix | 2 | 8 | 80 | Cardiac (Angina) | HADS | Yes | 13 | No |
| Blumenthal et al., 2005 | 90 | Centre-based | 3 | 16 | 30 | Cardiac (IHD) | BDI-II | Yes | 21 | Yes |
| Blumenthal et al., 2012 | 2322 | Centre-based | 3 | 12 | 35 | Cardiac (CHF) | BDI-II | Yes | 22 | Yes |
| Cadmus et al., 2009 | 75 | Mix | 5 | 24 | 30 | Cancer (Breast) | CES-D | Yes | 14 | Yes |
| Chen et al., 2015 | 116 | Home | 3 | 12 | 40 | Cancer (Lung) | HADS | Yes | 19 | Yes |
| Chrysohoou et al., 2014 | 100 | Centre-based | 3 | 12 | 45 | Cardiac (CHF) | ZDRS | Yes | 18 | Yes |
| Courneya et al., 2003 | 93 | Home | 3-5 | 16 | 20-30 | Cancer (Colorectal) | CES-D | Yes | 16 | Yes |
| Courneya et al., 2007 | 160 | Centre-based | 3 | 17 | 40 | Cancer (Breast) | CES-D | Yes | 15 | Yes |
| Courneya et al., 2009 | 122 | Centre-based | 3 | 12 | 30 | Cancer (Lymphoma) | CES-D-SF | Yes | 16 | Yes |
| Dodd et al., 2010 | 83 | Home | 4 | 16-24 | 25 | Cancer (Various) | CES-D | Yes | 20 | No |
| Ergun et al., 2013 | 40 | Home | 3 | 12 | 30 | Cancer (Breast) | BDI | Yes | 14 | Yes |
| Gary et al., 2010 | 33 | Home | 3 | 12 | 30 | Cardiac (HF) | HAM-D | Yes | 19 | Yes |
| Gayle et al., 1988 | 15 | Centre-based | 3 | 14 | 50 | Respiratory (COPD) | GHQ | Yes | 12 | No |
| Gokal et a., 2016 | 50 | Home | 3 | 12 | 60 | Cancer (Breast) | HADS | Yes | 23 | Yes |
| Gonçalves et al., 2008 | 20 | Centre-based | 2 | 12 | 30 | Respiratory (asthma) | BDI | Yes | 16 | Yes |
| Güell et al., 2006 | 35 | Centre-based | 5 | 8 | 30 | Respiratory (COPD) | SCL-90-R | Yes | 17 | Yes |
| Isaksen et al., 2016 | 30 | Home | 3 | 12 | 60 | Cardiac (HF) | HADS | No | 16 | Yes |
| Kitzman et a., 2010 | 46 | Centre-based | 3 | 16 | 60 | Cardiac (HF) | CES-D | Yes | 16 | Yes |
| Koukouvou et al., 2004 | 26 | Centre-based | 3 | 24 | 60 | Cardiac (CHF) | BDI | Yes | 14 | Yes |
| Kulcu et al., 2007 | 44 | Centre-based | 3 | 8 | 60 | Cardiac (HF) | BDI | Yes | 18 | Yes |
| Lennon et al., 2008 | 48 | Centre-based | 2 | 10 | 30 | Cardiac (Stroke) | HADS | Yes | 20 | No |
| Mendes et al., 2010 | 89 | Centre-based | 2 | 12 | 30 | Respiratory (asthma) | BDI | Yes | 13 | No |
| Monga et al., 2007 | 21 | Centre-based | 3 | 8 | 50 | Cancer (Prostate) | BDI | Yes | 18 | Yes |
| Payne et al., 2008 | 20 | Centre-based | 4 | 12 | 20 | Cancer (Breast) | CES-D | Yes | 18 | Yes |
| Roviaro et a., 1984 | 48 | Centre-based | 3 | 12 | 60 | Cardiac (MI) | BDI-II | No | 7 | No |
| Sardar et al., 2014 | 53 | N/A | 3 | 8 | 50 | Diabetes T2 | GHQ | Yes | 10 | Yes |
| Segar et al., 1998 | 15 | Home | 4 | 10 | 30 | Cancer (Breast) | BDI | Yes | 13 | Yes |
| Smith et al, 2007 | 66 | Centre-based | 3 | 24 | 55 | Cardiac (Hypertension) | BDI | Yes | 17 | No |
| Stern et al., 1983 | 71 | Centre-based | 3 | 12 | 60 | Cardiac (MI) | ZDRS | Yes | 15 | Yes |
| Topcuoglu et al., 2015 | 40 | Centre-based | 5 | 4 | 30 | Cardiac (Stroke) | BDI | Yes | 18 | No |
| van den Berg-Emons et al., 2004 | 34 | Centre-based | 2 | 12 | 60 | Cardiac (HF) | HADS | Yes | 17 | Yes |

Notes : UC = Usual care ; BDI = Beck Depression Inventory; CESD-SF = Short-form Center for Epidemiological Studies-Depression Scale ; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Rating Scale for Depression; ZDRS = Zung Depression Rating Scale, D&B = Downs and Black quality assessment; CHF = Chronic heart failure; COPD = Chronic obstructive pulmonary disorder; HF = Heart failure; IHD = Ischemic heart disease; MI = Myocardial infarction; N/A: Data not available. [a]Includes UC and AE groups only

Figure 2.2. Forest plot demonstrating the impact of aerobic exercise interventions on depressive symptoms




Note: Std diff = standardized difference; CI = confidence interval; AE = aerobic exercise; UC = usual care

was driven by the fact that the majority of the studies showed high levels of heterogeneity. It was also downgraded because of publication bias.

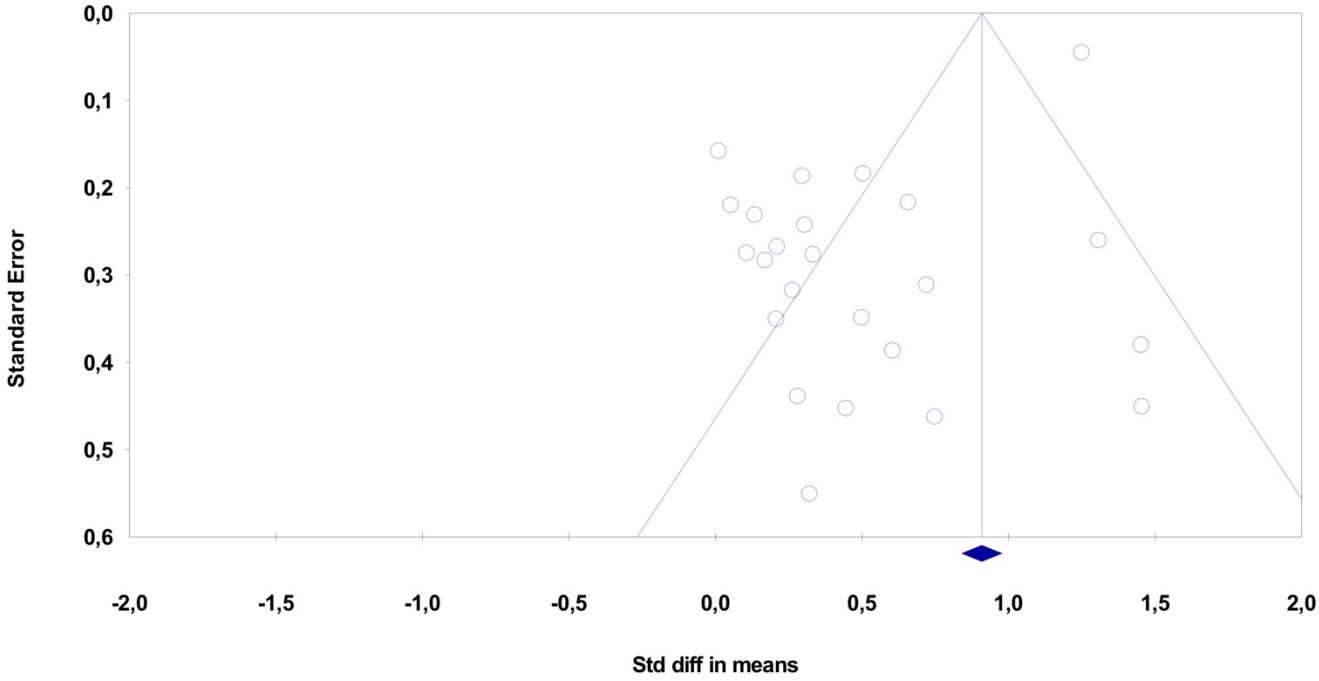
**Discussion**

This first systematic review of aerobic exercise and depressive symptoms in patients living with major NCDs (i.e., CVD, cancers, respiratory diseases, and T2D) extends previous studies by identifying that even short bouts of aerobic exercise on a regular basis may alleviate depressive symptoms and these changes may appear more rapidly than was previously reported.

The current National Institute for Health and Care Excellence (NICE) guidelines on the treatment of depression in adults living with a chronic illness recommend that patients participate in an exercise program two-three times a week, for 45-60 minutes per session, for an average of 12 weeks (The National Institute for Health and Care Excellence, 2010). The results of the current meta-analysis do not support the NICE recommendations. We did not find a specific number of weekly training days (2-3 times/week versus 4-5 times/week) to be more effective than another. Similarly, we did not find a specific amount of time per bouts of exercise (30 minutes or less, 31-60 minutes, 60+ minutes) to be better than another. This raises the question as to how much exercise may be needed to see a significant change in depression levels. It is possible that practicing short bouts of aerobic exercise on a regular basis may be enough to see a change. Additionally, the current results do not support the NICE recommendation that interventions should last at least 12 weeks (The National Institute for Health and Care Excellence, 2010). The results of our meta-analysis suggest that doing any aerobic exercise is better than nothing.

Most current national physical activity guidelines recommend at least 150 minutes of moderate intensity aerobic exercise per week for optimal health in adults (Tremblay et al., 2011; World Health Organization, 2010). The average weekly amount of aerobic exercise was 126 minutes in the meta-analysis, below recommendations. Furthermore, post hoc analyses revealed no statistical difference between the studies who met recommendations and those who did not. This result is consistent with other studies which find health benefits from exercising below the

Figure 2.3. Funnel plot of standardized difference in means versus the study standard error




Note: Std diff = standardized difference

current recommendations (Warburton & Bredin, 2016, 2017) and extends these to alleviating depressive symptoms.

It is important to note that most studies in this review did not target depression specifically; the average baseline scores across all studies fell within the 'normal' range on the various depression assessments. Thus, it is possible that there was a floor effect. Additionally, no included studies assessed depression using a clinical interview. To our knowledge, only one RCT looked at the efficacy of aerobic exercise on major depression disorder (MDD) using a valid psychiatric interview in people with a NCD (Blumenthal, Sherwood, et al., 2012). Among those with a MDD (47% of the sample), 40% of participants in the aerobic exercise group were remitted at 16 weeks, compared to 10% in the sertraline group and 0% in the placebo pill group (Blumenthal, Sherwood, et al., 2012). This study was not included in our systematic review since it did not include a usual care comparison group. The results of the aforementioned studies suggest that aerobic exercise could be efficacious for treating clinical depression in patients with CHD and may be superior to antidepressants. However, it is not possible to infer whether this holds true for other NCDs. Future studies targeting NCD participants with diagnosed clinical depression are therefore needed.

There was a moderate effect of aerobic exercise on depressive symptoms in cardiac patients. Additionally, the cardiac studies were of higher quality compared to studies with other types of NCDs. However, it should also be noted that there were more cardiac studies included in the meta-analysis ($n$=11) compared to other NCDs (respiratory, $n$=2, T2D, $n$=1). As per previous systematic reviews of all kinds of exercise (Brown et al., 2012; Craft et al., 2012; Herring et al., 2012), a small effect of aerobic exercise on depressive symptoms in cancer patients was seen. There was a moderate, non-significant effect of aerobic exercise on depressive symptoms in respiratory disease populations. However, only two studies in respiratory disease populations were included in the meta-analysis and thus, results should be interpreted with caution. Additionally, two other studies were included in the systematic review, but could not be included in the meta-analysis since it was not possible to calculate their effect sizes (Gayle et al., 1988; Mendes, Goncalves, et al., 2010). While only two COPD studies focused on aerobic exercise alone and qualified for this systematic review, there are several studies showing the beneficial

effect of multicomponent interventions (e.g., pulmonary rehabilitation, of which the key component is exercise training) on depressive symptoms in COPD populations (Coventry et al., 2013). Only one study with a T2D population was included in the current meta-analysis; therefore, it is not possible to draw any notable conclusions. Sardar and colleagues (2014) assessed the efficacy of 8-weeks of aerobic exercise on several mental health measures, including depression, in a cohort of men with type 2 diabetes. The authors did not find an advantage of aerobic exercise over usual care on depressive symptoms. There is a clear need for future research in diabetes. These results suggest that aerobic exercise is an efficacious treatment for depressive symptoms in cardiac populations and it may provide a small but significant beneficial effect in cancer populations. While encouraging, there is a need for more studies looking at the effect of aerobic exercise on depressive symptoms in respiratory diseases, especially in asthma, as well as in T2D.

*Quality of evidence*

Overall, most studies included in the meta-analysis had a small sample size, with 14 studies (Ergun et al., 2013; Gary et al., 2010; Gonçalves et al., 2008; Güell et al., 2006; Isaksen et al., 2016; Kitzman et al., 2010; Koukouvou et al., 2004; Kulcu et al., 2007; Monga et al., 2007; Payne et al., 2008; Sardar et al., 2014; Segar et al., 1998; Stern et al., 1983; Van Den Berg-Emons et al., 2004) not reaching the minimum recommendation of 30 participants per group (Cohen, 1988). Moreover, there was substantial heterogeneity, which could be explained by several factors, including variation in intervention length, minutes of training per session, and types of NCDs. It is also possible that other factors not included in the current systematic review may explain some of the heterogeneity.

Based on the GRADE system (Balshem et al., 2011), the strength of the evidence was low. Heterogeneity was high across the results and thus the quality of evidence was downgraded. Additionally, the funnel plot revealed high risk of bias of publication, which may affect the overall results. These findings reduce the confidence in our findings, and the estimates should be interpreted cautiously.

*Strengths and limitations*

We note several limitations of this review. First, there was a lack of homogeneity across studies, with differences on several levels, such as patient populations, length of intervention, and study quality, which reduces the clinical impact of the current findings. However, this variability does increase the potential generalizability of the findings. Second, the majority of the studies in the systematic review (62%) did not provide information regarding adverse events related to the intervention. Of those who mentioned adverse effects, only one reported minor issues. To be able to recommend aerobic exercise to help relieve depressive symptoms in patients living with a NCD, it is important to know whether there are important adverse effects or not. While exercise is considered safe for people living with a NCD (Carson et al., 2013; Colberg et al., 2010; Lavie et al., 2001; Schmitz et al., 2010), several factors such as previous activity levels and disease-specific limitations should be taken in to consideration when recommending an aerobic exercise regimen. Third, usual care groups may have differed across studies and NCDs. We tried to reduce the differences by choosing studies that did not encourage their patients to exercise and were just offered their usual health care. However, given the heterogeneity of the data, it was not possible to fully standardize the usual care group parameter. The present meta-analysis presented secondary analysis regarding duration of interventions, length of weekly sessions and duration of weekly sessions, but due to the limited data it was not able to provide any definitive recommendation about the optimal exercise prescription. Overall, because of the novelty of the subject, adopting a broad and inclusive approach in terms of NCDs was deemed more appropriate than a narrow approach, as it allows maximization of power and subgroup analyses (Gøtzsche, 2000).

## Conclusion

We conclude that aerobic exercise showed moderate and significant improvements in depressive symptoms when compared to usual care in people living with NCDs. Overall, our preliminary results suggest that aerobic exercise may be beneficial, safe, and contribute to the decrease in depressive symptoms in patients living with NCD, even in those without clinically significant levels of symptoms. Future studies should test the effect of aerobic exercise on patients with a clinical diagnosis of depression in populations with an NCD.

# CHAPTER 3

## Associations Between Leisure Time Physical Activity And Depressive Symptoms In Patients With Asthma

**Abstract**

**Background:** Depression is common in asthma patients and can have a negative impact on asthma outcomes, such as asthma control. Physical activity has been shown to reduce depressive symptoms and asthma symptoms. However, there is limited data on the association between physical activity and depression in adults with asthma.

**Objective:** Assess the cross-sectional relationship between leisure time physical activity and depressive symptoms in adults with asthma.

**Methods:** A total of 953 adult patients with objectively confirmed asthma from two asthma cohorts (PAL: *n*=640, mean age (SD)=49 (14) years, 60% women; and RESP: *n*=513, mean age (SD)=53 (16) years, 64% women) were included. All patients completed the Beck Depression Inventory (BDI) and a physical activity questionnaire to assess leisure time physical activity (LTPA), as well as a measure of asthma control (Asthma Control Questionnaire, ACQ).

**Results:** Engaging in any LTPA was associated with lower levels of depressive symptoms in adults with asthma (β=−1.272, $p = 0.008$). Moreover, in patients with high levels of depressive symptoms, engaging in vigorous LTPA was related to lower levels of depressive symptoms ($\beta$=−0.819, $p = .040$). These relationships were not statistically significant after adjustment for inhaled corticosteroid (ICS) dose and asthma control. No other patterns of LTPA were associated with depression in either study cohorts.

**Conclusions:** The current study is the first to look at the association between LTPA and depressive symptoms in adults with asthma. Results indicate that engaging in any LTPA is associated with lower levels of depressive symptoms and it seems to have a stronger effect in adults with asthma who have moderate to severe depressive symptoms. The associations were partially mediated by asthma control. Future studies are needed to better understand the role of asthma control and ICS in the relationship between physical activity and depression.

## Introduction

Depression, which is currently the leading cause of disability worldwide (World Health Organization, 2017), has been associated with higher rates of mortality (Cuijpers & Smit, 2002). Adults with asthma are 1.4 times more likely to suffer from depression compared to the general population (Alosco et al., 2012), with approximately a third of asthma patients currently suffering from depression (Ahmedani, Peterson, Wells, & Williams, 2013). Additionally, depression has been associated with worse asthma control (K. L. Lavoie et al., 2006) and an increased number of asthma exacerbations (Ahmedani et al., 2013). Given that depression can greatly impact the wellbeing of adults with asthma, it is important to understand the relationship between depression, asthma and factors that might influence this relationship.

In patients with asthma, engaging in physical activity has been associated with improved exercise capacity and quality of life, and reduced asthma symptoms (Eichenberger, Diener, Kofmehl, & Spengler, 2013; Mancuso et al., 2013). Additionally, engaging in physical activity has been associated with a lower risk of asthma exacerbation (Garcia-Aymerich, Varraso, Antó, & Camargo Jr, 2009) and lower health care use (Dogra, Baker, & Ardern, 2009).

Cross-sectional studies have suggested a negative association between physical activity and depressive symptoms in the general population (De Mello et al., 2013). For example, a Dutch population study found that participants who engaged in higher levels of physical activity had lower depressive symptoms than those who didn't exercise (De Moor, Beem, Stubbe, Boomsma, & De Geus, 2006). The difference between those who engaged and those who did not engage in physical activity was consistent across age and sex. Longitudinal studies have shown LTPA to be negatively associated with depression (Lindwall, Gerber, Jonsdottir, Börjesson, & Ahlborg Jr, 2014; Ströhle, 2009). For example, Ku and colleagues found similar findings, reporting that engaging in physical activity at baseline was associated with a decrease in depressive symptoms 11 years later (Ku, Fox, Chen, & Chou, 2012). Additionally, a recent study investigated the longitudinal association between physical activity and depressive symptoms in women over a 32-year period (Gudmundsson et al., 2015). The authors found that a decline in LTPA over time was associated with higher levels of depressive symptoms. Overall, the relationship between physical activity and depressive symptoms has been relatively well documented in the general population.

However, little is known about this relationship in asthmatic populations.

There is some evidence in the literature suggesting a beneficial effect of physical activity on depression in asthma patients (Gonçalves et al., 2008; Mendes et al., 2010; Turner, Eastwood, Cook, & Jenkins, 2011). For example, Mendes and colleagues (2010) assessed the efficacy of an aerobic exercise intervention compared to usual care in patients with moderate or severe persistent asthma. At the end of the three months intervention, only participants in the exercise group showed a significant reduction in depressive symptoms. While the previous studies were randomized controlled trials (RCTs) and showed promising results, they were limited by their small sample sizes (e.g., 20 to 101 participants per study). Results of the RCTs were also not adjusted for any potential confounders that may affect the association, such as sex. There is still much that has not been explored regarding the association between LTPA and depressive symptoms in asthma patients, such as the role of different patterns of exercise, which need to be addressed.

It has been suggested that the impact of physical activity on depression might be moderated by levels of intensity and different physical activity patterns. For example, a study investigated the dose-response relation of aerobic exercise and depression in a population diagnosed with major depressive disorder (MDD) (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005). Results showed that overall and independent of frequency, the public health dose was beneficial for reducing depressive symptoms, whereas low dose of exercise yielded results similar to the control group, showing no statistically significant improvement. To our knowledge, the role of physical activity dose has not been investigated in an asthma population. However, the roles of intensity and seasonal patterns of LTPA have been investigated in regard to its effects on asthma control. Bacon and colleagues (Bacon et al., 2015) found that engaging in more vigorous (rather than moderate or mild) LTPA was linked to better asthma control. Engaging in LTPA during the winter was also associated with better asthma control compared to engaging in LTPA during the summer (Bacon et al., 2015). To our knowledge, no studies have assessed how seasonal patterns and physical activity intensities might affect the relationship between physical activity and depression among adults with asthma, which could have implications in the development of physical activity interventions for patients with asthma.

The purpose of the study was to assess the cross-sectional relationship between physical activity and depressive symptoms using two cohorts of patients with asthma. It was hypothesized that there would be an association between physical activity and depressive symptoms, such that patients who engaged in more physical activity would report less depressive symptoms. Additionally, exploratory analyses were carried out to look at the relationship between seasonal patterns (summer/winter) and different levels of physical activity intensity (light, moderate, vigorous, very vigorous), and depressive symptoms.

**Methodology**

*Participants and procedure*

The present study was a sub-analysis of data from two different asthma cohorts: 1) the follow-up wave of the Psychological Risk Factors for Asthma Longitudinal (PAL) Study and 2) the baseline assessment of the Registre Épidémiologique en Santé Pulmonaire (RESP) Cohort.

The PAL study is a longitudinal cohort that aimed at understanding the role of psychological factors in asthma morbidity. A detailed procedure has been described elsewhere (Favreau, Bacon, Labrecque, & Lavoie, 2014). In brief, patients were recruited between 2003 and 2009 from a tertiary care asthma clinic. Baseline inclusion criteria included having objectively confirmed, physician diagnosed asthma, being at least 18 years of age, no comorbidity more important than asthma (e.g., cancer, recent history of stroke) and being fluent in either English of French. Patients were screened at their outpatient asthma clinic visit to verify their eligibility. Eligible and consenting patients completed a sociodemographic and medical history interview, which included the Primary Care Evaluation for Mental Disorders (PRIME-MD) to screen for mood and anxiety disorders. Following the interview, participants were asked to complete a battery of questionnaires followed by pulmonary function testing. Participants were contacted on average 4.5 years later by phone for a follow-up, which was treated as a cross-sectional cohort and was what was used for this study. This follow-up included re-administering the PRIME-MD and measuring asthma control (verbal administration of the Asthma Control Questionnaire [ACQ]) and levels of physical activity in the past 12 months (verbal administration of the 12-month Physical Activity Recall Interview (Pelaez, Lavoie, Gordon, Arsenault, & Bacon, 2010)

by a trained research assistant. In addition, patients were asked to complete a battery of asthma and psychological questionnaires including the Beck Depression Inventory [BDI], which were sent by mail. Prepaid stamped envelopes were included to facilitate the return of the questionnaire.

The RESP Study is a consecutive cohort of patients with asthma and chronic obstructive pulmonary disease (COPD) recruited from a tertiary care outpatient clinic in Montreal (Canada). Patients included in the current analyses were recruited between 2010 and 2014. Similar to PAL, patients were included in the asthma arm of RESP if they had objectively confirmed, physician diagnosed asthma, were at least 18 years of age, showed no comorbidity more important than asthma (e.g., cancer, recent history of stroke) and were fluent in either English of French. Eligible and consenting patients completed a sociodemographic and medical history interview, which included the PRIME-MD. Following the interview, participants were asked to complete a battery of questionnaires similar to PAL (including the ACQ and BDI-II), followed by pulmonary function testing. In RESP, physical activity was measured using the Godin-Shephard Leisure-Time Physical Activity Questionnaire (Godin & Shephard, 1985) which assesses PA levels in the past week. Unlike PAL, participants were only assessed at one time-point (baseline).

All clinical information (including medication status and dosage) for both studies was self-reported and verified by chart medical review. Both projects were approved by the Human Ethics Committee of Centre intégré universitaire de santé et de services sociaux du Nord-de-l'Île-de-Montréal (CIUSSS-NIM) and written informed consent was obtained from all participants.

*Assessments*

*Depression.* The BDI-II (Beck, 1996) is a 21-item questionnaire measuring the intensity of depressive symptoms over the past two weeks. The BDI-II comprises 21 items, ranging from 0 (absence of symptoms) to 3 (most severe symptoms). A cutoff score of 12 has been established as the optimal cut point to suggest the presence of major depressive disorder in patients with asthma (Plourde, Moullec, Bacon, Suarthana, & Lavoie, 2016). Internal consistency has been shown to be around 0.9 and retest reliability ranges from 0.73 to 0.96 (Wang, Booth-LaForce, Tang, Wu, & Chen, 2013). The French version also shows good internal consistency (Cronbach

$\alpha = 0.88$) and satisfactory test-retest reliability ($r = 0.82$) (Vézina, Landreville, Bourque, & Blanchard, 2010).

In order to assess clinical levels of depression, participants underwent a brief, structured psychiatric interview using the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al., 1994). The PRIME-MD was designed to detect the most common psychiatric disorders present in primary care settings and is based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 2000). The PRIME-MD has been validated and has been shown to be of comparable sensitivity (83%), specificity (88%), and reliability ($\alpha = 0.71$) as longer structured interviews such as the Structured Clinical Interview for DSM Disorders (Spitzer et al., 1994). It takes between 10 and 15 minutes to administer and score and consists of a structured interview that is used to follow-up patient responses. The PRIME-MD has been used previously in studies assessing psychiatric disorders in patients with chronic diseases (Gudmundsson et al., 2015; Lindwall et al., 2014).

