SEX DIFFERENCES IN PHYSIOLOGICAL RESPONSES AFTER CARDIAC REHABILITATION

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ABSTRACT

Background and Purpose: Heart disease (HD) is one of the leading causes of death in men and women in Canada. Many HD patients are referred for cardiac rehabilitation (CR) which is a multidisciplinary outpatient supervised exercise program consisting of aerobic and resistance training to improve cardiovascular health. Previous studies have shown that healthy men and women respond differently to aerobic and resistance training. The purpose of this systematic review is to discover any physiological differences in male and female HD patient responses to a CR program. **Methods and Results**: A search strategy was generated to investigate the relationships between heart disease patients, a supervised exercise program, physiological outcomes, and gender differences. **Conclusions:** This review presents that HD patients respond similarly in most physiological variables regardless of sex. Though, many studies discussing maximal oxygen consumption, functional capacity, six-minute walk distances, and grip strength strongly suggest that men benefit more.

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List of Abbreviations

6MWD: six-minute walk distance

6MWT: six-minute walk test

AF: atrial fibrillation

AMI: acute myocardial infarction

Anglt2: angiopoietin like 2

ACS: acute coronary syndrome

BCM: body cell mass

BF: breathing frequency

BMI: body mass index

BNP: brain natriuretic peptide

BP: blood pressure

CABG: coronary bypass graft surgery

CAD: coronary artery disease

CHF: chronic heart failure

CO: cardiac output

CR: cardiac rehabilitation

CRP: c-reactive protein

CVD: cardiovascular disease

DBP: diastolic blood pressure

EF: ejection fraction

E_{α}: estrogen receptor alpha

E_{β}: estrogen receptor beta

E/A: early filling to diastolic filling ratio

FBF: forearm blood flow

FBS: fasting blood sugar

FEV/FVC: forced expiratory volume/forced vital capacity

FVR: forearm vascular resistance

HAD: haloacid dehydrogenase

HD: heart disease

HF: heart failure

HDL: high density lipoprotein

HIIT: high intensity interval training

HR: heart rate

IMT: intima media thickness

LA: left atrium

LBM: lean body mass

LDL: low density lipoprotein

LF: low frequency

LV: left ventricle

LVEDD: left ventricular end diastolic diameter

LVEDVI: left ventricular end diastolic volume index

LVEF: left ventricular ejection fraction

LVESD: left ventricular end systolic diameter

LVESVI: left ventricular end systolic volume index

LVMI: left ventricular mass index

MAP: mean arterial pressure

METs: metabolic equivalents

MHC: myosin heavy chain form

MI: myocardial infarction

MSNA: muscle sympathetic nerve activity

NO: nitric oxide

NT-proBNP: N-terminal pro brain natriuretic peptide

NYHA: New York Association classification

PCI: percutaneous coronary intervention

PTCA: percutaneous transluminal coronary angioplasty

RER: respiratory exchange ratio

SBP: systolic blood pressure

SV: stroke volume

TBW: total body water

TGs: triglycerides

VO_2max: maximum rate of oxygen consumption

Vt1 and Vt2: first and secondary ventilatory thresholds

QA: quality assessment

Chapter 1: General Introduction

Cardiovascular disease (CVD) is the number one cause of premature death in women in Canada (Government of Canada, 2016). Specifically, ischemic heart disease (HD) and heart failure (HF) were the top two HD related deaths in Canada in the year of 2016 (as reviewed by Norris et al., 2020). Recent studies have shown that after being diagnosed with stable angina and nonobstructive coronary artery disease (CAD), women are three times more likely to experience a major adverse cardiac event following catheterization compared to men (Sedlak et al., 2013). This becomes alarming due to the lack of research on sex-specific factors of CVD in women, including prevention, diagnosis, clinical testing, treatment, and therapy (Gulati, 2017).

The cardiovascular anatomy and functioning in men and women have been shown to differ significantly across multiple areas of health or fitness research (reviewed in Kolar & Ostadal, 2013). Sex-specific differences have been demonstrated when comparing men and women in terms of anatomical size, bodily composition, sympathetic or parasympathetic responses to stressors, and hormone levels (Rossy & Thayer, 1998; Salton et al., 2002; Vitale et al., 2010). The disparity between male and female physiology should be further investigated in order to develop appropriate sex-specific medicine and interventions (Kautzky-Willer, 2014).

This thesis aims to complete a systematic review of the literature which investigates the different physiological responses of males and females with chronic HD after the completion of supervised exercise programs. Firstly, it is essential to understand the cardiovascular system in regards to both healthy and nonhealthy functioning, responses to exercise, and sex differences in exercise and training contexts. In addition, the topic of HD is to be explored and understood, along with specifically addressing women's cardiovascular health. Lastly, it is important to be conscious of the benefits of cardiac rehabilitation (CR) on HD patients to determine any physiological variation between men and women. Thus, if significant sex differences are discovered, they can be incorporated to improve HD therapy and treatment.

Chapter 2: Literature Review

2.1 General Understanding of the Cardiovascular System

The cardiovascular system is composed of the heart and blood vessels that deliver oxygen and nutrients via the blood to the body's core and periphery. The heart is a four-chambered muscular organ comprised of two atria and two ventricles that contract and expand in accordance with the electrical conduction pathway (i.e., heartbeat), and it is divided into a right and left side (reviewed in Sanz et al., 2019). The right side is responsible for delivering deoxygenated blood to the lungs starting from the vena cava returning blood to the right atrium, into the right ventricle and the pulmonary arteries. At the same time, the left side pumps oxygenated blood to the rest of the body beginning with the pulmonary veins which enter the left atrium, flowing into the left ventricle (LV), and eventually through the aorta (reviewed in Sanz et al., 2019). The LV contains a larger muscle mass that is required to generate a stronger force against the pressure in the aorta to allow for significant blood propagation to the periphery. Moreover, the heart is innervated with sympathetic nerves that come from the spinal ganglia, and the heart is also connected to parasympathetic nerve fibers originating from the brainstem to mediate the heart rate (HR) (reviewed in Pagani et al., 1973; Schwartz & Stone, 1979). Elevated HR occurs when norepinephrine is released by the sympathetic fibers onto adrenoreceptors on the heart. Norepinephrine initiates a faster release of sodium ions and calcium ions into pacemaker cells starting from the sinoatrial nodes and propagating to the atrioventricular nodes and down along the Purkinje fibers to the rest of the heart. On the contrary, the HR decreases when parasympathetic signals are sent through the vagus nerve, releasing acetylcholine, which induces hyperpolarization of pacemaker cells by reducing inner potassium levels in a similar pattern from the base to the apex of the heart (reviewed in Dusi et al., 2020).

2.2 Anatomical and Physiological Differences Between Men and Women

The heart consists of specialized contractile muscle cells called cardiac myocytes that allow the heart to stretch and contract in order to pump blood effectively throughout the body. Males and females are born with the same number and size of cardiac myocytes and there are no significant differences in structure or size before puberty (de Simone et al., 1995). Significant changes occur after puberty when cardiac myocytes undergo more instances of hypertrophy in men causing them to have larger heart masses (de Simone et al., 1995) During growth, heart mass is increased proportionally throughout the heart and is directly proportional to body size (Ford 1976).

Generally, women have smaller hearts and blood vessels than men. In a study conducted by Sheifer et al., intravascular ultrasound was used to examine and compare the left main and proximal left anterior descending arteries in both sexes. An immediate sex difference was determined when they noted that these two blood vessels were smaller in women than in men, with body size not being a determining factor (Sheifer et al., 2000). Another study conducted by Salton et al. investigated sex differences of the heart in healthy men and women free of CVD or abnormality. By using cardiovascular magnetic resonance imaging, the researchers were able to conclude that men typically have larger LVs, end-diastolic and end systolic volumes than women (Salton et al., 2002).

Since women have smaller hearts than men, they produce a smaller stroke volume (SV) and therefore require a faster HR in order to produce equivalent cardiac output (CO) (Umetani et al., 1998); The baroreflex is a homeostatic mechanism which maintains blood pressure (BP) levels through autonomic regulation by increasing HR during a decline in BP, and vice versa (reviewed in Eckberg et al., 1971). This regulation of BP is initiated by baroreceptors in the aorta and carotid sinus that detect changes in pressure when the vessel wall of the carotid artery stretches and relays this signal to the medulla which is responsible for sympathetic and parasympathetic output (Eckberg et al., 1971). Women have an overall increased parasympathetic and reduced sympathetic resting activity, lowering BP (Abdel-Rahman et al., 1994). Additionally, men may experience naturally higher levels of noradrenaline in the plasma. This was shown in a study by Geelen et al., comparing norepinephrine levels among men and women after a supine and 70° tilted position. It was theorized that there are differences in autonomic regulation between men and women, because higher levels of norepinephrine are indicative of higher levels of sympathetic activity (Geelen et al., 2002). This is further proven when looking at HR variability; a physiological response representing a balance of sympathetic and parasympathetic activity on the heart's beat-to-beat variation. The high frequency variable is indicative of parasympathetic control on the heart, and the low frequency variable (LF) is speculated to be correlated with both cardiac parasympathetic and sympathetic nerve activity (reviewed in Heathers, 2014; Ramaekers et al., 1998;). In a study by Ryne et. al, examining healthy men and women, it was discovered that women have a higher high frequency component of heart rate variability, indicating higher parasympathetic activity (Ryan et al., 1994).

Throughout aging both men and women experience an increase in LV wall and septal thickness, but males have shown an exaggeration in larger LV diameter. The larger LV diameter with aging might be due to the loss of myocardium creating a hollow, weaker-walled heart (de Simone et al., 1995). The loss of myocytes caused by aging in men allows for these cells to grow larger in size to compensate, however, usually women continue to have the same number and size of myocytes throughout their life (Olivetti e al., 1995). Young women may also exhibit enhanced diastolic function compared to young men, though both sexes are subject to a decline in diastolic function as a result of aging (Lakatta et al., 1990). Furthermore, a study by Redfield et al. has shown that women experience a greater reduction in systolic function compared to men due to aging (Redfield et al., 2010). There is a steeper correlation with aging and decreased diastolic compliance and larger ventricular stiffness in women compared to men, which could possibly be the reason for higher instances of women with diastolic HF (Redfield et al., 2005; Vasan et al., 1999).

2.3 Effect of Sex Hormones on the Cardiovascular System

Estrogen, most commonly found as 17β-estradiol in circulation, and progesterone are the main sex hormones found in women, with lower concentrations found in men (reviewed in Murphy, 2011; Salerni et al., 2015). Concentrations of estrogen and progesterone fluctuate in women across the duration of the menstrual cycle (reviewed in an Update in Obstetrics and Gynecology, 2005). Testosterone is the most abundant sex hormone in men (reviewed in Finkelstein et al., 2013). Both estrogen and testosterone are known to induce secondary sexual characteristics after puberty among other roles, whereas one of progesterone's main roles is to prepare the female body for pregnancy. Testosterone and estrogen also facilitate different processes as testosterone is known for increasing bone mass, muscle size, and increased erythropoietin production whereas estrogen regulates lipid metabolism by maintaining healthy cholesterol levels, promotes anti-inflammatory effects, along with initiating vasodilatory responses (reviewed in Finkelstein et al., 2013; Hayashi et al., 1995).

The heart has estrogen and testosterone receptors and studies have investigated the influence of these hormones on cardiac function. (Marsh et al., 1998; Nordmeyer et al., 2004).

Thus, in a study by Schaible et al., and another by Stauffer et al., gonadectomy was performed on rodents to investigate the sex hormone influence on cardiac physiology. The studies concluded that hearts from gonadectomized animals weighed considerably less than the sham controls in both female and male rats (Schaible et al., 1981; Stauffer, 2005). Additionally, both sexes displayed decreases in left ventricular contractility in the gonadectomized mice (Schaible et al., 1981). Another study involving ovariectomized mice with induced congestive HF displayed that the lack of estrogen resulted in increased left ventricular compliance and dilation and further increased HF due to pulmonary edema compared to the controls (Brower et al., 2003). These animal studies shed light on the impact that estrogen and testosterone may have on cardiovascular function and structure. It has been hypothesized that estrogen may have a cardioprotective property due to more incidence of cardiovascular diseases occurring in men and postmenopausal women compared to premenopausal women (reviewed in Gorodeski, 1994).

Other studies exploring the cardioprotective property of estrogen have shown that estrogen may play a role in inhibiting the presynaptic pathway of noradrenaline, therefore decreasing sympathetic influence on the heart (Du et al., 1991). Estradiol has been shown to increase levels of acetylcholine and acetyltransferase in various brain regions such as the hippocampus, caudate nucleus, frontoparietal cortex and hypothalamus (Kaufman et al., 1988). The increase in acetylcholine and acetyltransferase in these brain regions due to the presence of estradiol extrapolates the possibility that cardiac acetylcholine will also increase, potentially increasing parasympathetic influence on the heart. A study conducted by Du et al., investigated the sex differences of parasympathetic control on the heart by looking at rats and the relationship between estrogen and cholinergic nerve activity (Du et al., 1994). After comparing male and female rats, female rats had a stronger vagal activation causing an increased release of acetylcholine, stimulating cholinergic receptors on the heart (Du et al., 1994). Higher levels of choline uptake are evident in healthy normal cycling female mice which is important for promoting parasympathetic responses (O'Malley et al., 1987). Other mouse studies also have reported reductions of acetylcholine and acetyltransferase levels in male versus female mice and ovariectomized mice (Egozi et al., 1982; Kaufman et al., 1988; Loy & Sheldon, 1987; Luine, 1985). Furthermore, higher basal levels of noradrenaline are found in men compared to premenopausal women indicating higher levels of sympathetic output (Lenders et al., 1987). Similarly, under stress, postmenopausal women release larger amounts of noradrenaline compared to premenopausal women (Lindheim et al., 1992). Therefore, cycling females have greater parasympathetic control, whereas males and post-menopausal or ovariectomized females have greater sympathetic control.

The effect of progesterone is often grouped with the effect of estrogen and is understudied. (reviewed in Salerni et al., 2015). Like estrogen, progesterone induces a vasodilatory response by relaxing vascular smooth muscle cells and increasing NO synthesis in human endothelial cells (Barbagallo et al., 2001; reviewed in Pang et al., 2015) Additionally, progesterone inhibits vasoconstriction as it prevents excess calcium dependent vasoconstriction in vascular smooth muscle cells (Barbagallo et al., 2001). On the contrary, the influence of testosterone on the cardiovascular system can be conflicting. Studies have shown that testosterone can induce acute vasodilatory effects in men, however chronic exposure to testosterone can result in higher instances of vasoconstriction and higher blood pressure in men (reviewed in Iliescu & Reckelhoff, 2006). Furthermore, testosterone can increase the risk of cardiac arrythmia in men compared to women (reviewed in Sedlak et al.,2012). However, high levels of endogenous testosterone are speculated to be inversely proportional with carotid intima-media thickness (IMT), a measure of the thickness between the two innermost walls of an artery, which can indicate early signs of atherosclerosis (Fukui et al., 2003; Van den Beld et al., 2003). This suggests that testosterone in men may prevent the development of atherosclerosis though this hypothesis needs to be further investigated (reviewed in Lorigo et al., 2019). Although in women, an elevated level of endogenous testosterone is correlated with an increased risk of HD (reviewed in Salerni et al 2015).

2.4 Cardiovascular Disease

CVD can be defined as an impairment of the heart or blood vessel functioning (American Heart Association, 2017). More specifically, HD is when the heart and/or the cardiac blood vessels experience complications due to abnormal structure or function. CVD is an umbrella term encompassing the diseases that affect the cardiovascular system including the heart, whereas HD is limited to diseases that affect only the heart (American Heart Association, 2017). Some examples of HD include coronary artery disease, HF, valvular HD, and cardiac arrhythmia. Impairments in oxygen delivery to the heart and bodily tissues from these conditions can cause damage and sometimes sudden death. Multiple factors ranging from age, diet, family history, sedentary lifestyles and even menopause can increase the risks of developing HD (reviewed in Kannel et al., 1964)

One of the biggest risk factors for more serious CVD is hypertension, which can be clinically defined as a chronic increase of BP with a systolic BP of >130mmHg or a diastolic BP of >80mmHg (Arnett et al, 2019). The prevalence of hypertension is more common in women over the age of 65 partly due to declining levels of estrogen compared to premenopausal women (Heart and Stroke Statistics, 2017). Hypertension can cause arterial stiffness and remodeling, reducing efficient blood flow to the heart (O'Rourke, 1990). Moreover, lower levels of estrogen pose greater cardiovascular risks due to less vasodilatory effects, higher levels of angiotensinogen, higher low-density lipoprotein (LDL) and lower higher density lipoprotein (HDL) (Hokanson et al., 1996, Manolio et al., 1992; Shai et al., 2004). Higher levels of angiotensinogen promote the production of angiotensin II, which is known to increase BP by inducing vasoconstriction, along with aldosterone which is responsible for water retention (Curtiss et al., 1978). Higher levels of LDL contribute to plaque formation in arteries and lower levels of HDL allow for plaque buildup (reviewed in Kerenyi et al., 2006). Other risk factors for CVD include obesity, smoking, depression, and emotional stress (reviewed in Ostadal et al., 2020).

