Community-Based Exercise Rehabilitation in a Diverse Chronic Disease Population

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PhD

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Declaration

I hereby certify that this material, which I now submit for assessment on the program of study leading to the award of PhD is entirely my own work, that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Signed:  **ID No**. 10339729 **Date** 7/07/2020

Fiona Skelly (PhD Candidate)

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Abbreviations

6MTT = 6 minute time trial

6MWT = 6 minute walk test

ADL = Activities of daily living

AIC = Akaike Information Criterion

ANCOVA = Univariate analysis of covariance

BIC = Bayesian Information Criterion

BL = Baseline

BMI = Body mass index

BP = Blood pressure

CAD = Coronary artery disease

CBER = Community based exercise rehabilitation

CD = Chronic disease

COPD = Chronic obstructive pulmonary disease

CRF = Cardiorespiratory fitness

CRP = C-reactive protein

CVD = Cardiovascular disease

DBP = Diastolic blood pressure

DCU = Dublin City University

EQ-VAS = EuroQoL Visual Analogue Scale

EU = European Union

FEV_1 = Forced expiratory volume in 1 second

HbA_1c = glycated haemoglobin

HDL-C = High density lipoprotein cholesterol

hsCRP = high sensitivity c-reactive protein

HR = Hazard ratio

HRQoL = Health-related quality of life

LDL-C = Low density lipoprotein cholesterol

LIPA = Light intensity physical activity

LPL = lipoprotein lipase

MANCOVA = Multivariable analysis of covariance

MET = Metabolic equivalent

MM = Mulitmorbidity

MMA = Mixed model analysis

MSKF = Musculoskeletal fitness

MVPA = Moderate to vigorous physical activity

Neuro/MSK = neuromuscular/musculoskeletal disorders

PA = Physical Activity

PAD = Peripheral arterial disease

PCA = Principal component analysis

PHQ8 = 8-item Patient Health Questionnaire Depression Scale

QoL = Quality of life

OR = Odds ratio

SB = Sedentary behaviour

SBP = Systolic blood pressure

SCD = Single chronic disease

SCT = Social cognitive theory

SD = Standard deviation

SE = Standard error

SWEMWBS = The Short Warwick Edinburgh Mental Wellbeing Scale

SWLS = Satisfaction with Life Scale

T2DM = Type 2 diabetes mellitus

TG = Triglycerides

TRX = Total body resistance suspension training

UK = United Kingdom

US = United States

VO_{2max} = maximal oxygen uptake

VO_{2peak} = peak oxygen uptake

WHO = The World Health Organisation

WHR = Waist to hip ratio

Definition of Key Terms

Chronic disease (CD): complex long-term, progressive diseases that develop in response genetic, environmental, physiological or behavioural risk factors (Larsen & Lubkin, 2009).

Multimorbidity (MM): the presence of two or more chronic medical conditions (Wallace et al., 2015).

Cardiovascular disease (CVD): a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions (World Health Organization, 2020c).

Chronic obstructive pulmonary disease (COPD): a progressive disease of the lungs characterized by airflow limitation that is not fully reversible (World Health Organization, 2019b).

Type 2 Diabetes (T2D): a chronic metabolic disease, characterized by disruption of glucose homeostasis, resulting from defects in insulin secretion, insulin action, or both (American Diabetes Association, 2005; DeFronzo, 2004).

Cancer: is a generic term applied to a large group of diseases characterised by the growth of abnormal cells beyond their usual boundaries (World Health Organization, 2019b).

Physical Activity (PA): any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above basal level (Caspersen et al., 1985).

Light intensity physical activity (LIPA): activities <3.0 METs or that do not cause a noticeable change in breathing rate and can be sustained for prolonged periods (Haskell et al., 2007; Norton et al., 2010).

Moderate to vigorous physical activity (MVPA): activities >3.0 METs or that cause an increase in heart rate and breathing rate (Haskell et al., 2007; Norton et al., 2010).

Exercise: a sub-category of PA that is planned, structured, repetitive and is completed with the purpose of improving or maintaining one or more components of physical fitness (Caspersen et al., 1985).

Cardiorespiratory fitness (CRF): an integrated measure of the ability of the cardiovascular, respiratory and muscular systems to supply and utilise oxygen during sustained physical work.

Community-based exercise rehabilitation (CBER): exercise rehabilitation that is delivered in local fitness centres, gyms and community centres.

Sedentary behaviour: a range of human endeavours that result in an energy expenditure of no more than 1.5 times resting energy expenditure and typically includes time spent sitting or lying during waking hours (Matthews et al., 2008).

Abstract

Skelly, Fiona. Community-Based Exercise Rehabilitation in a Diverse Chronic Disease Population