*Leisure time physical activity.* At the follow-up, PAL participants were asked to complete the 12-month physical activity recall interview (12M-PAR), which assesses the average amount of leisure time physical activity (LTPA) that individuals perform over the course of a year (Bacon et al., 2015; Pelaez et al., 2010). This self-report scale includes activities at three intensity levels: moderate (e.g., brisk walking), vigorous (e.g., dancing) and very vigorous (e.g., swimming), and generates estimates of energy expenditure (metabolic equivalent (MET)-hrs/week). For this study, the questionnaire was adapted to ask about the summer (May–October) and winter (November–April) months separately, due to the extreme difference in temperature and weather conditions in Montreal.

LTPA was measured at baseline in the RESP cohort using the Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ). The GSLTPAQ consists of three items assessing the frequency of mild, moderate, and vigorous bouts of exercise of at least 15 minutes in duration for a typical week. The GSLTPAQ has been successfully used in different types of non-communicable chronic diseases, such as cancer, diabetes and COPD (Amireault & Godin, 2015; Franke et al., 2016; Thiel, Al Sayah, Vallance, Johnson, & Johnson, 2017).

Of note, both questionnaires generate a MET-hr/week score as the measure of LTPA, and a MET-hrs/week of 10 approximates to current guidelines for optimal activity levels of 30 min of at least moderate activity on most (i.e., five) days of the week (Pelaez et al., 2010).

*Asthma control.* The Asthma control questionnaire (ACQ-6) (Juniper, O'Byrne, Guyatt, Ferrie, & King, 1999) is a self-report questionnaire which assesses levels of asthma control in the last week according to standard criteria specified by international guidelines (Global Initiative for Asthma, 2017). Participants were asked to recall their symptoms (shortness of breath, wheezing, waking dyspnea, and nocturnal dyspnea), and activity limitations using six items rated on a 6-point scale (0 = no impairment, 6 = maximum impairment), which yields a mean score out of 6 (i.e. higher scores indicate worse asthma control). The ACQ-6 has been shown to be valid and reliable (Schuler, Faller, Wittmann, & Schultz, 2016) and has been used previously in other studies (Bacon et al., 2015; Meltzer et al., 2010). Scores of >0.8 indicate poor asthma control (Austin et al., 2014; Favreau et al., 2014) and a change of score of ≥ 0.5 has been identified as clinically significant (Juniper, Stahl, Mork, & Svensson, 2004). The ACQ has been validated in French (Juniper, 2005).

*Other measures.* Patient characteristics, such as sex, age, height and weight, which were used to calculate body mass index (BMI), were self-reported. Additionally, dosage of asthma-sepcific medications (e.g., inhaled corticosteroid (ICS) dose) were self-reported and then verified by medical chart review.

*Statistical analysis*

All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA). Missing data were imputed using PROC MI (SAS) and 20 independent data sets were generated. Variables that were imputed are indicated in table 3.1. For the main analyses, PROC MIANALYZE was used in order to generate estimations for model coefficients (Rubin, 2004).

For the reporting of demographics, group differences in continuous variables were tested using t-tests, while group differences in categorical variables were examined using Pearson's chi-squared

test using non-imputed variables. General linear models (GLM) were used to assess the association between LTPA (continuous variable) and depressive symptoms (continuous variable). A recent meta-analysis (Béland et al., 2019) suggested that being physically active, regardless of the frequency and duration, was more efficacious in reducing levels of depressive symptoms than being completely physically inactive. As such, GLMs were also assessed using LTPA as a dichotomous predictor (0=no LTPA and 1=any LTPA).

In addition, a series of exploratory analyses were performed. The different predictors included optimal LTPA (0 < less than 10 MET-hrs/week and 1 ≥ 10 MET-hrs/week and more), seasonal patterns (winter and summer LTPA; in PAL only), and different exercise intensities (light, moderate, vigorous, and very vigorous).

All initial models were adjusted for age, sex, and BMI, which were determined a priori (Lavoie et al., 2005; Strine, Mokdad, Balluz, Berry, et al., 2008). A second set of analyses were conducted adjusting for asthma characteristics (ICS dose and ACQ) which differed between those who engaged in any LTPA compared to those who did not (see Appendix F). Finally, for analyses where both cohorts were merged, we included a dummy variable for cohort (0 = RESP, 1 = PAL). All GLMs were performed using imputed data. All tests were two-sided and significance was set at $p < 0.05$. Effect sizes (omega-squared) were also calculated and values of 0.01, 0.06, and 0.14 represent small, medium, and large effects, respectively (Cohen, 1988).

Finally, to assess the potential mechanistic role of asthma control and ICS on the LTPA-depressive symptoms relationship, a series of moderation and mediation models were conducted, using Hayes' PROCESS (Field, 2013). Moderation analyses were conducted to analyze the potential interaction effects of LTPA and ICS on depressive symptoms; this approach was chosen based on previous findings suggesting a dose-response effect of ICS on depressive symptoms (Brown & Suppes, 1998; Warrington & Bostwick, 2006). Mediation analyses were used to examine if, and to what extent, asthma control mediated the direct effect of LTPA on depressive symptoms; this approach was chosen based on the literature, which suggest that engaging in LTPA is associated with better asthma control (Bacon et al., 2015), while better

asthma control is associated with lower levels of depressive symptoms (Ahmedani et al., 2013; Lavoie et al., 2005). The data was resampled with replacement using bootstrapping 1 000 times to test the indirect effect with a 95% confidence interval. The indirect effects were tested for statistical significance at $p < .05$.

**Results**

*Sample characteristics*

Demographics and study variables are presented in table 3.1. The PAL cohort included 640 participants, whom were primarily women (60%), and had a mean (SD) age of 49.0 (14.1). The RESP cohort included 513 participants (64% women) with a mean (SD) age of 52.7 (16.0). Patients in RESP were older and had a higher BMI compared to patients in PAL. With regards to asthma, patients in RESP tended to have worse asthma control and take more ICS.

*Physical activity.* The proportion of patients doing any physical activity did not differ between the two cohorts, with 62% of both cohorts engaging in any physical activity. However, PAL participants had a higher average LTPA score (4.77 vs 3.41 METhrs/wk, $p < .001$). When only moderate and vigorous physical activity levels were analyzed, a significant difference between the two cohorts was observed, with PAL patients more likely to engage in any moderate or vigorous physical activity than RESP patients (57% vs 38%, $p < .001$), even though they both had a similar mean moderate or vigorous activity level (6.87 vs 6.45 METhrs/wk, $p = .519$).

*Depression.* Participants from PAL showed significantly higher average BDI scores compared to participants from RESP (8.3 vs 6.8, $p < .001$), as well as a higher prevalence of PRIME-MD depression (20% vs 8%, $p < .001$).

Group differences for demographic and study characteristics, as a function of LTPA engagement are provided in Appendix F. In both cohorts, patients engaging in any LTPA had lower BMIs, smoked less, better asthma control, and less depressive symptoms than patients not engaging in any LTPA. Additionally, in PAL, patients engaging in any LTPA had lower prescribed doses of ICS compared to patients not engaging in LTPA, while patients in RESP engaging in any LTPA were younger and were less likely to have a mood disorder (based on the PRIME-MD).

*Associations between LTPA and depression*

*Continuous LTPA.* As seen in table 3.2, there were no associations between continuous measures of LTPA and BDI in neither RESP nor PAL. However, there was a trend showing a negative association between LTPA and depressive symptoms in the unadjusted model in RESP ($\beta$=–0.139, $p$ = .090). When different levels and seasonal patterns of LTPA were assessed in PAL, we did not find any statistical associations.

Table 3.1. Baseline characteristics of PAL (N = 640) and BD-ASTHMA (N = 513) study participants.

| | **PAL study (N = 640)** | **RESP study (N = 513)** | ***p* value** |
|---|---|---|---|
| | Means (SD) or % (n) | Means (SD) or % (n) | |
| **Demographics** | | | |
| Age (yrs) | 49.01 (14.12) | 52.73 (16.01) | < .001 |
| Sex (% women) | 60 (384) | 64 (328) | .255 |
| Ethnicity (% White) | 93 (595) | 94 (482) | .340 |
| BMI (kg/m2) | 27.82 (6.13) | 30.54 (7.25) | < .001 |
| Smoking (% yes) | 8 (51) | 10 (51) | .164 |
| **Asthma characteristics** | | | |
| ACQ | 0.99 (1.02) | 1.41 (1.14) | < .001 |
| ICS (mcg fluticasone equiv.) | 603.4 (504.32) | 794.1 (584.2) | < .001 |
| **Physical activity characteristics** | | | |
| Level of PA (MET-hours/week) | 4.77 (7.78)<br>Range: 0-48<br>Median: 1.35<br>Interquartile: 6.29 | 3.41 (4.17)<br>Range: 0-32<br>Median: 2.25<br>Interquartile: 5.25 | < .001 |
| Level of PA (MET-hours/week; only mod/vigorous) | 6.87 (8.49)<br>Range: 0-45<br>Median: 3.08<br>Interquartile: 8.62 | 6.45 (4.12)<br>Range: 1.5-26.25<br>Median: 4.5<br>Interquartile: 6 | .519 |
| Does any PA (% yes) | 62 (397) | 62 (318) | .924 |
| Does any PA (% yes; mod/vigorous only) | 57 (365) | 38 (195) | < .001 |
| Does Optimal PA (% yes) | 17 (109) | 8 (41) | < .001 |
| **Psychological characteristics** | | | |
| BDI | 8.3 (8.41)<br>Range: 0-52.5<br>Median: 6.3<br>Interquartile: 9.45 | 6.77 (6.76)<br>Range: 0-52<br>Median: 5<br>Interquartile: 8 | .026 |
| Mood Disorder (% yes) | 20 | 8 | < .001 |

Additional analyses were conducted in participants with a BDI ≥ 12 (table 3.3). Results showed a trend for negative associations between LTPA and depressive symptoms in the unadjusted model in RESP ($\beta$=–0.356, $p$ = .066) and in the model adjusted for patient characteristics (Model 2; age, sex, BMI) ($\beta$=–0.364, $p$ = .090).

*Dichotomous LTPA.* In RESP, the nature of the relationship between any LTPA or not (dichotomous) and BDI was in accordance with the hypothesis, that is, engaging in any LTPA was associated with lower levels of depressive symptoms ($\beta$=–1.803, $p$ = .003) (see table 3.4). The magnitude of the effect size was small. When adjusting for patient characteristics (Model 2; age, sex, BMI), the associations remained significant; however, it was no longer statistically significant after adjusting for asthma characteristics (Model 3; patient characteristics, ICS, ACQ), though there was still a trend ($\beta$=–1.116, $p$ = .066). There was a trend in the PAL cohort in which engaging in any LTPA was associated with lower depressive symptoms ($\beta$=–1.217, $p$ = .081). However, the association was non-significant after adjusting for covariates. When considering only moderate and vigorous intensity activities, there was a statistically significant negative association between LTPA (any or none) and depressive symptoms in both in the unadjusted model ($\beta$=–1.470, $p$ = .027) and the model adjusted for patient characteristics ($\beta$=–1.368, $p$ = .046) in RESP; the magnitude of these effect sizes were small. The association was no longer significant after adjusting for asthma characteristics. In PAL, engaging in any LTPA at the moderate or vigorous levels was not associated with BDI.

We did not find that engaging in optimal levels of physical activity (yes/no; 10 MET-hrs/week) was associated with depression in neither PAL ($\beta$=–0.679, $p$ = .443) nor RESP ($\beta$=–0.756, $p$ = .532). Moreover, an unadjusted model revealed a trend that practicing any vigorous LTPA (dichotomous) was negatively associated with depressive symptoms ($\beta$=–1.523) in the RESP cohort, such that engaging in any vigorous LTPA was associated with a 1.5 point reduction in BDI score. Exploratory analyses revealed an association between engaging in any LTPA during summer and lower depressive symptoms, both in the unadjusted model ($\beta$=–1.346, $p$ = .049) and in the model adjusted for patient characteristics ($\beta$=–1.337, $p$ = .050).

Table 3.2. GLM models of continuous LTPA, LTPA intensity, and season on depressive symptoms.

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | B (SE) | *p* value | ES | B (SE) | *p* value | ES | B (SE) | *p* value | ES |
| RESP | | | | | | | | | |
| LTPA (all intensities) | *-0.139 (0.396)* | *.090* | .001-.014 | -0.119 (0.083) | .152 | .001-.014 | -0.056 (0.081) | .489 | .001-.003 |
| LTPA (only moderate and vigorous) | -0.135 (0.084) | .109 | .002-.014 | -0.106 (0.086) | .216 | .001-.011 | -0.035 (0.085) | .676 | .001-.011 |
| *Intensity* | | | | | | | | | |
| Low | -0.088 (0.132) | .504 | .001-.002 | -0.086 (0.134) | .525 | .001-.002 | -0.093 (0.131) | .481 | .000-.003 |
| Moderate | -0.126 (0.192) | .512 | .000-.002 | -0.105 (0.191) | .584 | .000-.001 | -0.058 (0.188) | .757 | .000-.001 |
| Vigorous | -0.321 (0.226) | .157 | .000-.017 | -0.278 (0.240) | .248 | .000-.017 | -0.070 (0.238) | .768 | .002-.009 |
| PAL | | | | | | | | | |
| LTPA (all intensities) | -0.026 (0.395) | .550 | .000-.001 | -0.031 (0.043) | .475 | .000 | 0.003 (0.042) | .941 | .000 |
| LTPA (only moderate and vigorous) | -0.022 (0.047) | .645 | .000 | -0.024 (0.046) | .601 | .000 | -0.002 (0.044) | .967 | .000 |
| *Intensity* | | | | | | | | | |
| Moderate | -0.035 (0.110) | .751 | .000 | 0.003 (0.108) | .977 | .000 | 0.028 (0.104) | .790 | .000 |
| Vigorous | -0.394 (0.371) | .289 | .000-.003 | -0.427 (0.376) | .256 | .000-.004 | -0.338 (0.362) | .351 | .000-.004 |
| Very vigorous | -0.027 (0.048) | .568 | .000 | -0.026 (0.047) | .578 | .000 | -0.007 (0.045) | .880 | .000 |
| *Season* | | | | | | | | | |
| Summer | -0.030 (0.076) | .690 | .000 | -0.011 (0.075) | .882 | .000 | 0.026 (0.073) | .725 | .000 |
| Winter | -0.071 (0.092) | .440 | .000-.001 | -0.077 (0.091) | .398 | .000-.001 | -0.019 (0.088) | .828 | .000-.001 |

Note. Model 1 = general linear model (GLM) of main effects without covariates; Model 2 = GLM of main effects with covariates (age, sex, and BMI); Model 3 = GLM of main effects with covariates (age, sex, BMI, dose of inhaled corticosteroids, and ACQ score). ES = Effect size.

Table 3.3. GLM models of continuous LTPA, LTPA intensity, and season on depressive symptoms in patients with a BDI ≥ 12.

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | B (SE) | *p* value | ES | B (SE) | *p* value | ES | B (SE) | *p* value | ES |
| RESP | | | | | | | | | |
| LTPA (all intensities) | *-0.356 (0.192)* | *.066* | *.005-.095* | *-0.364 (0.213)* | *.090* | .014 .095 | -0.287 (0.261) | .187 | .003 .095 |
| LTPA (only moderate and vigorous) | -0.292 (0.186) | .118 | .003-.057 | -0.310 (0.209) | .140 | .003-.057 | -0.236 (.0213) | .268 | .006-.057 |
| *Intensity* | | | | | | | | | |
| Low | -0.341 (0.274) | .213 | .000-.030 | -0.317 (0.288) | .271 | .000-.028 | -0.242 (0.289) | .402 | .000-.025 |
| Moderate | -0.476 (0.421) | .259 | .000-.027 | -0.458 (0.427) | .283 | .000-.025 | -0.366 (0.432) | .397 | .000-.025 |
| Vigorous | -0.596 (0.536) | .267 | .000-.029 | -0.675 (0.637) | .291 | .000-.029 | -0.462 (0.635) | .467 | .000-.029 |
| PAL | | | | | | | | | |
| LTPA (all intensities) | 0.050 (0.079) | .525 | .000 | 0.042 (0.788) | .597 | .000 | 0.053 (0.078) | .497 | .000 |
| LTPA (only moderate and vigorous) | 0.026 (0.086) | .761 | .000 | 0.010 (0.086) | .912 | .000 | 0.025 (0.085) | .771 | .000 |
| *Intensity* | | | | | | | | | |
| Moderate | 0.129 (0.193) | .506 | .000 | 0.180 (0.194) | .353 | .000 | 0.234 (0.191) | .221 | .000 |
| Vigorous | -0.634 (0.618) | .305 | .000-.007 | -0.763 (0.629) | .225 | .000-.007 | -0.653 (0.617) | .290 | .000-.007 |
| Very vigorous | 0.035 (0.093) | .710 | .000 | 0.004 (0.093) | .966 | .000 | -0.002 (0.092) | .980 | .000 |
| *Season* | | | | | | | | | |
| Summer | 0.128 (0.133) | .337 | .000-.002 | 0.120 (0.133) | .365 | .000-.002 | 0.141 (0.132) | .286 | .000-.003 |
| Winter | 0.046 (0.174) | .781 | .000 | -0.002 (0.176) | .993 | .000 | 0.021 (0.175) | .905 | .000 |

Note. Model 1 = general linear model (GLM) of main effects without covariates; Model 2 = GLM of main effects with covariates (age, sex, and BMI); Model 3 = GLM of main effects with covariates (age, sex, BMI, dose of inhaled corticosteroids, and ACQ score).

Table 3.4. GLM models of dichotomous LTPA (y/n) and LTPA intensity on depressive symptoms.

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | B (SE) | *p* value | ES | B (SE) | *p* value | ES | B (SE) | *p* value | ES |
| RESP | | | | | | | | | |
| **LTPA (y/n)** | **-1.803 (0.601)** | **.003** | **.010-.025** | **-1.671 (0.612)** | **.006** | **.008-.025** | *-1.116 (0.608)* | *.066* | .005-.023 |
| **LTPA (y/n: moderate and vigorous only)** | **-1.470 (0.660)** | **.027** | **.007-.027** | **-1.368 (0.682)** | **.046** | **.007-.022** | -0.643 (0.674) | .341 | .001-.028 |
| Optimal LTPA (y/n) | -0.756 (1.207) | .532 | .000-.002 | -0.517 (1.232) | .675 | .000-.002 | 0.068 (1.211) | .956 | .000-.003 |
| *Intensity* | | | | | | | | | |
| Low (y/n) | -0.376 (0.676) | .578 | .000-.001 | -0.366 (0.684) | .593 | .000-.002 | -0.443 (0.667) | .506 | .000-.002 |
| Moderate (y/n) | -1.032 (0.730) | .157 | .000-.010 | -0.941 (0.727) | .196 | .000-.008 | -0.564 (0.712) | .431 | .000-.006 |
| Vigorous (y/n) | *-1.523 (0.836)* | *.071* | .001-.030 | -1.467 (0.903) | .106 | .001-.031 | -0.676 (0.886) | .446 | .001-.031 |
| PAL | | | | | | | | | |
| LTPA (y/n) | *-1.217 (0.696)* | *.081* | *.002-.006* | *-1.196 (0.691)* | *.084* | .002-.007 | -0.705 (0.667) | .291 | .002-.007 |
| LTPA y/n: moderate and vigorous only) | -0.588 (0.675) | .384 | .000-.003 | -0.816 (0.678) | .229 | .000-.003 | -0.406 (0.653) | .534 | .000-.003 |
| Optimal LTPA (y/n) | -0.679 (0.886) | .443 | .000 | -0.509 (0.874) | .560 | .000 | -0.113 (0.843) | .893 | .000 |
| *Intensity* | | | | | | | | | |
| Moderate (y/n) | -0.588 (0.675) | .384 | .000-.002 | -0.635 (0.671) | .345 | .000-.002 | -0.132 (0.646) | .838 | .000-.002 |
| Vigorous (y/n) | -0.446 (1.155) | .700 | .000 | -0.561 (1.167) | .631 | .000 | 0.033 (1.121) | .976 | .000 |
| Very vigorous (y/n) | -0.874 (0.758) | .249 | .000-.002 | -0.970 (0.761) | .203 | .000-.002 | -0.676 (0.734) | .357 | .000-.003 |
| *Season* | | | | | | | | | |
| Summer (y/n) | **-1.346 (0.466)** | **.049** | **.003-.008** | **-1.337 (0.682)** | **.050** | **.003-.008** | -1.005 (0.655) | .125 | .001-.009 |
| Winter (y/n) | -0.601 (0.698) | .390 | .000-.001 | -0.718 (0.698) | .304 | .000-.001 | -0.274 (0.672) | .684 | .000-.002 |

Note. Model 1 = general linear model (GLM) of main effects without covariates; Model 2 = GLM of main effects with covariates (age, sex, and BMI); Model 3 = GLM of main effects with covariates (age, sex, BMI, dose of inhaled corticosteroids, and ACQ score).

Table 3.5. GLM models of dichotomous LTPA (y/n) and LTPA intensity on depressive symptoms in patients with BDI ≥ 12.

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | B (SE) | *p* value | ES | B (SE) | *p* value | ES | B (SE) | *p* value | ES |
| RESP | | | | | | | | | |
| **LTPA (y/n)** | **-2.889 (1.147)** | **.012** | **.035 .097** | **-2.897 (1.224)** | **.018** | **.035-.097** | *-2.283 (1.326)* | *.085* | .021 .100 |
| LTPA (y/n: moderate and vigorous only) | *-2.408 (1.266)* | *.058* | *.009-.055* | *-2.513 (1.382)* | *.070* | .009-.055 | -1.920 (1.452) | .187 | .011-.064 |
| Optimal LTPA (y/n) | -1.928 (3.271) | .556 | .000-.010 | -1.715 (3.373) | .611 | .000-.010 | -1.160 (3.495) | .740 | .000-.010 |
| *Intensity* | | | | | | | | | |
| Low (y/n) | -1.434 (1.331) | .282 | .000-.016 | -1.292 (1.377) | .348 | .000-.024 | -0.946 (1.386) | .495 | .000-.016 |
| Moderate (y/n) | -1.843 (1.570) | .241 | .000-.030 | -1.723 (1.585) | .277 | .000-.030 | -1.321 (1.593) | .407 | .000-.026 |
| Vigorous (y/n) | -2.107 (1.592) | .186 | .000-.036 | -2.383 (1.858) | .200 | .000-.036 | -1.728 (1.883) | .359 | .000-.039 |
| PAL | | | | | | | | | |
| LTPA (y/n) | -1.294 (1.204) | .282 | .000-.004 | -1.180 (1.212) | .330 | .000-.004 | -0.614 (1.222) | .614 | .000-.004 |
| LTPA (y/n: moderate and vigorous only) | -1.000 (1.195) | .403 | .000-.002 | -1.001 (1.207) | .407 | .000-.002 | -0.372 (1.218) | .760 | .000-.002 |
| Optimal LTPA (y/n) | 0.595 (1.595) | .709 | .000 | 0.344 (1.597) | .830 | .000 | 0.561 (1.585) | .724 | .000 |
| *Intensity* | | | | | | | | | |
| Moderate (y/n) | -0.981 (1.194) | .411 | .000-.002 | -0.864 (1.217) | .478 | .000-.002 | -0.135 (1.235) | .913 | .000-.002 |
| Vigorous (y/n) | -2.055 (2.000) | .304 | .000-.006 | -2.532 (2.033) | .213 | .000-.006 | -1.933 (2.021) | .339 | .000-.006 |
| Very vigorous (y/n) | -0.162 (1.351) | .905 | .000 | -0.233 (1.347) | .863 | .000 | -0.467 (1.343) | .728 | .000 |
| *Season* | | | | | | | | | |
| Summer (y/n) | 0.690 (1.234) | .576 | .000-.002 | 0.847 (1.247) | .497 | .000-.002 | 1.071 (1.229) | .383 | .000-.002 |
| Winter (y/n) | -0.080 (1.240) | .949 | .000 | -0.026 (1.248) | .984 | .000 | 0.133 (1.229) | .914 | .000 |

Note. Model 1 = general linear model (GLM) of main effects without covariates; Model 2 = GLM of main effects with covariates (age, sex, and BMI); Model 3 = GLM of main effects with covariates (age, sex, BMI, dose of inhaled corticosteroids, and ACQ score).

Finally, additional analysis conducted in participants who had a BDI ≥12 (table 3.5) revealed a significant negative association in RESP between LTPA and depressive symptoms (yes/no) in unadjusted model ($\beta$=−2.889, $p$ = .012) as well as in the model adjusted for patient characteristics ($\beta$=−2.897, $p$ = .018); both associations showed small to moderate effect sizes. Additional adjustment for asthma-related variables showed a trend, but was not statistically significant ($\beta$=−2.283, $p$ = .085). There were no significant associations in PAL.

*Merged cohorts.* Given that both cohorts were recruited from the same hospital and measures were similar, RESP and PAL cohorts were merged together in order to run an additional series of analyses (see Appendice G). GLMs revealed a negative association between practicing any LTPA and depressive symptoms in an unadjusted model ($\beta$=−1.407, $p$ = 0.003) and in models adjusted for age, sex, BMI, and cohort ($\beta$=−1.237); however, the model did not reach statistical significance when additionally adjusted for asthma control and ICS dose ($\beta$=−0.673). In patients with high depressive symptomatology (BDI≥12), the association between any LTPA and depressive symptoms was significant in both the unadjusted model ($\beta$=−1.633, $p$ = 0.054) and in the model adjusted for patient characteristics ($\beta$=−1.786, $p$ = 0.042). The magnitude of effect size was small. Additionally, practicing any vigorous LTPA was also associated with depressive symptoms when the model was adjusted for patient characteristics ($\beta$=−2.981, $p$ = .034), resulting in a reduction in BDI score by 3 points.

*Mediation*

The mediation analyses revealed a significant, indirect effect of LTPA on depressive symptoms in RESP (Figure 3.1). Engaging in LTPA resulted, through asthma control, in a decrease in depressive symptoms by 2.05 units ($R^2$ = 0.03, $p$ < .001). Indirect effect of moderate/vigorous LTPA (RESP) and summer LTPA (PAL) on depressive symptoms were also significant (LTPA mod/vig, $R^2$ = 0.13, $p$ = .002; summer LTPA, $R^2$ = 0.10, $p$ < .001; see figures 3.2-3.3).

*Moderation*

There were no interaction effects between change in LTPA and change in ICS dose on decline in depressive symptoms in either RESP (LTAP y/n, b=0.00, t[235]=-0.24, $p$=.811; LTPA mod/vig, b=0.00, t[235]=-0.41, p=.683) or PAL (summer LTPA, b=0.00, t[455]=0.307, p=.759).