Coronary artery disease (CAD) occurs when the blood vessels in the heart are narrowed due to a build-up of plaque (Centers for Disease Control and Prevention, 2021). It is the most common type of CVD with higher occurrences of mortality and morbidity in men, however, the likelihood of mortality and morbidity increases in women after menopause (reviewed by Norris et al., 2020). One of the more obvious signs of CAD can be myocardial infarction (MI). MI occurs when the heart is in a state of ischemia causing death of the tissue distal to the site of a blockage (ESC Committee for Practical Guidelines, 2012). Fibrous scar tissue accumulates at the site of the injury, hindering cardiac function and structure (reviewed in Talman 2016). Next, HF is another common HD that can be categorized into two main types: HF with reduced ejection fraction (EF) and HF with preserved EF. HF with reduced EF happens when the ventricle does not contract properly with an EF of <40% (American Heart Association, 2017). HF with preserved ejection fraction has an EF of >50%, however diastolic function is impaired due to reduced compliance in the LV (American Heart Association, 2017). Interestingly, HF with preserved ejection fraction is more common in women, whereas HF with reduced ejection fraction is more common in men (Lam et al., 2019).

2.5 Women's Cardiovascular Health

CVD has been thought to be a "man's disease" due to higher reported incidents of adverse cardiac events in men. In reality, women are often underrepresented and underdiagnosed. Women usually report more severe symptoms that are usually due to a much older age at the time of diagnosis compared to men (as reviewed in Shaw et al., 2017). With this in mind, onset and symptoms of CVD may actually differ between men and women dramatically. For instance, symptoms of an MI are typically known to be chest pain, tightness, and numbness of the left side of the body. However, women can actually experience a whole different set of symptoms during a MI which include pain over the upper side of the body, nausea, dizziness, fatigue, and shortness of breath (Canto et al., 2012).

Similarly, the morphology of atherosclerosis can present itself differently in men and women as shown in multiple studies looking at sex differences in CAD outcomes. Firstly, men are more likely to display signs of obstructive CAD compared to women, on the basis that the plaque formation in men is more likely to have calcification with a larger plaque volume concentrated on one side of the artery making structural abnormality within the artery more visible when detected. (Kardys et al., 2007; Moreira et al., 2014; Vishram et al., 2014). Unlike men, most women with CAD have displayed less dense fibrous tissue in plaque formation appearing less detectable on an angiogram (Aguilar et al., 2015). This may be because the development of these plaques in some of these women disperse along the circumference of the artery walls instead of creating discernable obstructive plaques as seen in men (Lansky et al., 2012; Yahagi et al., 2015). Furthermore, women are also at a higher risk of plaque erosion than rupture, compared to men (Regitz-Zagrosek et al., 2006). Plaque erosion usually occurs when the plaque does not have a large lipid core but a proteoglycan rich composition instead (Virmani et al., 1999). Inflammation is lower in plaque erosions, and while they account for 20-40% of coronary thrombi, the mechanisms behind the thrombi in plaque erosions remain unclear (Burke et al., 1997; Farb et al., 1996; Virmani et al., 1999). Plaque rupture on the other hand, occurs when an inflammatory response is triggered, rupturing the plaque leading to thrombosis at the site (Falk et al., 1995). The characteristics of a plaque are also different than one more susceptible to erosion, as ruptures usually happen when the plaque has a large lipid core, thin fibrous cap, and positive remodeling towards the lumen (Falk et al., 1995; Felton et al., 1997, Lendon et al., 1991, Richardson et al., 1989). In the context of these occurrences in postmenopausal women compared to premenopausal women, Yahagi et al., suggests that plaque rupture seems to be just as evident in both of these groups (Yahagi et al., 2015). Postmenopausal women also have a three times greater risk of worse prognosis of CAD including sudden cardiac death and MIs, than premenopausal women (Lerner & Kannel, 1986).

Furthermore, differences between men and women are also recognized when developing cardiac comorbidities with HD (reviewed by Norris et al., 2020). In terms of developing other cardiac comorbidities when diagnosed with HD, sex differences also exist. For instance, women with valvular HD have a 47% higher chance of developing atrial fibrillation than men (Aggarwal et al., 2013). Women with HF also have a 24% higher chance of suffering from atrial fibrillation than men. Additionally, they also have higher rates of mortality within a year of experiencing an MI compared to men (reviewed by Norris et al., 2020).

Regarding HF with reduced EF women make up about 40% of those patients yet are more likely to develop severe symptoms of the disease, along with being diagnosed much later on in life compared to men (Ezekowitz et al., 2017). Women with this disease are much more likely to be obese, have hypertension, develop valvular HD and have more strokes than men (Dewan et al., 2019). There is a higher prevalence of hypertension among female patients with HF with reduced EF compared to males. About 71% of women with HF with reduced EF reported having hypertension compared to 66% of the men with this disease (Dewan et al., 2019). Moreover, according to the American Heart Association in 2017, 59% of hospitalized patients with HF with preserved EF were women (Heart and Stroke Statistics, 2017). Similarly, symptoms of HF with preserved EF in women are different from men and include abdominal discomfort, cognitive impairment, delirium, anorexia, and cyanosis (Ezekowitz et al., 2017). Furthermore, hypertension and diabetes were greater risk factors for women to develop HF with preserved EF compared to men (Hogg et al., 2004). On a similar note, approximately 48% of valvular HD patients are women and exhibit more severe aortic stenosis than men. Due to women having smaller hearts than men lower calcification levels can induce similar if not higher levels of aortic stenosis severity in women (Aggarwal et al., 2013).

2.6 Estrogen Receptors and Cardiovascular Benefits

Endogenous estradiol primarily found in premenopausal women can prevent hypertension by inducing acute and chronic vasodilator activity, ultimately reducing BP in some women (Mugge et al., 1993). This is due to the cascade of events that stimulate the production of nitric oxide (NO) causing vasodilation (C. P. Weiner et al., 1994; Kim & Levin, 2006;). Estradiol binds to estrogen receptor alpha (E_α) and estrogen receptor beta (E_β) that can be found in nuclei of vascular smooth muscle cells and endothelial cells. It also binds to g-protein coupled receptors found on the endoplasmic reticulum and plasma membrane in cardiomyocytes (Deschamps & Murphy; Wang et al., 2017). A study on female mice examining the effects of E_α found an increase in endothelial function in ovariectomized hypertensive mice through rising levels of endothelial NO synthase when administered estradiol (Widder et al., 2003). Activation of a g-protein coupled estrogen receptor by estradiol has also shown to slow down the proliferation and migration of vascular smooth muscle cells typically known for influencing vascular disease and developing atherosclerosis (Rubio-Gayosso et al., 2000). The g-protein coupled receptor responding to estradiol additionally activates endothelial NO synthase in human endothelial cells to increase vasodilation (Fredette et al., 2018). Specifically, activation of E_α reduces endothelial dysfunction and activation of E_β decreases BP by decreasing vascular resistance and vasoconstriction, and overall attenuating cardiac hypertrophy (reviewed in Aryan et al., 2020).

More young men than women die from atherosclerosis, though it becomes the leading cause of death in postmenopausal women possibly due to the loss of estrogen and estrogen receptor sensitivity (Vitale et al., 2009). In a study by Zhu et al., conducted on mice, they discovered that E_α signaling prevents accumulation of LDL during formation of early atherosclerosis (Zhu et al., 2018). However, in terms of E_β, there is some contradiction as to whether it has the same cardioprotective effect in atherosclerosis. Furthermore, a study by Christian et al., found that the expression of E_β is positively correlated with calcification and atherosclerosis in pre- and postmenopausal women (Christian et al., 2006). Though these controversial claims of E_β need to be further investigated and studied to understand whether E_β is less protective against disease development. Finally, the activation of these estrogen receptors has been proven to reduce inflammation, coronary artery smooth muscle cell proliferation, and reduce vasoconstriction as a protection from atherosclerosis (reviewed in Barton & Prossnitz, 2015). Therefore, the cardioprotective effect of estrogen can be seen through the functions of E_α, E_β and g-protein coupled receptors and why women are less likely to experience HD before menopause.

2.7 Cardiovascular Responses and Adaptations to Exercise Training

Aerobic exercise involves any exercise that requires continuous movement of muscles that increase HR and breathing. These exercises could be running, jogging, cycling, swimming, and dancing (reviewed by Nystoriak & Bhatnagar 2018). More importantly, aerobic exercise training has been proven to reduce BP (Cleroux et al., 1992). High BP or hypertension is a causal factor to many CVDs, thus reducing BP mitigates these risks (Kannel et al., 1964). It is theorized that after exercise, there is a direct drop in arterial pressure due to the increase in systemic vascular conductance from long-term relaxation of blood vessels (Halliwill, 2001). Post exercise vasodilation includes a reduction in sympathetic activity caused by a reset of the arterial baroreflex and an increase of vasodilatory metabolites leading to vasodilation (Chen & Bonham 2010). Recently, discoveries by Romero et al. also introduced that the vasodilatory responses after exercise are linked to the release of histamine in the active skeletal tissue (Romero et al., 2017).

Resting BP recorded after continuous exercise training drops overall due to the increased shear stress on the endothelial layer that occurred during exercise. This can be due to increasing levels of NO bioavailability which also contribute to reducing the risk of CVD (Kingwell, 2000). Through endothelial-dependent vasodilation, arterial diameter can undergo remodeling and become larger due to releases of both vascular endothelial growth factor and NO (Da Silva-Azevedo et al., 2002; Gavin et al., 2004). Chronic aerobic exercise training can increase NO production, a known vasodilator, via improved vascular endothelial function increasing blood flow (Duncker & Bache, 2008; Green et al., 2004). A study by Cononie et al., investigated the effects of endurance exercise training on elderly men and women and concluded that mean arterial pressure was reduced in both sexes by the end of the study (Cononie et al.,1991). Likewise, regular exercise reduces arterial stiffness by lowering oxidative stress and inflammation while increasing vascular compliance (Ashor et al., 2014; Martin et al., 1987). Furthermore, a study conducted by DeSouza et al., was the first to discover that aerobic exercise training can reverse the decline in endothelium dependent vasodilation caused by aging in men. They concluded that habitual aerobic exercise can be used as a primary and secondary prevention of the loss of endothelium-dependent vasodilation in middle and older sedentary men (DeSouza et al., 2000).

Moreover, the heart is a muscular organ that can increase in size, (i.e., hypertrophy) in response to regular exercise (R. B. Weiner & Baggish, 2012). Hypertrophy can be very beneficial (to an extent) because the increase in size of the LV can allow for improved myocardial contraction (i.e., a direct increase in SV). This was first discovered in 1899 by Henschen, who compared the hearts of cross-country skiers to sedentary individuals. When comparing these athletes to the non-athletes, there was a greater SV in the trained versus untrained (Henschen 1899). Though athletic individuals, in general, experience this enlargement in the heart, the largest LV cavity and wall dimensions have been recorded in top male cyclists, rowers, swimmers, and cross-country skiers with larger body sizes (Pelliccia et al., 1991; Pelliccia & Maron, 1999; Spirito et al., 1994). Hypertrophy in the LV results in a larger end-diastolic volume, which can be determined by diastolic filling, HR, compliance of the ventricles, ventricular filling pressures, atrial contraction, and myocardial relaxation. An increase in end-diastolic volume directly increases SV (Baggish & Wood, 2011). While the SV increases, the resting HR decreases when conditioned to aerobic exercise. The reduction in resting HR does not decrease the total CO due to the increased SV (Blomqvist & Saltin, 1983). This reduction in HR is also a result of an increased parasympathetic activity from the vagus nerve with slight reduction of sympathetic activity (Rosenwinkel et al., 2001). Similarly, this attenuation of sympathetic activity may also be caused by a reduction of visceral obesity or body weight after exercise training (Joyner & Green, 2009).

The rapid recovery of HR for the first minute after exercise is due to additional vagal control, and the slow recovery that continues after the first minute is due to a withdrawal of sympathetic output (Peçanha et al., 2017; Seiler et al., 2007). Improvements in HR recovery have also been shown to be affected by exercise training, as exercising individuals display a shorter HR recovery than those who are sedentary. Delayed HR recovery can be an indication of lack of fitness or even a precursor to HD (Kleiger et al., 1987). Further, multiple studies have shown that continuous exercise training can create a better cardiac autonomic balance, in which there is a higher parasympathetic output and a lower sympathetic one, overall improving HR variability (Galbreath et al., 2011; Levy et al., 1998; Iwasaki et al., 2003; Okazaki et al., 2005).

Studies have also shown that the renin-angiotensin-aldosterone system is also regulated by continuous exercise. Angiotensin II, a hormone that increases BP via systemic vasoconstriction, is shown to decrease after exercise training reducing the risk of vascular dysfunction (reviewed in Zucker et al., 2015). Angiotensin II typically increases in response to sympathetic stimulation when the baroreflex detects a drop in BP; however, an overproduction of angiotensin II can induce chronic hypertension (reviewed in Zucker et al., 2015). Higher levels of angiotensin II are linked to higher levels of sympathetic activity especially in patients with congestive HF because angiotensin II increases sympathetic outflow transmission, desensitizing sympatho-inhibitory mechanisms of the baroreflex and increasing the cardiac sympathetic afferent reflex (reviewed in Wang et al., 2012). A study by Mousa et al., determined that there is a link between reduced levels of angiotensin II and reduced sympathetic activity in HF patients after exercise training and saw improvements in baroreflex sensitivity (Mousa et al., 2008).

As a result of exercise training, athletes report having a larger blood volume and lower blood viscosity (Convertino 1991). The hypervolemia in athletes is beneficial for evaporative cooling across the skin through increased perspiration (Convertino, 1991; Convertino et al., 1980). Since hypervolemic blood reduces blood viscosity, it reduces workload on the heart by increasing filling and lowering peripheral resistance (El-Sayed et al., 2005). Higher blood plasma volume has been demonstrated to increase cardiac preload, ventricular filling, and SV (Fortney et al., 1983). Therefore, aerobic exercise training has been suggested to improve vascular and cardiac performance.

2.8 Sex Differences in Exercise Training

Individuals who incorporate exercise into their lifestyles tend to have a lower risk of CVD due to higher levels of cardiorespiratory fitness (reviewed in Collier 2008). Few studies have been conducted to compare men and women's physiological responses after periods of exercise training. For instance, VO_2max is a physiological variable representing oxygen consumption rate calculated during maximal exercise and has been shown to increase in both sexes after endurance training (Spina et al., 1993); VO_2max is representative of cardiorespiratory fitness and endurance capacity during exercise performance (reviewed in Spina et al., 1993). Howden et al., explored sex differences that can occur after one year of endurance training in young healthy men and women. In this paper, Howden mentions the differences in VO_2max values between the sexes at baseline, 3 months, 6 months, 9, months and 12 months after training. Women reached their peak VO_2max after the third month of training, whereas men continued to increase VO_2max until month 9. By the end of the training period at month 12, men had significantly greater increases of VO_2max than women (Howden et al., 2015). In another exercise training study conducted by Spina et al., men also had larger VO_2max values after training which were accounted for by larger increases in SV.

Women however, also had increasing levels of VO_2max after exercise but arteriovenous O_2 differences accounted for this increase, and not SV (Spina et al., 1993). Women attaining lower VO_2max levels compared to men could be due to lower concentrations of hemoglobin in women and higher body fat percentages (Rossy & Thayer, 1998). Lower hemoglobin can account for less oxygen carrying capacity, and body fat is inversely proportional to VO_2max (reviewed in Diaz-Canestro et al., 2021).

Both Spina et al. and Howden et al., looked at cardiovascular adaptations in healthy men and women after endurance training. When compared to women, men achieved a larger LV mass, SV, and right ventricular mass towards the end of the study, and women usually reached maximum values at 3 months of training (Howden et al., 2015). Both men and women were training at similar aerobic exercise intensity, thus these differences were deemed to be based on sex only (Howden et al., 2015). Howden et al. attributed the previously discussed higher aerobic power observed in men after 1 year of endurance training to the greater increase of LV mass experienced in men compared to women. Indeed, in the study by Spina et al., they suggest that men experience a larger overall CO after training, possibly due to more hypertrophy (Spina et al., 1993).