The effectiveness of physical activity (PA) for reducing the morbidity and mortality in individuals with chronic disease (CD) has been widely established. CD populations participate in lower levels of PA than their healthy counterparts. Currently research has focused on individual disease cohorts and limited evidence exists investigating levels of PA and SB in a mixed CD population. Study I used a cross-sectional study design to evaluate total daily PA and SB in men and women (62.98 ± 10.99 yr and 50.6% men) with a variety of CDs and examined the association between these behaviours and selected health indices. Participants spent 9.5 $h \cdot day^{-1}$, 4.1 $h \cdot day^{-1}$, 1.4 $h \cdot day^{-1}$, and 0.3 $h \cdot day^{-1}$ sedentary, standing, in light intensity PA (LIPA) and moderate to vigorous intensity PA (MVPA), respectively and on average took 6713 steps per day. The majority of SB was accumulated in bouts lasting ≥ 30 min. A higher daily step count was associated with more favourable measures of body composition, aerobic fitness and self-rated health. Increased daily sedentary time was associated with less favourable lower body strength. These findings highlighted that individuals with CD, regardless of specific condition, are a target cohort for intervention. Community-based exercise rehabilitation (CBER) programs have the potential to improve health outcomes in CD groups by increasing PA levels and reducing sedentary behaviour (SB). Historically such programs have involved single CDs. Given the similar programme design and the growing prevalence of multimorbidity (MM), an integrated model may be more suitable. MedEx Wellness is a novel CBER service in Ireland, which offers a shared programme to a range of CDs. In study II a quasi-experimental design was used to investigate the effects of a CBER program on levels of PA, SB and selected health indices, in men and women with a variety of CDs. There were significant improvements in LIPA, patterns of SB, physical function, body composition and psychological health following participation in a CBER program. A higher attendance to the CBER program was associated with improvements in measures of LIPA, MVPA, step count, time in sedentary bouts > 60 min, physical function, body composition and psychological health and psychosocial determinants of PA. These findings demonstrate that CBER is an effective approach to increasing PA and improving health related outcomes for individuals with CD, however statistically significant findings often mask the range of inter-individual variability that exists within response to CBER. In study III factors associated with an effective response to participation in a CBER, in terms of a measurable change, in men and women with a variety of CDs were explored. For measures of LIPA, strength, body composition and psychological health, a lower baseline (BL) value increased the likelihood of achieving a measurable change. A higher cardiorespiratory fitness (CRF) level at BL, increased the likelihood of achieving a measurable change. Individuals with cancer were more likely to improve measures lower body strength. Individuals with metabolic disease and respiratory disease were less likely to improve measures of LIPA and psychological health, respectively. Individuals with CD participate in low levels of PA and accumulate high levels of SB. A shared CBER program is an effective approach to inducing change in PA, SB, physical function and psychological health in a CD cohort. Identifying factors associated with a non-response to CBER could optimise program design and delivery.

Chapter 1

Introduction

Rationale

Chronic disease (CD) is an umbrella term that describe long-term progressive illnesses including cardiovascular disease (CVD), cancer, type 2 diabetes mellitus (T2DM) and chronic obstructive lung disease (COPD) (World Health Organization, 2013). Globally, CD is the leading cause of mortality accounting for > 70% of annual deaths (Roth et al., 2018; World Health Organization, 2018b) and > 60% of all adult (≥ 18 yr) deaths in Ireland in 2018 (Department of Health, 2019). CD represents the major driver of health care utilization and it is estimated that the management of CD accounts for 70% - 90% of healthcare budgets in Europe and the United States (US) (Cronin et al., 2017; National Center for Chronic Disease Prevention and Health Promotion, 2020).

Multimorbidity (MM) refers to the coexistence of two or more long-term medical conditions or diseases and is associated with a higher risk of premature death, hospital admission, reduced functional capacity and quality of life (QoL), compared to a single CD (SCD) (Bayliss et al., 2004; Fortin et al., 2005; Smith & O'Dowd, 2007; Wallace et al., 2015). Currently, > 90% of older adults in Ireland a living with at least one CD and 70% with MM (Hernández et al., 2019).

Maximizing disease outcomes requires a combination of medical management, primarily pharmacological strategies and lifestyle interventions including smoking cessation, dietary

changes, reducing SB and increasing physical activity (PA). PA is defined as any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above basal level (Caspersen et al., 1985). Exercise is a subcategory of PA that involves planned, structured, and repetitive body movements undertaken to improve and/or maintain physical fitness or health.

PA can be classified by the intensity of the activity, which in absolute terms is measured by the rate of energy expenditure, usually described in metabolic equivalents (METs). Moderate to vigorous intensity PA (MVPA), is identified as any activity that requires 3-6 METs (World Health Organization, 2020a). It is currently recommended that individuals with CD should accumulate at least 150 min per week of moderate to vigorous PA (MVPA) (US Department of Health and Human Services, 2018b). However, only a small proportion of individuals with CD meet the recommended PA guidelines (Bernard et al., 2018; Fox et al., 2015; Loprinzi et al., 2013; Morrato et al., 2007; Serrano-Sanchez et al., 2014). This may be due in part to the fact that many individuals living with CD have a low functional capacity, limiting their ability to participate in MVPA (Brown & Flood, 2013; Kujala et al., 2019; Welmer et al., 2013).

The health enhancing benefits of increasing light intensity PA (LIPA), which refers to activities performed at >1.5 METs to < 3 METs (Chastin et al., 2019) are now emerging. In a meta-analysis by Chastin *et al.,* (2019) evidence for beneficial acute and long-term cardiometabolic responses associated with LIPA are demonstrated. Furthermore, an association between LIPA and a reduced risk of mortality was found. Additional research has reported favourable associations between LIPA and body composition, blood lipids and glucose, systemic inflammation, depression, risk of hospitalization and all-cause mortality (Donaire-Gonzalez et al., 2015; Fuezeki et al., 2017a;

Gando et al., 2014; Healy et al., 2007; Loprinzi & Pariser, 2013; Park & Larson, 2014). A threshold for the amount of LIPA required to onset health benefits has yet to be established, however increasing LIPA by 2 min every hour was associated with a lower risk of mortality in individuals with chronic kidney disease (Beddhu *et al*., 2015). Recent evidence reports that reallocating 30 min of sleep, sedentary time or standing with LIPA is associated with significant decreases in BMI, body fat and fat mass in older adults (Powell et al, 2020). For some individuals with MM, LIPA or MVPA is potentially the most effective treatment option to positively impact all components of the illness (Barker et al., 2018) and the term 'polypill' has been used to describe the pleotropic effects of PA, which has been shown to include physical functioning, clinical and psychological enhancements in health (Pareja-Galeano et al., 2015).