**Figure 3.1** Mediation of asthma control on LTPA toward depressive symptoms

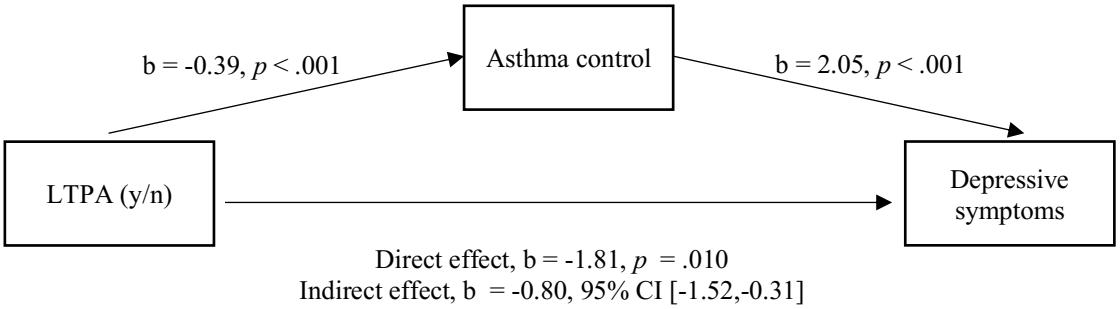



**Figure 3.2** Mediation of asthma control on moderate/vigorous LTPA toward depressive symptoms

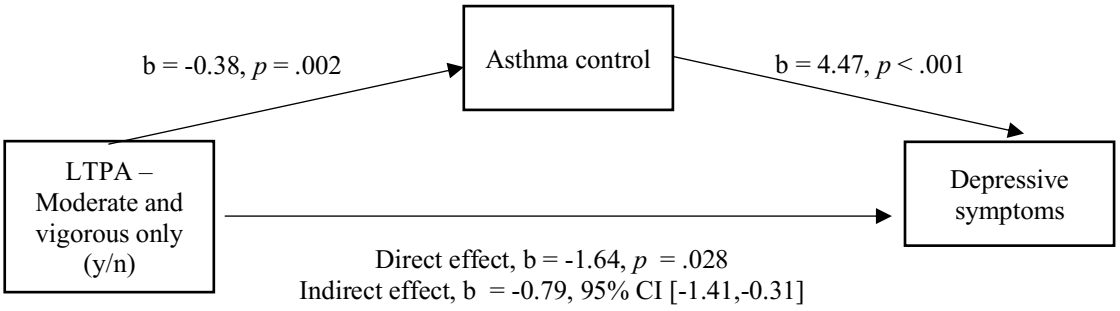
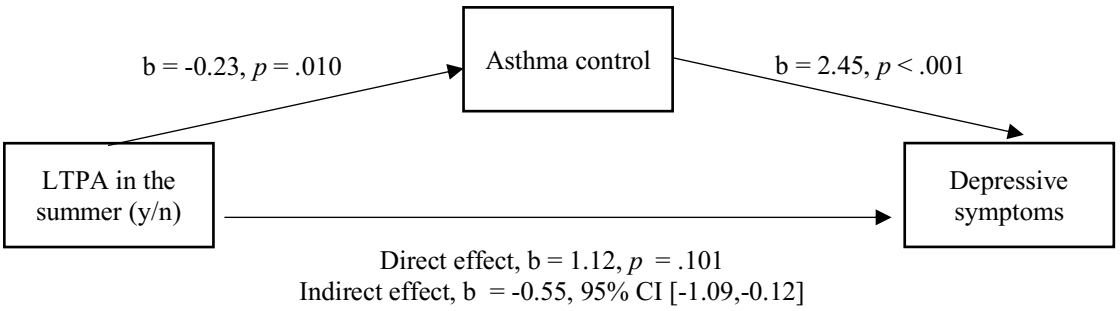



**Figure 3.3** Mediation of asthma control on summer LTPA toward depressive symptoms



**Discussion**

The current study assessed the cross-sectional relationship between LTPA and depressive symptoms in two cohorts of adult patients with asthma. Results showed that although patients engaging in any LTPA showed lower levels of depressive symptoms, the effect was lost once we adjusted for asthma control and prescribed ICS dose. The association was generally stronger in participants with higher levels of depressive symptoms. Further analyses revealed that vigorous LTPA was the only individual intensity which had any associations with lower depressive symptoms (and specifically in the combined cohort dataset). In contrast to engaging in any LTPA, we did not find that engaging in optimal levels of LTPA (i.e., 10 MET-hrs/week) was associated with depressive symptoms. Taken together, these results suggest that practicing any LTPA may be associated with lower levels of depressive symptoms, although asthma control and ICS dose may play a role in the relationship. These associations were small to moderate in effect.

Our findings are generally in line with previous studies showing a negative association between physical activity and depressive symptoms in patients with non-communicable chronic diseases, such as chronic obstructive pulmonary disease (COPD) (Loprinzi, Kane, & Walker, 2013). Loprinzi and colleagues (2013) reported an association between optimal levels of physical activity and depressive symptoms. The authors found that participants who reported meeting guideline levels of physical activity were 59% less likely to suffer from high levels of depressive symptoms than those who did not meet the guidelines. In our study, t-tests revealed significant differences in BDI scores between those who engaged in optimal levels of LTPA compared to those who did not in RESP (not optimal=6.86, optimal=4.38; $p$=0.026); however, these differences were no longer significant in the main analyses. The Loprinzi study (2013) reported that 45% of their sample met the PA guidelines, while in our study, only 17% in PAL and 8% in RESP met the guidelines. It is possible that the low numbers in our study may have decreased sensitivity of our analyses. However, such suppositions need to be formally tested. Overall, while the Loprinzi study provided valuable information regarding the association between physical activity and depressive symptoms in a respiratory disease population, to our knowledge, our study is the first to report the cross-sectional relationship between LTPA and depressive symptoms specifically in adults with asthma.

While there was a significant association between engaging in any LTPA and depressive symptoms in the RESP cohort when taking age, sex and BMI into account, the association lost significance when asthma control and ICS prescription were added as covariates. In the last five decades, studies have shown an association between ICS and depressive symptoms (Bonala et al., 2003; Naber, Sand, & Heigl, 1996; Smyllie & Connolly, 1968; Vanelle, Aubin, & Michel, 1990; Wada, Yamada, Suzuki, Lee, & Kuroda, 2000). Indeed, there has been numerous studies suggesting a dose-response effect of ICS on depressive symptoms, with long-term ICS therapy associated with more chances of developing depressive symptoms (Brown & Suppes, 1998; Warrington & Bostwick, 2006). It has been suggested that long-term exposure to corticosteroids may exert its effect through modification in hypothalamus-pituitary-adrenal (HPA) functioning including glucocorticoid resistance and reductions in serotonin levels (Pretorius, 2004). Glucocorticoid is a class of corticosteroids that contributes to the reduction of inflammation, which is associated with both depression and asthma (Rhen & Cidlowski, 2005). Thus, it is possible that some asthma patients who are prescribed larger amounts of ICS may become glucocorticoid resistant over time and may experience a reduction in serotonin levels, which may facilitate the apparition of depressive symptoms. However, it should be noted that in the current study, it was not possible to assess participants' adherence to medication, and thus it is not possible to know if the total ICS dose prescribed was actually taken. Similarly, poor asthma control has been associated with different psychological disorders including panic attacks, anxiety, and depression (Di Marco et al., 2014; Lavoie et al., 2006; Merghani & Alawad, 2017; Strine et al., 2008). A recent study assessed the long-term predictors of anxiety and depression in asthma patients found that asthma control and lung function were predictors of persistent depression over time (Labor et al., 2017). Poor asthma control may be conceptualized as an important stressor, which may negatively impact asthma symptoms and result in increased symptoms of depression (Merghani & Alawad, 2017).

Mediation analyses revealed that the effect of engaging in any LTPA on depressive symptoms was mediated by asthma control. As mentioned previously, exercise has been shown to improve asthma control (Toennesen et al., 2018; Wanrooij et al., 2014), while improved asthma control has been associated with lower levels of depression (Merghani & Alawad, 2017). Our results are

in line with the literature and add to it by suggesting that asthma control mediates the association between exercise and depressive symptoms. Another possible explanation may be the fact that asthma patients with worse asthma control are at greater risk of having an exacerbation and may avoid situations and activities, such as exercise, which could trigger an exacerbation (American Academy of Allergy, 2017; Disabella, Sherman, & DiNubile, 1998). Exercise-induced bronchoconstriction (EIB) may occur when an individual experiences asthma symptoms while exercising, such as wheezing and shortness of breath, and is often considered to be an important reason for restricting or avoiding sports and activity (American Academy of Allergy, 2017). The fear of exacerbation, real or perceived, may result in a decrease in physical conditioning that, in turn, can increase the risk of exacerbation and so on. It is possible that participants who did not engage in any LTPA limited their physical activity because of poor asthma control for the reasons above, which in turn lead to depressive symptoms. Due to the cross-sectional nature of this study, it is also possible that people with high levels of depressive symptoms due to their worse asthma control, which in turn may lead them to limit or avoid engaging in any LTPA in order to avoid exacerbations. This association warrants further investigation. Overall, our study is the first to suggest that asthma control play a role in the relationship between physical activity and depression.

Seasonal variations in LTPA were assessed in regard to depressive symptoms in the PAL cohort. Engaging in any LTPA during summer was associated with lower levels of depressive symptoms, while engaging in any LPTA during winter was not. To our knowledge, no other studies have assessed this relationship. A higher proportion of the participants engaged in LTPA during summer (47%) compared to winter (37%). Studies looking at seasonal effects on physical activity have found that levels of physical activity were at the highest in spring and summer and tended to decrease during winter (Tucker & Gilliland, 2007). This could be partially attributed to shorter days and adverse weather conditions that are more prominent during winter, thus summer may offer more opportunities to be physically active. Another potential explanation may be that adults with asthma take advantage of the summer, since there are lower risks of getting asthma exacerbations, as opposed to winter (Kippelen & Anderson). Moreover, winter has been shown to be associated with higher levels of depression (Harmatz et al., 2000) and more hospital admissions for depression than during the summer (Suhail & Cochrane, 1998). It is not clear how

engaging in any LTPA during summer may be associated with a decrease in depressive symptoms in adults with asthma; however, our results do suggest that there might be an association, which should be further investigated.

Additional analyses performed in participants with moderate to severe depressive symptoms (BDI≥12) revealed that among participants with a BDI score ≥12 in RESP, those who engaged in any LTPA had fewer depressive symptoms compared to those who did not, resulting in a reduction of 3 points in BDI score (table 3.4). In comparison, engaging in any LTPA in the PAL sample resulted in a reduction of 1.7 points in BDI score. Additionally, those who engaged in any vigorous levels of LTPA had fewer depressive symptoms compared to those who did not engaged in any vigorous levels of LTPA in the merged cohort (see Appendix G). These results are similar to those found by previous studies which have reported an inverse relationship between vigorous physical activity and depressive symptoms in healthy women and older individuals (Lampinen, Heikkinen, & Ruoppila, 2000; Wise, Adams-Campbell, Palmer, & Rosenberg, 2006). To our knowledge, our study is the first to suggest that engaging in LTPA, especially of vigorous intensity, may be effective in adults with asthma and higher levels of depression. Future research in asthma patients is needed to investigate the intensity-response to physical activity in patients clinically diagnosed with MDD.

One interesting finding was the difference in results across the 2 cohorts. As a whole, the PAL study did not yield any significant associations. In general, the results in PAL were in the same direction as the ones found in RESP, but of a lesser magnitude. Additionally, asthma control was worse and ICS dosage higher in the RESP cohort compared to PAL, while levels of LTPA and depressive symptoms were higher in PAL. Given the findings regarding the role of asthma control and ICS, it is possible that these differences might explain, in part, the discrepancy between the two cohorts. Moreover, there was a statistical difference between the two cohorts in regard to depression, with PAL participants reporting higher prevalence of mood disorders than RESP participants (20% vs 8%) as well as higher BDI scores (8.3 vs 6.7). It should be noted that participants in PAL were sent the BDI by mail, while participants in RESP were asked to answer the BDI questions verbally in a face-to-face interview. Studies have shown that participants who fill out questionnaires on their own may be more likely to reveal more personal and sensitive

information than participants who answer the same questions in a face-to-face or telephone interviews (Bowling, 2005). However, both cohorts also completed a face-to-face interview assessing mood disorders and results show consistency of the results with respective BDI results, thus it is unlikely that these account for the differences between the two cohorts in term of depression scores. In addition, it is worth noting that while PAL participants had a higher prevalence of mood disorder and higher BDI scores, there were no statistical differences between those who engaged in any LTPA and those who did not within the PAL cohort. This may explain why we were not able to find significant associations between LTPA and depressive symptoms in PAL.

*Limitations*

This study has some limitations. First, LTPA and depressive symptoms were both self-reported using questionnaires. However, BDI has been shown to be a valid and reliable measure of depressive symptomatology (Subica et al., 2014), while the leisure time physical activity questionnaires have been shown to be consistent with other valid and reliable measures of physical activity (Amireault & Godin, 2015; Camões, Severo, Santos, Barros, & Lopes, 2010). Second, the current study was a sub-analysis of pre-existing data; both PAL and RESP did not aim at recruiting participants with depression. Thus, on average, participants in both cohorts showed very low levels of depressive symptoms, within normal range (BDI scores between 0 and 12) which may have resulted in a floor effect. Third, the current study analyzed cohorts with cross-sectional data. Therefore, it is not possible to know the directionality of the association between LTPA and depressive symptoms. Indeed, while we assessed whether engaging in LTPA was associated with lower depressive symptoms, it is also possible that people with lower levels of depressive symptoms are more likely to engage in LTPA. Indeed, depression has been shown to be a risk factor for the development of a sedentary lifestyle and a decrease in physical activity levels (Roshanaei-Moghaddam, Katon, & Russo, 2009; Teychenne, Abbott, Lamb, Rosenbaum, & Ball, 2017). However, randomized controlled trials (RCTs) have found that the regular practice of moderate exercise results in a significant reduction in depressive symptoms in adults with asthma compared to those who do not exercise (Gonçalves et al., 2008; Mendes et al., 2010; Turner et al., 2011). While it is not possible to know whether LTPA affects depressive symptoms or if it is the other way around in the current study, the results are in line with the literature

which suggest engaging in physical activity may reduce levels of depressive symptoms.

*Strengths*

This study was conducted using two well characterized and large samples of patients with objectively-defined physician-diagnosed asthma. In addition, we measured and adjusted for a range of asthma variables that are important in the clinical management of the disease (i.e., asthma control and prescribed ICS dosage). Finally, this study also appears to be the first to have assessed the cross-sectional association between LTPA and depressive symptoms, as well as the role of seasonal patterns and LTPA intensities in adults with asthma.

*Clinical implications*

A better understanding of the association between LTPA and depressive symptoms in adult patients with asthma may have important clinical implications. For example, the current study provides evidence that patients who exhibit depressive symptoms may improve by engaging in any LTPA. This information would be important in the development of PA interventions for this population (Czajkowski et al., 2015). However, the potential to prescribe or recommend PA to treat depression in patients with asthma may be dependent of the patient's ICS dosage and asthma control level.

**Conclusion**

In summary, physical activity was associated with lower levels of depressive symptoms in two large tertiary-care samples of adults with asthma, although asthma control and ICS dose may play a role in the association. Furthermore, it would seem that vigorous physical activity was strongly associated with lower levels of depressive symptoms. Future studies should examine the potential mechanistic role of asthma control and ICS in the relationship between physical activity and depression in asthma patients. Finally, these results should be replicated in a longitudinal or intervention setting using asthma patients with high depressive symptoms or MDD in order to better understand the causal pathway and determine the minimal dose of physical activity required to render important changes in depressive symptoms.

# GENERAL DISCUSSION

This chapter summaries the findings from one systematic review and from an original research study undertaken in this thesis. Further, the importance of translating these findings into practice is addressed and suggestions for future research and in this area of enquiry as well as clinical implications are provided. The work conducted in this thesis was designed to address gaps within the research relating to the role of exercise to improve depression in people living with a NCD, particularly asthma.

## Summary of findings

In chapter 2, the beneficial effect of aerobic exercise interventions on depressive symptoms in people living with a NCD compared to usual care was investigated. The results suggest that aerobic exercise is efficacious in reducing depressive symptoms in people living with a NCD, especially in cardiovascular diseases and cancer. Further, the results provided preliminary evidence that people living with a NCD may not need to meet the current physical activity guidelines as proposed by NICE for individuals with NCDs (The National Institute for Health and Care Excellence, 2010) to see a benefit from an aerobic exercise intervention on depressive symptoms. Overall, the results of the systematic review and meta-analysis suggest that simply engaging in aerobic exercise may be enough to reduce depressive symptoms (The National Institute for Health and Care Excellence, 2010). Some limitations were noted, including the lack of homogeneity across studies, low number of included studies in respiratory diseases and in type 2 diabetes (T2D), and lack of studies including clinically depressed patients. Future research should be performed to validate these findings in a clinically depressed population living with a NCD and to determine whether aerobic exercise interventions are effective in respiratory diseases and T2D.

In chapter 3, the focus was narrowed to a group with a specific NCD – asthma. Adults with asthma were chosen given the lack of studies in this population about the relationship of aerobic exercise and depressive symptoms, as well as for practicality since data for this population was available in my research laboratory. This study was a cross-sectional examination performed to examine the association between leisure time physical activity (LTPA), a proxy of aerobic

exercise, and depressive symptoms in adults with asthma. This secondary data analysis included a total of 953 participants from two different databases (PAL and RESP) were analyzed. Findings revealed that there was a negative association between LTPA and depressive symptoms, with there being a statistically significant difference in those doing vs. not doing any LTPA. However, the relationship was no longer statistically significant when asthma control and ICS dosage were taken in account, a novel finding, given that none of the existing studies assessing the relationship, including intervention studies, had statistically adjusted or controlled for them. Further analyses revealed that asthma control mediated the relationship between LTPA and depressive symptoms. Finally, optimal LTPA was not statistically significantly related to depressive symptoms in adults with asthma; however, engaging in vigorous LTPA was associated with lower depressive symptoms in participants with high levels of depressive symptoms. Suggestions for future research recommended that the impact of asthma control on the association between aerobic exercise and depressive symptoms should be examined more closely. Future research should try to replicate the study goals and hypotheses in a longitudinal or intervention setting using clinically depressed asthma patients.

**Conclusion based on findings**

Taken together, the collective results from chapters 2 and 3 lend evidence to the notion that engaging in aerobic exercise is associated with a decrease in levels of depressive symptoms in adults living with a NCD.

*Effect of aerobic exercise on depressive symptoms in asthma population*

Findings from both chapters are consistent in showing a relationship between aerobic exercise and depressive symptoms in adults with asthma, both cross-sectionally (chapter 3) and using interventions (chapter 2). Two studies using asthma patients were included in the systematic review (chapter 2), although only one was included in the meta-analysis; thus it was not possible to get a pooled effect size (Gonçalves et al., 2008; Mendes et al., 2010). Overall, both studies found a beneficial effect of aerobic exercise on depressive symptoms. The results of the cross-sectional study in chapter 3 revealed an association between engaging in any LTPA and lower depressive symptoms in a large asthma cohort, adding to the previous findings from chapter 2. Taken together, the results are consistent with the body of evidence accumulated in healthy

population (Bernard et al., 2015; Cooney et al., 2013; De Mello et al., 2013) and in generally chronically ill populations (Herring et al., 2012; Stevinson et al., 2009), and suggest that exercising may be beneficial in reducing depressive symptoms in adults with asthma.

*Optimal physical activity and depressive symptoms*

The results from chapter 3 reinforces the theory elaborated in chapter 2, which states that engaging in some aerobic exercise may be sufficient in reducing depressive symptoms. This is contrary to the recommendations of the NICE guideline for treating depression in chronic disorders, which suggest that patients engage in a 10 to 14 weeks exercise intervention, consisting of two to three sessions per week, and for 45 to 60 minutes per session (The National Institute for Health Care Excellence, 2009). The NICE recommendations are similar to those of current physical activity guidelines (i.e., 150 minutes of moderate-to vigorous aerobic exercise accumulated over a week), which have been shown to be associated with health benefits (Tremblay et al., 2011). While it has been shown that meeting the physical activity guidelines is beneficial for health (Lee & Paffenbarger Jr, 2000; World Health Organization, 2010), it is possible that simply engaging in some form of exercise might be enough for someone with depressive symptoms to feel better (Warburton & Bredin, 2016).

As mentioned previously, the antidepressant mechanism of exercise is still unclear. However, exercise is associated with several positive psychological benefits including increased self-esteem, sense of control, feeling of success, increased sense of independence, and also the sense of belonging (Knapen et al., 2015). However, to date, there is no consensus regarding the duration, frequency, and intensity of exercise that has the best effect in reducing depressive symptoms. In line with current findings, both low and high levels of exercise have shown an antidepressant effect (Nyströmet al., 2015).

**Limitations of this thesis**

Several study limitations have been described in chapters 2 and 3. This section highlights some of the main thesis limitations, which are often common to depression research.

*Measurement of depression*

Identification of depression symptoms were based on self-report screening tools in the studies included both in chapters 2 and 3. A limitation of using self-report tools to assess depression in NCD populations is that the results can be complicated by the overlap of somatic symptoms of depression (e.g., changes in sleep, weight, and energy) and symptoms of NCDs, which may artificially inflate depressive scores in these population (Cusin, Yang, Yeung, & Fava, 2010). Most studies included in the systematic review (chapter 2) used questionnaires that suffer from this limitation, as well as the study in chapter 3, with the use of the Beck Depression Inventory. Some depression measures have been specifically designed to be assessed in a medical setting, like the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) and the Beck Depression Inventory for Primary Care (BDI-PC) (A. T. Beck, Guth, Steer, & Ball, 1997) and may be more suitable. Whichever screening tool is used, a clinical interview is likely to help provide a more specific depression diagnosis and account for multiple causes of symptoms.

Another issue concerns how the depression questionnaire was administered, which, depending on the mode of delivery, can elicit different responses. For example, self-administration of questionnaires has been shown to be associated with participants' willingness to reveal more personal and sensitive information compared to face-to-face or telephone interviews (Bowling, 2005). Most intervention studies in chapter 2 did not specify how the questionnaires were administered, whether the questionnaire was self-administered or administered by a researcher. However, the advantage of a meta-analysis is that by pooling together effect sizes of each included study, we obtain a weighted overall effect size and increase power of our results. In chapter 3, the two cohorts included the study differed in their way of administering the BDI; participants in PAL were sent the BDI by mail and were asked to return it, while participants in RESP answered the BDI questions verbally in an interview conducted by a research assistant. This may explain why participants in PAL had higher levels of depressive symptoms compared to RESP participants, they might have been more likely to share private information. Further, the study in chapter 3 was not initially designed to examine depression as a primary outcome and therefore, the majority of participants in the study had low levels of depressive symptoms which may have confounded the results. Additionally, no studies included in the systematic review (chapter 2) assessed the effect of exercise on clinical depression in NCDs. Only a few studies in

NCD populations have been specifically geared towards assessing the impact or association of aerobic exercise in clinically depressed patients. For example, Blumenthal and colleagues (2013) compared the efficacy of aerobic exercise to antidepressants (e.g., sertraline) as well as placebo in coronary heart disease patients with major depressive disorder (MDD) (Blumenthal, Sherwood, et al., 2012). The authors found that both exercise and sertraline were comparable in reducing depressive symptoms and both were superior compared to placebo group. Further research is required to explore the role of exercise for patients with clinical depression and a NCD.

*Randomized controlled trial in asthma patients*

This thesis fails to include a randomized controlled trial (RCT) in asthma patients, which could have reinforced the findings from chapter 2 and 3. Due to time constraints, it was not possible to include one. However, previous RCTs which have assessed the efficacy of exercise on depressive symptoms have revealed a positive effect of exercise on reducing depressive symptoms in adults with asthma (Gonçalves et al., 2008; Mendes et al., 2010; Turner et al., 2011). While the results of these studies are encouraging, none of the studies included patients with clinical depression. This issue was also noted in chapter 2; thus, a RCT in depressed patients with asthma would have been an interesting addition to this thesis.

**Recommendations for practitioners**

The examination of the role of aerobic exercise on depressive symptoms has important implications for the treatment of patients living with a NCD and depression. For example, practitioners can develop or promote interventions by providing opportunities for movement. Psychologists can also be instrumental in promoting change through cost-effective innovations that increase health and well-being and reduce depression.

*Exercise Promotion*

Promoting exercise and physical fitness may be just as important as psychotherapy or antidepressants in treating NCD patients with depression. Indeed, along with improved mood state, exercise is also the only treatment available that can reduce or delay the onset of secondary co-morbidities, whether they are disease-specific or not (Loprinzi & Davis, 2016). This suggest

that even if no antidepressant effects result from exercising, it is likely that other beneficial physiological outcomes will arise. Therefore, clinical psychologists and general practitioners should encourage individuals who consult them to engage in exercise.

Some of the most prevalent features of depression are fatigue, inertia, and decreased interest to engage in things previously thought of as enjoyable, which in turn leads to increased withdrawal and a more inactive lifestyle. One of the most promising ways to improve depressive symptoms is to break the pattern by reintroducing enjoyable activities in life (Dimidjian, Barrera, Martell, Muñoz, & Lewinsohn, 2011). Besides exercise, behavioural activation (BA) has also been shown to be efficacious in reducing depressive symptoms. BA is a structured brief psychotherapy which aims at reintroducing positive reinforcers in patients' daily life (Dimidjian et al, 2011). The main goals of BA are to: 1) increase activities that are associated with a sense of value to the client; 2) reduce activities that maintain or increase risk of depression; and 3) solve problems and change behaviours that limit the access to a sense of value of the client. Although BA strategies can be seen in other therapies, such as CBT and mindfulness (Dimidjian & Davis, 2009), BA has become a well-established stand-alone treatment for depression. The efficacy of BA is comparable to CBT and anti-depressants (Cuijpers, van Straten, & Warmerdam, 2007; Mazzucchelli, Kane, & Rees, 2009). Exercise and BA have been shown to offer similar benefit for depression. It is also not rare for a clinical psychologist who uses BA strategies to suggest to a client to engage in some form of exercise. However, it is not always the case since the target may not always be related to physical activity. Given that both exercise and BA have a similar target and have both been shown to help with depressive symptoms, and given the added health benefits of aerobic exercise in NCDs, BA strategies could be used to encourage clients with NCD to be reintroduce exercise in their daily routine.

Working with people who, for the most part, do not engage enough in exercise can be a challenge. However, practitioners can be instrumental in the promotion of exercise. Studies have shown that adherence and maintenance of physical activities may be increased by the use of motivational interviewing (O'Halloran et al., 2014), narratives (Falzon, Radel, Cantor, & d'Arripe-Longueville, 2015), self-efficacy promotion, social modeling, and support (McAuley et al., 2007). Additionally, the use of self-regulatory strategies (i.e., use of pedometers,

accelerometers) and self-promotion can increase the level of motivation in clients (Conn, Hafdahl, Brown, & Brown, 2008; Heath et al., 2012).