Possible sex differences in autonomic regulation such as heart rate variability have also been investigated (reviewed in Sloan et al., 2009). In a study conducted by Sloan et al., they compared healthy young men and women undergoing aerobic training and looked at HR variability. The measure of HR variability they used was the standard deviation of the R-R intervals (SDRR) and a higher value of SDRR represents a more parasympathetic control and a healthier beat-to beat variation. At baseline, women had slightly higher SDRR values than men but after training they reported that there was a significant improvement in men's SDRR and not much of an increase in women indicating improvement of the parasympathetic nervous system in men (Sloan et al., 2009). However, Schuit et al. conducted a longitudinal endurance training study in elderly men and women and saw a much larger decrease in resting HR and Q-T interval (the time it takes for the ventricles to contract and recover) in women (Schuit et al. 1998). Since the populations were elderly, the authors suggested that this larger decrease in HR and Q-T interval in women after training, may be due to the elderly women being less active at baseline and more sensitive to training effects (Schuit et al., 1998). Therefore, the extent of physiological improvements after endurance training can be heavily affected by sex, with men often displaying greater improvements in cardiovascular health.

2.9 Cardiac Rehabilitation

Patients diagnosed with HD or have suffered from a cardiac event in the past are usually eligible to participate in CR as referred by their physician (Canadian Guidelines for Cardiac Rehabilitation and Cardiovascular Disease Prevention, 2009). CR is a medical secondary prevention program that incorporates supervised exercise, diet recommendations, health education, smoking cessation, psychological counselling as well as lipid and BP management (McMahon et al., 2017). The goal of CR is to reduce mortality caused by CVD by improving cardiovascular function and overall health, while also aiming to improve quality of life. When a patient is referred to CR, it usually occurs in three phases. The first phase occurs at the time of hospitalization where patients are monitored closely to watch for changes in HR, BP, and oxygen saturation. During this phase, patients are assisted in carrying out daily tasks like sitting and standing. For phase 2, a cardiopulmonary exercise test (CPET) takes place as the initial measure of assessment of the patient's heart and lung function during exercise. Some of the parameters gathered during the CPET include VO_2max, HR, and BP to evaluate the patient's exercise capacity (Adachi, 2017). These parameters allow the team to determine personalized exercise training consisting of aerobic and resistance exercise optimal for the patient. Aerobic exercise consists of activities that require the movement of large muscles and is the main prescribed exercise of CR. Activities like running, jogging, dancing, swimming, and cycling improve cardiovascular health by enhancing the function of the heart, lungs, vessels, and muscles after training adaptations (reviewed in Nystoriak 2018). Resistance training, also known as strength training, includes activities that build muscle endurance by applying an external resistance force (Knuttgen and Kraemer, 1988). Examples of resistance exercise include weightlifting and using resistance bands.

Phase 2, or the outpatient phase of CR, generally includes a consistent supervised exercise program, attending multiple classes per week. Some CR programs can vary in terms of length of the program and can be offered onsite at the rehabilitation centre or patients can complete a home-based program. While performing exercise during phase 2, patients are asked to report their rating of perceived exertion which monitors how much exertion the patient is putting in per exercise, to either increase or decrease the intensity. Phase 2 of CR also includes setting and achieving realistic fitness goals by gradually increasing exercise intensity until the end of the program. Finally, an exit CPET test is taken towards the end of the program to examine how much the patient has improved in their cardiovascular and pulmonary health. The supervision and recommendations that are provided for the patient during phase 2 of CR can encourage the patient to undergo phase 3 which involves complete independent exercise and lifestyle modification (Canadian Guidelines for Cardiac Rehabilitation and Cardiovascular Disease Prevention, 2009).

2.10 Benefits of Cardiac Rehabilitation

CR has been proven to enhance cardiovascular functioning in cardiac patients by increasing vagal control and decreasing sympathetic modulation (Routledge et al., 2010). A study by Hambretch et al., concluded that higher SV was achieved in patients with HF after exercise, as well as a reduction in HR and total peripheral resistance. (Hambretch et al., 2000). In addition, after being diagnosed with HD, healthcare professionals often measure functional capacity and a six-minute walk test (6MWT). These are evaluations of a patient's exercise capacity as well as their physical and functional abilities. Thus, functional capacity was being assessed in a study by McKelvie et al., as measurements of VO_2max, muscular strength and 6MWT at baseline and compared after 12 months of exercise training in HF patients. In this study, exercise caused significant improvements in VO_2max and 6MWT (McKelvie et al., 2002). Another study conducted by Van Craenebroeck using patients with stable CAD underwent aerobic exercise for 12 weeks and looked at endothelial function via flow mediated dilation ultrasound measurements in addition to looking at circulating endothelial progenitor cells (Van Craenenbroeck et al., 2015). The results from this study suggested that although there was no correlation between level of progenitor cells and exercise training, flow mediated dilation and VO_2max had improved after this CR program. Additionally, Fujie et. al looked at serum adropin levels in the plasma of middle aged and older adults after undergoing 8 weeks of aerobic exercise. Adropin is a protein that circulates in the plasma and promotes NO release by regulating endothelial NO synthase, thus enhancing blood flow. Adropin levels often decline with age, and this study showed that aerobic exercise training decreases arterial stiffness due to elevations in adropin serum levels (Fujie et al., 2015). Furthermore, improvements in oxygen perfusion and diffusion were displayed in patients with chronic HF after aerobic exercise training similarly conducted in CR (Hirai et al., 2015).

Therefore, it is evident that CR has been proven to be a successful secondary prevention by its means of improving cardiovascular health and increasing fitness levels in HD patients. While multiple studies support the findings that men and women have physiological and anatomical differences in HD and they differ in terms of adaptations to exercise training, not many studies investigate the effect of sex on physiological responses after CR. Therefore, it is important to investigate sex differences in the responses to CR to determine the efficiency of programs and to potentially improve CR programs for both sexes.

Chapter 3: Methods

A systematic review that encompasses sex differences after completion of a standard CR program was conducted for the completion of this thesis. This systematic review was conducted by following the Preferred Reporting Items Systematic Reviews and Meta-Analyses [PRISMA] updated guidelines (Page et al., 2020). The details of the search strategy and data sources were discussed first, then Prospero registration and the usage of the Covidence software were introduced, and finally, each stage of screening was explored in detail to bring forth the finalized results. A Prisma flow diagram is attached to this thesis for a clear representation of the steps completed for the upcoming review in Appendix A.

3.1 Data Sources and Search Strategy

The search was inputted on April 9th, 2021, into seven scientific online databases which included: APA PsycInfo (Ovid), CINAHL Complete (EBSCOhost), Embase (Ovid), Emcare (Ovid), Medline (Ovid), PubMed (non-Medline), and Web of Science Core Collection. This search generated a grand total of 4673 citations including duplicates. This search was developed and finalized with the expertise of UHN Information Specialist Maureen Pakosh, and originally formulated by the PICO(S) framework comprising of concepts that relate to: Population or Problem, Intervention, Comparisons, Outcomes, and Study design. The PICO(S) used for this search strategy included heart disease as the population or problem, cardiac/exercise rehabilitation as the intervention and gender/sex as the comparisons. Since the project entails any physiological responses, all physiological Outcomes were of potential interest, so this concept was omitted in order to keep the search results as broad as possible. Additionally, medical subject headings

(MeSH terms) and keywords were included in each database to specify the search further for relevant results. Furthermore, the search strategy aimed to collect articles written in English and pertained to human subjects. An example of the search strategy input into the Medline database is shown in Appendix B. A hand search was also conducted but did not retrieve any additional articles.

3.2 Prospero and Covidence Registration

Prospero registration is essential for every systematic review, as it avoids duplicates of the same review and lays out a planning protocol. During registration, a central question for the review was formulated, along with necessary details such as the title of the review, authors, type of studies, search strategy and keywords. Moreover, a systematic review software program called Covidence was used to conduct the screening and further stages of the systematic review. Covidence is an online platform created for researchers who are part of academic institutions across the globe, which allows them to log in to collaborate and manage systematic reviews. It facilitates efficient title & abstract screening, full text screening, data extraction and supports accessible imports and exports of documents. It was established under the Cochrane Library, a renowned database for publishing systematic reviews and meta-analyses in health and medical research (Higgins et al., 2021). Thus, while the review was undergoing Prospero registration, it was also being set up as a project in Covidence to allow for other members of the systematic review team to access it during the screening stages. The systematic review team included the primary author and four other peer reviewers for screening, and if there was a discrepancy during any of the screening stages, two reviewers and the primary author would agree on a final consensus vote. Once Prospero registration and Covidence set up was complete, the finalized search strategy was converted into an XML file to remove duplicates prior being imported into Covidence for study selection. This reduced the number of citations from 4673 to 2802.

3.3 Study Selection

After inputting the search strategy, only certain studies were selected. According to the PICO concepts mentioned above, the studies avoided any healthy individuals and focused on male and female patients with cardiac disease. The intervention was any supervised exercise study, with a before and after assessment of any physiological variable in response to the intervention. A sex difference needed to be directly investigated, and not simply as a co-variate in the statistical analysis. The studies had to be original research studies and not excerpts from a book or case studies. Additionally, the papers had to be as objective as possible with quantitative direct measurements of physiological variables, as qualitative research or research focusing on psychosocial aspects and questionnaires were not of interest. At this stage, a screening pilot was created as a trial round of screening by examining twenty-five random articles to ensure that the appropriate studies were filtered. During the trial screening, all members on the systematic review team read titles and abstracts of the articles and answered either yes, no, or maybe to whether the article falls under the study selection criteria. All five reviewers at this stage compared votes to achieve a general consensus with each screening question. This also helped address any confusion that may occur during actual screening (i.e., understanding screening questions and criteria) with every member on the review team. Had any conflict between two or more votes at this stage occur, a discussion was held to depict the thought process of how to approach opposing votes in the legitimate stages. In the upcoming stages, a third person who was not a part of the conflict made the final decision between two votes. Now that guidelines were attained and understood by every member, the official stage one of title and abstract screening was conducted on Covidence.

3.4 Title and Abstract Screening

The Covidence software further deduplicated files from the search strategy in preparation for the first stage of screening. An additional 359 citations were removed, giving a starting number of 2443 to begin screening. This stage of screening involved all members of the group to review the titles and abstracts of each paper in the search before deciding to read the full text. The finalized criteria for title and abstract screening included cardiac/HD patients, a supervised exercise program, a physiological response before and after the supervised exercise program, and lastly, whether the mentioning of sex or gender or a comparison between men and women was present. The progression of an article from one stage to the next was dependent on identical responses from two independent screeners. If this was not the case, a third person had to resolve the conflict by ultimately choosing whether the article passed to the next stage. A total of 299 articles out of the 2443 that were uploaded to Covidence made it past this stage.

3.5 Full Text Screening

Full text screening required a more in-depth analysis of the studies of interest. The articles were uploaded using York University or University of Toronto Libraries. First and foremost, by screening the full text, screeners were able to identify if there were assessments of physiological variables at both baseline and program completion; variables such as mortality, program adherence or non-physiological variables were excluded. Additionally, sex differences were more scrutinized at this stage, as many studies may have men and women but do not actually conduct a direct sex comparison, but rather rely on co-variate analysis for sex differences; these latter studies were excluded from this review. Lastly, any review with no original data on sex differences was also excluded. Upon completion of this stage, only 102 out of the 299 progressed to the next round of screening.

3.6 Quality Assessment

Quality assessment (QA) was conducted to determine the validity of evidence in each article at this stage collected for the systematic review (Higgins et al., 2021). Strong evidence included eliminating risk of bias with both the researchers and participants of the trial, having an accurate intervention that could be applicable in real medical practice, representing apparent baselines and outcomes in relation to the intervention, and determining any possible confounding factors (Higgins et al., 2021). In order to assess the quality of a paper, a quality appraisal tool must be used and specified for the type of studies; in this case, a QA tool for cohort studies was used. The QA tool is a standardized reliable checklist usually containing questions that could be answered by yes, no, or unclear. Different QA tools for cohort studies from several research institutions were compared based on the suitability of the questions for these exercise trials. Among the QA tools compared, JBI for cohort studies was used to assess research aims, appropriate methods and significant measures of statistics per study (JBI, 2020). JBI, also known as Joanna Briggs Institute, is a research organization that aims to develop research practices that achieve evidence-based information for health outcomes (Santos et al., 2018). The JBI checklist is found attached in Appendix C. Furthermore, adjustments to the questions on the QA tool were made to make the checklist more specific if certain trends among papers are found that qualify them for elimination. For instance, adherence to CR is a factor to be wary of when assessing the results of the participants, along with the time follow-up assessment post rehabilitation was conducted. The modifications made to the QA checklist included an additional question regarding if empirical evidence was provided with sex difference conclusions. 102 papers gathered at the QA stage were assessed by the JBI checklist by two reviewers. No papers were eliminated based off a quality threshold, however; 31 articles were sent back to the previous screening stage due to missing requirements. Of the 31 articles that were filtered back, 12 were abstracts, 4 contained no information on sex comparisons, 1 was a thesis, 2 were systematic reviews, 7 included an inpatient rehab (phase 1-CR) instead of an outpatient intervention or did not include pre and/or post intervention data, 3 compared measures outside the scope of this review, and 2 were duplicates. Those papers that passed the QA stage were considered for data extraction in which the desired data were extracted and compared.

3.7 Data Extraction

Data extraction was achieved through constructing an appropriate template on Covidence to gather imperative summaries from the 71 final articles chosen for the review. By completing data extraction, relevant information from the approved articles included title of the article, authors, study design, country of trial, population description, inclusion and exclusion criteria, method of recruitment, total number of participants, intervention description and length of program, adherence rates, baseline measures, variables of interest and their respective values, how measurements of variables were defined, along with the type of statistical measures used and their significances. At this stage, the main reviewer concentrated on extracting comparable physiological variables collected in males and females pre and post CR to draw conclusions on whether significant changes were evident. After each extraction, the papers were categorized into groups of whether a sex difference was present or not.

3.8 Synthesis of Evidence and Knowledge Dissemination

Finally, a thematic synthesis was completed after assessing all the findings and data. Examples of some possible themes could be adherence to program, length of program, type of exercise used in rehabilitation programs, male to female participant ratio, or type of statistics (e.g. appropriate t-tests between sexes comparing the change of a variable pre-post CR or repeated measures ANOVAs). Major conclusions and discussions from relevant articles were summarized, drawing key links between sex differences and physiological responses after rehabilitation. Sex differences after CR is a current research issue that should be considered when implementing treatments in cardiovascular medicine to improve patient health outcomes.

<u>Chapter 4: Results</u>

4.1 Organization of Data

The final extracted data was compiled into Tables 1, 2, and Table 3. Table 1 includes a comparison of all the articles in regard to the study ID, study design, population description, method of recruitment, total number of participants, type of CR, length of CR, QA score, adherence rates and statistics used. The study ID was determined with the first author's last name and the year of publication. Additionally, the study design was selected among several choices: cohort study, retrospective cohort, retrospective cross sectional, or randomized/non-randomized controlled trial. Population description presented the type of HD that was diagnosed in the sample, with the majority of the studies investigating CAD populations. Next, total number of participants was listed, which included the number of participants along with the number of men and women stated in each population where available. Furthermore, the type of CR stated the nature of the exercise, including aerobic only, aerobic and strength, home-based, other, or non-specified. The length of CR specified the length of the intervention in weeks, ranging from two weeks to two hundred and sixty weeks. Additionally, the QA score was derived from the QA stage conducted prior to data extraction for quality comparison. The average QA for all articles was 10.9±1.1 out of 12. Lastly, the CR completion and adherence rates were calculated and separated based on men's and women's completion rates where available. The adherence rates were calculated based off the number of individuals that remained from the study out of the initial population number and expressed as a percentage. Additional information from certain studies involved the amount of CR sessions attended in men and women, also expressed as percentages. Lastly, the type of statistics was stated from every study, which included repeated measures ANOVAs between sexes over time (i.e. "ANOVAs"), t-tests within one sex only (i.e. "t-tests"), t-tests between sexes on the change from pre- to post-CR (i.e. "t-tests between deltas"), other types or unknown. While ANCOVAs using sex as a co-variate were excluded, we retained studies that analyzed sex as a main variable but had other factors such as age as a co-variate. Thus, when ANCOVA is noted in the Tables, the main variables are sex and CR.

Table 2 provides a visual comparison of the primary physiological variables indicating 1) a greater improvement in men, 2) only men improved, 3) greater improvement in women, 4) only women improved, or 5) no differences between the responses of men and women. The variables were divided into 6 physiological parameters including fitness, metabolic measures, body composition, respiratory, cardiac measures, and protein measures for appropriate comparisons. Specifically, Table 2 examines only the physiological variables that were measured in two or more studies and were marked by the study ID. With this grouping, 45 variables were examined in Table 2. The remaining variables that were discussed in only a single study were categorized and placed into Table 3. The same 6 physiological parameters that were used in Table 2 were used, with the addition of 2 more parameters: autonomic and muscle physiology. The remaining variables found in Table 3 were totaled to 98.