Sedentary behaviour (SB) refers to any waking behaviour characterized by an energy expenditure ≤ 1.5 METs while in a seated, reclined or lying posture (Tremblay et al., 2017). The specific postural component of SB (sitting activities), differentiates SB from physical inactivity. Physical inactivity refers to PA levels which are below the recommended guidelines. SB is associated with an increased risk of all-cause and CVD mortality, which appear to be independent of PA (Patterson et al., 2018; Rezende et al., 2014). Prolonged SB has been associated with detrimental effects on glycaemic control, lipid levels and body composition (Brocklebank et al., 2015; Powell et al., 2018; Wirth et al., 2017). The relative risks associated with prolonged sitting become more pronounced in individuals who are also insufficiently active (Biswas et al., 2015; Bouchard et al., 2015; Ekelund et al., 2016). Moreover, among CD populations, the number and length of sedentary periods along with frequency of interruptions with standing or LIPA are associated with an increase and a decrease, respectively in markers of cardiometabolic and

cardiovascular health in CD populations (Bankoski et al., 2011; Biswas et al., 2015). Interestingly, the negative effects of too much sitting may not exist on the same continuum as the health-enhancing benefits achieved through PA (Dempsey & Thyfault, 2018; Knaeps et al., 2018). Distinct genomic regions are linked to PA and SB and SB has detrimental cardiovascular and metabolic effects which are independent of PA (Hamilton et al., 2008). From a public health perspective, MVPA by itself may be insufficient to eliminate the negative health effects of SB and findings a health balance between sitting, standing and PA throughout the day may encompass a more integral public health recommendation for individuals with CD (Van der Ploeg et al., 2017).

Although several biological risk factors are shared across CD groups including hypertension, insulin resistance, hyperglycemia, dyslipidemia and chronic inflammation, all of which are positively impacted by PA and reduced SB (Koene et al., 2016; Nesto, 2019; Warburton et al., 2006; World Health Organization, 2005b), PA studies to date have largely focused on SCD cohorts, and comparison across disease groups are limited. Community-based exercise rehabilitation (CBER) programs are exercise rehabilitation services that take place in a local fitness centre, gym or community centre and have the potential to increase daily PA levels and improve health outcomes in CD cohorts (Moreton et al., 2018; Varas et al., 2018, Gallé et al., 2019; Marsden et al., 2016; Pang et al., 2005; Santa Mina et al., 2017) Although CBER programs have historically accommodated specific disease cohorts (Anderson et al., 2016; Dunlay et al., 2014; Houchen-Wolloff et al., 2018; McCarthy et al., 2015; Puhan et al., 2016; Shepherd & While, 2012) they often incorporate similar structures and primarily comprise of a combination of aerobic and resistance training (Bourke et al., 2016; Heiwe & Jacobson, 2011; Heran et al., 2011; Lane et al., 2014; Marsden et al., 2016; McCarthy et al., 2015). In addition, similar exercise training programs for

individuals with MM have been shown as effective therapeutic strategies (Barker et al., 2018; Ewanchuk et al., 2018; Zgibor et al., 2017). Given the commonality in program design and delivery, an integrated approach to CBER may offer a more resource efficient strategy for reducing SB and increasing PA. The effectiveness of a shared exercise rehabilitation program for CD and MM has yet to be established.

Wide-ranging responses exists within participant cohorts in response to pharmacologic treatments or lifestyle interventions and indeed, it is not uncommon for some participants to experience an adverse response to an intervention or treatment (Garrod et al., 2006; Gayda et al., 2008; Stoilkova-Hartmann et al., 2015). Reporting mean changes in health indices as a representative of the entire group usually has little clinical importance for individual patients (Jaeschke et al., 1989) and can often may mask adverse responses. In contrast, determining clinically meaningful changes in indices of health are of much greater importance in the management of CD (Cook, 2008). Research identifying factors associated with meaningful biological and behavioural responses could assist in program design and delivery.

The CD population is currently primarily segregated in terms of both research and healthcare. Research capturing PA levels and SB has focused on SCD populations and comparisons are limited as a result of different methodologies used to capture these outcomes. Moreover, individuals with MM are often excluded from SCD cohort studies. An integrated model of CBER has the potential to highly effective for improving PA and health related outcomes in the CD population, while also reducing a substantial burden on healthcare services. The evidence base for this approach to CBER currently does not exist. The purpose of this PhD was to determine the levels

of PA and SB in a mixed CD cohort and evaluate the efficacy of CBER on PA levels and SB within this cohort.

Aims

I. Determine the levels of PA and SB in a mixed CD cohort and to investigate the associations of PA and SB with selected indices of health

II. Evaluate the effects of CBER on PA levels, SB and selected indices of health in a mixed CD cohort

III. Investigate factors associated with a favourable response to CBER in a mixed CD cohort

Hypotheses

I. Total daily PA will be low, SB will be high and will be accumulated in prolonged bouts in men and women with CD and MM and higher PA and lower SB will be associated with more favourable measures of physical, clinical and psychological health

II. Participation in a CBER program will result in significant improvements in PA, SB, physical, clinical and psychological health

III. Inter-individual variability in physical (activity behaviours and physical functioning), clinical or psychological health between men and women with SCD and MM will predict response to CBER.

Chapter 2

Literature Review

Chronic Disease

CD, also known as a non-communicable diseases, are complex long-term, progressive diseases (Larsen & Lubkin, 2009) that develop in response to genetic, environmental, physiological or behavioural risk factors. There are a wide range of medical conditions which are captured under the umbrella term CD, with CVD, cancer, T2DM and chronic lung conditions being most prevalent (World Health Organization, 2013). CD require ongoing medical treatment, which can limit activities of daily living (ADL). Lifestyle behaviours such as smoking, poor nutrition, excessive weight, physical inactivity and alcohol consumption are the primary, preventable determinants of CD (Ezzati & Riboli, 2013).

Mortality Associated with Chronic Disease

More people worldwide die as a result of a CD than any other cause of mortality. In 2017, CDs were responsible for > 73% of global deaths (figure 2.1) (Roth et al., 2018). According to the World Health Organisation (WHO) (World Health Organization, 2018b), CD are responsible for 75% of premature adult deaths, i.e., death occurring between the ages of 30-69 yr. CDs develop at a younger age in low and middle income countries (World Health Organization, 2005a) resulting in a higher rate of premature death compared to developed countries.

With the number of people over the age of 65 yr increasing in the developed and developing world, the proportion of the population living with a CD is growing. Approximately half of all Americans and one-third of adults in EU member states are living with at least one CD (Raghupathi & Raghupathi, 2018, OECD/European Observatory on Health Systems and Policies, 2019b). The primary causes of death in European Union (EU) countries are circulatory disease, cancers and respiratory diseases (OECD/European Union, 2018).