*Exercise preference*

In this thesis, the type of exercise was mainly aerobic. However, there wasn't a focus on any specific type of aerobic exercise (e.g., walking, treadmill); thus, the results may apply to diverse type of aerobic exercises. Given that aerobic exercise has the potential to be flexible and accessible, and can be conducted in a group setting or alone, with both shown to have positive effects on depressive symptoms (Legrand & Heuze, 2007), practitioners could play a role in guiding patients in finding an exercise program that may correspond to their preferences and specific needs.

*Exercise as an alternative treatment for depression*

While this thesis did not focus on clinical depression, the results suggest that aerobic exercise is a relevant way to help relieve depressive symptoms in people living with a NCD. Additionally, results from chapter 3 showed that the effect of LTPA on depressive symptoms was strong in patients who had high levels of depressive symptoms, a finding that has been also found in intervention studies using chronically ill populations (Herring et al., 2012). Therefore, it could be worth considering aerobic exercise as a potential adjuvant to traditional therapies for depression or possibly even as an alternative. Indeed, exercise may benefit people who choose not to use traditional interventions, such as cognitive behavioural intervention and antidepressants, either because of a previous failed attempt or because of a perceived negative social stigma associated with these methods. For example, less than 50% of people who are prescribed an antidepressant are adherent in the long term and less than 20% use it as prescribed (Hunot, Horne, Leese, & Churchill, 2007). Moreover, stigma, the belief that most people will have a negative attitude towards the people who have a mental illness and/or use mental health service, has a negative impact on patients seeking care (Cooper-Patrick et al., 1997), medication adherence (Hodgkin, Volpe-Vartanian, & Alegría, 2007), and contribute to treatments dropouts (Bados, Balaguer, & Saldaña, 2007; Sirey et al., 2001). Therefore, using exercise as an alternative therapeutic option for depression would provide these individuals with access to acceptable treatment.

**Recommendations for future research**

Results from this thesis provide some basis for further investigation of the impact of aerobic exercise on depression in people living with a NCD. For example, the cross-sectional study which examined the association between leisure-time physical activity and depressive symptoms in asthma patients (chapter 3) provided encouraging results that warrant further investigation and validation in longitudinal studies or large randomised trials in the same population. Furthermore, given that neither chapters included clinical population, and upon further research, there doesn't seem to be many intervention studies which have assessed the effect of aerobic exercise on depression in a clinical sample of adults living with a NCD, future research on depression in NCD should focus on patients with clinical depression.

The majority of studies in chapter 2 were of short duration (1-3 months) and long-term follow-up data (>12 months) was lacking in the majority of interventions, thus failing to evaluate whether aerobic exercise was sustained over time and whether levels depressive symptoms remained stable. Isaksen and colleagues (2016) looked at the effect of an aerobic exercise intervention on depressive symptoms in patients with heart failure and included a 2-years follow-up (Isaksen et al., 2016). The authors reported that the levels of depressive symptoms after 2 years were no longer different from baseline in the intervention group, while there was a significant increase in the control group. Future intervention studies should systematically include a long-term follow-up and subsequently report the findings in order to better assess the long-term effects. Additionally, the dose-response relationships between aerobic exercise and depressive symptoms have yet to be established in patients with NCDs. While previous studies have suggested that moderate to vigorous intensity was associated with lower depressive symptoms, compared to low intensity, in people with chronic illnesses (Herring et al., 2012), it was not the case in either studies in the current thesis, which both suggested that engaging in some levels of aerobic exercise may be enough. More studies need to investigate the dose-response association, as the results may later guide exercise interventions

Overall, there is still much work to be done and many unanswered questions that remain about the relationship between aerobic exercise and depression in people living with a NCD. Since

depression can be debilitating and may worsen NCD outcomes, it is imperative to further investigate the effect of aerobic exercise on depression in people living with a NCD.

## REFERENCES


Abramson, L. Y., Metalsky, G. I., & Alloy, L. B. (1989). Hopelessness depression: A theory-based subtype of depression. *Psychological Review, 96,* 358-372.

Abramson, L. Y., Alloy, L. B., Hogan, M. E., Whitehouse, W. G., Donovan, P., Rose, D., Panzarella, C., & Raniere, D. (1999). Cognitive vulnerability to depression: Theory and evidence. *Journal of Cognitive Psychotherapy*, *13*, 5–20.

Ahmedani, B. K., Peterson, E. L., Wells, K. E., & Williams, L. K. (2013). Examining the relationship between depression and asthma exacerbations in a prospective follow-up study. *Psychosomatic Medicine, 75*(3), 305.

Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clinical Psychology Review*, *30*(2), 217–237.

Alesci, S., Martinez, P. E., Kelkar, S., Ilias, I., Ronsaville, D.S., … Gold, P. W. (2005). Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. *Journal of Clinical Endocrinology & Metabolism*, *90*, 2522–2530

Ali, S., Stone, M., Peters, J., Davies, M., & Khunti, K. (2006). The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabetic Medicine, 23*(11), 1165-1173.

Almagro, P., Calbo, E., Ochoa de Echaguïen, A., Barreiro, B., Quintana, S., Heredia, J. L., & Garau, J. (2002). Mortality After Hospitalization for COPD. *Chest, 121*(5), 1441-1448. doi:https://doi.org/10.1378/chest.121.5.1441

Alosco, M. L., Spitznagel, M. B., Miller, L., Raz, N., Cohen, R., Sweet, L. H., . . . Hughes, J. (2012). Depression is associated with reduced physical activity in persons with heart failure. *Health Psychology, 31*(6), 754.

American Academy of Allergy, A. I. (2017). *Exercise-Induced Bronchoconstriction (EIB)*. Retrieved from http://www.aaaai.org/conditions-and-treatments/asthma

American College of Sports Medicine. (1998). American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. (0195-9131 (Print)).

American Psychiatric, A. (2010). American Psychiatric Association Practice Guidelines for the Treatment of Patients With Major Depressive Disorder. *Practice, 150*(October), 1-28. doi:10.1176/appi.books.9780890423387.654001

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed, text rev ed.). Washington, DC: Author.

American Psychiatric Association. (2010). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, D.C.: Author.

Amireault, S., & Godin, G. (2015). The Godin-Shephard leisure-time physical activity questionnaire: validity evidence supporting its use for classifying healthy adults into active and insufficiently active categories. *Perceptual and Motor Skills, 120*(2), 604-622.

Anand, P., Kunnumakara, A. B., Sundaram, C., Harikumar, K. B., Tharakan, S. T., Lai, O. S., . . . Aggarwal, B. B. (2008). Cancer is a Preventable Disease that Requires Major Lifestyle Changes. *Pharmaceutical Research, 25*(9), 2097-2116. doi:10.1007/s11095-008-9661-9

Annesi, J. J. (2004). Relationship between Self-Efficacy and Changes in Rated Tension and Depression for 9- to 12-Yr.-Old Children Enrolled in a 12-Wk. after-School Physical Activity Program. *Perceptual and Motor Skills*, *99*(1), 191–194.

Antó, J. M., Vermeire, P., Vestbo, J., & Sunyer, J. (2001). Epidemiology of chronic obstructive pulmonary disease. *European Respiratory Journal, 17*(5), 982.

Asbury, E. A., Slattery, C., Grant, A., Evans, L., Barbir, M., & Collins, P. (2008). Cardiac rehabilitation for the treatment of women with chest pain and normal coronary arteries. *Menopause, 15*(3), 454-460. doi:http://dx.doi.org/10.1097/gme.0b013e31815982eb

Asbury, E. A., Webb, C. M., Probert, H., Wright, C., Barbir, M., Fox, K., & Collins, P. (2012). Cardiac Rehabilitation to Improve Physical Functioning in Refractory Angina: A Pilot Study. *Cardiology, 122*(3), 170-177. doi:10.1159/000339224

Austin, A. W., Gordon, J. L., Lavoie, K. L., Arsenault, A., Dasgupta, K., & Bacon, S. L. (2014). Differential association of insulin resistance with cognitive and somatic symptoms of depression. *Diabetic Medicine, 31*(8), 994-1000.

Avallone, K. M., & McLeish, A. C. (2013). Asthma and aerobic exercise: a review of the empirical literature. *Journal of Asthma, 50*(2), 109-116.

Bacon, S. L., Lemiere, C., Moullec, G., Ninot, G., Pepin, V., & Lavoie, K. L. (2015). Association between patterns of leisure time physical activity and asthma control in adult patients. *BMJ open respiratory research, 2*, e000083. doi:10.1136/bmjresp-2015-000083

Bados, A., Balaguer, G., & Saldaña, C. (2007). The efficacy of cognitive–behavioral therapy and the problem of drop-out. *Journal of Clinical Psychology, 63*(6), 585-592. doi:10.1002/jclp.20368

Baillet, A., Zeboulon, N., Gossec, L., Combescure, C., Bodin, L.-A., Juvin, R., . . . Gaudin, P. (2010). Efficacy of cardiorespiratory aerobic exercise in rheumatoid arthritis: Meta-analysis of randomized controlled trials. *Arthritis Care & Research, 62*(7), 984-992. doi:10.1002/acr.20146

Balducci, S., Zanuso, S., Cardelli, P., Salvi, L., … Pugliese, G. (2012). Effect of high- versus low-intensity super-vised aerobic and resistance training on modifiable cardiovascular risk factors in type 2 diabetes; the Italian Diabetes and Exercise Study (IDES). *PLoS ONE*, 7:e49297.

Balshem, H., Helfand, M., Schünemann, H. J., Oxman, A. D., Kunz, R., Brozek, J., . . . Guyatt, G. H. (2011). GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol, 64*(4), 401-406. doi:10.1016/j.jclinepi.2010.07.015

Bandura, A. (1997). *Self-efficacy: The exercise of control*. New York, NY: W.H. Freeman and Company.

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosomatic Medicine, 66*(6), 802-813. doi:10.1097/01.psy.0000146332.53619.b2

Beck, A. T. (1976). *Cognitive Therapy and the Emotional Disorders*. New York, NY : Meridian.

Beck, A. T., Guth, D., Steer, R. A., & Ball, R. (1997). Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Behaviour Research and Therapy, 35*(8), 785-791. doi:https://doi.org/10.1016/S0005-7967(97)00025-9

Beck, A. T., Steer, R.A., & Brown, G.K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Bedard, G., Hawley, P., Zhang, L., Slaven, M., Gagnon, P., Bisland, S., . . . Chow, E. (2013). A survey of Canadian cancer patients' perspectives on the characteristics and treatment of

breakthrough pain. *Supportive Care in Cancer, 21*(9), 2557-2563. doi:10.1007/s00520-013-1817-4

Bernard, P., Ninot, G., Bernard, P. L., Picot, M. C., Jaussent, A., Tallon, G., & Blain, H. (2015). Effects of a six-month walking intervention on depression in inactive post-menopausal women: a randomized controlled trial. *Aging & Mental Health, 19*(6), 485-492. doi:10.1080/13607863.2014.948806

Biostat. (2015). Comprehensive Meta-Analysis software. Englewood: Englewood, New Jersey.

Blake H. (2012). Physical activity and exercise in the treatment of depression. *Frontiers in psychiatry, 3*, 106. doi:10.3389/fpsyt.2012.00106

Blumenthal, J. A., Babyak, M. A., Doraiswamy, P. M., Watkins, L., Hoffman, B. M., Barbour, K. A., . . . others. (2007). Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosomatic Medicine, 69*(7), 587-587.

Blumenthal, J. A., Babyak, M. A., O'Connor, C., Keteyian, S., Landzberg, J., Howlett, J., . . . Whellan, D. J. (2012). Effects of exercise training on depressive symptoms in patients with chronic heart failure: the HF-ACTION randomized trial. *JAMA, 308*(5), 465-474. doi:10.1001/jama.2012.8720

Blumenthal, J. A., Lett, H. S., Babyak, M. A., White, W., Smith, P. K., Mark, D. B., . . . Newman, M. F. (2003). Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet, 362*(9384), 604-609. doi:10.1016/S0140-6736(03)14190-6

Blumenthal, J. A., Sherwood, A., Babyak, M. A., Watkins, L. L., Smith, P. J., Hoffman, B. M., . . . Hinderliter, A. L. (2012). Exercise and Pharmacological Treatment of Depressive Symptoms in Patients With Coronary Heart Disease: Results From the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) Study. *Journal of the American College of Cardiology, 60*(12), 1053-1063. doi:https://doi.org/10.1016/j.jacc.2012.04.040

Blumenthal, J. A., Sherwood, a., Babyak, M. a., Watkins, L. L., Waugh, R., Georgiades, a., . . . Hinderliter, a. (2005a). Effects of Exercise and Stress Management Training on Markers of Cardiovascular Risk in Patients With Ischemic Heart Disease. *Journal of Cardiopulmonary Rehabilitation, 25*(4), 235-235. doi:10.1097/00008483-200507000-00012

Blumenthal, J. A., Sherwood, A., Babyak, M. A., Watkins, L. L., Waugh, R., Georgiades, A., . . . Hinderliter, A. (2005b). Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: a randomized controlled trial. *JAMA, 293*(13), 1626-1634. doi:10.1001/jama.293.13.1626

Bodin, T., & Martinsen, E. W. (2004). Mood and self-efficacy during acute exercise in clinical depression. A randomized, controlled study. *Journal of Sport & Exercise Psychology*, *26*, 623–633.

Bonala, S. B., Pina, D., Silverman, B. A., Amara, S., Bassett, C. W., & Schneider, A. T. (2003). Asthma severity, psychiatric morbidity, and quality of life: correlation with inhaled corticosteroid dose. *The Journal of asthma : official journal of the Association for the Care of Asthma, 40*(6), 691-699.

Bond, S., Stonebridge, C., & Theriault, L. (2010). *The Canadian Heart Health Strategy: Risk Factors and Future Cost Implications*. Retrieved from https://sencanada.ca/content/sen/committee/412/SOCI/Briefs/2015-05-07ReportCdnCardiovascularSociety-AddInfoConferenceBoardofCanada_e.pdf

Booth, F. W., Roberts, C. K., & Laye, M. J. (2012). Lack of exercise is a major cause of chronic diseases. *Comprehensive Physiology*, *2*(2), 1143-1211.

Bowling, A. (2005). Mode of questionnaire administration can have serious effects on data quality. *Journal of Public Health, 27*(3), 281-291. doi:10.1093/pubmed/fdi031

Brown, G. W., & Harris, T. 0. (1978). *Social origins of depression: A study of of psychiatric disorder in women*. New York: Free Press.

Brown, E. S., & Suppes, T. (1998). Mood Symptoms during Corticosteroid Therapy: A Review. *Harvard Review of Psychiatry, 5*(5), 239-246. doi:10.3109/10673229809000307

Brown, G. W., Harris, T. 0., & Peto, J. (1973). Lifeevents and psychiatric disorder: 2. Nature of causal link. *Psychological Medicine*, *3*, 159-176.

Brown, J. C., Huedo-Medina, T. B., Pescatello, L. S., Ryan, S. M., Pescatello, S. M., Moker, E., . . . Johnson, B. T. (2012). The efficacy of exercise in reducing depressive symptoms among cancer survivors: a meta-analysis. *PLoS One, 7*(1), e30955-e30955. doi:10.1371/journal.pone.0030955

Brummett, B. H., Babyak, M. A., Siegler, I. C., Mark, D. B., Williams, R. B., & Barefoot, J. C. (2003). Effect of smoking and sedentary behavior on the association between depressive symptoms and mortality from coronary heart disease. *The American Journal of Cardiology, 92*(5), 529-532. doi:https://doi.org/10.1016/S0002-9149(03)00719-7

Burr, J. F., Davidson, W., Shephard, R. J., & Eves, N. (2012). Physical activity in chronic respiratory conditions: Assessing risks for physical activity clearance and prescription. *Canadian Family Physician, 58*(7), 761-764.

Byrne, a., & Byrne, D. G. (1993). The effect of exercise on depression, anxiety and other mood states: A review. *Journal of Psychosomatic Research, 37*(6), 565-574. doi:10.1016/0022-3999(93)90050-P

Cadmus, L. A., Salovey, P., Yu, H., Chung, G., Kasl, S., & Irwin, M. L. (2009). Exercise and quality of life during and after treatment for breast cancer: results of two randomized controlled trials. *Psycho-Oncology, 18*(4), 343-352. doi:10.1002/pon.1525

Camões, M., Severo, M., Santos, A. C., Barros, H., & Lopes, C. (2010). Testing an adaptation of the EPIC physical activity questionnaire in Portuguese adults: a validation study that assesses the seasonal bias of self-report. *Annals of human biology, 37*(2), 186-198.

Canadian Cancer Society's Advisory Committee on Cancer Statistics. (2017). *Canadian Cancer Statistics 2017*. Retrieved from Tonronto, Ontario: http://www.cancer.ca/Canadian-CancerStatistics-2017-EN.pdf

Canadian Institute for Health Information. (2008). *Health indicators 2008*. Retrieved from https://secure.cihi.ca/free_products/HealthIndicators2008_ENGweb.pdf

Canadian Lung Association. (2016). *Asthma Control in Canada Survey*. Retrieved from https://www.lung.ca/news/advocacy-tools/our-publications

Canadian Society for Exercise Physiology. (2011). *Canadian Physical Activity Guidelines for Adults 18-64 years*. Retrieved from http://www.csep.ca/view.asp?ccid=580

Canadian Thoracic Society. (2010). *The Human and Economic Burden of COPD: A Leading Cause of Hospital Admission in Canada*. Retrieved from https://www.lung.ca/news/advocacy-tools/our-publications

Canadian Thoracic Society. (n.d.). *Facts about COPD*. Retrieved from https://cts.lung.ca/cts-sct/pdf/COPDFactSheet_E.pdf

Carek, P. J., Laibstain, S. E., & Carek, S. M. (2011). Exercise for the Treatment of Depression and Anxiety. *The International Journal of Psychiatry in Medicine, 41*(1), 15-28. doi:10.2190/PM.41.1.c

Carson, K. V., Chandratilleke, M. G., Picot, J., Brinn, M. P., Esterman, A. J., & Smith, B. J. (2013). Physical training for asthma. *The Cochrane Library*.

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public health Reports, 100*(2), 126.

Celli, B. R., MacNee, W., Agusti, A., Anzueto, A., Berg, B., Buist, A. S., . . . ZuWallack, R. (2004). Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *European Respiratory Journal, 23*(6), 932.

Chaouloff, F. (1997). Effects of acute physical exercise on central serotonergic systems. *Medicine & Science in Sports & Exercise*, *29*(1), 58–62.

Chen, H. M., Tsai, C. M., Wu, Y. C., Lin, K. C., & Lin, C. C. (2015). Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. *British journal of cancer, 112*(3), 438-445. doi:10.1038/bjc.2014.612

Chrysohoou, C., Tsitsinakis, G., Vogiatzis, I., Cherouveim, E., Antoniou, C., Tsiantilas, a., . . . Stefanadis, C. (2014). High intensity, interval exercise improves quality of life of patients with chronic heart failure: a randomized controlled trial. *Qjm, 107*(1), 25-32. doi:10.1093/qjmed/hct194

Chudyk, A., & Petrella, R. J. (2011). Effects of Exercise on Cardiovascular Risk Factors in Type 2 Diabetes. *Diabetes Care, 34*(5), 1228.

Clark, A. M., Haykowsky, M., Kryworuchko, J., MacClure, T., Scott, J., DesMeules, M., . . . McAlister, F. A. (2010). A meta-analysis of randomized control trials of home-based secondary prevention programs for coronary artery disease. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 17*(3), 261-270.

Clark, C. J., & Cochrane, L. M. (1988). Assessment of work performance in asthma for determination of cardiorespiratory fitness and training capacity. *Thorax, 43*(10), 745-749.

Cohen, J. (1988). Statistical power analysis for the behavioral sciences. Erlbaum. *Hillsdale, NJ*.

Colberg, S. R., & Grieco, C. R. (2009). Exercise in the Treatment and Prevention of Diabetes. *Current Sports Medicine Reports, 8*(4).

Colberg, S. R., Sigal, R. J., Fernhall, B., Regensteiner, J. G., Blissmer, B. J., Rubin, R. R., . . . Braun, B. (2010). Exercise and Type 2 Diabetes: The American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care, 33*(12), e147-e167. doi:10.2337/dc10-9990

Conn, V. S., Hafdahl, A. R., Brown, S. A., & Brown, L. M. (2008). Meta-analysis of patient education interventions to increase physical activity among chronically ill adults. *Patient Education and Counseling, 70*(2), 157-172.

Cooney, G., Dwan, K., & Mead, G. (2014). Exercise for depression. *JAMA, 311*(23), 2432-2433.

Cooney, G. M., Dwan, K., Greig, C. A., Lawlor, D. A., Rimer, J., Waugh, F. R., . . . Mead, G. E. (2013). Exercise for depression. *The Cochrane Database of Systematic Reviews, 9*, CD004366-CD004366. doi:10.1002/14651858.CD004366.pub6

Cooper-Patrick, L., Powe, N. R., Jenckes, M. W., Gonzales, J. J., Levine, D. M., & Ford, D. E. (1997). Identification of Patient Attitudes and Preferences Regarding Treatment of Depression. *Journal of General Internal Medicine, 12*(7), 431-438. doi:10.1046/j.1525-1497.1997.00075.x

Cornelissen, V. A., & Smart, N. A. (2013). Exercise training for blood pressure: a systematic review and meta-analysis. *Journal of the American Heart Association, 2*(1), e004473.

Courneya, K. S., Friedenreich, C. M., Quinney, H. A., Fields, A. L. A., Jones, L. W., & Fairey, A. S. (2003). A randomized trial of exercise and quality of life in colorectal cancer survivors. *European Journal of Cancer Care, 12*(4), 347-357. doi:10.1046/j.1365-2354.2003.00437.x

Courneya, K. S., Katzmarzyk, P. T., & Bacon, E. (2008). Physical activity and obesity in Canadian cancer survivors. *Cancer, 112*(11), 2475-2482. doi:10.1002/cncr.23455

Courneya, K. S., Segal, R. J., Mackey, J. R., Gelmon, K., Reid, R. D., Friedenreich, C. M., . . . McKenzie, D. C. (2007). Effects of Aerobic and Resistance Exercise in Breast Cancer Patients Receiving Adjuvant Chemotherapy: A Multicenter Randomized Controlled Trial. *Journal of Clinical Oncology, 25*(28), 4396-4404. doi:10.1200/JCO.2006.08.2024

Courneya, K. S., Sellar, C. M., Stevinson, C., McNeely, M. L., Peddle, C. J., Friedenreich, C. M., . . . Reiman, T. (2009). Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *Journal of Clinical Oncology, 27*(27), 4605-4612. doi:10.1200/JCO.2008.20.0634

Coventry, P. A., Bower, P., Keyworth, C., Kenning, C., Knopp, J., Garrett, C., . . . Dickens, C. (2013). The effect of complex interventions on depression and anxiety in chronic obstructive pulmonary disease: systematic review and meta-analysis. *PLoS One, 8*(4), e60532-e60532. doi:10.1371/journal.pone.0060532

Coventry, P. A., & Hind, D. (2007). Comprehensive pulmonary rehabilitation for anxiety and depression in adults with chronic obstructive pulmonary disease: Systematic review and meta-analysis. *Journal of Psychosomatic Research, 63*(5), 551-565. doi:10.1016/j.jpsychores.2007.08.002

Craft, L. L. (2005). Exercise and clinical depression: examining two psychological mechanisms. *Psychology of Sport and Exercise*, *6*(2), 151-171.

Craft, L. L., Vaniterson, E. H., Helenowski, I. B., Rademaker, A. W., & Courneya, K. S. (2012). Exercise effects on depressive symptoms in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention, 21*(1), 3-19. doi:10.1158/1055-9965.EPI-11-0634

Cronin-Stubbs, D., de Leon, C. F., Beckett, L. a., Field, T. S., Glynn, R. J., & Evans, D. a. (2000). Six-year effect of depressive symptoms on the course of physical disability in community-living older adults. *Archives of Internal Medicine, 160*(20), 3074-3080. doi:10.1001/archinte.160.20.3074

Cuijpers, P., & Smit, F. (2002). Excess mortality in depression: A meta-analysis of community studies. *Journal of Affective Disorders, 72*(3), 227-236. doi:10.1016/S0165-0327(01)00413-X

Cuijpers, P., van Straten, A., & Warmerdam, L. (2007). Behavioral activation treatments of depression: A meta-analysis. *Clinical Psychology Review, 27*(3), 318-326. doi:https://doi.org/10.1016/j.cpr.2006.11.001

Cusin, C., Yang, H., Yeung, A., & Fava, M. (2010). Rating Scales for Depression. In L. Baer & M. A. Blais (Eds.), *Handbook of Clinical Rating Scales and Assessment in Psychiatry and Mental Health* (pp. 7-35). Totowa, NJ: Humana Press.

Czajkowski, S. M., Powell, L. H., Adler, N., Naar-King, S., Reynolds, K. D., Hunter, C. M., . . . Peterson, J. C. (2015). From ideas to efficacy: the ORBIT model for developing behavioral treatments for chronic diseases. *Health Psychology, 34*(10), 971-982.

Daar, A. S., Singer, P. A., Leah Persad, D., Pramming, S. K., Matthews, D. R., Beaglehole, R., . . . Bell, J. (2007). Grand challenges in chronic non-communicable diseases. *Nature, 450*, 494. doi:10.1038/450494a

Daley, A. J. (2008). Exercise and Depression: A Review of Reviews. *Journal of clinical Psychology in Medical Settings, 15*(2), 140. doi:10.1007/s10880-008-9105-z

Daley, A. J., Crank, H., Saxton, J. M., Mutrie, N., Coleman, R., & Roalfe, A. (2007). Randomized trial of exercise therapy in women treated for breast cancer. *Journal of Clinical Oncology, 25*(13), 1713-1721. doi:10.1200/JCO.2006.09.5083

Dang-Tan, T., Ismaila, A., Zhang, S., Zarotsky, V., & Bernauer, M. (2015). Clinical, humanistic, and economic burden of chronic obstructive pulmonary disease (COPD) in Canada: a systematic review. *BMC Research Notes, 8*(1), 464. doi:10.1186/s13104-015-1427-y

Dantzer, R., Connor, J. C. O., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience*, *9*(1), 46–56.

de Groot, M., Anderson, R., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). Association of depression and diabetes complications: a meta-analysis. *Psychosomatic Medicine, 63*(4), 619-630.

De Mello, M. T., de Aquino Lemos, V., Antunes, H. K. M., Bittencourt, L., Santos-Silva, R., & Tufik, S. (2013). Relationship between physical activity and depression and anxiety symptoms: a population study. *Journal of Affective Disorders, 149*(1), 241-246.