4.2 Additional Study Characteristics

The data extracted from the final studies included research conducted globally. The studies stated similar purposes to investigate gender-related differences among heart disease patients and were published in the following countries: United States, Canada, Australia, Portugal, Brazil, Germany, Iran, Poland, Costa Rica, Egypt, Israel, Italy, Korea, Ireland, France, Sweden, and Denmark. Furthermore, most studies commonly shared retrospective cohort study designs, along with prospective cohort and randomized controlled trials being the next prevalent.

The median number of weeks of CR intervention was 12 with every intervention incorporating at least aerobic exercise (unless the intervention was unknown). The most prevalent type of CR was aerobic only, followed by aerobic and strength exercise. Other CR interventions included home-based, high or moderate intensity interval training, and only knee extensor exercise. Additional information provided by the articles defined training exercises and patient agendas throughout the intervention. In other words, information such as the specific exercises during CR were mentioned such as using a cyclometer or treadmill for performing aerobic exercise, how many CR sessions were prescribed per week, structured exercise plans for the day/week, and/or recommendations for additional physical activity outside patient rehab programs. Furthermore, the study populations generally had higher enrollment and participation rates in men compared to women whereas adherence appeared similar among both genders. In regards to the QA, 27 articles scored a perfect score of 12/12, 21 articles scored 11/12, 14 scored 10/12, 7 scored 9/12 and only 2 scored 8/12.

4.3 Analysis of Results

Comparisons and final conclusions of the results were based on the categorization of variables discussed in Table 2, focusing on the 6 physiological parameters: fitness, metabolic, body composition, respiratory, cardiac, and protein measures. Interpretations of the results were also established by using the study characteristics listed in Table 1 to examine and describe the differences pertaining to common variables from paper to paper. Factors from Table 1 that were used for analysis of the results ranged from type of HD population, methodological differences, and limitations of the study. Overall, male and female HD patients engaging in CR tended to respond similarly, though some studies highlight why that may not always be the case.

Table 1: Study Characteristics

Study ID	Study Design	Population description	Method of recruitment of participants	Total number of participants	Type of CR	Length of CR	Completion and/or Adherence (sex presented separately where available)	Quality Assessment (out of 12)	Statistics
Adams 1999	Cohort Study	Patients with CABG, MI, PTCA, cardiomyopathy, and stable angina.	Clinic patients	n=74	HIIT & Aerobic	8 Weeks	CR Completion 82% 61/74 patients	11	ANOVA
Ades 1992	Cohort Study	All patients (hospitalized from AMI or CABG) interviewed were candidates for participation in cardiac rehabilitation	Clinic patients	n= 57 (39 men, 18 women)	Aerobic	12 Weeks	CR Completion 95% 37/39 men, 94% 17/18 women	11	t-test
Anjo 2014	Retrospective cohort study	Patients with CAD who attended a cardiac rehab program after an ACS or elective PCI.	Clinic patients	n=386 (301 men, 85 women)	Aerobic and Strength	8-12 Weeks	> 80% sessions attended	11	t-test
Antunes-Correa 2010	Randomized Controlled Trial	Patients with clinically stable HF, aged between 40 to 70 years, in NYHA functional class II to III and with an ejection fraction<40%	Clinic patients	n=21 (12 men, 9 women)	Aerobic and Strength	16 Weeks	85-100% of sessions attended.	12	ANOVA
Araya-Ramirez 2021	Retro-spective Study	Cardiac patients enrolled in a university-based CR program	Clinic patients	n=311 (237 men, 74 women)	Aerobic	12 Weeks	92% adherence for men and women	12	ANCOVA

Balady 1996	Cohort Study	Patients experiencing MI, CABG, or PTCA within 6 months of program	Clinic patients	n=778 (558 men, 220 women)	Aerobic	10 ± 2 weeks	CR completion: 33% 182/558 men, 28% 61/220 women; 83% adherence rate for men and women	12	t-test
Bellet 2015	Non-randomized Controlled Trial	Patients with a diagnosis of MI, angina, controlled arrhythmia, CAD or PCI, CABG, or experienced cardiac valve surgery, defibrillator, or pacemaker implantation. Patients were either divided in a fast track CR or a traditional CR program.	Clinic patients	n=197 (130 men, 67 women) Fast Track CR, n=423 (332 men, 91 women) Traditional CR	Aerobic and Strength	6 Weeks	CR completion: 58% 115/197 fast track CR patients and 60% 254/423 traditional CR patients.	10	ANOVA
Braga 2021	Retrospective Study	Patients were diagnosed with ACS	Clinic patients	n=731 (633 men, 98 women)	Aerobic and Strength	Up to 12 Weeks	>50% sessions attended	12	t-test
Branco 2016	Cross sectional descriptive retrospective study	Patients diagnosed with CAD who have been referred to cardiac rehabilitation.	Clinic patients	n=1399 (1068 men, 330 women)	Aerobic and Strength	8-12 Weeks	CR completion: 83% 886/1068 men, 72% 238/330 women	10	t-test
Brochu 2000	Cohort Study	Patients with AMI, CABG, unstable angina, and CHF	Clinic patients	n=82 (59 men, 23 women)	Aerobic and Strength	12 Weeks	CR completion: 100%	10	ANOVA

Candelaria 2020	Retrospective Cross-sectional study	Patients were eligible if they were attending CR for CAD, arrhythmia, heart failure and implantable devices.	Clinic patients	n=849 (604 men, 245 women)	Aerobic and Strength	6-12 Weeks	CR completion: 71% 426/604 men, 74% 181/245 women	10	t-test
Cannistra 1992	Cohort Study	Patients with heart disease: MI +- revascularization, CABG, coronary angioplasty, or angina pectoris.	Clinic patients	n=225 (174 men, 51 women)	Aerobic	12 Weeks	CR completion: 63% 110/174 men, 51% 26/51 women. Adherence was 85 ± 11% for women and 89 ± 13% for men	10	t-test
Casey 2009	Cohort Study	Patients were CAD outpatients and as well as diagnosed with stable angina, MI, PCI, CABG, cardiomyopathy, or CHF	Clinic patients	n=637 (459 men, 178 women)	Aerobic	13 Weeks	CR completion: 92% of men completed study, 88% of women completed study	11	t-test between deltas
Caulin-Glaser 2005	Retrospective Cohort Study	Patients with CAD who participated in a CR program.	Clinic patients	n=172 (134 men, 38 women)	Not specified	12 Weeks	CR completion: 100%	11	t-test between deltas
Caulin-Glaser 2007	Retrospective Cohort Study	Patients with CABG, PTCA, MI/CAD, or Valve disease	Clinic patients	n=348 (248 men, 100 women)	Not specified	12 Weeks	CR completion: 90% 224/248 men, 71% 71/100 women	12	t-test between deltas

Chai 1999	Cohort Study	Patients with recent MI, CABG or angioplasty or stable angina pectoris.	Clinic patients	n=113	Aerobic and Strength	12 Weeks	CR completion: 100%	8	t-test
ElMissiri 2020	Cohort Study	Patients with CAD and underwent PCI 3 months prior to their enrollment in the study.	Clinic patients	n=60 (30 men, 30 women)	Aerobic	12 Weeks	CR completion: 100% Adherence rate for men was 79.6% and 65.4% for women	12	t-test
Fiorina 2007	Cohort Study	Patients had either CABG, valve replacement, or AMI	Clinic patients	n=2500	Aerobic	15±3 Days	CR completion: 55%	12	t-test
Freene 2018	Cohort Study	Patients with stable CAD with/ without a revascularization procedure.	Clinic patients	n=72 (57 men, 15 women)	Aerobic and Strength	6 Weeks	CR completion: 88%	11	t-test between deltas
Gee 2014	Retrospective Cohort Study	Patients with stable angina, MI, PCI, or CABG	Clinic patients	n=1104 (758 men, 346 women)	Not specified	12 Weeks	CR completion: 73% 554/758 men, 66% 227/346 women. Adherence rate for men was 73.1% and was 65.6% for women	12	t-test
Ghashghaei 2012	Cohort Study	Patients with CAD including having history of one or more of the	Clinic patients	n=156 (men=72, women n=84)	Aerobic and Strength	8 Weeks	CR completion: 100%	11	t-test between deltas

		following: MI, CABG, PCI, and chronic stable angina.							
Goldhammer 2007	Cohort Study	Patients with CAD, having a history of MI, PCI, and/or CABG 21 to 45 days prior to inclusion to study.	Clinic patients	n=37 (23 men, 14 women)	Aerobic	12 Weeks	CR completion: 100%	12	ANOVA
Gupta 2007	Cohort Study	Patients with CAD and had either diabetes, dyslipidemia, hypertension or were obese.	Clinic patients	n=601	Aerobic	8-12 Weeks	CR completion: 89% 533/601 patients	11	t-test
Keating 2013	Cohort Study	Patients with CAD and had not had a MI or been hospitalized within the past 3 months. Patients also had a BMI > 27 kg/m 2, and waist circumference > 102 cm (men) or > 88 cm (women).	Clinic patients	n=46 (35 men, 11 women)	Aerobic; Home based	16 Week exercise + 4 Week weight control and exercise	CR completion: 100%	9	ANOVA
Keteyian 2003	Cohort Study	Patients with chronic heart failure caused by left ventricular systolic dysfunction (New York Heart As-sociation class II or III, a resting ejection fraction of<35%)	Clinic patients	n=15 (10 men and 5 women)	Aerobic	14-24 weeks	CR completion: 100%	11	t-test between deltas

Kim 2019	Cohort Study	Patients who underwent PCI after MI or unstable angina visited the CR center at 4 weeks after being discharged from the hospital.	Clinic patients	n=586 (451 men, 135 women)	Aerobic	36 Weeks	CR completion: 25% 114/451 men, 21% 30/145 women. Adherence rates between men and women were similar	11	t-test
Kligfield 2003	Cohort Study	Patients who were referred for a 12-week program of CR because of stable angina or after they experienced MI, CABG, or PCI	Clinic patients	n=81 (58 men, 23 women)	Aerobic	12 Weeks	CR completion: 100%	9	Unknown
Kodis 2001	Retrospective Cohort Study	Patients with CABG.	Clinic patients	n=1042- 713 in person CR (612 men; 101 women) 329 home based (296 men; 33 women)	Aerobic and Strength or Home-Based	24 Weeks	In person CR completion: 84% 516/612 men, 82% 83/101 women; Home-based CR completion: 97% 288/296 men, 91% 30/33 women	9	ANOVA

Korzeniowska-Kubacka 2015	Cohort Study	Patients with stable angina pectoris (CCS class I or II), sinus rhythm, preserved left ventricular function (ejection fraction > 50%), no evidence of right ventricular dysfunction on echocardiography, and those who were qualified for phase II of a comprehensive, post-MI, CR program	Clinic patients	n=87	1/2 Aerobic, 1/2 Home Based	8 Weeks	CR completion: 100%	12	t-test
Korzeniowska-Kubacka 2017	Cohort Study	Patients who experienced MI within last 3 months, sinus rhythm, preserved left ventricular function (ejection fraction >50%), and referred to CR	Clinic patients	n=62 (32 men, 30 women)	Aerobic	8 Weeks	CR completion: 100%	12	t-test /ANOVA
Lavie 1995	Cohort Study	Patients with CAD	Clinic patients	n=458 (375 men, 83 women)	Aerobic	12 Weeks	CR completion: 100%	12	t-test /ANOVA
Lee 2018	Cohort Study	Patients with CAD	Clinic patients	n=7726	Aerobic + Strength Vs Aerobic Interval Training	24 Weeks	CR completion: 73% (5,640/7726 patients)	10	t-test
MacMillan 2006	Retrospective Cohort Study	Patients who suffered from MI, CABG, PCI, stable	Clinic patients	n=100	Aerobic	12 Weeks	CR completion: 100%	11	t-test

		angina, revascularization, chronic heart failure or valve replacement.							
McConnell 1997	Cohort Study	Patients had to have a diagnosis of MI or coronary artery revascularization bypass surgery.	Clinic patients	n=581 (456 men, 125 women)	Aerobic	12 Weeks	76% adherence for body composition, 36% for lipid measures, 20% for VO_2	10	ANOVA
Mertens 1996	Cohort Study	Patients with chronic AF, and/or had a history of valvular disease, or CAD	Clinic patients	n=20	Aerobic	52 Weeks	CR completion: 100%	8	Unknown
Mittag 2006	Randomized Controlled Trial	Patients suffered with MI, CABG, and PCI	Clinic patients	n=343	Not specified (Home-Based)	52 Weeks	CR completion: 87%	9	t-test
Mroszczyk-McDonald 2007	Cohort Study	Patients who suffered from CABG, MI, PCI, heart failure, and/or diagnosed with stable angina	Clinic patients	n=1960 (men=1479, women=481)	Aerobic and Strength	12 Weeks	CR completion: 34% 505/1479 men, 33% 161/481 women	10	t-test /ANOVA
Nguyen 2020	Cohort Study	Patients who had undergone CABG surgery, CAD, MI, or PCI	Clinic patients	n=63 (40 men, 23 women)	Aerobic and Strength	24 Weeks	CR completion: 100%	11	t-test
Nguyen 2021	Cohort Study	Patients diagnosed with CAD	Clinic patients	n= 63 (40 men, 23 women)	Aerobic and Strength (in month 2-S)	24 Weeks	CR completion: 100%	12	Unknown

Ocallaghan 1984	Cohort Study	Patients who had MI or PCI	Clinic patients	n=264 (227 men, 37 women)	Aerobic	8 Weeks	CR completion: 92% of men completed the study, 81% of women completed. Men had an attendance rate of 87 ± 14% and women 77±16%.	11	t-test
O'Farrell 2000	Retrospective Cohort Study	Patients with either angina, MI, PTCA, CABG, CHF, cardiomyopathy, valvular disease, or heart transplantation	Clinic patients	n=387 (317 men, 70 women)	Aerobic	12 Weeks	CR completion: 100%. Men attended 83%, while women attended 76%.	10	t-test
Pabisiak 2013	Cohort Study	Patients who suffered a MI.	Clinic patients	n=61 (34 men, 27 women)	Aerobic and Strength	8 Weeks	CR completion: 100%	11	t-test
Piepoli 1998	Randomized Controlled Trial	Patients with heart failure (NYHA class III)	Clinic patients	n=134	Aerobic	6-16 Weeks	CR completion: 94% (126/134 patients)	10	t-test /ANOVA
Pina 2014	Randomized Controlled Trial	Patients with heart failure, patients with left ventricular dysfunction (ejection fraction <35%) and NYHA class 2 to 4	Clinic patients	n=2331 (1670 men, 661 women)	Aerobic	12 Weeks	CR completion: 81% of men and 79% of women. Adherence was 45% for men and	12	t-test

							37% for women		
Pischke 2006	Randomized Controlled Trial	Patients had a diagnosis of CAD, and a history of CABG, PTCA, angina or MI.	Clinic patients	n=343 (286 men, 57 women)	Aerobic	12 Weeks	CR completion: 95% of men completed the study and 95% of women.	12	ANOVA
Rejeski 2002	Randomized Controlled Trial	Patients with a history of MI, PTCA, chronic stable angina, New York Heart Association Class I or Class II congestive heart failure, cardiovascular surgery (coronary artery or valvular heart disease) in the past 6 months	Other: Recruitment strategies consisted of mass mailings, mass media advertisements, and requests from local physicians	n=147 (76 men, 71 women)	Aerobic and Strength	12 Weeks	CR completion: 88%	10	ANOVA
Rengo 2020	Cohort Study	Patients with a history of cardiac surgery and MI	Clinic patients	n=3925(2985 men, 940 women)	Aerobic (some CR had HIIT)	12-16 Weeks	CR completion: 46% of men, 43% of women	12	t-test /ANOVA
Sadeghi 2012	Cohort Study	Patients with a history of MI, CABG, PCI, and chronic stable angina.	Clinic patients	n=585 (men=464, women=121)	Aerobic and Strength	8 Weeks	CR completion: 100%	9	t-test between deltas
Saeidi 2013	Cohort Study	Patients with a history of MI, PTCA, CABG, and CAD	Clinic patients	n=100 (69 men, 31 women)	Aerobic	8 Weeks	CR completion: 100%	9	t-test
Sarrafzadegan 2008	Cohort Study	Patients had a history of MI, CABG, PCI or CAD	Clinic patients	n=1220	Aerobic	8 Weeks	CR completion: 45%	12	t-test /ANOVA