In Ireland, around 50% of men and women aged 65 yr and over, reported to have at least one CD (OECD/European Observatory on Health Systems and Policies, 2019a). In 2018, CD accounted for 61.4% of all deaths in the population between the ages of 0 – 64 yr and 64.7% of all deaths in adults aged ≥65 yr in Ireland with CVD, cancer and respiratory diseases the most common cause of death (Department of Health, 2019).

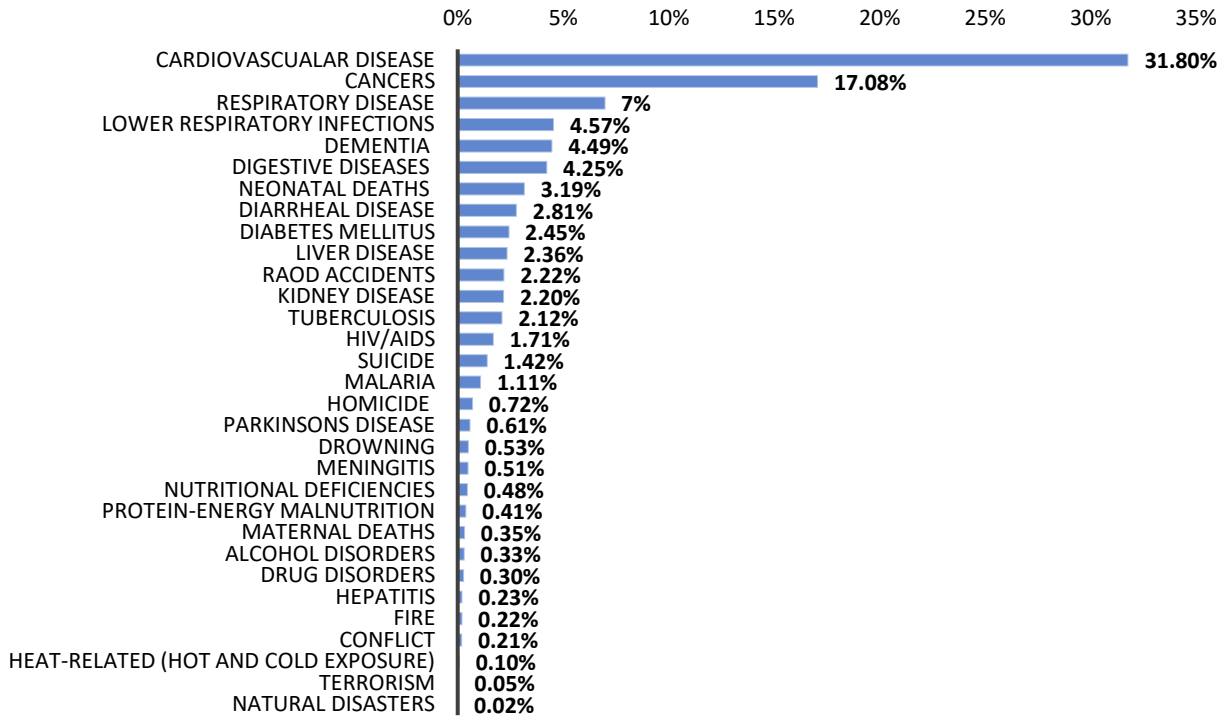

Figure 2.1 Global causes of death in 2017
Adapted from Ritchie (2018)

Prevalence of Chronic Disease

The prevalence of CD in the UK is expected to increase by more than 50% between 2015 and 2035 (Kingston et al., 2018). Specifically, by 2035 the number of people diagnosed with cancer, diabetes and coronary artery disease (CAD) is expected to increase by 179%, 118% and 22% respectively. Likewise, the number of older adults in the US living with a CD is expected to double and reach close to 71 million by 2030 (Centers for Disease Control and Prevention, 2011). A 40% increase in the number of adults in Ireland living with a CD is expected in the next decade (Government of Ireland, 2018).

Economic Burden of Chronic Disease

The cost of CD encompasses direct costs (e.g., medical care, including ambulances services, inpatient or outpatient care, rehabilitation and medication), indirect costs (e.g., loss of human resources caused by morbidity, reduced working population) and intangible costs (e.g., the impact on mental health, bereavement, and suffering, which can result in low productivity). Examining healthcare expenditure alone illustrates the magnitude of the burden of CD. It is estimated that 90% of the US $3.5 trillion annual health care expenditure and 70%-80% of healthcare budgets in the EU are spent caring for individuals with CD (National Center for Chronic Disease Prevention and Health Promotion, 2020, Cronin et al., 2017). In Ireland, approximately 90% of the total healthcare budget is spent treating CD (Smyth, 2017). The management of CD is Ireland has been described as inadequate and the present system is unsustainable. Public outpatient services in Ireland are overwhelmed and constantly operating off waiting lists (Irish College of General Practitioners, 2018). Unless urgently addressed, it is expected that CD will have profound social and economic consequences (Riley et al., 2016).

Patient Burden of Chronic Disease

Living with a CD is associated with considerable burden. All CDs have the potential to limit the quality of life (QoL) of the people who live with them (Harris & Wallace, 2012). Functional capacity can be impacted which in turn effects independence (Nihtilä et al., 2008). CD impacts the general wellbeing of individuals across a variety of components including functional capacity and psychological health.

Functional capacity and functional independence

Functional capacity can be defined as an individual's ability to independently carry out ADL (Liang & Jette, 1981) and a single CD (SCD) is a significant predictor of functional status decline (Stuck et al., 1999). Furthermore, loss of mobility over a 4 yr follow-up period in adults ≥ 65 yr is highly predicted by the presence of CD (Guralnik et al., 1993). Approximately 80% of older adults with a CD are unable to perform some ADL unaided. (Júnior et al., 2017). Among community-dwelling women with CD, three-quarters indicated that the illness had a significant impact on daily life, including reducing activity participation, necessitating modifications to their usual routine and affecting future plans (Restorick Roberts et al., 2017). A decrease in independence can significantly impact QoL. The presence of a CD appears to accelerate the normal decline in functional capacity associated with ageing. This is of concern considering that a decline in functional capacity is a major cause of disability and increases ADL dependency (Hou et al., 2018).