De Moor, M., Beem, A., Stubbe, J., Boomsma, D., & De Geus, E. (2006). Regular exercise, anxiety, depression and personality: a population-based study. *Preventive Medicine, 42*(4), 273-279.

de Voogd, J. N., Wempe, J. B., Postema, K., van Sonderen, E., Ranchor, A. V., Coyne, J. C., & Sanderman, R. (2009). More evidence that depressive symptoms predict mortality in COPD patients: is type D personality an alternative explanation? *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine, 38*(2), 86-93. doi:10.1007/s12160-009-9105-8

Deaton, C., Froelicher, E. S., Wu, L. H., Ho, C., Shishani, K., & Jaarsma, T. (2011). The Global Burden of Cardiovascular Disease. *European Journal of Cardiovascular Nursing, 10*(2_suppl), S5-S13. doi:10.1016/S1474-5151(11)00111-3

Deeks, J. J., Dinnes, J., D'Amico, R., Sowden, A. J., Sakarovitch, C., Song, F., . . . Altman, D. G. (2003). Evaluating non-randomised intervention studies. *Health Technology Assessment, 7*(27), iii-x, 1-173.

Di Marco, F., Terraneo, S., Roggi, M. A., Repossi, A. C., Pellegrino, G. M., Veronelli, A., . . . Centanni, S. (2014). Physical Activity Impairment in Depressed COPD Subjects. *Respiratory Care, 59*(5), 726-734. doi:10.4187/respcare.02848

DiMatteo, M. R., Haskard, K. B., & Williams, S. L. (2007). Health Beliefs, Disease Severity, and Patient Adherence: A Meta-Analysis. *Medical Care, 45*(6).

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine, 160*(14), 2101-2107. doi:10.1001/archinte.160.14.2101

Dimidjian, S., Barrera, M., Martell, C., Muñoz, R. F., & Lewinsohn, P. M. (2011). The Origins and Current Status of Behavioral Activation Treatments for Depression. *Annual Review of Clinical Psychology, 7*(1), 1-38. doi:10.1146/annurev-clinpsy-032210-104535

Dimidjian, S., & Davis, K. J. (2009). Newer variations of cognitive-behavioral therapy: Behavioral activation and mindfulness-based cognitive therapy. *Current Psychiatry Reports, 11*(6), 453. doi:10.1007/s11920-009-0069-y

Disabella, V., Sherman, C., & DiNubile, N. A. (1998). Exercise for asthma patients: little risk, big rewards. *The Physician and Sports Medicine, 26*(6), 75-84.

Disner, S. G., Beevers, C. G., Haigh, E. a P., & Beck, A. T. (2011). Neural mechanisms of the cognitive model o f depression. Nature Reviews. *Neuroscience*, *72*(8), 467-77. doi:10.1038/nm3027

Dodd, M. J., Cho, M. H., Miaskowski, C., Painter, P. L., Paul, S. M., Cooper, B. A., . . . Bank, K. A. (2010). A randomized controlled trial of home-based exercise for cancer-related fatigue in women during and after chemotherapy with or without radiation therapy. *Cancer Nursing, 33*(4), 245-257. doi:10.1097/NCC.0b013e3181ddc58c

Dogra, S., Baker, J., & Ardern, C. I. (2009). The role of physical activity and body mass index in the health care use of adults with asthma. *Annals of Allergy, Asthma & Immunology, 102*(6), 462-468.

Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health, 52*(6), 377-384. doi:10.1136/jech.52.6.377

Dunn, A. L., Trivedi, M. H., Kampert, J. B., Clark, C. G., & Chambliss, H. O. (2005). Exercise treatment for depression: efficacy and dose response. *American Journal of Preventive Medicine, 28*(1), 1-8.

Duval, S., & Tweedie, R. (2000). Trim and fill: a simple funnel-plot--based method of testing and adjusting for publication bias in meta-analysis. *Biometrics, 56*(2), 455-463.

Egede, L. E. (2007). Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. *General Hospital Psychiatry, 29*(5), 409-416.

Egede, L. E., & Hernandez-Tejada, M. A. (2013). Effect of comorbid depression on quality of life in adults with Type 2 diabetes. *Expert Review of Pharmacoeconomics & Outcomes Research, 13*(1), 83-91. doi:10.1586/erp.12.86

Eichenberger, P. A., Diener, S. N., Kofmehl, R., & Spengler, C. M. (2013). Effects of exercise training on airway hyperreactivity in asthma: a systematic review and meta-analysis. *Sports Medicine, 43*(11), 1157-1170.

Emtner, M., Herala, M., & Stålenheim, G. (1996). High-intensity physical training in adults with asthma: a 10-week rehabilitation program. *Chest, 109*(2), 323-330.

Ergun, M., Eyigor, S., Karaca, B., Kisim, A., & Uslu, R. (2013). Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients. *European Journal of Cancer Care, 22*(5), 626-637. doi:10.1111/ecc.12068

Evenson, K. R., Butler, E. N., & Rosamond, W. D. (2014). United States Prevalence of Physical Activity and Sedentary Behavior Among Adults with Cardiovascular Disease. *Journal of Cardiopulmonary Rehabilitation and Prevention, 34*(6), 406-419. doi:10.1097/HCR.0000000000000064

Evidence Prime, I. (2015). GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University. Retrieved from http://gradepro.org

Eyre, H. A., Papps, E., & Baune, B. T. (2013). Treating depression and depression-like behavior with physical activity: An immune perspective. *Frontiers in Psychiatry*, *4*, 1–27.

Falzon, C., Radel, R., Cantor, A., & d'Arripe-Longueville, F. (2015). Understanding narrative effects in physical activity promotion: the influence of breast cancer survivor testimony on exercise beliefs, self-efficacy, and intention in breast cancer patients. *Supportive Care in Cancer, 23*(3), 761-768. doi:10.1007/s00520-014-2422-x

Faulkner, G. & Carless, D. (2006). Physical activity in the process of psychiatric rehabilitation: theoretical and methodological issues. *Psychiatric Rehabilitation Journal, 29*(4), 258–266.

Favreau, H., Bacon, S. L., Labrecque, M., & Lavoie, K. L. (2014). Prospective impact of panic disorder and panic-anxiety on asthma control, health service use, and quality of life in adult patients with asthma over a 4-year follow-up. *Psychosomatic Medicine, 76*(2), 147-155.

Fenton, W. S., & Stover, E. S. (2006). Mood disorders: cardiovascular and diabetes comorbidity. *Current opinion in psychiatry, 19*(4), 421-427. doi:10.1097/01.yco.0000228765.33356.9f

Ferguson, J. M. (2001). SSRI Antidepressant Medications: Adverse Effects and Tolerability. *Primary Care Companion to the Journal of Clinical Psychiatry, 3*(1), 22-27.

Fiske, A., Wetherell, J. L., & Gatz, M. (2009). Depression in Older Adults. *Annual Review of Clinical Psychology*, *5*(1), 363–389.

FitzGerald, J. M., Boulet, L. P., Mclvor, R. A., Zimmerman, S., & Chapman, K. R. (2006). Asthma control in Canada remains suboptimal: The reality of asthma control (TRAC) study. *Canadian Respiratory Journal, 13*, 253-259. doi:10.1155/2006/753083

Ford, E. S., Bergmann, M. M., Kröger, J., Schienkiewitz, A., Weikert, C., & Boeing, H. (2009). Healthy living is the best revenge: Findings from the european prospective investigation into cancer and nutrition–potsdam study. *Archives of Internal Medicine, 169*(15), 1355-1362. doi:10.1001/archinternmed.2009.237

Franke, K. J., Domanski, U., Schroeder, M., Jansen, V., Artmann, F., Weber, U., . . . Nilius, G. (2016). Telemonitoring of home exercise cycle training in patients with COPD. *Int J International Journal of Chronic Obstructive Pulmonary Disease, 11*, 2821-2829. doi:10.2147/COPD.S114181

Ganga, H. V., Leung, A., Jantz, J., Choudhary, G., Stabile, L., Levine, D. J., . . . Wu, W. C. (2017). Supervised exercise training versus usual care in ambulatory patients with left ventricular assist devices: A systematic review. *PLoS One, 12*(3), e0174323. doi:10.1371/journal.pone.0174323

Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I.-M., . . . Swain, D. P. (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and Science in Sports and Exercise, 43*(7), 1334-1359.

Garcia-Aymerich, J., Varraso, R., Antó, J. M., & Camargo Jr, C. A. (2009). Prospective study of physical activity and risk of asthma exacerbations in older women. *American Journal of Respiratory and Critical Care Medicine, 179*(11), 999-1003.

Gary, R. A., Dunbar, S. B., Higgins, M. K., Musselman, D. L., & Smith, A. L. (2010). Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. *Journal of Psychosomatic Research, 69*(2), 119-131. doi:10.1016/j.jpsychores.2010.01.013

Gayle, R. C., Spitler, D. L., Karper, W. B., Jaeger, R. M., & Rice, S. N. (1988). Psychological changes in exercising COPD patients. *International journal of rehabilitation research, 11*(4), 335-342.

Gibb, B. E., Beevers, C. G., & McGeary, J. E. (2013). Toward an integration o f cognitive and genetic models o f risk for depression. *Cognition & Emotion*, *27*(2), 193-216. doi: 10.1080/02699931.2012.712950

Gimeno-Santos, E., Frei, A., Steurer-Stey, C., de Batlle, J., Rabinovich, R. A., Raste, Y., . . . Garcia-Aymerich, J. (2014). Determinants and outcomes of physical activity in patients with COPD: a systematic review. *Thorax, 69*(8), 731.

Global Initiative for Asthma. (2017). *Global strategy for asthma management and prevention*. Retrieved from http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/

Glynn, M. G., McFarlin, B. K., & Markofski, M. M. (2007). The anti-inflammatory actions of exercise training. *American Journal of Lifestyle Medicine*, *1*, 220–235.

Godin, G., & Shephard, R. (1985). A simple method to assess exercise behavior in the community. *Canadian Journal of Applied Sport Sciences, 10*(3), 141-146.

Gokal, K., Wallis, D., Ahmed, S., Boiangiu, I., Kancherla, K., & Munir, F. (2015). Effects of a self-managed home-based walking intervention on psychosocial health outcomes for breast cancer patients receiving chemotherapy: a randomised controlled trial. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. doi:10.1007/s00520-015-2884-5

Gonçalves, R., Nunes, M., Cukier, A., Stelmach, R., Martins, M., & Carvalho, C. (2008). Effects of an aerobic physical training program on psychosocial characteristics, quality-of-life, symptoms and exhaled nitric oxide in individuals with moderate or severe persistent asthma. *Brazilian Journal of Physical Therapy, 12*(2), 127-135.

Gosselin, C., & Taylor, A. (1999). Exercise as a stress management tool. *Stress News*, *11*(4).

Gøtzsche, P. C. (2000). Why we need a broad perspective on meta-analysis: it may be crucially important for patients. *British Medical Journal, 321*(7261), 585-585.

Greist, J. H., Klein, M. H., Eischens, J. F., Gurman, A. S., Morgan, W. P. (1979). Running as treatment for depression. *Compr. Psychiatry, 20*, 41–54.

Grenard, J. L., Munjas, B. A., Adams, J. L., Suttorp, M., Maglione, M., McGlynn, E. A., & Gellad, W. F. (2011). Depression and Medication Adherence in the Treatment of Chronic Diseases in the United States: A Meta-Analysis. *Journal of General Internal Medicine, 26*(10), 1175-1182. doi:10.1007/s11606-011-1704-y

Grundy, A., Poirier, A. E., Khandwala, F., Grevers, X., Friedenreich, C. M., & Brenner, D. R. (2017). Cancer incidence attributable to lifestyle and environmental factors in Alberta in 2012: summary of results. *CMAJ Open, 5*(3), E540-E545. doi:10.9778/cmajo.20160045

Gudmundsson, P., Lindwall, M., Gustafson, D. R., Östling, S., Hällström, T., Waern, M., & Skoog, I. (2015). Longitudinal associations between physical activity and depression scores in Swedish women followed 32 years. *Acta Psychiatrica Scandinavica, 132*(6), 451-458. doi:10.1111/acps.12419

Güell, R., Resqueti, V., Sangenis, M., Morante, F., Martorell, B., Casan, P., & Guyatt, G. H. (2006). Impact of Pulmonary Rehabilitation on Psychosocial Morbidity in Patients With Severe COPD. *Chest, 129*(4), 899-904. doi:10.1378/chest.129.4.899

Gunter, J. (2008, November). *Examining the cognitive theory of depression using descriptive experience sampling*. Unpublished master‘s thesis, University of Nevada, Las Vegas.

Haeffel, G. J., & Hames, J. L. (2014). Cognitive vulnerability to depression can be contagious. *Clinical Psychological Science*, *2*, 75–85.

Hamer, M., Sabia, S., Batty, G. D., Shipley, M. J., Tab.k, A. G., … Kivimaki, M. (2012). Physical activity and inflammatory markers over 10 years: Follow-up in men and women from the whitehall II cohort study. *Circulation*, *126*, 928–933.

Harmatz, M. G., Well, A. D., Overtree, C. E., Kawamura, K. Y., Rosal, M., & Ockene, I. S. (2000). Seasonal Variation of Depression and Other Moods: A Longitudinal Approach. *Journal of Biological Rhythms, 15*(4), 344-350. doi:10.1177/074873000129001350

Haskell, W. L., Lee, I.-M., Pate, R. R., Powell, K. E., Blair, S. N., Franklin, B. A., . . . Bauman, A. (2007). Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation, 116*(9), 1081.

Health Canada. (2013). *Respiratory Effects of Air Pollution*. Retrieved from Ottawa: http://www.hc-sc.gc.ca/ewh-semt/air/out-ext/health-sante/respir-eng.php

Heath, G. W., Parra, D. C., Sarmiento, O. L., Andersen, L. B., Owen, N., Goenka, S., . . . Group, L. P. A. S. W. (2012). Evidence-based intervention in physical activity: lessons from around the world. *The Lancet, 380*(9838), 272-281.

Heijnen, S., Hommel, B., Kibele, A., & Colzato, L. S. (2016). Neuromodulation of Aerobic Exercise-A Review. *Frontiers in psychology*, *6*, 1890. doi:10.3389/fpsyg.2015.01890

Herring, M. P., Puetz, T. W., O'Connor, P. J., & Dishman, R. K. (2012). Effect of Exercise Training on Depressive Symptoms Among Patients With a Chronic Illness: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Archives of Internal Medicine, 172*(2), 101-111. doi:10.1001/archinternmed.2011.696

Higgins, J. P. T., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions* (Vol. 4): John Wiley & Sons.

Higgins, J. P. T., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine, 1558*, 1539-1558. doi:10.1002/sim.1186

Hiles, S. A., Baker, A. L., de Malmanche, T., & Attia, J. (2012). A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. *Brain, Behavior, and Immunity*, *26*(7), 1180–8.

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic Medicine*, *71*(2), 171–86.

Hodgkin, D., Volpe-Vartanian, J., & Alegría, M. (2007). Discontinuation of Antidepressant Medication Among Latinos in the USA. *The Journal of Behavioral Health Services & Research, 34*(3), 329-342. doi:10.1007/s11414-007-9070-6

Hooper, P., Jutai, J. W., Strong, G., & Russell-Minda, E. (2008). Age-related macular degeneration and low-vision rehabilitation: a systematic review. *Canadian Journal of Ophthalmology/Journal Canadien d'Ophtalmologie, 43*(2), 180-187.

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosomatic Medicine*, *71*, 171–186.

Hung, C., Daub, B., Black, B., Welsh, R., Quinney, A., & Haykowsky, M. (2005). Exercise Training Improves Overall Physical Fitness and Quality of Life in Older Women with Coronary Artery Disease. *Cardiopulmonary Physical Therapy Journal, 16*(1), 35.

Hunot, V. M., Horne, R., Leese, M. N., & Churchill, R. C. (2007). A Cohort Study of Adherence to Antidepressants in Primary Care: The Influence of Antidepressant Concerns and Treatment Preferences. *Primary Care Companion to the Journal of Clinical Psychiatry, 9*(2), 91-99.

Husky, M., Mazure, C., Maciejewski, P., and Swendsen J. (2007) A Daily Life Comparison of Sociotropy-Autonomy and Hopelessness Theories of Depression. *Cognitive Therapy and Research*, *31*, 659-676.

Hynninen, K. M. J., Breitve, M. H., Wiborg, A. B., Pallesen, S., & Nordhus, I. H. (2005). Psychological characteristics of patients with chronic obstructive pulmonary disease: a review. *Journal of Psychosomatic Research, 59*(6), 429-443. doi:10.1016/j.jpsychores.2005.04.007

Isaksen, K., Munk, P. S., Giske, R., & Larsen, A. I. (2016). Effects of aerobic interval training on measures of anxiety, depression and quality of life in patients with ischaemic heart failure and an implantable cardioverter defibrillator: A prospective non-randomized trial. *Journal of Rehabilitation Medicine, 48*(3), 300-306. doi:10.2340/16501977-2043

Jehn, C. F., Kuehnhardt, D., Bartholomae, A., Pfeiffer, S., Krebs, M., Regierer, A. C., . . . Flath, B. C. (2006). Biomarkers of depression in cancer patients. *Cancer, 107*(11), 2723-2729. doi:10.1002/cncr.22294

Juniper, E. F. (2005). Asthma-related quality of life. Retrieved from http://www.qoltech.co.uk/language_lists.html - aqlq

Juniper, E. F., O'Byrne, P. M., Guyatt, G. H., Ferrie, P. J., & King, D. R. (1999). *European Respiratory Journal, 14*(4), 902.

Juniper, E. F., Stahl, E., Mork, A. C., & Svensson, K. (2004). Minimal important difference for the asthma control questionnaire. *European Respiratory Journal, 24*, 460s.

Just, N., & Alloy, L. B. (1997). The response styles theory of depression: Tests and an extension of the theory. *Journal o f Abnormal Psychology*, *106*, 221-229.

Katon, W. J. (2011). Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues in Clinical Neuroscience, 13*(1), 7-23.

Katon, W. J., Lin, E. H., & Kroenke, K. (2007). The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *General Hospital Psychiatry, 29*(2), 147-155.

Katon, W. J., & Sullivan, M. D. (1990). Depression and chronic medical illness. *Journal of Clinical Psychiatry, 51*(Suppl 6), 3-11.

Kavanagh, D. J., & Wilson, P. H. (1989). Prediction of outcome with a group version of cognitive therapy for depression. *Behaviour Research and Therapy*, *27*, 333-347.

Kelley, G. A., Kelley, K. A., & Vu Tran, Z. (2001). Aerobic Exercise and Resting Blood Pressure: A Meta-Analytic Review of Randomized, Controlled Trials. *Preventive cardiology, 4*(2), 73-80. doi:10.1111/j.1520-037X.2001.00529.x

Kendler, K. (2008). Explanatory models for psychiatric illness. *American Journal of Psychiatry*, *165*(6), 695-702.

Kendler, K. (2011). Levels of explanation in psychiatric and substance use disorders: Implications for the development of an etiologically based nosology. *Molecular Psychiatry*, *17*(1), 11-21.

Khan, A., & Brown, W. A. (2015). Antidepressants versus placebo in major depression: an overview. *World Psychiatry, 14*(3), 294-300.

King, D. E., Carek, P., Mainous, A. G. I., & Pearson, W. S. (2003). Inflammatory markers and exercise: differences related to exercise type. *Medicine and Science in Sports & Exercise*, *35*, 575-581.

Kippelen, P., & Anderson, S. D. (2013). Pathogenesis of Exercise-Induced Bronchoconstriction. *Immunology and Allergy Clinics, 33*(3), 299-312. doi:10.1016/j.iac.2013.02.002

Kirsch, I. (2015). Antidepressants and the placebo effect. *Zeitschrift f{ü}r Psychologie*.

Kitzman, D. W., Brubaker, P. H., Morgan, T. M., Stewart, K. P., & Little, W. C. (2010). Exercise training in older patients with Heart failure and preserved ejection fraction: A randomized, controlled, single-blind trial. *Circulation: Heart Failure, 3*(6), 659-667. doi:10.1161/CIRCHEARTFAILURE.110.958785

Koukouvou, G., Kouidi, E., Iacovides, A., Konstantinidou, E., Kaprinis, G., & Deligiannis, A. (2004). Quality of life, psychological and physiological changes following exercise training in patients with chronic heart failure. *Journal of Rehabilitation Medicine, 36*(1), 36-41. doi:10.1080/11026480310015549

Ku, P.-W., Fox, K. R., Chen, L.-J., & Chou, P. (2012). Physical activity and depressive symptoms in older adults: 11-year follow-up. *American Journal of Preventive Medicine, 42*(4), 355-362.

Kulcu, D. G., Kurtais, Y., Tur, B. S., Gülec, S., & Seckin, B. (2007). The effect of cardiac rehabilitation on quality of life, anxiety and depression in patients with congestive heart failure. A randomized controlled trial, short-term results. *Europa medicophysica, 43*(4), 489-497.

Labor, M., Labor, S., Jurić, I., Fijačko, V., Popović Grle, S., & Plavec, D. (2017). Long-term predictors of anxiety and depression in adult patients with asthma. *Wiener klinische Wochenschrift, 129*(19), 665-673. doi:10.1007/s00508-017-1203-1

Laframboise, M. A., & deGraauw, C. (2011). The effects of aerobic physical activity on adiposity in school-aged children and youth: a systematic review of randomized controlled trials. *The Journal of the Canadian Chiropractic Association, 55*(4), 256-268.

Lampinen, P., Heikkinen, R.-L., & Ruoppila, I. (2000). Changes in Intensity of Physical Exercise as Predictors of Depressive Symptoms among Older Adults: An Eight-Year Follow-Up. *Preventive Medicine, 30*(5), 371-380. doi:https://doi.org/10.1006/pmed.2000.0641

Lane, A. M., Jackson, A., & Terry, P. C. (2005). Preferred modality influences on exercise-induced mood changes. *Journal of Sports Science & Medicine, 4*(2), 195.

Lanting, S. M., Johnson, N. A., Baker, M. K., Caterson, I. D., & Chuter, V. H. (2017). The effect of exercise training on cutaneous microvascular reactivity: A systematic review and meta-analysis. *Journal of Science & Medicine in Sport, 20*(2), 170-177.

Laurin, C., Labrecque, M., Dupuis, G., Bacon, S. L., Cartier, A., & Lavoie, K. L. (2009). Chronic Obstructive Pulmonary Disease Patients With Psychiatric Disorders Are at Greater Risk of Exacerbations. *Psychosomatic Medicine, 71*(6).

Lavie, C. J., Milani, R. V., Marks, P., & de Gruiter, H. (2001). Exercise and the Heart: Risks, Benefits, and Recommendations for Providing Exercise Prescriptions. *The Ochsner Journal, 3*(4), 207-213.

Lavoie, K. L., Bacon, S. L., Barone, S., Cartier, A., Ditto, B., & Labrecque, M. (2006). What is worse for asthma control and quality of life: depressive disorders, anxiety disorders, or both? *Chest, 130*(4), 1039-1047.

Lavoie, K. L., Cartier, A., Labrecque, M., Bacon, S. L., Lemière, C., Malo, J.-L., . . . Ditto, B. (2005). Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? *Respiratory Medicine, 99*(10), 1249-1257. doi:https://doi.org/10.1016/j.rmed.2005.03.003

Lee, I.-M., & Paffenbarger Jr, R. S. (2000). Associations of light, moderate, and vigorous intensity physical activity with longevity: the Harvard Alumni Health Study. *American Journal of Epidemiology, 151*(3), 293-299.

Legrand, F., & Heuze, J. P. (2007). Antidepressant effects associated with different exercise conditions in participants with depression: a pilot study. *Journal of Sport and Exercise Psychology, 29*(3), 348-364.

Leith, L. M. (1994). *Foundations of exercise and mental health*. Morgantown, WV: Fitness Information Technology.

Lennon, O., Carey, A., Gaffney, N., Stephenson, J., & Blake, C. (2008). A pilot randomized controlled trial to evaluate the benefit of the cardiac rehabilitation paradigm for the non-acute ischaemic stroke population. *Clinical Rehabilitation, 22*(2), 125-133. doi:10.1177/0269215507081580

Lepore, S. J. (1997). Expressive writing moderates the relation between intrusive thoughts and depressive symptoms. *Journal of Personality and Social Psychology*, *73*(5), 1030-1037.

Lett, H. S., Blumenthal, J. A., Babyak, M. A., Sherwood, A., Strauman, T., Robins, C., & Newman, M. F. (2004). Depression as a Risk Factor for Coronary Artery Disease: Evidence, Mechanisms, and Treatment. *Psychosomatic Medicine, 66*(3).

Lewinsohn, P. M., & Graf, M. (1973). Pleasant activities and depression. *Journal of Consulting and Clinical Psychology*, *41*(2), 261–268.

Lichtman, J. H., Bigger, J. T., Blumenthal, J. A., Frasure-Smith, N., Kaufmann, P. G., Lespérance, F., . . . Froelicher, E. S. (2008). Depression and Coronary Heart Disease. *Circulation, 118*(17), 1768.

Lin, E. H. B., Katon, W., Von Korff, M., Rutter, C., Simon, G. E., Oliver, M., . . . Young, B. (2004). Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care, 27*(9), 2154-2160.

Lin, T.-W. & Yu-Min Kuo, Y.-M. (2013). Exercise Benefits Brain Function: The Monoamine Connection. *Brain Science*, *3*, 39-53; doi:10.3390/brainsci3010039.

Lin, E. H. B., Rutter, C. M., Katon, W., Heckbert, S. R., Ciechanowski, P., Oliver, M. M., . . . McCulloch, D. K. (2010). Depression and advanced complications of diabetes. *Diabetes Care, 33*(2), 264-269.

Lindwall, M., Gerber, M., Jonsdottir, I. H., Börjesson, M., & Ahlborg Jr, G. (2014). The relationships of change in physical activity with change in depression, anxiety, and burnout: A longitudinal study of Swedish healthcare workers. *Health Psychology, 33*(11), 1309.

Liu, R. T., Kleiman, E. M., Nestor, B. A., & Cheek, S. M. (2015). The hopelessness theory of depression: A quarter century in review. *Clinical Psychology*, *22*, 345–365.

Liubaoerjijin, Y., Terada, T., Fletcher, K., & Boulé, N. G. (2016). Effect of aerobic exercise intensity on glycemic control in type 2 diabetes: A meta-analysis of head-to-head randomized trials. *Acta Diabetol*, *53*, 769–781.

Loprinzi, P. D., Cardinal, B. J., Winters-Stone, K., Smit, E., & Loprinzi, C. L. (2012). *Physical activity and the risk of breast cancer recurrence: a literature review.* Paper presented at the Oncology Nursing Forum.