Savage 2004	Cohort Study	Patients had a history of MI, CABG, CHF, unstable angina or CAD.	Clinic patients	n=340 (263 men, 77 women)	Aerobic + Strength	12 Weeks	CR completion: 100%	12	t-test /ANOVA
Schultz 2010	Cohort Study	Patients who had a history of CABG, MI, PTCA and/or valve surgery.	Clinic patients	n=109 (60 men, 49 women)	Aerobic	12 Weeks	CR completion: 100%	9	t-test
Socha 2017	Cohort Study	Patients with CAD following CABG	Clinic patients	n=65 (44 men, 21 women)	Aerobic	3 Weeks	CR completion: 66% of men, 52% of women	11	Other
Soleimani 2009	Cohort Study	Patients with CAD who had previously undergone elective PTCA	Clinic patients	n=440 (339 men, 101 women)	Aerobic	8 Weeks	CR completion: 59% of men, 85% of women. 19.3% of patients attended 24 or more sessions)	10	t-test
Soleimani-Netajian 2009	Retrospective Cohort Study	Patients with CAD	Clinic patients	n=216 (168 men, 48 women) - nondiabetics	Aerobic	8 Weeks	CR completion: 100% of men, 81% of women	11	t-test /Other
Swank 2010	Cohort Study	Patients with CHF, ejection fraction<35%, with systolic dysfunction	Clinic patients	n=42 (27 men, 15 women)	Aerobic and Strength	14 Weeks	CR completion: 100%	12	ANOVA
Temfemo 2011	Cohort Study	Patients who had a history of CABG, artery angioplasty, MI, or valve replacement.	Clinic patients	n=188	Aerobic	8 Weeks	CR completion: 100%	12	ANOVA

Terada 2019	Randomized Controlled Trial	Patients with CAD	Clinic patients	n=120 (60 men, 60 women)	Aerobic (Either AIT or MICE)	8 Weeks	CR completion: 100%	11	t-test /ANCOVA
Terada-Chirico 2019	Retrospective Cohort	Patients diagnosed with angina, CABG, PCI, CAD, CHF, cardiomyopathy, heart murmur, carotid disease, or transient ischemic attack.	Clinic patients	n=591 (436 men, 155 women)	Aerobic (On site, home based, or brief)	4-12 weeks	CR completion: 100%	12	t-test /ANCOVA
Thorin-Trescases 2016	Cohort Study	Patients diagnosed with ACS	Clinic patients	n=40 (30 men, 10 women)	Aerobic	12 Weeks	CR completion: 100%. Adherence rate for men was 98.9±3.0% and for women 97.0±3.4%	10	ANCOVA/Other
Trachsel 2020	Randomized Controlled Trial	Patients with CAD	Clinic patients	n=116 (64 men, 19 women)	Aerobic and Strength	12 Weeks	CR completion: 88% of men, 86% of women completed	12	ANOVA
Turk-Adawi 2016	Retrospective Cohort Study	Patients with ACS, revascularization, stable heart failure, and heart valve repair or replacement	Clinic patients	n=12976 (8,836 men, 4,140 women)	Not specified	12 Weeks	CR completion: 71% of men, 65% of women completed	12	Other

Tyni-Lenne 1998	Cohort Study	Patients with CHF, ejection fraction<40%, New York Heart Association (NYHA) functional class II and class III	Clinic patients	n=24 (12 men, 12 women)	Knee extensor exercise	8 Weeks	CR completion: 92% of men, 100% of women. Adherence to program ranged from 86% to 100% with no sex-related differences.	12	t-test /ANOVA
Verrill 2003	Cohort Study	Patients with CAD, and/or angina, valvular disease or replacement, CHF or MI	Clinic patients	n=630 (424 men and 206 women)	Aerobic and Strength	10-12 Weeks	CR completion: 100%	10	ANOVA
Vilela 2020	Retrospective cohort	Patients who suffered from AMI	Clinic patients	n=379 (307 men, 72 women)	Aerobic and Strength	8 Weeks	CR completion: 100%	12	t-test
Wagner 2018	Randomized Controlled Trial	Patients with AF	Clinic patients	n=210 (151 men, 59 women)	Aerobic and Strength	12 Weeks	CR completion: 82% of men, 88% of women. Adherence to the training sessions was higher in men (47%) than in women (40%)	11	t-test
Warner 1995	Retrospective Cohort	Patients were referred after MI, CABG, percutaneous	Clinic patients	n=719 (553 men 166 women)	Aerobic	260 Weeks	CR completion: 12% 69/553 men, 8%	11	t-test /ANCOVA

		balloon angioplasty, cardiomyopathy, and/or stable angina					14/166 women. Adherence was 70% for men and 68% for women		
Weinberger 2014	Retrospective Cohort Study	Patients with PTCA, CABG, MI, valve replacement, CAD, CHF, angina or cardiomyopathy	Clinic patients	n=2339	Not Specified	≥ 7weeks; average 11 weeks	CR completion: 49% Adherence was 11.5 weeks for men and 11.4 weeks for women	12	Other
Willenheimer 1998	Randomized Controlled Trial	Patients with heart failure and ejection fraction <45%	Clinic patients	n=54	Aerobic	16 Weeks	CR completion: 91% Adherence for men was 78% and for 67% women	11	t-test
Wise 2012	Cohort Study	Patients with CHF (NYHA level I-III) also diagnosed with CAD, cardiomyopathy, valvular disease, and or/tachycardia	Clinic patients	n=232 (172 males, 60 females)	Aerobic and Strength	12 Weeks + median of 4 extra weeks	CR completion: 100% All patients attended at least 40% of sessions.	11	Other

ACS; acute coronary syndrome, AF; atrial fibrillation, AMI; acute myocardial infarction, BMI; body mass index, CABG; coronary artery bypass grafting, CAD; coronary artery disease, CHF; chronic heart failure, CR; cardiac rehabilitation, HF; heart failure, HIIT; high intensity interval training, MI; myocardial infarction, NYHA; New York heart association PCI; percutaneous coronary intervention, PTCA; percutaneous transluminal coronary angioplasty

Table 2: Statistically Significant ($p<0.05$) Sex Differences or Similarities in the Physiological Responses to CR Completion

Physiological response	Greater improvement in men	Only men improved	Greater improvement in women	Only women improved	Both men and women improved similarly	No improvement in either sex
Fitness						
Maximal exercise VO_2 (ml/kg/min)	Keteyian 2003, Kodis 2001, Lee 2018, Mroszczyk-McDonald 2007, Nguyen 2020, Nguyen 2021, Rengo 2020, Savage 2004, Schultz 2010, Thorin-Trescases 2016 **(10 studies)**	Kim 2019, Willenheimer 1998 **(2 studies)**		Tyni-Lenne 1998 **(1 study)**	Ades 1992, Antunes-Correa 2010, Brochu 2000, MacMillan 2006, Piepoli 1998, Pina 2014, Temfemo 2011, Trachsel 2020, Vilela 2020, Wagner 2018 **(9 studies)**	
Percent-predicted peak VO_2 (%)	Mertens 1996 **(1 study)**				Trachsel 2020, Vilela 2020 **(2 studies)**	
RER ratio			Rengo 2020 **(1 study)**		Trachsel 2020, Vilela 2020 **(2 studies)**	Ades 1992 **(1 study)**
Functional Capacity (METS)	Caulin-Glaser 2007, Chai 1999, Gee 2014, Ghashghaei 2012, Kligfield 2003, Kodis 2001, Lavie 1995, Sadeghi 2012, Saeidi 2013, Sarrafzadegan 2008, Wise 2012 **(11 studies)**	Willenheimer 1998 **(1 study)**			Anjo 2014, Balady 1996, Branco 2016, Cannistra 1992, Korzeniowska-Kubacka 2015, MacMillan 2006, Pischke 2006, Rejeski 2002 **(9 studies)**	
6MWD (m)	Araya-Ramirez 2021, Bellet 2015 Candelaria 2020, Gupta 2007,		Wagner 2018, Wise 2012 **(2 studies)**		Fiorina 2007, Freene 2018, Kim 2019 Rejeski 2002 **(4 studies)**	

	Tyni-Lenne 1998, Verrill 2003 **(6 studies)**					
Peak workload/LBM (W/kg)	Kodis 2001 **(1 study)**				Trachsel 2020, Tyni-Lenne 1998 **(2 studies)**	
HR at rest (bpm)	ElMissiri 2020, O'Farrell 2000, Saeidi 2013 **(3 studies)**	Anjo 2014 **(1 study)**	Korzeniowska-Kubacka 2017 **(1 study)**		Goldhammer 2007, Pischke 2006, , Soleimani- Nejatian 2009, Swank 2010, Temfemo 2011, Terada 2019 **(6 studies)**	Ades 1992, Antunes-Correa 2010, Araya-Ramirez 2021, Korzeniowska-Kubacka 2015, Lavie 1995, MacMillan 2006, Sarrafzadegan 2008, Tyni-Lenne 1998 **(8 studies)**
Maximal HR (bpm)				Keteyian 2003, Lavie 1995 **(2 studies)**	Goldhammer 2007, Korzeniowska-Kubacka 2015, MacMillan 2006, Soleimani-Netajian 2009, Temfemo 2011 **(5 studies)**	Ades 1992 **(1 study)**

Difference in HRR (bpm)	Kligfield 2003 **(1 study)**				Anjo 2014, Araya-Ramirez 2021, MacMillan 2006, Soleimani-Nejatian 2009 **(4 studies)**	
DBP with effort (mm Hg)	Korzeniowska-Kubacka 2017 **(1 study)**					Korzeniowska-Kubacka 2015 **(1 study)**
Exercise time (s)			Wagner 2018 **(1 study)**		Balady 1996, Cannistra 1992, Goldhammer 2007, Korzeniowska-Kubacka 2015, Ocallaghan 1984, Vilela 2020 **(6 studies)**	
Absolute energy expenditure (kcal/wk)					O'Farrell 2000, Schultz 2010, Soleimani 2009 **(3 studies)**	
Sit to stand (number)	Wagner 2018 **(1 study)**	Kim 2019 **(1 study)**				
Functional Reach (cm)		Kim 2019 **(1 study)**			Adams 1999 **(1 study)**	
Leg press (number)					Adams 1999, Swank 2010 **(2 studies)**	
Leg extension (number)					Adams 1999, Swank 2010 **(2 studies)**	

Grip strength (kg)	Mroszczyk-McDonald 2007, Rengo 2020 **(2 studies)**	Kim 2019 **(1 study)**				
Metabolic Measures						
HDL (mg/dl)	Weinberger 2014 **(1 study)**	Gupta 2007, Sadeghi 2012 **(2 studies)**	Casey 2009, Savage 2004, Terada-Chirico 2019 **(3 studies)**	Warner 1995 **(1 study)**	Anjo 2014, Brochu 2000, Caulin-Glaser 2007, Ghashghaei 2012, , Kim 2019, Lavie 1995, Mittag 2006, O'Farrell 2000, Pischke 2006, Sarrafzadegan 2008, Schultz 2010 **(11 studies)**	Goldhammer 2007, Thorin-Trescases 2016, Turk-Adawi 2016 **(3 studies)**
Total cholesterol: HDL ratio					O'Farrell 2000, Warner 1995 **(2 studies)**	Brochu 2000, Thorin-Trescases 2016 **(2 studies)**
Total Cholesterol (mg/dl)	Casey 2009, ElMissiri 2020, Ghashghaei 2012 **(3 studies)**				Anjo 2014, Brochu 2000, Gupta 2007, Kim 2019, Lavie 1995, McConnell 1997, Mittag 2006, O'Farrell 2000, Pischke 2006, Sadeghi 2012, Sarrafzadegan 2008, Savage 2004, Turk-Adawi 2016, Warner 1995 **(14 studies)**	Goldhammer 2007, Thorin-Trescases 2016 **(2 studies)**

LDL (mg/dl)					Anjo 2014, Casey 2009, Caulin-Glaser 2007, ElMissiri 2020, Ghashghaei 2012, Goldhammer 2007, Gupta 2007, O'Farrell 2000, Pischke 2006, Sadeghi 2012, Sarrafzadegan 2008, Savage 2004,Terada-Chirico 2019, Thorin-Trescases 2016, Turk-Adawi 2016, Warner 1995 **(16 studies)**	Brochu 2000, Kim 2019, Schultz 2010 **(3 studies)**
LDL-C/HDL-C					Ghashghaei 2012, Lavie 1995, O'Farrell 2000 **(3 studies)**	
TGs (mg/dl)	ElMissiri 2020, Turk-Adawi 2016 **(2 studies)**				Anjo 2014, Casey 2009, Lavie 1995, McConnell 1997, Pischke 2006, Sadeghi 2012, Sarrafzadegan 2008 Savage 2004, Schultz 2010, Terada-Chirico 2019, Turk-Adawi 2016, Warner 1995 **(12 studies)**	Brochu 2000, Caulin-Glaser 2007, Goldhammer 2007, Kim 2001, O'Farrell 2000, Thorin-Trescases 2016, **(6 studies)**
SBP (mmHg)	Mittag 2006		O'Farrell 2000, Turk-Adawi 2016		Araya-Ramirez 2021, Casey 2009, Pischke 2006, Sarrafzadegan	Ades 1992, Kim 2019, Korzeniowska-

	(1 study)		**(2 studies)**		2008, Schultz 2010, Swank 2010, Terada-Chirico 2019, Thorin-Trescases 2016 **(8 studies)**	Kubacka 2015, Lavie 1995, Terada 2019, Trachsel 2020 **(6 studies)**
DBP (mmHg)			ElMissiri 2020, Trachsel 2020 **(2 studies)**		Araya-Ramirez 2021, Casey 2009, Pischke 2006, Sarrafzadegan 2008, Terada-Chirico 2019, Thorin-Trescases 2016, **(6 studies)**	Kim 2019, Korzeniowska-Kubacka 2015, O'Farrell 2000, Schultz 2010, Swank 2010, Terada 2019, Turk-Adawi 2016 **(7 studies)**
Glucose (mg/dl)			Anjo 2014, **(1 study)**		Schultz 2010, Terada-Chirico 2019 **(2 studies)**	Brochu 2000, Goldhammer 2007, O'Farrell 2000, Thorin-Trescases 2016 **(4 studies)**
Insulin (mg/dl)						Brochu 2000, Thorin-Trescases 2016 **(2 studies)**
Changes in Glycated					Anjo 2014, Terada-Chirico 2019, Turk-Adawi 2016	

hemoglobin A1C (%)					**(3 studies)**	
Body Composition						
Weight (kg)	Ghashghaei 2012, Terada-Chirico 2019 **(2 studies)**				Casey 2009, McConnell 1997, Mroszczyk-McDonald 2007, Pischke 2006, Rengo 2020, Savage 2004, Socha 2017, Temfemo 2011, Terada 2019, Thorin-Trescases 2016 **(13 studies)**	Araya-Ramirez 2021, Brochu 2000, Schultz 2010 **(3 studies)**
Waist Circumference (cm)	Brochu 2000 **(1 study)**		Braga 2021 **(1 study)**		Casey 2009, ElMissiri 2020, Mroszczyk-McDonald 2007, Rengo 2020, Sarrafzadegan 2008, Savage 2004, Schultz 2010, Terada 2019, Thorin-Trescases 2016 **(9 studies)**	Kim 2019, Turk-Adawi 2016 **(2 studies)**
BMI (kg/m^2)			Sarrafzadegan 2008 **(1 study)**		Anjo 2014, Brochu 2000, Casey 2009, Caulin-Glaser 2007, ElMissiri 2020, Gupta 2007, Lavie 1995, Mroszczyk-McDonald 2007, Rengo 2020, Savage 2004, Socha 2017, Terada 2019, Thorin-Trescases 2016	Araya-Ramirez 2021, O'Farrell 2000, Schultz 2010, Turk-Adawi 2016 **(4 studies)**

					(13 studies)	
Body fat (%)	Brochu 2000 **(1 study)**				Lavie 1995, McConnell 1997, Pischke 2006, Socha 2017, Thorin-Trescases 2016 **(5 studies)**	Kim 2019 **(1 study)**
Hip circumference (cm)	Brochu 2000 **(1 study)**				Sarrafzadegan 2008 **(1 study)**	
Total fat mass (%)	Brochu 2000 **(1 study)**				Thorin-Trescases 2016 **(1 study)**	
Fasting Blood Sugar (mg/dl)		Ghashghaei 2012 **(1 study)**			Sarrafzadegan 2008 **(1 study)**	
Waist-to-hip ratio		Brochu 2000 **(1 study)**			Sarrafzadegan 2008 **(1 study)**	
Fat-free mass (%)		Brochu 2000 **(1 study)**			Socha 2017 **(1 study)**	
Respiratory						
Forced Vital Capacity (L)					Temfemo 2011 **(1 study)**	Ades 1992 **(1 study)**
VE/VCO$_2$ slope					Antunes-Correa 2010 **(1 study)**	Trachsel 2020 **(1 study)**
VE at peak (L/min)						Ades 1992, Trachsel 2020 **(2 studies)**
Cardiac Measures						

LVEF (%)					ElMissiri 2020, , Saeidi 2013, Sarrafzadegan 2008 **(3 studies)**	Antunes-Correa 2010, Goldhammer 2007, Trachsel 2020 **(3 studies)**
Peak rate pressure product (beats/min x mm Hg)	Cannistra 1992 **(1 study)**					Lavie 1995 **(1 study)**
LVEDD (mm)						ElMissiri 2020, Trachsel 2020 **(2 studies)**
LVESD (mm)					ElMissiri 2020 **(1 study)**	Trachsel 2020 **(1 study)**
Protein Measures						
CRP (mg/L)		Thorin-Trescases 2016 **(1 study)**			Caulin-Glaser 2005, Goldhammer 2007, Sheikhian 2018 **(3 studies)**	

Anglt2; angiopoietin like 2, BMI; body mass index, CRP; c-reactive protein, DBP; diastolic blood pressure, FBS; fasting blood sugar, LBM; lean body mass, LVEDD; left ventricular end diastolic diameter, LVEF; left ventricular ejection fraction, LVESD; left ventricular end systolic diameter, MAP; mean arterial pressure, METS; metabolic equivalents, NYHA class; New York Heart Association classification, RER; respiratory exchange ratio, SBP; systolic blood pressure, TGs; triglycerides, 6MWD; 6-minute walk distance, 6MWT; 6-minute walk time.