Quality of life and psychological health

Treatment priorities for CD populations have shifted over the decades as increased survivorship and non-fatal health outcomes, including HRQoL and psychological health, are now a major factor for consideration in healthcare. Health-related quality of life (HRQoL) is based on an individual's level of satisfaction with their current level of functioning in terms of physical, social and psychological health (Stenman et al., 2010). The CD population have a lower HRQoL than healthy age and gender matched counterparts (Alonso et al., 2004). An increased life expectancy is likely to result in a large proportion of the CD population, particularly those > 50 years of age,

living with a reduced HRQoL (Siegel et al., 2012; Wilmot et al., 2015). Across a range of CDs, Lam and Launder, (2000) reported adverse effects on HRQoL in a number of physical, social and psychological health components including physical fitness, emotional health, limitations in daily activities, limitations in social activities and overall health.

Rates of depression and decreased life satisfaction are increased in individuals with CD (Hébert, 1997; Mhaoláin et al., 2012). Chapman *et al.,* (2005) reported elevated rates of depressive disorders across a range of CDs including asthma, arthritis, CVD, cancer and diabetes. Among T2DM, the presence of depression and anxiety is significantly higher than in healthy age-matched controls (Rajput et al., 2016) and is related to risk of mortality in this population (Naicker et al., 2017). A high proportion individuals with COPD report having a persistent low mood and lack of interest (Kotrotsiou et al., 2017). Furthermore, individuals with depressive symptoms following a myocardial infarction are less likely to adhere to lifestyle and behavioural therapies, which potentially will increase their risk of additional cardiac events (Ziegelstein et al., 2000).

Multimorbidity

MM, defined as the presence of two or more chronic medical conditions has been shown to have a significant impact on QoL, functional capacity, risk of depression, and health care utilization (Wallace et al., 2015, Marengoni et al., 2011). Furthermore, the presence of MM is associated with increased likelihood of hospital admissions, length of stay and readmission, polypharmacy, and increased healthcare costs, dependency, and risk of mortality (Marengoni et

al., 2011; Salive, 2013). Studies in both the UK and US have found the patients with MM contribute largely to healthcare expenditure (Safran et al., 2005; Sum et al., 2018).

MM affects a substantial percentage of the population and the burden is expected to grow, owing to the aging population (Laires & Perelman, 2019). More than half of the UK population (54%) over the age of 65 yr were reported to have ≥ 2 CDs in 2015 and this is expected to increase to 67% by 2035 (Kingston et al., 2018). In a representative sample of the Irish population > 50 yr, it was estimated that 66.2% of individuals have MM, with 11% having > 4 chronic conditions (Glynn et al., 2011). Currently, > 70% of older adults in Ireland are classified as having MM (Hernández et al., 2019).

Risk Factors associated with Chronic Disease

A number of non-modifiable and modifiable risk factors are shared across many CDs. Non-modifiable risk factors include age, gender, race and family history. Modifiable risk factors include depression, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, hypertension, obesity, unhealthy diet, smoking, physical inactivity and excessive alcohol (World Health Organization, 2020b). At least 80% of CAD, 90% of T2DM and 30% of cancers could be avoided with lifestyle modifications (Waxman, 2004). SB is also a lifestyle behaviour that is associated with the development of CD (Owen et al., 2014). In the US > 95% of the adult population have at least one modifiable risk factor, > 70% have two or more and > 45% have three or more (Adams et al., 2019). Approximately 17% of the Irish population are smokers and 37% and 23% are considered

overweight and obese respectively (Healthy Ireland, 2019). In addition, 69% do not get the recommended levels of daily physical activity (PA) (World Health Organization, 2018c).

Physical Activity, Inactivity and Sedentary Behaviour

PA is defined as any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above basal level (Caspersen et al., 1985) and includes occupational, household (e.g. caregiving, household cleaning, gardening), transport (e.g. walking or cycling to work) and leisure time activities (Booth et al., 2011). Exercise is a sub-category of PA that is planned, structured, repetitive and is completed with the purpose of improving or maintaining one or more components of physical fitness (Caspersen et al., 1985). The current minimum recommended amount of PA is 150 min of moderate PA, 75 min of vigorous PA or an equivalent combination totalling ≥600 MET-min per week (US Department of Health and Human Services, 2018a). Subsequentially, physical inactivity refers to PA levels which are below the recommended guidelines and hence, less than those required for optimal health and prevention of premature death (Booth et al., 2011).

A continuum depiction based on intensity is frequently used where physical activity lies at the lower end. Research investigating the underlying mechanisms of physical inactivity as a risk factor and PA as a primary prevention tool have challenged the continuum theory of these two behaviours. The effects of inactivity are not simply a mirror image of the effects of activity. One example is their differing effects on vascular function. Inactivity results in immediate (within days) increases in the vasoconstrictor tone due to an inward remodelling mechanism in the arteries

(Thijssen et al., 2010). The primary mechanisms involved with exercise training in enhancing vasodilator activity is outwards remodelling, which requires 4-6 weeks. Comparing the response to bed rest and exercise training also highlights the non-parallel association between activity and inactivity. Alibegovic *et al*., (2010) found that 9 days of bed rest induced insulin resistance in 20 healthy males and altered the expression of more than 4,500 genes and a subsequent 4 weeks of exercise training only partially recovered these adaptations.

The term physical inactivity can be defined in different ways. It can refer to individuals who are insufficiently active to meet the recommended levels of PA (Thivel et al., 2018). Given the established dose-response relation between PA and health, defining physical inactivity in a similar manner suggest a continuum theory. Physical inactivity, defined in terms of non-active behaviours characterized by a lack of motion, distinguishes the unique nature of inactivity. This behaviour is now more commonly described as sedentary behaviour (SB).