Loprinzi, P. D., & Davis, R. E. (2016). Bouted and non-bouted moderate-to-vigorous physical activity with health-related quality of life. *Preventive Medicine Reports, 3*(Supplement C), 46-48. doi:https://doi.org/10.1016/j.pmedr.2015.12.005

Loprinzi, P. D., Kane, C., & Walker, J. F. (2013). Association between physical activity and major depressive disorder among current or former smokers with pulmonary disease. *Preventive Medicine, 57*, 545-549. doi:10.1016/j.ypmed.2013.07.009

Maj, M. (2011). When does depression become a mental disorder? *The British Journal of Psychiatry, 199*(2), 85.
Mancuso, C. A., Choi, T. N., Westermann, H., Wenderoth, S., Wells, M. T., & Charlson, M. E. (2013). Improvement in asthma quality of life in patients enrolled in a prospective study to increase lifestyle physical activity. *Journal of Asthma, 50*(1), 103-107.
Massie, M. J. (2004). Prevalence of Depression in Patients With Cancer. *JNCI Monographs, 2004*(32), 57-71. doi:10.1093/jncimonographs/lgh014
Mazzucchelli, T., Kane, R., & Rees, C. (2009). Behavioral Activation Treatments for Depression in Adults: A Meta-analysis and Review. *Clinical Psychology: Science and Practice, 16*(4), 383-411. doi:10.1111/j.1468-2850.2009.01178.x
McAuley, E., (1992). *Understanding exercise behavior: A self-efficacy perspective*. In G.C. Roberts (Ed.), Understanding motivation in exercise and sport (pp. 107-128).
McAuley, E., Lox, C., & Duncan, T. E. (1993). Long-term maintenance of exercise, self-efficacy, and physiological change in older adults. *Journal of Gerontology: Psychological Sciences*, *48*, 218-224.
McAuley, E., Morris, K. S., Motl, R. W., Hu, L., Konopack, J. F., & Elavsky, S. (2007). Long-term follow-up of physical activity behavior in older adults. *Health Psychology, 26*(3), 375-380. doi:10.1037/0278-6133.26.3.375
McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., & Lacasse, Y. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews,* (2). doi:10.1002/14651858.CD003793.pub3
McDonnell, M. N., Smith, A. E., & Mackintosh, S. F. (2011). Aerobic Exercise to Improve Cognitive Function in Adults With Neurological Disorders: A Systematic Review. *Archives of Physical Medicine and Rehabilitation, 92*(7), 1044-1052. doi:https://doi.org/10.1016/j.apmr.2011.01.021
McFarlin, B. K., Flynn, M. G., Campbell, W. W., Craig, B. A., Robinson, J. P., … Coen, P. M. (2006). Physical activity status, but not age, influences inflammatory biomarkers and toll-like receptor 4. *The Journals of Gerontology: Series A, Biological Sciences and Medical Sciences*, *61*, 388-393.
Mead, K., Theadom, A., Byron, K., & Dupont, S. (2007). Pilot study of a 4-week Pain Coping Strategies (PCS) programme for the chronic pain patient. *Disability and Rehabilitation, 29*(3), 199-203. doi:10.1080/09638280600756117
Meltzer, E. O., Busse, W., Wenzel, S. E., Belozeroff, V., Weng, H. H., Feng, J., . . . Lin, S. (2010). Use Of Asthma Control Questionnaire (ACQ) Score To Predict Future Risk Of Asthma Exacerbation *D101. Diagnosis And Treatment Of Asthma* (pp. A6858-A6858): American Thoracic Society.
Melzack, R., Wall, P. D., & Ty, T. C. (1982). Acute pain in an emergency clinic: Latency of onset and descriptor patterns related to different injuries. *Pain, 14*(1), 33-43. doi:https://doi.org/10.1016/0304-3959(82)90078-1
Mendes, F. A., Gonçalves, R. C., Nunes, M. P., Saraiva-Romanholo, B. M., Cukier, A., Stelmach, R., . . . Carvalho, C. R. (2010a). Effects of aerobic training on psychosocial morbidity and symptoms in patients with asthma: a randomized clinical trial. *Chest, 138*(2), 331-337. doi:10.1378/chest.09-2389
Mendes, F. A., Lunardi, A. C., Silva, R. A., Cukier, A., Stelmach, R., Martins, M. A., & Carvalho, C. R. (2013). Association between maximal aerobic capacity and psychosocial

factors in adults with moderate-to-severe asthma. *Journal of Asthma, 50*(6), 595-599. doi:10.3109/02770903.2013.786724

Mendis, S., Puska, P., & Norrving, B. (2011). *Global Atlas on Cardiovascular Disease Prevention and Control*. Geneva: World Health Organization.

Merghani, T. H., & Alawad, A. O. (2017). Indicators of Asthma Control in Asthmatic Patients: Are they related to Depression? *Open Access Macedonian Journal of Medical Sciences, 5*(5), 673-676. doi:10.3889/oamjms.2017.091

Mezuk, B., Eaton, W. W., Albrecht, S., & Golden, S. H. (2008). Depression and type 2 diabetes over the lifespan: A meta-analysis. *Diabetes Care, 31*(12), 2383-2390. doi:10.2337/dc08-0985

Miller, A. H. & Raison, C. L. (2016). The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, *16*(1), 22–34.

Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B. (2011). Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. *Biological Psychiatry*, *70*(7), 663–671.

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biological Psychiatry, 65(9), 732–41.

Miller, M., Mogun, H., Azrael, D., Hempstead, K., & Solomon, D. H. (2008). Cancer and the Risk of Suicide in Older Americans. *Journal of Clinical Oncology, 26*(29), 4720-4724. doi:10.1200/JCO.2007.14.3990

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The Prisma, G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses : The PRISMA Statement. *PLoS medicine, 6*(7). doi:10.1371/journal.pmed.1000097

Möller, H.-J. (2008). Outcomes in major depressive disorder: The evolving concept of remission and its implications for treatment. *The World Journal of Biological Psychiatry, 9*(2), 102-114. doi:10.1080/15622970801981606

Monga, U., Garber, S. L., Thornby, J., Vallbona, C., Kerrigan, A. J., Monga, T. N., & Zimmermann, K. P. (2007). Exercise prevents fatigue and improves quality of life in prostate cancer patients undergoing radiotherapy. *Archives of Physical Medicine and Rehabilitation, 88*(11), 1416-1422. doi:10.1016/j.apmr.2007.08.110

Morrato, E. H., Hill, J. O., Wyatt, H. R., Ghushchyan, V., & Sullivan, P. W. (2007). Physical Activity in U.S. Adults With Diabetes and At Risk for Developing Diabetes, 2003. *Diabetes care, 30*(2), 203.

Morrow, J., & Nolen-Hoeksema, S. (1990). Effects of responses to depression on the remediation of depressive affect. *Journal of Personality and Social Psychology*, *58*, 519-527.

Mössner, R., Mikova, O., Koutsilieri, E., Saoud, M., Ehlis, A.-C., Müller, N., . . . Riederer, P. (2007). Consensus paper of the WFSBP Task Force on Biological Markers: Biological Markers in Depression. *The World Journal of Biological Psychiatry, 8*(3), 141-174. doi:10.1080/15622970701263303

Moy, M. L., Teylan, M., Weston, N. A., Gagnon, D. R., & Garshick, E. (2013). Daily Step Count Predicts Acute Exacerbations in a US Cohort with COPD. *PLoS One, 8*(4), e60400. doi:10.1371/journal.pone.0060400

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., . . . Turner, M. B. (2016). Heart Disease and Stroke Statistics—2016 Update. *Circulation, 133*(4), e38.

Naber, D., Sand, P., & Heigl, B. (1996). Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. *Psychoneuroendocrinology, 21*(1), 25-31. doi:https://doi.org/10.1016/0306-4530(95)00031-3

Nan, H., Lee, P. H., McDowell, I., Ni, M. Y., Stewart, S. M., & Lam, T. H. (2012). Depressive symptoms in people with chronic physical conditions: prevalence and risk factors in a Hong Kong community sample. *BMC Psychiatry, 12*, 198-198. doi:10.1186/1471-244X-12-198

Narayan, K., Boyle, J. P., Thompson, T. J., Sorensen, S. W., & Williamson, D. F. (2003). Lifetime risk for diabetes mellitus in the united states. *JAMA, 290*(14), 1884-1890. doi:10.1001/jama.290.14.1884

Nolen-Hoeksema, S., Morrow, J., & Fredrickson, B. L. (1993). Response styles and the duration of episodes of depressed mood. *Journal o f Abnormal Psychology*, *102*, 20-28.

Norton, K., Norton, L., & Sadgrove, D. (2010). Position statement on physical activity and exercise intensity terminology. *Journal of Science and Medicine in Sport, 13*(5), 496-502. doi:https://doi.org/10.1016/j.jsams.2009.09.008

O Brien, K., Nixon, S., Tynan, A.-M., & Glazier, R. H. (2004). Effectiveness of aerobic exercise in adults living with HIV/AIDS: systematic review. *Medicine and Science in Sports and Exercise, 36*, 1659-1666.

O'Donnell, D. E., Hernandez, P., Kaplan, A., Aaron, S., Bourbeau, J., Marciniuk, D., . . . Voduc, N. (2008). Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2008 update – highlights for primary care. *Canadian respiratory journal : journal of the Canadian Thoracic Society, 15*(Suppl A), 1A-8A.

O'Halloran, P. D., Blackstock, F., Shields, N., Holland, A., Iles, R., Kingsley, M., . . . Taylor, N. F. (2014). Motivational interviewing to increase physical activity in people with chronic health conditions: a systematic review and meta-analysis. *Clinical Rehabilitation, 28*(12), 1159-1171. doi:10.1177/0269215514536210

Omachi, T. A., Katz, P. P., Yelin, E. H., Gregorich, S. E., Iribarren, C., Blanc, P. D., & Eisner, M. D. (2009). Depression and Health-Related Quality of Life in Chronic Obstructive Pulmonary Disease. *The American Journal of Medicine, 122*(8), 778.e779-778.715. doi:10.1016/j.amjmed.2009.01.036

Ouellet, K., Bacon, S. L., Boudreau, M., Plourde, A., Moullec, G., & Lavoie, K. L. (2012). Individual and combined impact of cigarette smoking, anxiety, and mood disorders on asthma control. *Nicotine & Tobacco Research, 14*(8), 961-969.

Paluska, S. A., & Schwenk, T. L. (2000). Physical activity and mental health current concepts. *Sports Medicine*, *29*(3), 167–180.

Pasquini, M., & Biondi, M. (2007). Depression in cancer patients: a critical review. *Clinical Practice and Epidemiology in Mental Health, 3*(1), 2. doi:10.1186/1745-0179-3-2

Payne, J. K., Held, J., Thorpe, J., & Shaw, H. (2008). Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. *Oncology Nursing Forum, 35*(4), 635-642. doi:10.1188/08.ONF.635-642

Pearson, C., Janz, T., & Ali, J. (2013). *Mental and substance use disorders in Canada*. (Catalogue no.82-624-X ). Retrieved from http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11855-eng.pdf.

Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., … Vinicor, F. (2003). Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*, *107*, 499-511.

Pedersen, B. K., Fischer, C. P., (2007). Physiological roles of muscle-derived inter-leukin-6 in response to exercise. *Current Opinion in Clinical Nutritionand Metabolic Care*, *10*, 265–271.

Pedersen, M., Bruunsgaard, H., Weis, N., Hendel, H. W., Andreassen, … Pedersen, B. K. (2003). Circulating levels of TNF-alpha and IL-6-relation to Truncal fat mass and muscle mass in healthy elderly individuals and inpatients with type 2 diabetes. *Mechanisms of Ageing and Development*, *124*, 495–502.

Pelaez, S., Lavoie, K. L., Gordon, J. L., Arsenault, A., & Bacon, S. L. (2010). Social networks and exercise in coronary heart disease patients. *Journal of Cardiopulmonary Rehabilitation and Prevention, 30*(5), 324-328. doi:10.1097/HCR.0b013e3181d8dd12

Peters, J. L., Sutton, A. J., Jones, D. R., Abrams, K. R., Rushton, L., & Moreno, S. G. (2010). Assessing publication bias in meta-analyses in the presence of between-study heterogeneity. *Journal of the Royal Statistical Society: Series A (Statistics in Society), 173*(3), 575-591.

Philip, E. J., Merluzzi, T. V., Zhang, Z., & Heitzmann, C. A. (2013). Depression and cancer survivorship: importance of coping self-efficacy in post-treatment survivors. *Psycho-Oncology, 22*(5), 987-994.

Pinquart, M., & Duberstein, P. R. (2010). Depression and cancer mortality: a meta-analysis. *Psychological Medicine, 40*(11), 1797-1810. doi:10.1017/S0033291709992285

Pirl, W. F., Greer, J., Temel, J. S., Yeap, B. Y., & Gilman, S. E. (2009). Major depressive disorder in long-term cancer survivors: analysis of the National Comorbidity Survey Replication. *Journal of Clinical Oncology, 27*(25), 4130-4134.

Plotnikoff, R. C., Costigan, S. A., Karunamuni, N. D., & Lubans, D. R. (2013). Community-Based Physical Activity Interventions for Treatment of Type 2 Diabetes: A Systematic Review with Meta-Analysis. *Frontiers in Endocrinology, 4*, 3. doi:10.3389/fendo.2013.00003

Plotnikoff, R. C., Taylor, L. M., Wilson, P. M., Courneya, K. S., Sigal, R. J., Birkett, N., . . . Svenson, L. W. (2006). Factors associated with physical activity in Canadian adults with diabetes. *Medicine & Science in Sports & Exercise, 38*(8), 1526-1534. doi:10.1249/01.mss.0000228937.86539.95

Plourde, A., Moullec, G., Bacon, S. L., Suarthana, E., & Lavoie, K. L. (2016). Optimizing screening for depression among adults with asthma. *Journal of Asthma, 53*(7), 736-743. doi:10.3109/02770903.2016.1145692

Polenick, C. A., & Flora, S. R. (2013). Behavioral Activation for Depression in Older Adults: Theoretical and Practical Considerations. *The Behavior Analyst*, *36*(1), 35.

Pradhan, A. D., Manson, J. E., Rifai, N., Buring, J. E., & Ridker, P. M. (2001). C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*, *286*, 327–334.

Pretorius, E. (2004). Corticosteroids, Depression and the Role of Serotonin *Reviews in the Neurosciences* (Vol. 15, pp. 109).

Public Health Agency of Canada. (2011). *Fast facts about Chronic Obstructive Pulmonary Disease (COPD) 2011*. Retrieved from https://www.canada.ca/en/public-health/services/chronic-diseases/reports-publications/fast-facts-about-chronic-obstructive-pulmonary-disease-copd-2011.html

Public Health Agency of Canada. (2016). *Health Status of Canadians 2016: Report of the Chief Public Health Officer - How are we unhealthy? - Cardiovascular disease*. Retrieved from https://www.canada.ca/en/public-health/corporate/publications/chief-public-health-officer-reports-state-public-health-canada/2016-health-status-canadians/page-17-how-are-we-unhealthy-cardiovascular-disease.html

Raedler, T. J. (2011). Inflammatory mechanisms in major depressive disorder. *Current Opinion in Psychiatry*, *24*(6), 519–525.

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology*, *27*(1), 24–31.

Raison, C. L., & Miller, A. H. (2011). Is depression an inflammatory disorder? *Current Psychiatry Reports*, *13*(6), 467–475.

Reed, J., & Buck, S. (2009). The effect of regular aerobic exercise on positive-activated affect: A meta-analysis. *Psychology of Sport and Exercise, 10*(6), 581-594.

Rehm, J., Baliunas, D., Brochu, S., Fischer, B., Gnam, W., Patra, J., . . . Adlaf, E. (2006). The costs of substance abuse in Canada 2002. *Ottawa: Canadian Centre on Substance Abuse*, 1-14.

Rhen, T., & Cidlowski, J. A. (2005). Antiinflammatory Action of Glucocorticoids — New Mechanisms for Old Drugs. *New England Journal of Medicine, 353*(16), 1711-1723. doi:10.1056/NEJMra050541

Rosenberg, M. S. (2005). The File-Drawer Problem Revisited: A General Weighted Method for Calculating Fail-Safe Numbers in Meta-Analysis. *Evolution, 59*(2), 464-468.

Roshanaei-Moghaddam, B., Katon, W. J., & Russo, J. (2009). The longitudinal effects of depression on physical activity. *General Hospital Psychiatry, 31*(4), 306-315.

Roviaro, R., Holmes, D. S., & Holmsten, R. D. (1984). Influence of a Cardiac Rehabilitation Program on the Cardiovascular, Psychological, and Social Functioning of Cardiac Patients. *Journal of Behavioral Medicine, 7*(1), 61-61.

Rozanski, A., Blumenthal, J. A., & Kaplan, J. (1999). Impact of Psychological Factors on the Pathogenesis of Cardiovascular Disease and Implications for Therapy. *Circulation, 99*(16), 2192.

Rubin, D. B. (2004). *Multiple imputation for nonresponse in surveys* (Vol. 81): John Wiley & Sons.

Sardar, M. A., Boghrabadi, V., Sohrabi, M., Aminzadeh, R., & Jalalian, M. (2014). The Effects of Aerobic Exercise Training on Psychosocial Aspects of Men with Type 2 Diabetes Mellitus. *6*(2), 196-202. doi:10.5539/gjhs.v6n2p196

Schane, R. E., Woodruff, P. G., Dinno, A., Covinsky, K. E., & Walter, L. C. (2008). Prevalence and Risk Factors for Depressive Symptoms in Persons with Chronic Obstructive Pulmonary Disease. *Journal of General Internal Medicine, 23*(11), 1757-1762. doi:10.1007/s11606-008-0749-z

Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvão, D. A., Pinto, B. M., . . . others. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine & Science in Sports & Exercise, 42*(7), 1409-1426.

Schmitz, N., Gariepy, G., Smith, K. J., Clyde, M., Malla, A., Boyer, R., . . . Wang, J. (2014). Recurrent subthreshold depression in type 2 diabetes: an important risk factor for poor health outcomes. *Diabetes Care, 37*(4), 970-978. doi:10.2337/dc13-1832

Schuler, M., Faller, H., Wittmann, M., & Schultz, K. (2016). Asthma Control Test and Asthma Control Questionnaire: factorial validity, reliability and correspondence in assessing status and change in asthma control. *Journal of Asthma, 53*(4), 438-445.

Scullion, J. E., & Holmes, S. (2011). Palliative care in patients with chronic obstructive pulmonary disease. *Nursing Older People, 23*(4), 32-39.

Segar, M. L., Katch, V. L., Roth, R. S., Garcia, A. W., Portner, T. I., Glickman, S. G., . . . Wilkins, E. G. (1998). The effect of aerobic exercise on self-esteem and depressive and anxiety symptoms among breast cancer survivors. *Oncology Nursing Forum, 25*(1), 107-113.

Seligman, M. (1975). *Helplessness: On depression, development, and death*. San Francisco: Freeman.

Semenkovich, K., Brown, M. E., Svrakic, D. M., & Lustman, P. J. (2015). Depression in type 2 diabetes mellitus: prevalence, impact, and treatment. *Drugs, 75*(6), 577-587.

Singh, N. A., Clements, K. M., & Fiatarone, M. A. (1997). A randomized controlled trial of progressive resistance training in depressed elders. *Journal of Gerontology*, *52*, M27-M35.

Singh, N. A., Stavrinos, T. M., Scarbek, Y., Galambos, G., Liber, C., & Fiatarone Singh, M. A. (2005). A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. *The Journals of Gerontology Series A, Biological Sciences and Medical Sciences*, *60*, 768–776.

Singh, N. A., Stavrinos, T. M., Scarbek, Y., Galambos, G., Liber, C., Fiatarone Singh, M. A., & Morley, J. E. (2005). A Randomized Controlled Trial of High Versus Low Intensity Weight Training Versus General Practitioner Care for Clinical Depression in Older Adults. *The Journals of Gerontology: Series A, 60*(6), 768-776. doi:10.1093/gerona/60.6.768

Sirey, J. A., Bruce, M. L., Alexopoulos, G. S., Perlick, D. A., Raue, P., Friedman, S. J., & Meyers, B. S. (2001). Perceived Stigma as a Predictor of Treatment Discontinuation in Young and Older Outpatients With Depression. *American Journal of Psychiatry, 158*(3), 479-481. doi:10.1176/appi.ajp.158.3.479

Slavich, G. M., & Irwin, M. R. (2014). From Stress to Inflammation and Major Depressive Disorder: A Social Signal Transduction Theory of Depression. Psychological Bulletin. doi:10.1037/a0035302.

Smith, P. J., Blumenthal, J. a., Babyak, M. a., Georgiades, A., Hinderliter, A., & Sherwood, A. (2007). Effects of exercise and weight loss on depressive symptoms among men and women with hypertension. *Journal of Psychosomatic Research, 63*(5), 463-469. doi:10.1016/j.jpsychores.2007.05.011

Smyllie, H. C., & Connolly, C. K. (1968). Incidence of serious complications of corticosteroid therapy in respiratory disease. *Thorax, 23*(6), 571.

Sowers, J. R., Epstein, M., & Frohlich, E. D. (2001). Diabetes, Hypertension, and Cardiovascular Disease. *Hypertension, 37*(4), 1053.

Speck, R. M., Courneya, K. S., Mâsse, L. C., Duval, S., & Schmitz, K. H. (2010). An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Journal of Cancer Survivorship, 4*(2), 87-100. doi:10.1007/s11764-009-0110-5

Spitzer, C., Barnow, S., Völzke, H., Wallaschofski, H., J., U., Freyberger, H. J., … Grabe, H. J. (2010). Association of posttraumatic stress disorder with low-grade elevation of Creactive protein: evidence from the general population. *Journal of Psychiatric Research*, *44*(1), 15–21. doi:10.1016/j.jpsychires.2009.06.002

Spitzer, R. L., Williams, J. B. W., Kroenke, K., Linzer, M., deGruy, F. V., & Hahn, S. R. (1994). *JAMA, 272*(22), 1749.

Spoletini, I., Gianni, W., Repetto, L., Bria, P., Caltagirone, C., Bossù, P., & Spalletta, G. (2008). Depression and cancer: An unexplored and unresolved emergent issue in elderly patients. *Critical Reviews in Oncology/Hematology, 65*(2), 143-155. doi:https://doi.org/10.1016/j.critrevonc.2007.10.005

Statistics Canada. (2014a). *Asthma, 2014*. Retrieved from http://www.statcan.gc.ca/pub/82-625-x/2015001/article/14179-eng.htm

Statistics Canada. (2014b). *Diabetes, by age group and sex*. Retrieved from http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health53b-eng.htm

Statistics Canada. (2014c). *Leading causes of death, by sex* Retrieved from http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/hlth36a-eng.htm

Statistics Canada. (2017). *Canadian Health Measures Survey: Activity monitor data*. Retrieved from http://www.statcan.gc.ca/daily-quotidien/170419/dq170419e-eng.htm

Stefani, L., Galanti, G., & Klika, R. (2017). Clinical implementation of exercise guidelines for cancer patients: Adaptation of ACSM's guidelines to the Italian model. *Journal of Functional Morphology and Kinesiology, 2*(1), 4-4.

Stern, M. J., Gorman, P. A., & Kaslow, L. (1983). The group counseling v exercise therapy study. A controlled intervention with subjects following myocardial infarction. *Archives of Internal Medicine, 143*(9), 1719-1725.

Stevinson, C., Steed, H., Faught, W., Tonkin, K., Vallance, J. K., Ladha, A. B., . . . Courneya, K. S. (2009). Physical activity in ovarian cancer survivors: associations with fatigue, sleep, and psychosocial functioning. *International Journal of Gynecological Cancer, 19*(1), 73-78.

Strine, T. W., Mokdad, A. H., Balluz, L. S., Berry, J. T., & Gonzalez, O. (2008). Impact of Depression and Anxiety on Quality of Life, Health Behaviors, and Asthma Control Among Adults in the United States with Asthma, 2006. *Journal of Asthma, 45*(2), 123-133. doi:10.1080/02770900701840238

Strine, T. W., Mokdad, A. H., Balluz, L. S., Gonzalez, O., Crider, R., Berry, J. T., & Kroenke, K. (2008). Depression and anxiety in the United States: findings from the 2006 behavioral risk factor surveillance system. *Psychiatric Services, 59*(12), 1383-1390.

Ströhle, A. (2009). Physical activity, exercise, depression and anxiety disorders. *Journal of Neural Transmission, 116*(6), 777.

Subbarao, P., Mandhane, P. J., & Sears, M. R. (2009). Asthma: epidemiology, etiology and risk factors. *Canadian Medical Association Journal, 181*(9), E181-E190.

Subica, A. M., Fowler, J. C., Elhai, J. D., Frueh, B. C., Sharp, C., Kelly, E. L., & Allen, J. G. (2014). Factor structure and diagnostic validity of the Beck Depression Inventory–II with adult clinical inpatients: Comparison to a gold-standard diagnostic interview. *Psychological Assessment, 26*(4), 1106.

Suhail, K., & Cochrane, R. (1998). Seasonal variations in hospital admissions for affective disorders by gender and ethnicity. *Social Psychiatry and Psychiatric Epidemiology, 33*(5), 211-217. doi:10.1007/s001270050045

Teychenne, M., Abbott, G., Lamb, K. E., Rosenbaum, S., & Ball, K. (2017). Is the link between movement and mental health a two-way street? Prospective associations between physical activity, sedentary behaviour and depressive symptoms among women living in socioeconomically disadvantaged neighbourhoods. *Preventive Medicine, 102*, 72-78.

The National Institute for Health and Care Excellence. (2010). *Depression in adults with a chronic physical health problem. The NICE guideline on treatment and management*. Retrieved from http://guidance.nice.org.uk/CG91/QuickRefGuide/pdf/English

The National Institute for Health Care Excellence. (2009). *The NICE Guideline on the Treatment and Depression the Treatment and Management of Depression*.

Thiel, D. M., Al Sayah, F., Vallance, J. K., Johnson, S. T., & Johnson, J. A. (2017). Association between Physical Activity and Health-Related Quality of Life in Adults with Type 2 Diabetes. *Canadian Journal of Diabetes, 41*(1), 58-63. doi:https://doi.org/10.1016/j.jcjd.2016.07.004

Topcuoglu, A., Gokkaya, N. K. O., Ucan, H., & Karakuş, D. (2015). The effect of upper-extremity aerobic exercise on complex regional pain syndrome type I: A randomized controlled study on subacute stroke. *Topics in Stroke Rehabilitation, 22*(4), 253-261. doi:10.1179/1074935714Z.0000000025

Tortora, G. J., & Derrickson, B. H. (2008). *Principles of anatomy and physiology*: John Wiley & Sons.