Table 3: Additional Statistically Significant ($p<0.05$) Physiological Response Comparisons (i.e. only one article per investigated variable)

Physiological Response	Greater improvement in men	Only men improved	Greater improvement in women	Only women improved	Both Men and women improved similarly	Neither sexes improved
Fitness						
VO_2 relative (ml/kg/min)		Keteyian 2003				
VO_2/LBM @ Vt1 (ml/min x kg)						Trachsel 2020
VO_2/LBM at Vt2 (ml/min x kg)						Trachsel 2020
Treadmill duration (min)					Ades 1992	
Treadmill velocity (km/hr)					Soleimani 2009	
Peak Power Output (W)					Temfemo 2011	
Peak power (% change)					Mertens 1996	

Oxygen uptake efficiency slope						Trachsel 2020
VO_2/Workload slope						Trachsel 2020
O_2 Pulse (mL/beat)						Trachsel 2020
Maximum HR (%)	Cannistra 1992					
Post-exercise heart rate					Soleimani-Netajian 2009	
HRR in the first min (bpm)						Korzeniowska-Kubacka 2015
Changes in HRR in the second minute (%)	Korzeniowska-Kubacka 2017					
HR x BP						Ades 1992
Submaximal HR (bpm)						Ades 1992
Maximal HR x BP						Ades 1992
Submaximal HR x BP						Ades 1992
Submaximal Systolic BP (mm Hg)						Ades 1992
Peak SBP (mm Hg)						Lavie 1995
SBP effort (mm Hg)		Korzeniowska-Kubacka 2015				
Submaximal exercise rate pressure product					Casey 2009	
Rate pressure product					Swank 2010	
Change in physical activity (min/week)	Turk-Adawi 2016					

Relative energy expenditure (kcal/kg/wk)					Schultz 2010	
Flexibility (cm)		Kim 2019				
Balance (s)					Kim 2019	
Horizontal squat (number)					Adams 1999	
Shoulder press (% change)					Swank 2010	
Latissimus pulldown (% change)					Swank 2010	
Bicep curl (% change)					Swank 2010	
Triceps extension (% change)					Swank 2010	
Timed up and go (s)					Kim 2019	
Gait velocity (m/s)	Tyni-Lenne 1998					
Heart rate in gait (bpm)	Tyni-Lenne 1998					
Post-6MWT DBP (mm Hg)			Araya-Ramirez 2021-			
Post-6MWT SBP (mm Hg)			Araya-Ramirez 2021			
Post-6MWT HR (bpm)					Araya-Ramirez 2021	
Heart rate at equal workloads (bpm)					Ocallaghan 1984	
Metabolic Measures						
FBF (ml/min/100 Ml tissue)					Antunes-Correa 2010	
FVR (U)					Antunes-Correa 2010	

TGs: HDL						Thorin-Trescases 2016
MAP (mm Hg)						Antunes-Correa 2010
Body Composition						
Trunk fat mass (%)					Thorin-Trescases 2016	
Lean Body Mass (kg)					McConnell 1997	
BCM (%)	Socha 2017					
TBW (%)					Socha 2017	
Respiratory						
Breathing Frequency (breaths/min)						Trachsel 2020
Tidal volume (L)						Trachsel 2020
Ventilation (L/min)						Ades 1992
Ventilatory threshold (ml/kg/min)					Temfemo 2011	
Peak Expiratory flow (L)						Temfemo 2011
Submaximal exercise Ventilation (L/min)						Ades 1992
FEV/FVC (%)					Temfemo 2011	
Forced expiratory volume in 1 second (L/s)					Temfemo 2011	
Cardiac Measures						

NYHA class					Antunes-Correa 2010	
EF <50% (n values)					Pabisiak 2013	
Changes in Chronotropic index (%)		Anjo 2014				
LVMI (g/m^2)						Trachsel 2020
LVEDVI (ml/m^2)						Trachsel 2020
LVESV (ml)						Trachsel 2020
LVESVi (ml/m^2)						Trachsel 2020
E/A ratio						Trachsel 2020
early to late diastolic filling velocity						Trachsel 2020
Mean peak early diastolic mitral annulus velocity						Trachsel 2020
LA diameter (mm)						Trachsel 2020
Stroke volume index						Trachsel 2020
Cardiac Index						Trachsel 2020
Muscle Physiology						
MHC-1 (% Change)		Keteyian 2003				
MHC- 2a (% Change)						Keteyian 2003
MHC-2x (% Change)						Keteyian 2003
Capillary density (endothelial/muscle fiber)						Keteyian 2003
Blood lactate baseline (nmol/L)					Tyni-Lenne 1998	

Blood lactate at 15 min point (nmol/L)					Tyni-Lenne 1998	
Autonomic						
MSNA frequency (bursts/min)					Antunes-Correa 2010	
MSNA incidence (bursts/100 heart beats)					Antunes-Correa 2010	
Plasma Norepinephrine baseline (nmol/L)					Tyni-Lenne 1998	
Plasma Norepinephrine 15 min point (nmol/L)					Tyni-Lenne 1998	
Protein Measures						
Paraoxonase (μm/ml)					Goldhammer 2007	
p-selectin expression (%)				Keating 2013		
BNP (ng/L)	Sheikhian 2018					
NT-proBNP (pg/ml)			Anjo 2014			
Angptl2 (ng/ml)		Thorin-Trescases 2016				
Cytochrome C Oxidase Change (mol/protein x h)					Keteyian 2003	
HAD Change (mol/kg protein x h)					Keteyian 2003	
Citrate Synthase Change (mol/ protein x h)					Keteyian 2003	

BCM; body cell mass, BF; breathing frequency, BNP;brain natriuretic peptide, DBP; diastolic blood pressure, E/A; early filling to late diastolic filling ratio, FBF; forearm blood flow, FVR; forearm vascular resistance, FEV/FVC; forced expiratory volume/forced vital capacity, HAD: haloacid dehydrogenase, LA diameter; left atrium diameter, LVEDVI; left ventricular end diastolic volume index, LVESV; left ventricular end systolic volume, LVESVI; left ventricular end systolic volume index, LVMI: left ventricular mass index, MHC: myosin heavy chain form, MSNA; muscle sympathetic nerve activity, NT-proBNP: N-terminal pro brain natriuretic peptide, SBP; systolic blood pressure, TBW: total body water, Vt1 and Vt2; first and secondary ventilatory thresholds.

Chapter 5: Discussion

In this section, a comparison of articles in Table 1 is thoroughly discussed, tackling multiple variables in several categories. Firstly, the discussion pertains to only fitness variables, then metabolic variables, body composition, respiratory variables, cardiac measures and lastly protein measures. The main consensus among the fitness variables was that men and women responded similarly to CR, yet a few variables strongly suggested a sex difference. As found in numerous articles maximal exercise VO_2, measures of functional capacity (METS-metabolic equivalents), 6-minute walk distances (6MWD) and grip strengths suggest that men may improve to a greater degree than women.

5.1 Fitness

5.1.1 Oxygen at Maximal Exercise

As previously discussed, VO_2max is a measure of peak oxygen consumption at maximal exercise. Many studies have indicated that there was a greater improvement in VO_2 max in men compared to women. (Keteyian et al., 2003; Kodis et al., 2001; Lee et al., 2018; Mroszczyk-McDonald et al., 2007; Nguyen et al., 2020, 2021; Rengo et al., 2020; Savage et al., 2004; Schultz et al., 2010; Thorin-Trescases et al., 2016). However, many studies also argued that there is no sex difference in this physiological response (Ades et al., 1992; Antunes et al., 2010; Brochu et al., 2000; MacMillan et al., 2006; Piepoli et al., 1998; Pina et al., 2014; Temfemo et al., 2011; Trachsel et al., 2020; Vilela et al., 2020; Wagner et al., 2018). Among the studies that found that men improved more than women, Kodis et al., Lee et al., Mroszczyk-McDonald et al., Nguyen et al., and Savage et al., included CR interventions of aerobic and strength training, and Keteyian et al., Schultz et al., and Thorin-Trescases et al., included only aerobic training (Kodis et al., 2001; Lee et al., 2018; Mroszczyk-McDonald et al., 2007; Nguyen et al., 2020, 2021; Savage et al., 2004; Schultz et al., 2010; Thorin-Trescases et al., 2016). Kodis et al., and Lee et al., also included a home-based program and aerobic interval training, respectively (Kodis et al., 2001; Lee et al., 2018). Furthermore, Rengo et al. was the only study in this group that included some aspects of high intensity interval training (HIIT) (Rengo et al., 2020). While comparing it was noted that for the studies that did not see a difference, Ades et al., MacMillan et al., Pina et al., Temfemo et al., had purely aerobic interventions, and Antunes-Correa et al., Brochu et al., Trachsel et al., Vilela et al., and Wagner et al., had a combination of strength and aerobic (Ades et al., 1992; Antunes et al., 2010; Brochu et al., 2000; MacMillan et al., 2006; Pina et al., 2014; Temfemo et al., 2011; Trachsel et al., 2020; Vilela et al., 2020; Wagner et al., 2018). Although both sets of articles have different outcomes regarding maximal oxygen consumption, the types of exercise were generally similar, including either aerobic and/or strength. Thus, the type of exercise is not a strong enough factor to predict why some articles reported the greater response in men compared to women, and why some articles did not.

VO_2max was found to only improve in men and not women in 2 additional studies (Kim & So, 2019; Willenheimer et al., 1998). A factor that may account for sex differences described in Kim & So, could be the extended program length of 36 weeks. This was the longest intervention duration among articles that compared VO_2max responses and could be a determining factor, as many articles stating no sex difference had interventions ranging only from 8-12 weeks (Ades et al., 1992; Brochu et al., 2000; MacMillan et al., 2006; Pina et al., 2014; Temfemo et al., 2011; Trachsel et al., 2020; Vilela et al., 2020; Wagner et al., 2018). Secondly, in the Willenheimer study, only patients with HF were studied, whereas the remainder of studies concluding no sex difference looked at populations with various heart diseases. Thus, program length or type of HD could play a role in the observation of sex differences.

A surprising finding was in a study by Tyni-Lenne et al. investigating patients diagnosed with HF enrolled in an 8-week intervention of knee extensor exercise. They observed an improvement of VO_2max only in women (Tyni-Lenne et al., 1998) which is contrary to most other articles. The only differing factor was the intervention type, for knee extensor exercise was the only one of its kind in comparison to the common aerobic and/or strength interventions discussed in the other studies arguing for a greater effect in men or no sex difference.

Furthermore, %-predicted peak VO_2, which represents maximal oxygen consumption as a predicted percentage, was observed by Mertens & Kavanagh who found a greater improvement in men versus women, however two other studies by Trachsel et al., and Vilela et al., concluded that this percentage improves equally in both sexes (Mertens & Kavanagh, 1996; Trachsel et al., 2020; Vilela et al., 2020). This could have been due to a population of atrial fibrillation patients being studied for a year-long aerobic intervention by Mertens & Kavanagh in comparison to Trachsel et al. and Vilela et al., whom had aerobic and strength interventions of shorter durations (12 and 8 weeks, respectively) (Mertens & Kavanagh, 1996; Trachsel et al., 2020; Vilela et al., 2020).

5.1.2 Functional Capacity

Functional capacity is often expressed as a measure of metabolic equivalents (METS) and defined as a person's capability to complete necessary tasks and activities. Several studies have collectively concluded that men experience a greater improvement in METS than women post CR intervention (Caulin-Glaser et al., 2007; Chai et al., 1999; Gee et al., 2014; Ghashghaei et al., 2012; Kligfield et al., 2003; Kodis et al., 2001; Lavie & Milani, 1995; Sadeghi et al., 2012; Saeidi et al., 2013; Sarrafzadegan et al., 2008; Willenheimer et al.,1998; Wise et al., 2012) . All these studies had either aerobic and strength interventions, purely aerobic interventions and in one case, a combination of home-based and in person aerobic and strength training (Kodis et al., 2001). Most of these studies had an intervention of either 8 or 12 weeks in length, with the exception of Kodis et al., who had an intervention of 24 weeks and Willenheimer et al., who had 16 weeks. (Kodis et al., 2001; Willenheimer et al., 1998). Patients in these trials had various HD diagnoses, including MI, CABG, CAD, percutaneous coronary intervention (PCI), stable angina, and HF. Thus, the greater improvement in functional capacity in men was prevalent across men and women with different cardiac conditions. Moreover, completion and participation ranged from as low as 45% to as high as 100% in these studies and these studies included a variety of statistics including t-tests, t-tests between deltas, and ANOVAS. Though these twelve studies stated that there is indeed a sex difference in METS, nine other articles that discussed functional capacity stated that both men and women improve equally after CR (Anjo et al., 2014; Balady et al., 1996; Branco et al., 2016; Cannistra et al., 1992; Korzeniowska-Kubacka et al., 2015; MacMillan et al., 2006; McConnell et al., 1997; Pischke et al., 2006; Rejeski et al., 2002). The studies that refuted a sex difference similarly had either aerobic, aerobic and strength, or home-based interventions ranging from 8 to 12 weeks, along with completion rates ranging as low as 31% to as high as 100%. Thus, the interventions among the two sets of studies were fairly similar. Furthermore, a deeper analysis was conducted by observing any differences in the types of statistical methods. The statistical analyses were also common, as both ANOVAs and t-tests were completed. Thus, statistical methods in this case would also be unlikely to determine the disparities between sex differences or similarities in functional capacity. Based on the parameters collected in the scope of this review, it is ambiguous as to what may distinguish the articles which found a sex difference from the articles which found similar responses between the sexes in regards to MET outcomes in functional capacity post CR.

5.1.3 Six Minute Walk Distance (6MWD)

6MWD is known as a test that measures aerobic capacity and endurance through attaining how much distance is covered when walking for six minutes. Many of the compiled studies found that men experienced a greater improvement in the 6MWD in comparison to women after CR (Araya-Ramirez et al., 2021.; Bellet et al., 2015; Candelaria et al., 2020; Gupta et al., 2007; Tyni-Lenne et al., 1998; Verrill et al., 2003). The populations of interest therein included participants of various heart diagnoses in addition to being exposed to different CR interventions, including aerobic, aerobic and strength or knee extensor exercise. Four other studies refuted the sex difference in 6MWD and reported similar improvements between men and women. These studies also included only aerobic, or aerobic and strength interventions. (Fiorina et al., 2007; Freene et al., 2018; Kim & So, 2019; Rejeski et al., 2002). These studies investigated populations with a combination of varying cardiac conditions, instead of specifying the HD type, thus disease state or intervention type could not predict whether there is a sex difference in 6MWD outcomes. Additionally, both groups of articles either used ANOVAs or t-tests. If the articles that stated a sex difference only used ANOVAs, or only used t-tests, then statistical measures could be a predicting factor for group differences. Another predicting factor could be adherence rates; however, it was generally high in all these articles, (at least 70% either fully completed the study or attended at least 70% of the sessions). Thus, adherence may not be a reason for these differences as both sets of articles shared similar adherence rates.

On the contrary, two additional studies by Wagner et al., and Wise et al., have reported that women actually have a greater improvement than men in 6MWD outcomes post CR (Wagner et al., 2018; Wise & Patrick, 2012). In the study by Wagner et al., they only investigated individuals with atrial fibrillation and the study design was a randomized controlled trial. In the study by Wise & Patrick, they investigated patients with HF with a cohort study design. In these cases, both studies investigated a specific HD type, which could be a determining factor as to why it was observed that women improved more than men. However, like the rest of the articles that stated no difference, or that men improved more, they shared similar methodology with an average of 12 week CR with both aerobic and strength exercise.