SB can include a range of human endeavours that result in an energy expenditure of no more than 1.5 times resting energy expenditure and typically includes time spent sitting or lying during waking hours (Matthews et al., 2008). SB refers to too much sitting rather than too little PA and is thought to be a distinct set of behaviours. A physically inactive person is someone who does not meet the recommended levels of PA. However this does not characterize them as sedentary. To date there has been no threshold established to characterize an individual as sedentary.

Physical Inactivity

Physical inactivity has been identified as a primary risk factor for the development of CD (Booth et al., 2017; González et al., 2017). Indeed the risk of CD development associated with physical inactivity is similar to the risk associated with obesity or smoking (Lee et al., 2012b). Globally, physical inactivity is accountable for 6-10% of CD (Lee et al., 2012b), and 30% of the burden of ischemic heart disease, 27% of T2DM, and 21-25% of breast cancer and colon cancer (World Health Organization, 2009). Booth *et al*., (2011) concluded that physical inactivity is one of the most important causes of most CDs and have identified 35 conditions highly associated with physical inactivity (Figure 2.2)

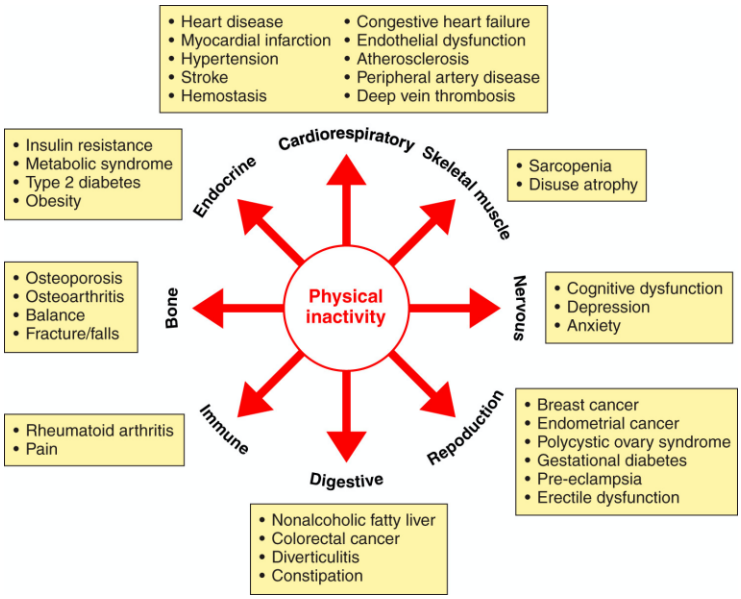

Figure 2.2. Chronic diseases associated with physical inactivity
(Booth et al., 2011)

Technological advances in modern society have greatly contributed to the growing prevalence of physical inactivity. Since the introduction of powered machinery, daily step counts

are estimated to have dropped approximately 50-70% (Booth et al., 2011). A third of adults globally are physically inactive (Hallal et al., 2012). Almost 70% of the adult population in Ireland are insufficiently active (World Health Organization, 2018c). It is estimated that reducing physical inactivity by 10% - 25% would avert 533,000 to 1.3 million global deaths annually (Lee et al., 2012).

Physical Activity

Participation in PA can be classified in terms of absolute and relative intensity. The absolute intensity of an activity is measured by the rate of energy expenditure associated with that activity, usually described in metabolic equivalents of task (METs) (Miles, 2007). A limitation associated with the measurement of PA intensity on an absolute scale is that a particular activity might require quite different physical effort between individuals with varying fitness levels (Lee et al., 2003). For example, walking at 3 to 4 mph (brisk walking), on an absolute scale, is classified as moderate intensity or requiring 4 METs, regardless of whether it is performed by a young man or elderly women. PA can be also be expressed in relative terms, where the intensity of an activity is classified by measuring the energy requirement in a particular individual compared to their level of fitness (Howley, 2001). The relative intensity of an aerobic activity can be described in terms of percentage of maximal oxygen uptake (VO_{2max}), oxygen uptake reserve, heart rate reserve or maximal heart rate. Likewise, intensity can be classified relative to an individual's subjective perceptions of effort or intensity.

Categories along this continuum can be described as follows:

Light: activities < 3.0 METs or that do not cause a noticeable change in breathing rate and can be sustained for prolonged periods.

Moderate: activities 3.0 – 5.9 METs or that cause an increase in heart rate and breathing rate but where one can still hold a conversation. This intensity can generally be sustained for 30-60 minutes.

Vigorous: activities ≥ 6.0 METs or in which a conversation could not be maintained and activity can usually be sustained for up to 20 minutes.

(Haskell et al., 2007; Norton et al., 2010)

Light intensity physical activities (LIPA) can include, but are not limited to, activities that involve casual walking, stretching, light weight bearing activities and can be performed as part of ADL or as leisure time pursuits. Observational evidence reporting that LIPA can confer health benefits is accumulating. Cross-sectional and longitudinal research reports that LIPA is positively associated cardiometabolic health, lipid metabolism, glucose metabolism, bone mineral density and functional capacity and inversely associated with adiposity, T2DM, metabolic syndrome, C-reactive protein, levels of depression (Fuezeki *et al*., 2017a) and all-cause mortality (Beddhu et al., 2015; Loprinzi, 2017). Increasing LIPA by 2 min every hour was associated with a lower risk of mortality in individuals with chronic kidney disease (hazard ratio (HR), 0.59; 95% CI, 0.35 to 0.98) (Beddhu *et al*., 2015) however findings were based off observational data, prohibiting

interpretation beyond an association. LIPA is associated with a reduced risk of hospitalization (HR 0.79, 95% CI 0.67 to 0.93), lower waist circumference and blood glucose levels in individuals with COPD (Donaire-Gonzalez et al., 2015; Park & Larson, 2014); cholesterol (odds ratio (OR) 0.99; 95% CI 0.99 to 0.99), waist circumference (OR 0.98; 95% CI 0.97 to 0.99) and risk of visual impairments (OR 0.62; 95% CI 0.42 to 0.92) in individuals with T2DM (Loprinzi et al., 2014; Loprinzi & Pariser, 2013); and high density lipoprotein cholesterol (HDL-C) (ß=1.23; 95% CI 0.46 to 2.05) and total cholesterol (ß=2.72; 95% CI 0.53 to 4.90) in individuals with MM (Li et al., 2019). In a recent study which employed a composite data analysis approach, that accounted for device-measured sleep, sedentary time, standing time, LIPA and MVPA, greater LIPA was strongly associated with favourable measures of adiposity in older adults (Powell et al., 2020). The results demonstrated that reallocating 30 min of sleep, sedentary time or standing with LIPA was associated with marked improvements in BMI (0.63, 0.96 and 1.08 kg/m^2, respectively), body fat (1.58, 1.61 and 1.73%, respectively) and fat mass (1.92, 2.12 and 2.26 kg, respectively). The current evidence promoting the benefits of LIPA remains predominantly observational and interventional studies are warranted to further investigate the health enhancing potential of LIPA.