Tremblay, M. S., Warburton, D. E. R., Janssen, I., Paterson, D. H., Latimer, A. E., Rhodes, R. E., . . . Duggan, M. (2011b). New Canadian Physical Activity Guidelines. *Applied Physiology, Nutrition, and Metabolism, 36*(1), 36-46. doi:10.1139/H11-009

Tu, R.-H., Zeng, Z.-Y., Zhong, G.-Q., Wu, W.-F., Lu, Y.-J., Bo, Z.-D., . . . Yao, L.-M. (2014). Effects of exercise training on depression in patients with heart failure: a systematic review and meta-analysis of randomized controlled trials. *European Journal of Heart Failure, 16*(7), 749-757. doi:10.1002/ejhf.101

Tucker, P., & Gilliland, J. (2007). The effect of season and weather on physical activity: A systematic review. *Public Health, 121*(12), 909-922. doi:https://doi.org/10.1016/j.puhe.2007.04.009

Turner, S., Eastwood, P., Cook, A., & Jenkins, S. (2011). Improvements in symptoms and quality of life following exercise training in older adults with moderate/severe persistent asthma. *Respiration, 81*(4), 302-310.

Umpierre, D., Ribeiro, P.A., Kramer, C.K., Leitão, C.B., Zucatti, A.T.N., … Schaan, B.D. (2011). Physical activity advice only or struc-tured exercise training and association with HbA1c levels in type 2 diabetes: A systematic review and meta-analysis. *JAMA*, *305*, 1790–1799.

U.S. Department of Health and Human Services. (1984). *The Health Consequences of Smoking: Chronic Obstructive Lung Disease. A Report of the Surgeon General*. Washington, DC: U.S. Department of Health and Human Services.

Urrutia, I., Aguirre, U., Pascual, S., Esteban, C., Ballaz, A., Arrizubieta, I., & Larrea, I. (2012). Impact of anxiety and depression on disease control and quality of life in asthma patients. *Journal of Asthma, 49*(2), 201-208.

Van Den Berg-Emons, R., Balk, A., Bussmann, H., & Stam, H. (2004). Does aerobic training lead to a more active lifestyle and improved quality of life in patients with chronic heart failure? *European Journal of Heart Failure, 6*(1), 95-100. doi:10.1016/j.ejheart.2003.10.005

van der Heijden, M. M., van Dooren, F. E., Pop, V. J., & Pouwer, F. (2013). Effects of exercise training on quality of life, symptoms of depression, symptoms of anxiety and emotional well-being in type 2 diabetes mellitus: a systematic review. *Diabetologia, 56*(6), 1210-1225. doi:10.1007/s00125-013-2871-7

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., & Beekman, A. (2007). Depression and the risk for cardiovascular diseases: systematic review and meta analysis (Vol. 22, pp. 613-626).

Vanelle, J. M., Aubin, F., & Michel, F. (1990). [Psychiatric complications of corticotherapy]. *La Revue du Praticien, 40*(6), 556-558.

Vézina, J., Landreville, P., Bourque, P., & Blanchard, L. (2010). Questionnaire de Dépression de Beck: Etude psychométrique auprès d'une population âgée francophone. *Canadian Journal on Aging / La Revue Canadienne du Vieillissement, 10*(1), 29-39. doi:10.1017/S0714980800007236

Vijayasaratha, K., & Stockley, R. A. (2008). Reported and unreported exacerbations of COPD: analysis by diary cards. *CHEST, 133*(1), 34-41.

Vollmer, W. M., Markson, L. E., O'connor, E., Sanocki, L. L., Fitterman, L., Berger, M., & Sonia Buist, A. (1999). Association of asthma control with health care utilization and quality of life. *American Journal of Respiratory and Critical Care Medicine, 160*(5), 1647-1652.

Vorrink, S. N. W., Kort, H. S. M., Troosters, T., & Lammers, J.-W. J. (2011). Level of daily physical activity in individuals with COPD compared with healthy controls. *Respiratory Research, 12*(1), 33. doi:10.1186/1465-9921-12-33

Wada, K., Yamada, N., Suzuki, H., Lee, Y., & Kuroda, S. (2000). Recurrent cases of corticosteroid-induced mood disorder: clinical characteristics and treatment. *The Journal of Clinical Psychiatry, 61*(4), 261-267.

Wang, H.-L., Booth-LaForce, C., Tang, S.-M., Wu, W.-R., & Chen, C.-H. (2013). Depressive symptoms in Taiwanese women during the peri- and post-menopause years: associations with demographic, health, and psychosocial characteristics. *Maturitas, 75*(4), 355-360. doi:10.1016/j.maturitas.2013.04.021

Wanrooij, V. H. M., Willeboordse, M., Dompeling, E., & van de Kant, K. D. G. (2014). Exercise training in children with asthma: a systematic review. *British Journal of Sports Medicine, 48*(13), 1024.

Warburton, D. E. R., & Bredin, S. S. D. (2016). Reflections on physical activity and health: what should we recommend? *Canadian Journal of Cardiology, 32*(4), 495-504.

Warburton, D. E. R., & Bredin, S. S. D. (2017). Health benefits of physical activity: a systematic review of current systematic reviews. *Current Opinion in Cardiology, 32*(5), 541-556.

Warburton, D. E. R., Charlesworth, S., Ivey, A., Nettlefold, L., & Bredin, S. S. D. (2010). A systematic review of the evidence for Canada's Physical Activity Guidelines for Adults. *International Journal of Behavioral Nutrition and Physical Activity, 7*(1), 39. doi:10.1186/1479-5868-7-39

Warburton, D. E. R., Nicol, C. W., & Bredin, S. S. (2006). Health benefits of physical activity: the evidence. *Canadian Medical Association Journal, 174*(6), 801-809.

Warrington, T. P., & Bostwick, J. M. (2006). Psychiatric Adverse Effects of Corticosteroids. *Mayo Clinic Proceedings, 81*(10), 1361-1367. doi:https://doi.org/10.4065/81.10.1361

Waschki, B., Kirsten, A., Holz, O., Muller, K.-C., Meyer, T., Watz, H., & Magnussen, H. (2011). Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest, 140*(2), 331-342. doi:10.1378/chest.10-2521

Waschki, B., Kirsten, A. M., Holz, O., Mueller, K.-C., Schaper, M., Sack, A.-L., . . . Watz, H. (2015). Disease Progression and Changes in Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. *American journal of respiratory and critical care medicine, 192*(3), 295-306. doi:10.1164/rccm.201501-0081OC

Whang, W., Kubzansky, L. D., Kawachi, I., Rexrode, K. M., Kroenke, C. H., Glynn, R. J., . . . Albert, C. M. (2009). Depression and Risk of Sudden Cardiac Death and Coronary Heart Disease in Women. Results From the Nurses' Health Study. *Journal of the American College of Cardiology, 53*(11), 950-958. doi:10.1016/j.jacc.2008.10.060

Willett, W. C., Koplan, J. P., Nugent, R., Dusenbury, C., Puska, P., & Gaziano, T. A. (2006). Prevention of chronic disease by means of diet and lifestyle changes. In D. T. Jamison, J. G. Breman, & A. R. Measham (Eds.), *Disease Control Priorities in Developing Countries* (2nd ed.). New York, N.Y.: Oxford University Press.

Williams, D. M., Lewis, B. A., Dunsiger, S., Whiteley, J. A., Papandonatos, G. D.,… Marcus, B. H. (2008). Comparing psychosocial predictors of physical activity adoption and maintenance. *Annals of Behavioral Medicine*, *36*, 186-194.

Williams, L. H., Miller, D. R., Fincke, G., Lafrance, J.-P., Etzioni, R., Maynard, C., . . . Reiber, G. E. (2011). Depression and incident lower limb amputations in veterans with diabetes. *Journal of Diabetes and its Complications, 25*(3), 175-182.

Williams, P. T. (2001). Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Medicine & Science in Sports & Exercise, 33*(5), 754-761.

Williams, S. A., Wagner, S., Kannan, H., & Bolge, S. C. (2009). The association between asthma control and health care utilization, work productivity loss and health-related quality of life. *Journal of Occupational and Environmental Medicine, 51*(7), 780-785.

Win, S., Parakh, K., Eze-Nliam, C. M., Gottdiener, J. S., Kop, W. J., & Ziegelstein, R. C. (2011). Depressive symptoms, physical inactivity and risk of cardiovascular mortality in older adults: the Cardiovascular Health Study. *Heart, 97*(6), 500-505.

Wise, L. A., Adams-Campbell, L. L., Palmer, J. R., & Rosenberg, L. (2006). Leisure time physical activity in relation to depressive symptoms in the black women's health study. *Annals of Behavioral Medicine, 32*(1), 68-76. doi:10.1207/s15324796abm3201_8

World Health Organization. (2010). *Global recommendations on Physical Activity for health*: World Health Organization.

World Health Organization. (2012). *World Health Statistics 2012* (Vol. 27).

World Health Organization. (2013). *Diabetes - Fact Sheet*. Retrieved from https://web.archive.org/web/20130826174444/http://www.who.int/mediacentre/factsheets/fs312/en/

World Health Organization. (2014a). *Global Status Report on Noncommunicable Diseases 2014*. Retrieved from http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf

World Health Organization. (2014b). *World Health Organization - Cancer Country Profiles, 2014 - Canada*. Retrieved from http://www.who.int/cancer/country-profiles/can_en.pdf?ua=1

World Health Organization. (2017a). Depression. Retrieved from http://www.who.int/mediacentre/factsheets/fs369/en/

World Health Organization. (2017b). Global Strategy on diet, physical activity and health. Retrieved from http://www.who.int/dietphysicalactivity/pa/en/

World Health Organization. (2017c). Noncommunicable diseases. Retrieved from http://www.who.int/mediacentre/factsheets/fs355/en/

World Health Organization. (n.d.). *Physical Activity*. Retrieved from http://www.who.int/mediacentre/factsheets/fs385/en/

Wright, A., Lavoie, K. L., Jacob, A., Rizk, A., & Bacon, S. L. (2010). Effect of body mass index on self-reported exercise-triggered asthma. *The Physician and Sports Medicine, 38*(4), 61-66.

Wulsin, L. R., & Singal, B. M. (2003). Do Depressive Symptoms Increase the Risk for the Onset of Coronary Disease ? A Systematic Quantitative Review. *Psychosomatic Medicine, 65*, 201-210. doi:10.1097/01.PSY.0000058371.50240.E3

Yang, P.-Y., Ho, K.-H., Chen, H.-C., & Chien, M.-Y. (2012). Exercise training improves sleep quality in middle-aged and older adults with sleep problems: a systematic review. *Journal of Physiotherapy, 58*(3), 157-163.

Yohannes, A., Willgoss, T., Baldwin, R., & Connolly, M. (2010). Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *International Journal of Geriatric psychiatry, 25*(12), 1209-1221.

Yu, S., Yarnell, J. W., Sweetnam, P. M., & Murray, L. (2003). What level of physical activity protects against premature cardiovascular death? The Caerphilly study. *Heart, 89*.

Yusuf, S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., . . . Lisheng, L. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet, 364*(9438), 937-952. doi:https://doi.org/10.1016/S0140-6736(04)17018-9

Ziegelstein, R. C., Fauerbach, J. a., Stevens, S. S., Romanelli, J., Richter, D. P., & Bush, D. E. (2000). Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Archives of Internal Medicine, 160*(12), 1818-1823. doi:10.1001/archinte.160.12.1818

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta psychiatrica Scandinavica, 67*(6), 361-370. doi:10.1111/j.1600-0447.1983.tb09716.x

# APPENDICES

**Appendix A: Systematic review search terms**

("Depressive Disorder, Major"[Mesh] AND "Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR (depressive AND symptoms) OR (unipolar AND depression) OR melancholia OR "Mood Disorders"[Mesh] OR (Beck AND Depression AND inventory) OR BDI OR (Hospital AND anxiety AND depression AND scale) OR HADS OR PHQ-9 OR (Hamilton AND Depression AND Rating AND Scale) OR (Primary AND Care AND Evaluation AND Mental AND Disorders) OR PRIME-MD OR (Centre AND Epidemiological AND Studies AND Depression AND Scale) OR CES-D OR (Structured AND Clinical AND Interview AND DSM-IV) OR SCID OR (World AND Health AND Organization AND Composite AND International AND Diagnostic AND Interview) OR CIDI OR (Schedule AND Affective AND Disorders AND Schizophrenia) OR SADS)

AND

("Chronic Disease"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR (Heart AND (Failure OR attack)) OR (myocardial AND infarction) OR "Cerebrovascular Disease"[Mesh] OR "Cardiomyopathies"[Mesh] OR PCI OR "Percutaneous Coronary Intervention"[Mesh] OR (Percutaneous AND transluminal AND coronary AND angioplasty) OR PCTA OR angioplasty OR Stent OR "Coronary artery bypass"[Mesh] OR CABG OR "Lung Diseases, Obstructive"[Mesh] OR asthma OR COPD OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR (respiratory AND disease) OR "Cancer" OR "Diabetes Mellitus, Type 2"[Mesh] OR "Diabetes Insipidus"[Mesh] OR "Diabetes Mellitus"[Mesh] OR DMT2)

AND

("Exercise"[Mesh] OR "Exercise Therapy"[Mesh] exercise OR (Physical AND (activity OR fitness)) OR running OR (physical AND therapy))

## Appendix B: Articles included in Herring et al. (2012) only

| Articles | Chronic illness | Reason for exclusion |
|---|---|---|
| Aylin K, Arzu D, Sabri S, Handan TE, Ridvan A. The effect of combined resistance and home-based walking exercise in type 2 diabetes patients. Int J Diab Dev Ctries. 2009;24(4):159-165. | Diabetes | Resistance training + aerobic exercise |
| Dugmore LD, Tipson RJ, Phillips MH, et al. Changes in cardiorespiratory fitness, psychological wellbeing, quality of life, and vocational status following a 12 month cardiac exercise rehabilitation programme. Heart. 1999;81(4):359-366. | Cardiac | Resistance training + aerobic exercise |
| Flynn KE, Pina IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301(14):1451-1459. | Cardiac | Depression at baseline only |
| Gary R, Lee SY. Physical function and quality of life in older women with diastolic heart failure: Effects of a progressive walking program on sleep patterns. Prog Cardiovasc Nurs. 2007;22(2):72-80. | Cardiac | Control group includes education program (but not in intervention group) |
| Jolly K, Taylor RS, Lip GYH, et al. A randomized trial of the addition of home-based exercise to specialist heart failure nurse care: the Birmingham Rehabilitation Uptake Maximisation study for patients with Congestive Heart Failure (BRUM-CHF) study. Eur J Heart Fail. 2009;11(2):205-13. | Cardiac | Resistance training + aerobic exercise |
| Lai SM, Studenski S, Richards L, et al. Therapeutic exercise and depressive symptoms after stroke. J Am Geriatr Soc. 2006;54(2):240-247. | Cardiac | Resistance training + aerobic exercise |
| Moug SJ, Grant S, Creed G, Boulton Jones M. Exercise during haemodialysis: West of Scotland pilot study. Scott Med J. 2003;49(1):14-17. | Kidney-related | Not NCD |
| Ouzouni S, Kouidi E, Sioulis A, Grekas D, Deligiannis A. Effects of intradialytic exercise training on health-related quality of life indices in haemodialysis patients. Clin Rehabil. 2009;23(1):53-63. | Kidney-related | Not NCD |
| Scholz U, Knoll N, Sniehotta FF, Schwarzer R. Physical activity and depressive symptoms in cardiac rehabilitation: Long-term effects of a self-management intervention. Soc Sci Med. 2006;62(12):3109-3120. | Cardiac | Not exercise intervention |
| Seki E, Watanabe Y, Sunayama, et al. Effects of phase III cardiac rehabilitation programs on health-related quality of life in elderly patients with coronary artery disease: Juntendo Cardiac Rehabilitation Program (J-CARP). Circ J. 2003;67(1):73-77. | Cardiac | Aerobic exercise not main component |
| Sorensen M, Anderssen S, Hjerman I, Holme I, Ursin H. The effect of exercise and diet on mental health and quality of life in middle-aged individuals with elevated risk factors for cardiovascular disease. J Sports Sci. 1999;17(5):369-377. | Cardiac | Resistance training + aerobic exercise |
| van Vilsteren MCBA, de Greef MHG, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counseling for sedentary haemodialysis patients in The Netherlands: Results of a randomized clinical trial. Nephrol Dial Transplant. 2005;20(1):141-146. | Kidney-related | Not NCD |
| Witham MD, Gray JM, Argo IS, Johnston DW, Struthers AD, McMurdo MET. Effect of a seated exercise program to improve physical function and health status in frail patients ≥ 70 years of age with heart failure. Am J Cardiol. 2005;95(9):1120-1124. | Cardiac | Resistance training + aerobic exercise |

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| Yu CM, Lau CP, Chau J, et al. A short course of cardiac rehabilitation program is highly cost effective in improving long-term quality of life in patients with recent myocardial infarction or percutaneous coronary intervention. Arch Phys Med Rehabil. 2004;85(12):1915-1922. | Cardiac | Resistance training + aerobic exercise |
| Belza B, Topolski T, Kinne S, Patrick DL, Ramsey SD. Does adherence make a difference? Results from a community-based aquatic exercise program. Nurs Res. 2002;51(5):285-291. | Chronic pain other than fibromyalgia | Not NCD |
| Clark DI, Downing N, Mitchell J, Coulson L, Syzpryt EP, Doherty M. Physiotherapy for anterior knee pain: A randomized controlled trial. Ann Rheum Dis. 2000;59(9):700-704. | Chronic pain other than fibromyalgia | Not NCD |
| Daltroy LH, Robb-Nicholson C, Iversen MD, Wright EA, Liang MH. Effectiveness of minimally supervised home aerobic training in patients with systemic rheumatic disease. Br J Rheumatol. 1995;34(11):1064-1069. | Chronic pain other than fibromyalgia | Not NCD |
| Fransen M, Nairn L, Winstanley J, Lam P, Edmonds J. Physical activity for osteoarthritis management: A randomized controlled clinical trial evaluating hydrotherapy or Tai Chi classes. Arthritis Care Res. 2007;57(3):407-414. | Chronic pain other than fibromyalgia | Not NCD |
| Giubilei G, Mondani N, Minervini A, et al. Physical activity of men with chronic prostatitis/chronic pelvic pain syndrome not satisfied with conventional treatments – Could it represent a valid option? The physical activity and male pelvic pain trial: A double-blind, randomized study. J Urol. 2007;177:159-165. | Chronic pain other than fibromyalgia | Not NCD |
| Hurley MV, Walsh NE, Mitchell HL, et al. Clinical effectiveness of a rehabilitation program integrating exercise, self-management, and active coping strategies for chronic knee pain: A cluster randomized trial. Arthritis Care Res. 2007;57(7):1211-1219. | Chronic pain other than fibromyalgia | Not NCD |
| Jessep SA, Walsh NE, Ratcliffe J, Hurley MV. Long-term clinical benefits and costs of an integrated rehabilitation programme compared with outpatient physiotherapy for chronic knee pain. Physiotherapy. 2009;95(2):94-102. | Chronic pain other than fibromyalgia | Not NCD |
| Leibetseder V, Strauss-Blasche G, Marktl W, Ekmekcioglu C. Does aerobic training enhance effects of spa therapy in back pain patients? A randomized, controlled clinical trail. Forsch Komplementarmed. 2007;14(4):202-206. | Chronic pain other than fibromyalgia | Not NCD |
| Lim H-J, Moon Y-I, Lee MS. Effects of home-based daily exercise therapy on joint mobility, daily activity, pain, and depression in patients with ankylosing spondylitis. Rheumatol Int. 2005;25(3):225-229. | Chronic pain other than fibromyalgia | Not NCD |
| Neuberger GB, Aaronson LS, Gajewski B, et al. Predictors of exercise and effects of exercise on symptoms, function, aerobic fitness, and disease outcomes of rheumatoid arthritis. Arthritis Care Res. 2007;57(6):943-952. | Chronic pain other than fibromyalgia | Not NCD |
| O'Reilly SC, Muir KR, Doherty M. Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: A randomized controlled trial. Ann Rheum Dis. 1999:58(1):15-19. | Chronic pain other than fibromyalgia | Not NCD |
| Patrick DL, Ramsey SD, Spencer AC, Kinne S, Belza B, Topolski TD. Economic evaluation of aquatic exercise for persons with osteoarthritis. Medical Care. 2001;39(5):413-424. | Chronic pain other than fibromyalgia | Not NCD |
| Pengel LHM, Refshauge KM, Maher CG, Nicholas MK, Herbert RD, McNair P. Physiotherapist-directed exercise, advice, or both for subacute low back pain: A randomized trial. Ann Intern Med. 2007;146(11):787-796. | Chronic pain other than fibromyalgia | Not NCD |
| Penninx BWJH, Rejeski WJ, Pandya J, et al. Exericse and depressive symptoms: A comparison of aerobic and resistance exercise effects on emotional and physical function in older persons with high and low | Chronic pain other than fibromyalgia | Not NCD |

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| depressive symptomatology. J Gerontol B Psychol Sci Soc Sci. 2002;57B(2):P124-P132. | | |
| Smeets RJEM, Vlaeyen JWS, Hidding A, Kester ADM, van der Heijden GJMG, Knottnerus JA. Chronic low back pain: Physical training, graded activity with problem solving training, or both? The one-year post-treatment results of a randomized controlled trial. Pain. 2008;134(3):263-276. | Chronic pain other than fibromyalgia | Not NCD |
| Strombeck BE, Theander E, Jacobsson LTH. Effects of exercise on aerobic capacity and fatigue in women with primary Sjogren's syndrome. Rheumatology. 2007;46(5):868-871. | Chronic pain other than fibromyalgia | Not NCD |
| Tench CM, McCarthy J, McCurdie I, White PD, D'Cruz DP. Fatigue in systemic lupus erythematosus: A randomized controlled trial of exercise. Rheumatology (Oxford). 2003;42(9):1050-1054. | Chronic pain other than fibromyalgia | Not NCD |
| Wand BM, Bird C, McAuley JH, Dore CJ, MacDowell, De Souza LH. Early intervention for the management of acute low back pain. A single-blind randomized controlled trial of biopsychosocial education, manual therapy, and exercise. Spine. 2004;29(21):2350-2356. | Chronic pain other than fibromyalgia | Not NCD |
| Wang C, Schmid CH, Hibberd PL, et al. Tai Chi is effective in treating knee osteoarthritis: A randomized controlled trial. Arthritis Rheum. 2009;61:1545-1553. | Chronic pain other than fibromyalgia | Not NCD |
| Weiner DK, Perera S, Rudy TE, Glick RM, Shenoy S, Delitto A. Efficacy of percutaneous electrical nerve stimulation and therapeutic exercise for older adults with chronic low back pain: A randomized controlled trial. Pain. 2008;140(5):344-357. | Chronic pain other than fibromyalgia | Not NCD |
| Williams K, Abildso C, Steinberg L, et al. Evaluation of the effectiveness and efficacy of iyengar yoga therapy on chronic low back pain. Spine. 2009;34:2066-2076. | Chronic pain other than fibromyalgia | Not NCD |
| Etnier JL, Karper WB, Gapin JI, Barella LA, Chang YK, Murphy KJ. Exercise, fibromyalgia, and fibrofog: A pilot study. J Phys Act Health. 2009;6(2):239-246. | Fibromyalgia | Not NCD |
| Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: Results of a randomized trial. Arthritis Res Ther. 2010;12(2):R55-R63. | Fibromyalgia | Not NCD |
| Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity in adults with fibromyalgia. J Clin Rheumatol. 2011;17:64-68. | Fibromyalgia | Not NCD |
| Gowans SE, deHueck A, Voss S, Silaj A, Abbey SE, Reynolds WJ. Effect of randomized, controlled trial of exercise on mood and physical function in individuals with fibromyalgia. Arthritis Care Res. 2001;45(6):519-529. | Fibromyalgia | Not NCD |
| Hakkinen A, Hakkinen K, Hannonen P, Alen M. Strength training induced adaptations in neuromuscular function of premenopausal women with fibromyalgia: Comparison with health women. Ann Rheum Dis. 2001;60(1):21-26. | Fibromyalgia | Not NCD |
| Jones KD, Burckhardt CS, Deodhar AA, Perrin NA, Hanson GC, Bennett RM. A six-month randomized controlled trial of exercise and pyridostigmine in the treatment of fibromyalgia. Arthritis Rheum. 2008;58(2):612-622. | Fibromyalgia | Not NCD |
| Mannerkorpi K, Nyberg B, Ahlmen M, Ekdahl C. Pool exercise combined with an education program for patients with fibromyalgia syndrome. A prospective, randomized study. J Rheumatol. 2000;27(10):2473-2481. | Fibromyalgia | Not NCD |
| Mannerkorpi K, Nordeman L, Ericsson A, et al. Pool exercise for patients with fibromyalgia or chronic widespread pain: A randomized controlled trial and subgroup analyses. J Rehabil Med. 2009;41(9):751-760. | Fibromyalgia | Not NCD |