5.1.4 Heart Rate Measures

Though men and women have shown to differ in heart size and adaptation to exercise, many studies have revealed a sex difference in HR related measures. To begin, multiple variables involving HR such as HR at rest have shown a greater improvement in men (ElMissiri et al., 2020; O'Farrell et al., 2000; Saeidi et al., 2013). In all three of these studies, the interventions were purely aerobic, had 100% adherence rates in both sexes yet only had t-tests conducted for the statistics. The t-tests in these studies were conducted by comparing changes within each sex only and did not compare between sexes thus compromising the quality of the analysis supporting a sex difference. All 3 studies had purely aerobic interventions of 8-12 weeks. It's possible that an aerobic based intervention may not be sufficient to induce an improvement in women, as stated in the literature review by Howden et al. (Howden et al., 2015). Nonetheless, the majority of the articles that discussed HR at rest showed no sex difference (Ades et al., 1992; Antunes-Correa et al., 2010; Araya-Ramirez et al., n.d.; Goldhammer et al., 2007; Korzeniowska-Kubacka et al., 2015; Lavie & Milani, 1995; MacMillan et al., 2006; Pischke et al., 2006; Sarrafzadegan et al., 2008; Soleimani, Nejatian, et al., 2009; Swank et al., 2010; Temfemo et al., 2011; Terada, Chirico, et al., 2019; Tyni-Lenne et al., 1998). In these studies, only Lavie et al., Soleimani et al., and Terada et al., looked at patients with CAD, and Antunes-Correa et al., Swank et al., and Tyni-Lenne et al., looked at patients with HF, whereas the remaining included multiple HD types. Thus, studies that looked at one group of HD patients or a mix of diagnoses, posed the same result. Furthermore, interventions were similar lengths compared to articles arguing for a sex difference, ranging from 8-12 weeks, with the exception of the study by Antunes-Correa having an intervention of 16 weeks. There were no striking differences in terms of adherence rates and exercise type between articles that stated a sex difference in HR at rest and those that do not.

A further study by Anjo et al., found that only men improved resting HR, and they included an intervention for CAD patients whom underwent aerobic and strength CR for up to 12 weeks (Anjo et al., 2014). A possible reason for men improving in this study whereas women did not, could be because women were significantly older in the study population which could have hindered their ability to respond to the CR program. On the contrary, HR at rest was shown to improve more in women than men in a study by Korzeniowska-Kubacka et al. under purely aerobic CR conditions for an intervention of 8 weeks (Korzeniowska-Kubacka et al., 2017). It is unclear as to why this sex difference had occurred in this particular study.

Keteyian et al. examined CHF patients and found that only men experienced an increase in their maximum HR during peak exercise after aerobic based rehabilitation (Keteyian et al., 2003). In addition, research conducted by Lavie & Milani looking at CAD patients, stated that after CR men also experienced an increase in maximal HR, and women experienced a decrease (Lavie & Milani, 1995). However, remaining studies indicated no difference between the two sexes (Ades et al., 1992; Goldhammer et al., 2007; Korzeniowska-Kubacka et al., 2015; MacMillan et al., 2006; Soleimani, Nejatian, et al., 2009; Temfemo et al., 2011). Every article that discussed maximal HR had purely aerobic interventions, however, the studies that did not see a sex difference, had populations of multiple HD types as opposed to studies by Keteyian et al., and Lavie & Milani who looked at CHF and CAD patients, respectively. It is likely that changes in maximal HR are due to changes in maximal effort since maximum HR is dictated primarily by age. That is, for Keteyian et al. and Lavie & Milani we suggest that the men in those studies increased their effort from the baseline to post-CR testing whereas in the bulk of studies that found no sex differences there was equivalent effort.

Kligfield et al. looked at differences in heart rate variability in HD patients and concluded that there was a greater improvement in heart rate recovery (HRR) after CR in men compared to women (Kligfield et al., 2003). The major difference between this study and those that did not see a sex difference could be due to the unspecified statistical methods mentioned in Kligfield et al. Studies by Anjo et al., Araya-Ramirez et al., MacMillan et al., and Soleimani et al., had statistics of either ANOVAs or t-tests and did not support this conclusion, instead they expressed that men and women experienced similar changes in heart rate variability post CR (Anjo et al., 2014; Araya-Ramirez et al., n.d.; MacMillan et al., 2006; Soleimani, Nejatian, et al., 2009).

5.1.5 Other Fitness Variables

Men and women responded similarly in studies that compared values of absolute energy expenditure, leg press, leg extension and diastolic blood pressure at maximum workload (Adams et al., 1999; Korzeniowska-Kubacka et al., 2015; O'Farrell et al., 2000; Schultz et alk., 2010; Soleimani, Abbasi, et al., 2009; Swank et al., 2010). The remaining fitness variables included respiratory exchange ratio (RER; i.e. the ratio of oxygen consumption to carbon dioxide production during exercise), peak workload/lean body mass, exercise time, absolute energy expenditure, sit to stand, functional reach, leg press, leg extension, diastolic blood pressure during effort, and grip strength. RER was found to improve more in women than men in a study by Rengo et al., though studies by Ades et al., Trachsel et al., and Vilela et al., expressed no differences in improvement between men and women (Ades et al., 1992; Rengo et al., 2020; Trachsel et al., 2020; Vilela et al., 2020). Interestingly, in the study by Rengo et al., the CR intervention included some high intensity interval training as compared to the studies by Ades et al., Trachsel et al., and Vilela et al., who followed a typical continuous aerobic only or aerobic and strength-based CR. Next, peak workload which can be defined as the maximum amount of work performed at given time, was discussed, and compared in studies by Trachsel et al., Kodis et al., and Tyni-Lenne et al. Both studies by Trachsel et al., and Tyni-Lenne et al., indicated no sex difference in peak workload, however Kodis et al., suggested a greater improvement in men compared to women (Kodis et al., 2001; Trachsel et al., 2020; Tyni-Lenne et al., 1998). This could be due to numerous reasons. In the study by Kodis et al., only patients with CABG were studied, and patients were either divided into a home-based or in person intervention, along with incorporating a 24-week exercise training program, which is a longer period of time compared to the 12 week and 8 week interventions by Trachsel et al., and Tyni-Lenne et al., respectively.

Exercise time in seconds was also compared and Wagner et al., stated that women experienced a greater improvement in exercise time than men (Wagner et al., 2018). The population in the Wagner et al. study included only those with atrial fibrillation, yet men had a higher adherence rate than women to the program (Wagner et al., 2018). Studies with opposing findings included a variety of aerobic, strength and home-based programs with other HD populations and found that men and women had similar exercise time outcomes (Balady et al., 1996; Cannistra et al., 1992; Goldhammer et al., 2007; Korzeniowska-Kubacka et al., 2015; Ocallaghan et al., 1984; Vilela et al., 2020). Thus, improvement in exercise time outcomes may be dependent on the type of cardiac disease.

Sex differences are found in two studies discussing the number of sit to stand transitions completed. Sit to stand is calculated by counting the number of times an individual can change from a seated to a standing position in a thirty second window (Wagner et al., 2018). Only two studies investigated this variable, and both stated that men benefited more than women. Interestingly, the studies were different in methodologies, with Wagner et al. looking at AF patients in an aerobic and strength intervention, and Kim & So looking at various HD patients after an aerobic intervention (Kim & So, 2019; Wagner et al., 2018).

Kim & So compared functional reach, a measure of stability, between men and women and concluded that only men improved after CR intervention (Kim & So, 2019). However, a study by Adams et al., stated that there is no sex difference in this outcome. The difference between these two studies that could lead to different results in functional reach was that Kim & So had a 36-week aerobic only intervention, whereas Adams et al. had an 8-week high intensity strength training combined with aerobic. Further, in the study by Adams et al., they had much higher completion rates, and conducted ANOVAs as compared to t-tests to reach this conclusion of no sex difference (Adams et al., 1999; Kim & So, 2019). Lastly, a measure of upper body strength called grip strength was another fitness variable measured (Kim & So, 2019; Mroszczyk-McDonald et al., 2007; Rengo et al., 2020). Men experienced a greater improvement than women in both studies by Mroszczyk-McDonald et al. and Rengo et al. while Kim & So stated only an improvement in men. Both studies by Mroszczyk-McDonald et al. and Rengo et al., looked at patients with various cardiac conditions, similar adherence rates and statistical methods to achieve the same conclusion. While no other current studies discussed sex differences in grip strength outcomes post CR, the consensus from this review is that men experienced a significantly greater improvement as compared to women.

5.2 Metabolic

5.2.1 Cholesterol and Triglycerides

Weinberger et al. concluded that HDL levels improved more in men compared to women after CR intervention (Weinberger et al., 2014). However, the type of exercise prescribed during CR intervention was not specified in this study. Similarly, studies by Gupta et al., and Sadeghi et al., expressed that only men improved in HDL levels post CR (Gupta et al., 2007; Sadeghi et al., 2012). Both interventions were approximately 8 weeks long, and the study by Gupta et al. included aerobic in comparison to aerobic and strength prescribed in the study by Sadeghi et al (Gupta et al., 2007; Sadeghi et al., 2012). On the contrary, studies by Savage et al., and Terada et al. found that women had a greater improvement in HDL levels compared to men. (Savage et al., 2004; Terada, Chirico, et al., 2019). Furthermore, a 5-year long cohort study by Warner et al., stated that only women improve their HDL levels after a CR intervention (Warner et al., 1995). A reason for these findings could be because women began the study with less favourable body composition, allowing them to benefit more in HDL (Terada et al., 1995). Despite these conflicting views on sex-related HDL improvement, the general consensus stated by many articles was that men and women appear to improve equally in HDL levels post CR (Anjo et al., 2014; Brochu et al., 2000; Casey et al., 2009; Caulin-Glaser et al., 2007; Ghashghaei et al., 2012; Goldhammer et al., 2007; Kim et al., 2019; Lavie et al., 1995; Mittag et al., 2006; O'Farrell et al., 2000; Pischke et al., 2006; Sarrafzadegan et al., 2008; Schultz et al., 2010; Thorin-Trescases et al., 2016; Turk-Adawi et al., 2016). In terms of study methodologies, no apparent differences stood out in comparison to articles that did not find a sex difference. Unlike HDL, all the articles in this review discussing LDL, LDL:HDL, and total cholesterol:HDL concluded that no sex differences in the response to CR were found (Ghashghaei et al., 2012; Lavie & Milani, 1995; O'Farrell et al., 2000). While the majority of studies found that no sex differences were evident in the improvement of total cholesterol after CR, ElMissiri et al., and Ghasghaei et al. concluded that men experienced a greater improvement in total cholesterol levels compared to women (ElMissiri et al., 2020; Ghashghaei et al., 2012). The study by ElMissiri et al. found that women had a much lower adherence rate compared to men (79.6% vs 65.4%), however, adherence was not discussed in the study by Ghashghaei et al.

Two studies by ElMissiri et al., and Turk-Adawi et al. stated that there was a greater reduction in trigylceride levels in men compared to women post CR. Though the intervention type was not specified in the study by Turk-Adawi et al., the intervention is purely aerobic in the ElMissiri study, which could be a reason for observing an improvement in men only as previously mentioned by Howden et al., that women may require strength training to illicit an improvement (Howden et al., 2015). Although this may be true, the remainder of these studies that indicate no sex difference also had only aerobic interventions, as well as a few aerobic and strength interventions (Anjo et al., 2014; Brochu et al., 2000; Casey et al., 2009; Goldhammer et al., 2007; Kim & So, 2019; Lavie & Milani, 1995; McConnell et al., 1997; O'Farrell et al., 2000; Pischke et al., 2006; Sadeghi et al., 2012; Sarrafzadegan et al., 2008; Savage et al., 2004; Terada, Chirico, et al., 2019; Thorin-Trescases et al., 2016; Turk-Adawi et al., 2016; Warner et al., 1995). Therefore, we are unable to determine the reasoning behind the similarities or differences in men and women in triglyceride levels except for identifying that 17 articles refute the sex difference.

5.2.3 Systolic and Diastolic Blood Pressure

Multiple references proposed that men and women improve equally in systolic blood pressures after CR (Ades et al., 1992; Araya-Ramirez et al., 2021; Casey et al., 2009; Kim & So et al., 2019; Korzeniowska-Kubacka et al., 2015; Lavie & Milani, 1995; Pischke et al., 2006; Sarrafzadegan et al., 2008; Schultz et al., 2010; Swank et al., 2010; Terada, Beanlands et al.,. 2019; Terada, Chirico, 2019; Thorin-Trescases et al., 2016; Trachsel et al., 2020). However, O'Farrell et al. and Turk-Adawi et al. observed a greater reduction in systolic blood pressure in women compared to men after CR. This could possibly be due to poor statistics, as O'Farrell et al. only used t-tests in their findings, and the statistics by Turk-Adawi et al., are unspecified.

The majority of the research leaned towards no sex difference in regards to diastolic blood pressure response to CR as well (Araya-Ramírez et al., 2021; Casey et al., 2009; Kim & So, 2019; Korzeniowska-Kubacka et al., 2015; O'Farrell et al., 2000; Pischke et al., 2006; Sarrafzadegan et al., 2008; Swank et al., 2010; Terada, Beanlands, et al., 2019; Terada, Chirico, et al., 2019; Thorin-Trescases et al., 2016; Turk-Adawi et al., 2016). However, two studies by ElMissiri et al., and Trachsel et al., stated that women improved their diastolic blood pressure more than men do after CR (ElMissiri et al., 2020; Trachsel et al., 2020). These studies do not appear to be distinguished from the rest, thus it is difficult to identify the factor driving this sex difference.

5.2.4 Glucose, Insulin, & Glycated Hemoglobin

Anjo et al., claimed that glucose measures were shown to improve more in women after completion of CR (Anjo et al., 2014). This study proposed that women expressed worse glucose levels at baseline, thus having a greater improvement after CR (Anjo et al., 2014). Ultimately, however, several other studies argued that there was no sex difference in glucose level improvement after CR (Brochu et al., 2000; Goldhammer et al., 2007; O'Farrell et al., 2000; Schultz et al., 2010; Terada, Chirico, et al., 2019; Thorin-Trescases et al., 2016). As Anjo et al. hypothesized, this could also be because baseline glucose levels were not found to be as low in the studied women. Similarly, insulin levels and changes in glycated hemoglobin were found to have similar improvements in men and women (Anjo et al., 2014; Brochu et al., 2000; Terada, Beanlands, et al., 2019; Thorin-Trescases et al., 2016; Turk-Adawi et al., 2016).

5.3 Body Composition

Research by Terada et al. suggested that women may need more intense exercise interventions to induce a similar reduction in weight loss as seen in men. Indeed, improvements in body weight were more significant in men than women in a study by a Terada et al. (Terada, Chirico, et al., 2019). Furthermore, a study by Brochu et al., stated that men also improved their waist circumference to a greater degree compared to women, yet a study by Braga et al., reported the contrary, with women improving more (Braga et al., 2021; Brochu et al., 2000). Nonetheless, most studies agreed that reductions in body weight and waist circumference were similar among both sexes (Araya-Ramirez et al., 2021; Brochu et al., 2000; Casey et al., 2009; McConnell et al., 1997; ElMissiri 2020; Kim & So, 2019; Mroszczyk-McDonald et al., 2007; Pischke et al., 2006; Rengo et al., 2020; Sarrafzadegan et al., 2008; Savage et al., 2004; Schultz et al., 2010; Socha et al., 2017; Temfemo et al., 2011; Terada et al., 2019; Thorin-Trescases et al., 2016, Turk-Adawi et al., 2016).

BMI measures appeared to improve significantly more in women compared to men in only a single study by Sarrafzadegan et al.; however, the majority of research did not achieve the same conclusion and stated that the response was equal in men and women (Anjo et al., 2014; Araya-Ramirez et al., 2021; Brochu et al., 2000; Casey et al., 2009; Caulin-Glaser et al., 2007; ElMissiri 2020; Gupta et al., 2007; Mroszczyk-McDonald et al., 2007; O'Farrell et al., 2000; Rengo et al., 2020; Sarrafzadegan et al., 2008; Savage et al., 2004; Schultz et al., 2010; Socha et al., 2017; Terada, Beanlands et al., 2019; Thorin-Trescases et al., 2016, Turk-Adawi et al., 2016). This could be because women presented significantly worse baseline measures compared to men in Sarrafzadegan et al. Multiple studies also did not find sex differences in body fat percentage outcomes (Kim & So 2019; Lavie et al., 1995; McConnell et al., 1997; Pischke et al., 2006; Socha et al., 2017; Thorin-Trescases 2016). In contrast, a study by Brochu et al., indicated that body fat percentage, hip circumference, and total fat mass improved more in men than women (Brochu et al., 2000). Since methodology did not strongly differ in comparison to the articles that saw no difference, Brochu et al., stated that this sex difference could be because women in this study were generally less fit than men.