The benefits associated with participation in MVPA have been extensively investigated. In 1995, the American College of Sports Medicine issued the first public health recommendations on PA, stating that every adult should accumulate 30 min or more of moderate intensity PA on most days of the week to promote and maintain health (Pate et al., 1995). The current minimum recommended amount of PA is 150 min of moderate PA, 75 min of vigorous PA or an equivalent combination totalling ≥600 MET-min per week. Previously, research suggested that each bout of

MVPA must be a minimum of 10 min in duration to be health enhancing (Physical Activity Guidelines Advisory Committee, 2008). However, subsequent research has established that a bout of MVPA of any duration can contribute to meeting the recommended target (US Department of Health and Human Services, 2018a).

A meta-analysis of 44 studies found a 20-30% reduced risk of all-cause mortality among those meeting the MVPA guidelines (Lee and Skerrett 2001). Based on the analysis of the pooled results from 6 population-based studies, Arem *et al*., (2015) reported that individuals meeting the PA guidelines had a 20% reduced risk of mortality compared to those reporting no leisure time MVPA. The risk was further reduced to 31%, 37% and 39% from those achieving 1-2 times, 2-3 times and 3-5 times the recommended minimum, respectively.

An abundance of research has demonstrated the protective benefits of PA for mental health among adult populations. Meeting the PA guidelines was associated with decreased odds of elevated depressive symptoms in a study involving over 10,000 Irish adults (McDowell et al., 2018a). In a study by McDowell *et al*., (2018b) a 40% reduction in prevalence of depression was observed in those meeting the PA guidelines compared to those below the guidelines. Available evidence suggests an inverse association between PA and both anxiety symptoms and disorders. The longitudinal associated of PA and anxiety were examined in a systematic review and meta-analysis by McDowell *et al*., (2019a). Similarly in a study with over 4,000 Irish adults ≥ 50 yrs, PA was cross-sectionally associated with lower anxiety symptoms and status, and a potential dose-response relation was identified (McDowell et al., 2019b). In a recent study with over 7,000 Irish

adults, meeting the PA guidelines was associated with a 13.5% lower odds of anxiety (McDowell et al., 2020). Specifically in patients with CD, exercise training has been shown to significantly reduce symptoms of anxiety (Herring et al., 2010) and depression (Herring et al., 2012).

Among individuals who participate in some MVPA but who fail to reach the recommended amount, there is a 22% reduced risk of mortality (Hupin et al., 2015) and greater survival (Loprinzi, 2015) compared to those who undertake no MVPA. A recent review by the American College of Sports Medicine, highlighted the potential health benefits of adding a little daily MVPA in those who currently perform little or no MVPA (US Department of Health and Human Services, 2018a). Similarly, the current Australian PA guidelines state that "*if you currently do no physical activity, start by doing some"* (Australian Department of Health, 2019). In Ireland, the PA guidelines recommendations are at least 30 min a day of moderate activity on 5 days a week, but add that "*some physical activity is better than none, more is better than some, and any amount of physical activity you do gains health benefits*" (Department of Health & Children & Health Service Executive, 2009).

Physical Activity and Health-related Physical Fitness

Health-related physical fitness is a state of wellbeing that reflects an individual's ability to perform ADL with vigour and is related to their current and future health. It encompasses CRF, musculoskeletal fitness, body composition, flexibility and balance (US Department of Health and Human Services, 2018a). Regular PA can enhance or maintain the various components of health-related physical fitness. Physical fitness is an outcome associated with a variety of behaviours,

with PA considered a major contributing behaviour (figure 2.3). Physical fitness a key predictor of health and improving physical fitness is central to how PA impacts health.

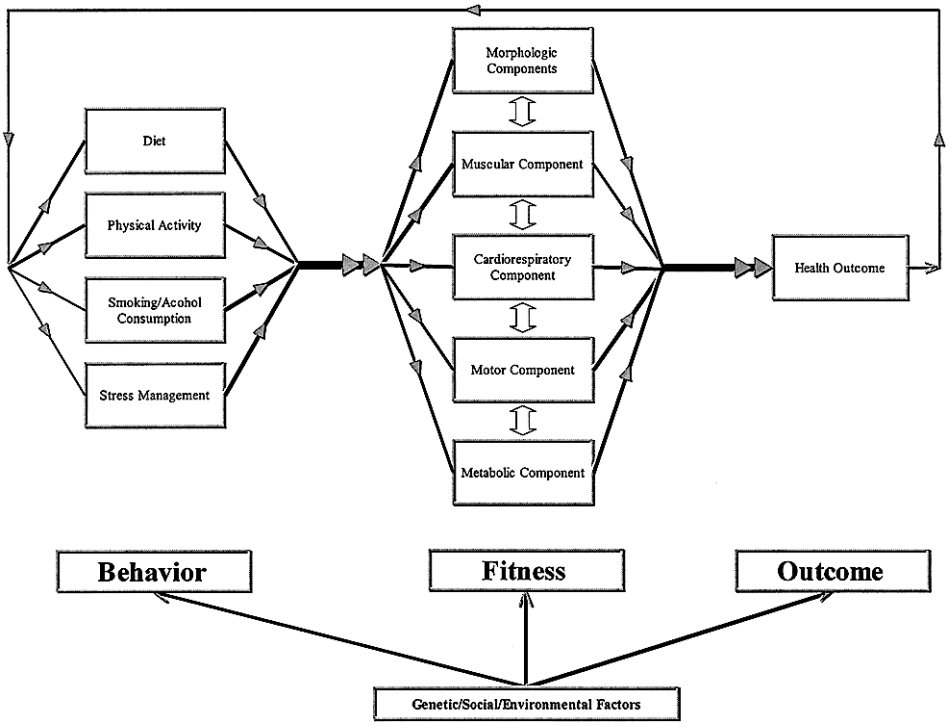

Figure 2.3 The relation between behaviour, fitness and health
(Blair et al., 2001)