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| Rooks DS, Gautam S, Romeling M, et al. Group exercise, education, and combination selfmanagement in women with fibromyalgia. Arch Intern Med. 2007;167(20):2192-2200. | Fibromyalgia | Not NCD |
| Schachter CL, Busch AJ, Peloso PM, Sheppard MS. Effects of short versus long bouts of aerobic exercise in sedentary women with fibromyalgia: A randomized controlled trial. Phys Ther. 2003;83(4):340-358. | Fibromyalgia | Not NCD |
| Tomas-Carus P, Gusi N, Hakkinen A, Hakkinen K, Leal A, Ortega-Alonso A. Eight months of physical training in warm water improves physical and mental health in women with fibromyalgia: A randomized controlled trial. J Rehabil Med. 2008;40(4):248-252. | Fibromyalgia | Not NCD |
| Valim V, Oliveira L, Suda A, et al. Aerobic fitness effects in fibromyalgia. J Rheumatol. 2003;30:1060-1069. | Fibromyalgia | Not NCD |
| Wang C, Schmid, Rones R, et al. A randomized trial of tai chi for fibromyalgia. N Eng J Med. 2010;363:743-754. | Fibromyalgia | Not NCD |
| Daley AJ, Copeland RJ, Wright NP, Roalfe A, Wales JKH. Exercise therapy as a treatment for psychopathologic conditions in obese and morbidly obese adolescents: A randomized controlled trial. Pediatrics. 2006;118(5):2126-2134. | Obesity | Not NCD/Not adults |
| Ghroubi S, Elleuch H, Chikh T, Kaffel N, Abid M, Elleuch MH. Physical training combined with dietary measures in the treatment of adult obesity. A comparison of two protocols. Ann Phys Rehabil Med. 2009;52(5):394-413. | Obesity | Not NCD |
| Gusi N, Reyes MC, Gonzalez-Guerrero JL, Herrera E, Garcia JM. Cost-utility of a walking programme for moderately depressed, obese, or overweight elderly women in primary care: A randomized controlled trial. BMC Public Health. 2008;8:231-240. | Obesity | Not NCD |
| Kiernan M, King AC, Stefanick ML, Killen JD. Men gain additional psychological benefits by adding exercise to a weight-loss program. Obes Res. 2001;9(12):770-777. | Obesity | Not NCD |
| Nieman DC, Custer WF, Butterworth DE, Utter AC, Henson DA. Psychological response to exercise training and/or energy restriction in obese women. J Psychosom Res. 2000;48(1):23-29. | Obesity | Not NCD |
| Sarsan A, Ardic F, Ozgen M, Topuz O, Sermez Y. The effects of aerobic and resistance exercise in obese women. Clin Rehabil. 2006;20(9):773-782. | Obesity | Not NCD |
| Thomson RL, Buckley JD, Lim SS, et al. Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome. Fertil Steril. 2010;94:1812-1816. | Obesity | Not NCD |
| Daley AJ, Crank H, Saxton JM, Mutrie N, Coleman R, Roalfe A. Randomized trial of exercise therapy in women treated for breast cancer. J Clin Oncol. 2007;25(13):1713-1721. | Cancer | Control group included stretching but not intervention |
| Dimeo FC, Stieglitz RD, Novelli-Fischer U, Fetscher S, Keul J. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. Cancer. 1999;85(10):359-366. | Cancer | Intervention less than 4 weeks |
| Mutrie N, Campbell AM, Whyte F, et al. Benefits of supervised group exercise programmefor women being treated for early stage breast cancer: pragmatic randomised controlled trial. BMJ. 2007;334(7592):517-523. | Cancer | Resistance training + aerobic exercise |
| Thorsen L, Skovlund E, Stromme SB, Hornslein K, Dahl AA, Fossa SD. Effectiveness of physical activity on cardiorespiratory fitness and health-related quality of life in young middleaged cancer patients shortly after chemotherapy. J Clin Oncol. 2005;23(10):2378-2388. | Cancer | Not specifically aerobic exercise intervention (multicomponent) |
| Haworth J, Young C, Thornton E. The effects of an 'exercise and education' programme on exercise self-efficacy and levels of | Neurological disorder | Not NCD |

| | | |
|---|---|---|
| independent activity in adults with acquired neurological pathologies: An exploratory, randomized study. Clin Rehabil. 2009;23(4):371-383. | | |
| Hicks AL, Martin KA, Ditor DS, et al. Long-term exercise training in persons with spinal cord injury: Effects on strength, arm ergometry performance and psychological well-being. Spinal Cord. 2003;41(1):34-43. | Neurological disorder | Not NCD |
| Rolland Y, Pillard F, Klapouszczak A, et al. Exercise program for nursing home residents with Alzheimer's disease: A 1-year randomized, controlled trial. J Am Geriatr Soc. 2007;55(2):158-165. | Neurological disorder | Not NCD |
| Cakit BD, Nacir B, Genc H, et al. Cycling progressive resistance training for people with multiple sclerosis. Am J Phys Med Rehabil. 2010;89:446-457. | Multiple sclerosis | Not NCD |
| Dalgas U, Stenager E, Jakobsen J, et al. Fatigue, mood and quality of life improve in MS patients after progressive resistance training. Mult Scler. 2010;16:480-490. | Multiple sclerosis | Not NCD |
| Oken BS, Kishiyama S, Zajdel D, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. Neurology. 2004;62(11):2058-2064. | Multiple sclerosis | Not NCD |
| Neidig JL, Smith BA, Brashers DE. Aerobic exercise training for depressive symptom management in adults living with HIV infection. J Assoc Nurses AIDS Care. 2003;14(2):30-40. | AIDS | Not NCD |
| White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behavior therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): A randomized trial. Lancet. 2011;377:823-836. | Chronic fatigue | Not NCD |
| Anderson RT, King A, Stewart AL, Camacho F, Rejeski WJ. Physical activity counseling in primary care and patient well-being: Do patients benefit? Ann Behav Med. 2005;30(2):146-154. | Any CI | Not just one NCD |
| Carei TR, Fyfe-Johnson AL, Breuner CC, Brown MA. Randomized controlled clinical trial of yoga in the treatment of eating disorders. J Adolesc Health. 2010;46(4):346-351. | Eating disorder | Not NCD |
| Merom D, Phongsavan P, Wagner R, et al. Promoting walking as an adjunct intervention to group cognitive behavioral therapy for anxiety disorders – A pilot group randomized trial. J Anxiety Disord. 2008;22(6):959-968. | Anxiety disorder | Not NCD |
| Skrinar GS, Huxley NA, Hutchinson DS, Menninger E, Glew P. The role of a fitness intervention on people with serious psychiatric disabilities. Psychiatr Rehabil J. 2005;29(2):122-127. | Psychiatric disorders | Not NCD |
| Donesky-Cuenco D, Nguyen HQ, Paul S, Carrieri-Kohlman V. Yoga therapy decreases dyspnea-related distress and improves functional performance in people with chronic obstructive pulmonary disease: A pilot study. J Altern Complement Med. 2009;15(3):225-234. | COPD | Not aerobic exercise |
| Emery CF, Schein RL, Hauck ER, MacIntyre NR. Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. Health Psychol. 1998;17(3):232-240. | COPD | Resistance training + aerobic exercise; multicomponent intervention |
| Hospes G, Bossenbroek L, ten Hacken NHT, van Hengel P, de Greef MHG. Enhancement of daily physical activity increases physical fitness of outclinic COPD patients: Results of an exercise counseling program. Patient Educ Couns. 2009;75(2):274-278. | COPD | Counselling intervention; no structured intervention |
| Paz-Diaz H, Montes de Oca M, Lopez JM, Celli BR. Pulmonary rehabilitation improves depression, anxiety, dyspnea and health status in patients with COPD. Am J Phys Med Rehabil. 2007;86(1):30-36. | COPD | Resistance training + aerobic exercise; multicomponent intervention |

## Appendix C: Articles included both in Herring et al. (2012) and thesis systematic review

| Articles | Chronic illness | Total n |
|---|---|---|
| Blumenthal JA, Sherwood A, Babyak MA, et al. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: A randomized controlled trial. JAMA. 2005;293(13):1626-1634. | Cardiac | 90 |
| Gary RA, Dunbar SB, Higgins MK, Musselman DL, Smith AL. Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. J Psychosom Res.2010;69(2):119-131. | Cardiac | 35 |
| Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: A randomized, controlled, singleblind trial. Circ Heart Fail. 2010;3:659-667. | Cardiac | 46 |
| Koukouvou G, Kouidi E, Iacovides A, Konstantinidou E, Kaprinis G, Deligiannis A. Quality of life, psychological and physiological changes following exercise training in patients with chronic heart failure. J Rehabil Med. 2004;36(1):36-41. | Cardiac | 26 |
| Kulcu DG, Kurtais Y, Tur BS, Gulec S, Seckin B. The effect of cardiac rehabilitation on quality of life, anxiety and depression in patients with congestive heart failure. A randomized controlled trial, short-term results. Eura Medicophys. 2007;43(4):489-497. | Cardiac | 44 |
| Smith PJ, Blumenthal JA, Babyak MA, Georgiades A, Hinderliter A, Sherwood A. Effects of exercise and weight loss on depressive symptoms among men and women with hypertension. J Psychosom Res. 2007;63(5):463-469. | Cardiac | 66 |
| van den Berg-Emons R, Balk A, Bussmann H, Stam H. Does aerobic training lead to a more active lifestyle and improved quality in patients with chronic heart failure? Eur J Heart Fail. 2004;6(1):95-100. | Cardiac | 34 |
| Monga U, Garber SL, Thornby J, et al. Exercise prevents fatigue and improves quality of life in prostate cancer patients undergoing radiotherapy. Arch Phys Med Rehabil. 2007;88(11):1416-1422. | Cancer | 21 |
| Cadmus LA, Salovey P, Yu H, Chung G, Kasl S, Irwin ML. Exercise and quality of life during and after treatment for breast cancer: Results of two randomized controlled trials. Psychooncology. 2009;18(4):343-352. | Cancer | 75 |
| Courneya KS, Friedenreich CM, Quinney HA, Fields ALA, Jones LW, Fairey AS. A randomized trial of exercise and quality of life in colorectal cancer survivors. Eur J Cancer Care. 2003;12(4):347-357. | Cancer | 93 |
| Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. J Clin Oncol. 2007;25(28):4396-4404. | Cancer | 160 |
| Courneya KS, Sellar CM, Stevinson C, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. J Clin Oncol. 2009;27(27):4605-4612. | Cancer | 122 |
| Payne JK, Held J, Thorpe J, Shaw H. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncol Nurs Forum. 2008;35(4):635-642. | Cancer | 20 |
| Segar ML, Katch VL, Roth RS, et al. The effect of aerobic exercise on self-esteem and depressive and anxiety symptoms among breast cancer survivors. Oncol Nurs Forum. 1998;25(1):107-113. | Cancer | 15 |
| Guell R, Resqueti V, Sangenis M, et al. Impact of pulmonary rehabilitation on psychosocial morbidity in patients with severe COPD. Chest. 2006;129(4):899-904. | COPD | 35 |

## Appendix D: Articles included in thesis systematic review only

| Articles | Chronic illness | Reason for exclusion in Herring et al. |
|---|---|---|
| Gonçalves RC, Nunes MPT, Cukier A, Stelmach R, Martins MA, Carvalho CRF. Effects of an aerobic physical training program on psychosocial characteristics, quality-of-life, symptoms and exhaled nitric oxide in individuals with moderate or severe persistent asthma. Brazilian J. Phys. Ther. SciELO Brasil; 2008;12:127–35. | Asthma | Unknown |
| Mendes FAR, Goncalves RC, Nunes MPT, Saraiva-Romanholo BM, Cukier A, Stelmach R, et al. Effects of aerobic training on psychosocial morbidity and symptoms in patients with asthma: a randomized clinical trial. Chest. United States; 2010;138:331–7. | Asthma | Unknown |
| Gayle RC, Spitler DL, Karper WB, Jaeger RM, Rice SN. Psychological changes in exercising COPD patients. Int. J. Rehabil. Res. Int. Zeitschrift fur Rehabil. Rev. Int. Rech. Readapt. 1988;11:335–42. | COPD | Unknown |
| Blumenthal J a, Babyak M a, O'Connor C, Keteyian S, Landzberg J, Howlett J, et al. Effects of exercise training on depressive symptoms in patients with chronic heart failure: the HF-ACTION randomized trial. Jama [Internet]. 2012;308:465–74. | Cardiac | Published after June 1st, 2011 |
| Isaksen K, Munk PS, Giske R, Larsen AI. Effects of aerobic interval training on measures of anxiety, depression and quality of life in patients with ischaemic heart failure and an implantable cardioverter defibrillator: A prospective non-randomized trial. J. Rehabil. Med. [Internet]. Sweden: Foundation of Rehabilitation Information; 2016;48:300–6. | Cardiac | Published after June 1st, 2011 |
| Stern MJ, Gorman PA, Kaslow L. The group counseling v exercise therapy study. A controlled intervention with subjects following myocardial infarction. Arch. Intern. Med.; 1983;143:1719–25. | Cardiac | Unknown |
| Roviaro R, Holmes DS, Holmsten RD. Influence of a Cardiac Rehabilitation Program on the Cardiovascular, Psychological, and Social Functioning of Cardiac Patients. J Beh Med. 1984;7:61. | Cardiac | Not RCT |
| Chrysohoou C, Tsitsinakis G, Vogiatzis I, Cherouveim E, Antoniou C, Tsiantilas A, et al. High intensity, interval exercise improves quality of life of patients with chronic heart failure: a randomized controlled trial. QJM. England; 2014;107:25–32. | Cardiac | Published after June 1st, 2011 |
| Lennon O, Carey A, Gaffney N, Stephenson J, Blake C. A pilot randomized controlled trial to evaluate the benefit of the cardiac rehabilitation paradigm for the non-acute ischaemic stroke population. Clin. Rehabil. England; 2008;22:125–33. | Cardiac | Unknown |
| Asbury EA, Slattery C, Grant A, Evans L, Barbir M, Collins P. Cardiac rehabilitation for the treatment of women with chest pain and normal coronary arteries. Menopause. 2008;15:454–60. | Cardiac | Unknown |
| Asbury E a., Webb CM, Probert H, Wright C, Barbir M, Fox K, et al. Cardiac Rehabilitation to Improve Physical Functioning in Refractory Angina: A Pilot Study. Cardiology. Switzerland; 2012;122:170–7. | Cardiac | Published after June 1st, 2011 |
| Topcuoglu A, Gokkaya NKO, Ucan H, Karakuş D. The effect of upper-extremity aerobic exercise on complex regional pain syndrome type I: A randomized controlled study on subacute stroke. Top. Stroke Rehabil. United Kingdom: Maney Publishing; 2015;22:253–61. | Cardiac | Published after June 1st, 2011 |
| Dodd MJ, Cho MH, Miaskowski C, Painter PL, Paul SM, Cooper BA, et al. A randomized controlled trial of home-based exercise for cancer-related fatigue in women during and after chemotherapy with or without radiation therapy. Cancer Nurs. United States; 2010;33:245–57. | Cancer | Unknown |
| Ergun M, Eyigor S, Karaca B, Kisim A, Uslu R. Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients. Eur. J. Cancer Care (Engl). England; 2013;22:626–37. | Cancer | Published after June 1st, 2011 |

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|---|---|---|
| Chen H-M, Tsai C-M, Wu Y-C, Lin K-C, Lin C-C. Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. Br. J. Cancer. England; 2015;112:438–45. | Cancer | Published after June 1st, 2011 |
| Gokal K, Wallis D, Ahmed S, Boiangiu I, Kancherla K, Munir F. Effects of a self-managed home-based walking intervention on psychosocial health outcomes for breast cancer patients receiving chemotherapy: a randomised controlled trial. Support. care cancer Off. J. Multinatl. Assoc. Support. Care Cancer. 2015; | Cancer | Published after June 1st, 2011 |
| Sardar MA, Boghrabadi V, Sohrabi M, Aminzadeh R, Jalalian M. The Effects of Aerobic Exercise Training on Psychosocial Aspects of Men with Type 2 Diabetes Mellitus. 2014;6:196–202. | Diabetes | Published after June 1st, 2011 |

## Appendix E: Mean scores of depression questionnaires

| | | | Control | | Intervention | |
|---|---|---|---|---|---|---|
| **Study** | **Type of NCD** | **Depression assessment** | **Baseline** | **Post** | **Baseline** | **Post** |
| Cadmus et al., 2009 | Cancer (Breast) | CES-D | 9.2 (8.6) | 10.8 (10.1) | 9.3 (3.6) | 9.6 (9.3) |
| Chen et al., 2015 | Cancer (Lung) | HADS | 4.74 (3.73) | 4.92 (3.14) | 5.67 (3.57) | 4.92 (3.14) |
| Courneya et al., 2003 | Cancer (Colorectal) | CES-D | 10.1 (12) | 9.6 (10.9) | 9.6 (8.1) | 8.6 (8.7) |
| Courneya et al., 2007 | Cancer (Breast) | CES-D | 13.9 (9.7) | 10.8 (9.4) | 12.8 (9.8) | 9.7 (9.3) |
| Courneya et al., 2009 | Cancer (Lymphoma) | CES-D-SF | 6 (4.5) | 6.1 (5) | 7.7 (5.7) | 5.4 (4.5) |
| Dodd et al., 2010 | Cancer (various) | CES-D | N/A | N/A | N/A | N/A |
| Ergun et al., 2013 | Cancer (Breast) | BDI | 7.5 (7.95) | 5.15 (5.18) | 9.05 (8.18) | 8.88 (10.48) |
| Gokal et a., 2016 | Cancer (Breast) | HADS | 6.68 (4) | 6.16 (3.23) | 5.52 (3.79) | 4.44 (3.37) |
| Monga et al., 2007 | Cancer(Prostate) | BDI | 3.6 (5.0) | 4.2 (3.4) | 3.5 (5.4) | 2.8 (5.5) |
| Payne et al., 2008 | Cancer (Breast) | CES-D | 10 | 10 | 15 | 8 |
| Segar et al., 1998 | Cancer (Breast) | BDI | 10 | 10 | 8.5 | 5.5 |
| Asbury et al., 2008 | Cardiac (Chest pain) | HADS | 4.2 (2.7) | 3.9 (2.5) | 5.4 (3.6) | 4.4 (3.4) |
| Asbury et al., 2012 | Cardiac (Angina) | HADS | 6.60 (4.13) | N/A | 5.90 (3.83) | N/A |
| Blumenthal et al., 2005 | Cardiac (IHD) | BDI-II | 8.9 (7.9) | 10.01 (0.6) | 9.8 (7.7) | 8.2 (0.6) |
| Blumenthal et al., 2012 | Cardiac (CHF) | BDI-II | 8 | 9.7 | 8 | 8.95 |
| Chrysohoou et al., 2014 | Cardiac (CHF) | ZDRS | 37 (8) | 41 (10) | 37 (8) | 30 (6) |
| Gary et al., 2010 | Cardiac (HF) | HAM-D | 15.2 (3.6) | 9.3 (4.9) | 15.4 (3.4) | 8.4 (5.6) |
| Isaksen et al., 2016 | Cardiac (HF) | HADS | 2.7 | 3.6 | 2.8 | 1.8 |
| Kitzman et a., 2010 | Cardiac (HF) | CES-D | 2.2 (2) | 1.4 (1.5) | 2.5 (2.2) | 1.2 (1.5) |
| Koukouvou et al., 2004 | Cardiac (CHF) | BDI | 18.5 (5.1) | 18.8 (5.1) | 18.6 (4.65) | 13.1 (3.13) |
| Kulcu et al., 2007 | Cardiac (HI) | BDI | 20.2 (12.5) | 22.5 (11.8) | 18.4 (9.3) | 13.5 (8) |
| Lennon et al., 2008 | Cardiac (Stroke) | HADS | 7 (median) | 6 (median) | 5 (median) | 4 (median) |
| Roviaro et a., 1984 | Cardiac (MI) | BDI-II | N/A | N/A | N/A | N/A |
| Smith et al, 2007 | Cardiac (Hypertension) | BDI | 5.7 | N/A | 5.2 | N/A |
| Stern et al., 1983 | Cardiac (MI) | ZDRS | 34.9 | 33.5 | 37.33 | 38.33 |
| Topcuoglu et al., 2015 | Cardiac (Stroke) | BDI | N/A | N/A | N/A | N/A |
| van den Berg-Emons et al., 2004 | Cardiac (HF) | HADS | 4.3 (3.2) | 4.8 (3.1) | 4.7 (5.2) | 3.4 (4.0) |
| Sardar et al., 2014 | Diabetes T2 | GHQ | 7.25 (7.95) | 7.44 (0.89) | 7.18 (0.52) | 7.29 (0.58) |
| Gayle et al., 1988 | Respiratory (COPD) | GHQ | 41.46 | 42.08 | 44.17 | 43.75 |
| Güell et al., 2006 | Respiratory (COPD) | SCL-90-R | 0.6 (0.6) | 0.9 (0.6) | 1.3 (0.8) | 0.8 (0.5) |
| Gonçalves et al., 2008 | Respiratory (asthma) | BDI | 12.45 | 9.05 | 11 | 6.6 |
| Mendes et al., 2010 | Respiratory (asthma) | BDI | N/A | N/A | N/A | N/A |

Notes : UC = Usual care ; BDI = Beck Depression Inventory; CESD-SF = Short-form Center for Epidemiological Studies-Depression Scale ; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; SCL-90-R = The Revised Symptom Checklist (Depression scale); ZDRS = Zung Depression Rating Scale; CHF = Chronic heart failure; COPD = Chronic obstructive pulmonary disorder; HF = Heart failure; IHD = Ischemic heart disease; MI = Myocardial infarction; N/A: Data not available.

**Appendix F: Baseline characteristics of PAL (N = 640) and RESP (N = 513) cohorts according to whether they engaged in LTPA or not**

| | PAL cohort (N = 640) | | | RESP cohort (N = 513) | | | |
|---|---|---|---|---|---|---|---|
| | No LTPA *Mean (SD) or % (n)* (*n* = 244) | Any LTPA *Mean (SD) or % (n)* (*n* = 396) | ***p* value** | No LTPA *Mean (SD) or % (n)* (*n* = 197) | Any LTPA *Mean (SD) or % (n)* (*n* = 316) | ***p* value** | **Between-groups *p* value** |
| **Demographics** | | | | | | | |
| Age (yrs) | 54.23 (13.78) | 53.72 (14.31) | .657 | 55.04 (15.52) | 51.28 (16.16) | .010 | < .001 |
| Sex (% women) | 40 (98) | 39 (155) | .797 | 68 (134) | 61 (193) | .161 | .255 |
| Ethnicity (% White) | 93 (227) | 92 (365) | .682 | 92 (181) | 95 (300) | .126 | .340 |
| BMI | 28.87 (6.57) | 27.11 (5.76) | .002 | 32.09 (7.80) | 29.58 (6.73) | < .001 | < .001 |
| Smoking (% yes) | 12 (30) | 5 (20) | .003 | 16 (32) | 7 (22) | .001 | .164 |
| **Asthma characteristics** | | | | | | | |
| ACQ | 1.11 (1.10) | 0.91 (0.97) | .020 | 1.65 (1.22) | 1.25 (1.06) | < .001 | < .001 |
| ICS | 660.40 (532.80) | 567.30 (489.00) | .043 | 876.40 (656.00) | 741.60 (538.50) | .050 | < .001 |
| **Physical activity characteristic** | | | | | | | |
| Level of PA (MET-hours/week) | 0 | 7.70 (0.436) | < .001 | 0 | 5.54 (0.228) | < .001 | < .001 |
| **Psychological characteristics** | | | | | | | |
| BDI | 9.18 (8.91) | 7.76 (8.06) | .050 | 8.22 (7.84) | 5.61 (5.50) | .001 | .026 |
| Mood Disorder (% yes) | 15 (37) | 17 (68) | .645 | 12 (24) | 5 (16) | .003 | < .001 |

## Appendix G: GLM models for merged cohorts (RESP and PAL)

Table 3.6. GLM models of continuous LTPA and LTPA intensity on elevated depressive symptoms

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | B (SE) | *p* value | ES | B (SE) | *p* value | ES | B (SE) | *p* value | ES |
| LTPA | -0.035 (0.036) | .336 | .000-.004 | -0.027 (0.037) | .461 | .000-.003 | 0.007 (0.036) | .853 | .000-.003 |
| I*ntensity* | | | | | | | | | |
| Moderate | -0.024 (0.094) | .802 | .000-.005 | -0.028 (0.095) | .769 | .000-.005 | -0.004 (0.091) | .968 | .000-.005 |
| Vigorous | *-0.362 (0.195)* | *.064* | .000-.007 | -0.267 (0.202) | .187 | .000-.006 | -0.069 (0.196) | .725 | .000-.006 |

Note. Model 1 = general linear model (GLM) of main effects without covariates; Model 2 = GLM of main effects with covariates (age, sex, BMI, and cohort); Model 3 = GLM of main effects with covariates (age, sex, BMI, cohort, dose of ICS, and ACQ score).

Table 3.7. GLM models of continuous LTPA and LTPA intensity on elevated depressive symptoms (BDI ≥ 12)

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | B (SE) | *p* value | ES | B (SE) | *p* value | ES | B (SE) | *p* value | ES |
| LTPA | 0.052 (0.074) | .483 | .000-.001 | 0.042 (0.074) | .573 | .000-.001 | 0.056 (0.073) | .446 | .000-.001 |
| *Intensity* | | | | | | | | | |
| Moderate | 0.161 (0.169) | .338 | .000-.025 | 0.094 (0.168) | .574 | 000-.025 | 0.125 (0.166) | .451 | .000-.025 |
| Vigorous | *-0.748 (0.382)* | *.051* | .000-.001 | -0.612 (0.397) | .124 | .000-.001 | -0.475 (0.400) | .235 | .000-.001 |

Note. Model 1 = general linear model (GLM) of main effects without covariates; Model 2 = GLM of main effects with covariates (age, sex, BMI, and cohort); Model 3 = GLM of main effects with covariates (age, sex, BMI, cohort, dose of ICS, and ACQ score).

Table 3.8. GLM models of dichotomous LTPA (y/n) and LTPA intensity on depressive symptoms

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | B (SE) | *p* value | ES | B (SE) | *p* value | ES | B (SE) | *p* value | ES |
| **LTPA (y/n)** | **-1.407 (0.478)** | **.003** | **.005-.013** | **-1.237 (0.479)** | **.010** | **.005-.013** | -0.673 (0.463) | .146 | .005-.013 |
| Optimal LTPA (y/n) | -0.383 (0.714) | .592 | .000-.002 | -0.254 (0.729) | .728 | .000-.003 | 0.227 (0.706) | .748 | .000-.003 |
| *Intensity* | | | | | | | | | |
| Moderate (y/n) | -0.517 (0.494) | .295 | .000-.004 | -0.729 (0.512) | .154 | .000-.004 | -0.313 (0.492) | .525 | .000-.004 |
| Vigorous (y/n) | *-1.165 (0.700)* | *.096* | .001-.006 | -0.873 (0.713) | .221 | .002-.006 | -0.080 (0.686) | .909 | .001-.006 |

Note. Model 1 = general linear model (GLM) of main effects without covariates; Model 2 = GLM of main effects with covariates (age, sex, BMI, and cohort); Model 3 = GLM of main effects with covariates (age, sex, BMI, cohort, dose of ICS, and ACQ score).

Table 3.9. GLM models of dichotomous LTPA (y/n) and LTPA intensity on depressive symptoms (BDI ≥ 12)

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | B (SE) | *p* value | ES | B (SE) | *p* value | ES | B (SE) | *p* value | ES |
| LTPA (y/n) | **-1.633 (0.848)** | **0.054** | **.004-.016** | **-1.786 (0.876)** | **0.042** | **.005-.018** | -1.341 (0.891) | 0.132 | .005-.018 |
| Optimal LTPA (y/n) | 0.881 (1.353) | 0.515 | .000-.004 | 0.402 (1.363) | 0.768 | .000-.004 | 0.619 (1.350) | 0.646 | .000-.004 |
| *Intensity* | | | | | | | | | |
| Moderate (y/n) | 0.563 (0.947) | 0.534 | .000-.003 | -0.720 (0.984) | 0.456 | .000-.005 | 0.003 (0.991) | 0.997 | .000-.005 |
| Vigorous (y/n) | -0.308 (1.033) | 0.765 | .000 | -0.467 (1.080) | 0.665 | .000 | -0.393 (1.064) | 0.712 | .000 |

Note. Model 1 = general linear model (GLM) of main effects without covariates; Model 2 = GLM of main effects with covariates (age, sex, BMI, and cohort); Model 3 = GLM of main effects with covariates (age, sex, BMI, cohort, dose of ICS, and ACQ score).