5.4 Respiratory

Respiratory measures such as forced vital capacity, minute ventilation response to carbon dioxide production, and peak minute ventilation have shown similar responses to CR completion in men and women across multiple articles. Studies by Ades et al., and Temfemo et al., have reported no differences in forced vital capacity in men and women after undergoing an aerobic only CR intervention (Ades et al., 1992; Temfemo et al., 2011) . Two studies by Antunes-Correa et al. and Trachsel et al. which examined the ratio of minute ventilation to carbon dioxide production in HF patients and CAD patients respectively (with similar aerobic and strength interventions), stated that this response also improved similarly among men and women (Antunes-Correa et al., 2010; Trachsel et al., 2020). Finally, peak minute ventilation was compared in studies by Ades et al., and Trachsel et al., and they reported equal improvements among men and women despite the study by Ades et al. incorporating only an aerobic intervention, and Trachsel et al. having both aerobic and strength interventions (Ades et al., 1992; Trachsel et al., 2020).

5.5 Cardiac Measures

In general, most cardiac measures were found to improve similarly in men and women post CR. Five studies comparing left ventricular ejection fraction in HD patients reported no sex differences (Antunes-Correa et al., 2010; Goldhammer et al., 2007; Saeidi et al., 2013; Sarrafzadegan et al., 2008; Trachsel et al., 2020). Similarly, two studies by ElMissiri et al., and Trachsel et al., looked at left ventricular diastolic diameter and left ventricular systolic diameter and found no differences were reported due to CR between men and women (ElMissiri et al., 2020, Trachsel et al., 2020).

5.6 Protein Measures

The only protein measure commonly compared in multiple articles collected from this review was the C-reactive protein (CRP). CRP is a protein that is released during spikes of inflammation. A study by Thorin-Trescases et al., stated that the levels of CRP were reduced in men after CR, but not women. This study only looked at individuals with acute coronary syndrome, and were enrolled in a 10 week aerobic intervention (Thorin-Trescases et al., 2016). Three other studies, however, expressed that no sex difference was found in CRP levels after CR. Two of these studies by Goldhammer et al., and Sheikhian et al. had 12-week interventions of aerobic exercise, and the third study by Caulin-Glaser et al., had an 8 week intervention but the exercise was unspecified (Caulin-Glaser et al., 2005; Goldhammer et al., 2007; Sheikhian et al., 2018). While these latter 3 studies used a combination of either t-tests or ANOVAs, the study by Thorin-Trescases et al., used different statistical approaches including ANCOVAs. The discrepancy in statistical measures could account for the different results seen in CRP levels in men and women, as other factors such as sample size and adherence rates were similar among these 4 articles (Caulin-Glaser et al., 2005; Goldhammer et al., 2007; Sheikhian et al., 2018; Thorin-Trescases et al., 2016).

5.7 Table 3

Table 3 as discussed previously, organized the data that included a variable discussed by only one article. Thus, with only one article examining a sex difference or similarity, further research is needed to support any claims.

Fitness variables including multiple measures of VO_2 , treadmill duration & velocity, measures of peak power, slopes of oxygen uptake and oxygen to workload, along with O_2 pulse were similar in men and women post CR (Ades et al., 1992; Mertens & Kavanagh, 1996; Soleimani, Abbasi, et al., 2009; Temfemo et al., 2011; Trachsel et al., 2020). Similarily, other measures such HRR in the first minute post exercise, measures of HR x BP, submaximal and peak systolic BP, submaximal exercise rate product and rate product, also showed no sex differences (Ades et al., 1992; Casey et al., 2009; Lavie & Milani, 1995; Soleimani, Nejatian, et al., 2009; Swank et al., 2010). Measures of changes in physical activity, relative energy expenditure, balance, horizontal squat, shoulder press, latissimus pulldown, bicep curl, tricep extension, timed up and go, post 6MWT HR and lastly, HR at equal workloads all had equal responses among men and women (Adams et al., 1999; Araya-Ramírez et al., 2021; Kim & So, 2019; Ocallaghan et al., 1984; Schultz et al., 2010; Swank et al., 2010).

A few variables, however, indicated sex differences. For instance, in the study by Keteyian et al., looking at patients with CHF after undergoing an aerobic intervention, only men improved in relative VO_2 , which is absolute VO_2 normalized to body weight (Keteyian et al., 2003). Next, maximal HR percentage during exercise studied in Cannistra et al., claimed that men experienced a greater increase than women after a 12 week aerobic intervention (Cannistra et al., 1992). A study by Korzeniowska-Kubacka et al., looking at changes in HRR in the second minute and a study by Turk-Adawi looking at changes in physical activity also stated that men experienced a greater improvement in these variables as well (Korzeniowska-Kubacka et al., 2017; Turk-Adawi et al., 2016). Furthermore, studies by Kim & So, along with Tyni-Lenne et al., indicated that men improve better in measures of flexibility, gait velocity and heart rate in gait (Kim & So, 2019; Tyni-Lenne et al., 1998). Lastly, a study by Araya-Ramirez et al., looking at diastolic and systolic BP measures after a 6MWT, stated that women exhibited an improved response compared to men (Araya-Ramírez et al., 2021). These results indicate that the bulk of fitness measurements indicate that men improve to a greater degree than women after CR except BP measurements after 6MWT.

Improvements in body composition measurements such as trunk fat mass, lean body mass, and total body water were reported to be similar in men and women post CR in three studies (McConnell et al., 1997; Socha et al., 2017; Thorin-Trescases et al., 2016). However, body cell mass was reported to improve more in men (Socha et al., 2017). Moreover, remaining metabolic measures such as forearm blood flow, forearm vascular resistance and mean arterial pressure, all collected in the study by Antunes et al., saw no sex differences in HF patients undergoing a 4 month aerobic and strength training program (Antunes-Correa et al., 2010). In addition, a study by Thorin-Trescases et al., whom looked at the ratio of triglycerides to HDL, indicated that men and women showed similar responses (Thorin-Trescases et al., 2016).

The physiological responses to CR of all respiratory variables were independent of sex. Breathing frequency, tidal volume, ventilation, peak expiratory flow, forced expiratory volume, forced expiratory ratio did not improve differently in men and women after CR (Ades et al., 1992; Temfemo et al., 2011; Trachsel et al., 2020). The improvements of multiple cardiac responses including ejection fraction, chronotropic index and measures of left atrium and ventricle dimensions were also similar between men and women (Antunes-Correa et al., 2010; Pabisiak et al., 2013; Trachsel et al., 2020).

Two studies by Keteyian et al., and Tyni-Lenne et al., examined muscle physiology variables (e.g. blood lactate, capillary density and myosin) and both found that there were no reported sex differences except in myosin heavy chain isoform examined in the study by Keteyian et al., stating that men had a greater increase (Keteyian et al., 2003; Tyni-Lenne et al., 1998) Moreover, all autonomic responses including muscle sympathetic nerve activity frequency, incidence and levels of plasma norepinephrine did not have any sex differences in improvement post CR (Antunes-Correa et al., 2010; Tyni-Lenne et al., 1998).

Lastly, protein measures such as changes in citrate synthase, cytochrome c oxidase, hydroxylacyl-CoA dehydrogenase; and paraoxonase after CR had similar responses in both sexes (Goldhammer et al., 2007; Keteyian et al., 2003). However, sex differences were reported in the B-natriuretic peptide and angiopoietin-like 2 protein where both variables improved in men after CR (Sheikhian et al., 2018; Thorin-Trescases et al., 2016). On the contrary, women were more likely to improve p-selectin protein levels and n-terminal pro-B natriuretic peptide after CR completion (Anjo et al., 2014; Keating et al., 2013)

Limitations

An essential factor that could play a role in the outcomes of these variables is the type of statistical analysis conducted in each study. In this review, repeated measures ANOVAs, t-tests, and t-tests between deltas were the most frequently used statistics. In the ideal case of comparing the changes between two groups at two different time points, repeated measures ANOVAs should be conducted to obtain the most accurate conclusions. A study that conducted ANOVAs was regarded to be a higher quality article due to using appropriate statistics. Similarly, t-tests that were conducted on the changes from pre to post intervention values between sexes were also considered as appropriate measures of statistics. This is because the changes were directly compared between sexes, in comparison to just analyzing pre and post measures within each sex. Unfortunately, most of the studies in this current literature review used t-tests within each sex, instead of directly comparing both sexes to obtain the significance of their results. Thus, due to the possibility that t-tests may reflect an inaccuracy of the results, many of the physiological responses to CR which do not show a sex difference, may in fact have a sex difference which could be obscured due to poor statistics.

Furthermore, another possibility for the lack of sex differences in these HD populations after exercise could be due to the generalization of HD populations. For example, many of the articles that proposed a physiological sex difference were often seen in populations with only CHF or only atrial fibrillation, as compared to a combination of patients with CABG, CAD, history of MI, and/or angina. Secondly, another limitation for these negative results could be the fact that most HD patients are older and are likely to have passed menopause and progressed through andropause. Thus, estrogen and testosterone and their effects on the human body have been minimized, making men and women less distinct in terms of their responses to exercise training.

Similarly, the physiological effects of aging can make men and women more similar to one another in regard to their overall fitness, metabolism, body composition, vasculature, and autonomic function. Lastly, psychosocial factors were beyond the scope of this review, but could also impede the improvement of physiological responses after CR.

Conclusions

Based on the overall consensus of this systematic review, men and women with HD respond similarly to CR. However, some articles have found larger improvements in men compared to women in measures of maximal oxygen consumption, functional capacity, 6MWD and grip strength. Reasons for such findings may be physiologically attributed to larger muscle masses and muscle capacity found in men compared to women. Though many other responses to CR have weakly suggested a sex difference, limitations such as statistics, intervention type, type of HD population, adherence rates, and program length could prevent a sex difference from being unanimously concluded.

Appendix A: PRISMA diagram

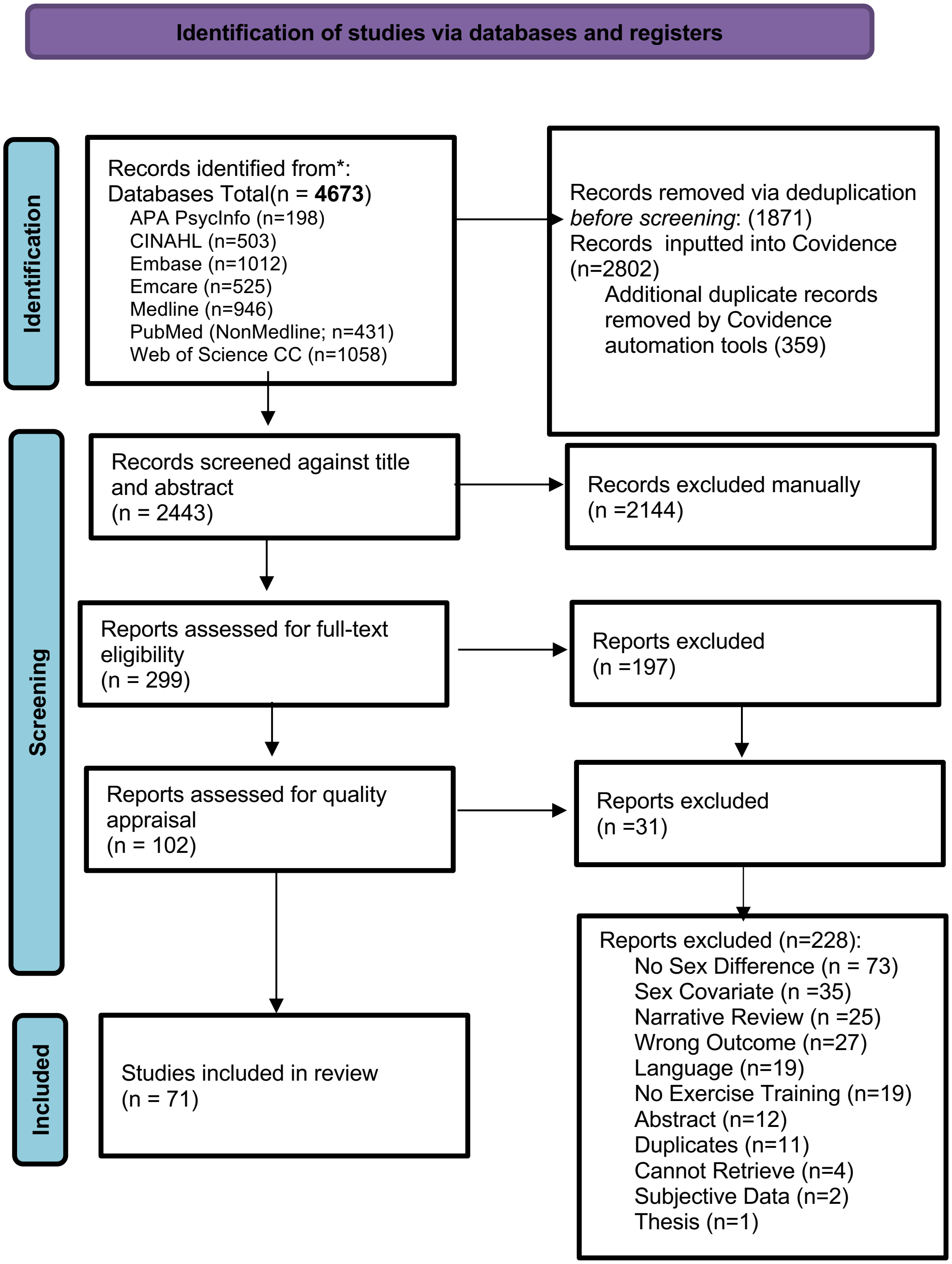

Figure 1: Prisma Flow Diagram. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. Doi: 10.1136/bmj.n71For more information, visit: http://www.prisma-statement.org/

Appendix B: Search strategy applied into Medline Database on April 12. 2021

Ovid® My Account JBI Admin Support & Training UHN Help Feedback Wolters Kluwer

Logged in as Maureen Pakosh at University Health Network Logoff

Ask A Librarian

Search Journals Books Multimedia My Workspace EBP Tools What's New

Search History saved as "HD_CR_Gender_Medline_04.12.21"

▼ Search History (22) View Saved

# ▲	Searches	Results	Type	Actions	Annotations
1	[Population: Heart Patients]	0	Advanced	Save | More	
2	exp Heart Diseases/	1156318	Advanced	Display Results | More	
3	((cardiac or heart or coronary or myocardi*) adj3 (disease* or disorder* or anomol* or disturbance* or deficien* or deformit* or dysfunction* or ischemi* or patient*)).tw,kw.	528258	Advanced	Display Results | More	
4	((rehab* or intervention*) adj3 (cardiac or cardiovascular or heart or coronary or infarct* or myocardi*)).tw,kw.	57943	Advanced	Display Results | More	
5	or/2-4	1347151	Advanced	Display Results | More	
6	[Intervention: Cardiac/Exercise Rehab]	0	Advanced	Save | More	
7	Cardiac Rehabilitation/	2707	Advanced	Display Results | More	
8	exp Exercise Therapy/	53653	Advanced	Display Results | More	
9	(exercis* adj3 (training or therap* or program* or rehab*)).tw,kw.	49084	Advanced	Display Results | More	
10	(training adj4 (resistanc* or weight* or strength* or interval* or intermittent* or cardio* or aerobic)).tw,kw.	30358	Advanced	Display Results | More	
11	(rehab* adj3 (cardiac or cardio* or program* or exercis*)).tw,kw.	29351	Advanced	Display Results | More	
12	or/7-11	121835	Advanced	Display Results | More	
13	[Comparator: Gender]	0	Advanced	Save | More	
14	Sex characteristics/	55979	Advanced	Display Results | More	
15	sex factors/	270356	Advanced	Display Results | More	
16	Sexism/	2327	Advanced	Display Results | More	
17	gender*.tw,kw.	353956	Advanced	Display Results | More	
18	(sex* adj3 (differen* or compar* or between or impact* or barrier* or analys* or both or bias or disparit* or discriminat* or factor* or variable* or issue* or specific*)).tw,kw.	205085	Advanced	Display Results | More	
19	((men or male) adj3 (compar* or versus or between or differen* or both) adj3 (women or female)).tw,kw.	66650	Advanced	Display Results | More	
20	or/14-19	768196	Advanced	Display Results | More	
21	5 and 12 and 20	958	Advanced	Display Results | More	
22	limit 21 to "humans only (removes records about animals)"	946	Advanced	Display Results | More	

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Advanced Search | Basic Search | Find Citation | Search Tools | Search Fields | Multi-Field Search

1 Resource selected | Hide | Change

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Enter keyword or phrase (* or $ for truncation) ◉ Keyword ○ Author ○ Title ○ Journal Search | Expand Term Finder ›

Appendix C: Quality Appraisal Tool from Joanna Briggs Institute

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer____________________________________Date____________________________

Author____________________________________Year________ Record Number________

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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