CRF is an integrated measure of the ability of the cardiovascular, respiratory and muscular systems to supply and utilise oxygen during sustained physical work. It is an excellent marker of functional capacity and one of the strongest independent predictors of all-cause mortality and CVD mortality (Lee et al., 2010). Small improvements in CRF are associated with significant health benefits. An increase in functional capacity of one metabolic equivalent of task (MET) is associated with a 13% and 15% reduction in the risk of all-cause and CVD mortality, respectively (Kodama, 2009). Importantly, the greatest mortality benefits are achieved by those with the lowest initial level of CRF.

CRF is a stronger predictor of current health than PA levels (Warburton & Bredin, 2016; Blair et al., 2001; Myers et al., 2004; Williams, 2001). CRF and PA have independent and interrelated associations with health, in particular disease risk and premature mortality (DeFina et al., 2015; Myers et al., 2015). PA and CRF have parallel benefits in relation to CVD outcomes (DeFina et al., 2015). However, their beneficial effect on cardiovascular health may be explained by mechanisms specific to each activity.

The physiological adaptations associated with increasing CRF include altered autonomic tone, improved endothelial function and altered thrombotic potential (Willerson et al., 2007). Resting heart rate is a well-recognised indicator of CRF, where a lower resting heart rate suggests better cardiac autonomic control. In a study by Carroll *et al*., (2012), resting heart rate was not found to be a factor that explained the relation between PA and cardiovascular health. Instead metabolic and inflammatory emerging were potential mechanisms.

Among obese individuals, CRF and high levels of PA were found to be more important for improving health than improvements in body composition (Gill & Malkova, 2006; Lee et al., 2012a; Pedersen, 2007). The risk for all-cause and CVD mortality are lower in individuals with a high BMI and optimal fitness than those with a normal BMI and poor fitness (Fogelholm, 2010). However, physically active individuals with a high BMI have a greater risk of T2DM, and CVD than those individuals with a normal BMI and low PA. Regular PA improves CVD risk factors including blood pressure (BP), HDL-C, low density lipoprotein cholesterol (LDL-C), triglycerides (TG), CRP, and

glucose tolerance. While increasing PA levels can have a positive effect on health, improving CRF can evoke additional health benefits.

Musculoskeletal fitness (MSKF) can be described as a combination of muscular strength, muscular endurance and muscular power along with joint flexibility (Katzmarzyk & Craig, 2002). Optimal MSKF is strongly related with functional capacity, reduced risk for CVD and fracture, functional independence, improved QoL and cognitive function (Pate et al., 2012; Warburton et al., 2001; Warburton & Bredin, 2016) and is an important determining factor in the ability to perform ADL (Kell et al., 2001). In CD patients, reduced skeletal muscle mass and accompanying loss in strength and function is related to impaired QoL and increased risk of institutionalization (Wolfe, 2006).

Resistance training is an effective approach to maintaining and/or improving MSKF (Abernethy et al., 1994; Reid & Fielding, 2012; Williams et al., 2007). Numerous national guidelines for PA for both healthy adults and those with CD include recommendations for muscle-strengthening exercise. The guidelines suggest that 8-10 resistance training exercises, of at least a moderate intensity for 8-12 repetitions, which targets all major muscle groups on 2 or more days a week should be conducted (Australian Department of Health, 2019; Chodzko-Zajko et al., 2009; Department of Health & Children & Health Service Executive, 2009; Tremblay et al., 2011; US Department of Health and Human Services, 2018b).

Physical Activity in the Primary Prevention of Chronic Disease

Primary prevention of CD refers to activities that aim to limit the incidence of disease, mainly by reducing risk factors that can negatively impact health and promoting factors that are protective of health (Gilford, 1988). There is a strong evidence base linking PA to primary prevention of most CDs and all-cause mortality (Blair et al., 2001, Reiner et al., 2013). A graded linear relation between the volume of PA and health status exists, where the most physically active people are at the lowest risk of disease development. Indeed, PA is believed to be an essential components in the primary prevention of at least 35 CDs (Booth et al., 2011).

The role of PA in the primary prevention of CVD has been widely established. CVD is a progressive disease, with numerous manifestations across patient cohorts, often beginning with cardiovascular risk factors such as dyslipidemia and hypertension, which are known to induce oxidative stress and endothelial dysfunction. Classes of disorders under the umbrella term of CVD are diseases affecting the heart or circulatory system and includes CAD, cerebrovascular disease, peripheral arterial disease (PAD), rheumatic heart disease, congenital heart disease, heart failure and deep venous thrombosis. Although CVD is preventable, it is the leading cause of global mortality. The role PA plays the primary and secondary prevention of CVD is well established. The seminal work by Morris *et al*., (1953) on London bus drivers and conductors was perhaps the first to establish the link between PA and CVD. Bus conductors, who spend the day walking up and down double-decker buses, had a 30% lower incidence rate of CAD than sedentary drivers. Subsequently, large scale epidemiology studies such as the Harvard Alumni Study (Paffenbarger &

Lee Jr, 1998; Sesso et al., 2000) and the Nurses' Health Study (Manson et al., 2002) have determined that meeting the recommendations for PA is associated with a reduction in relative risk of CVD of 20-35%. A meta-analysis of 26 studies reporting on over 510,000 individuals found significant protection against CVD in those reporting moderate to high levels of leisure time PA (Sofi et al., 2008). Greater engagement in MVPA is associated with more favourable cardiovascular biomarkers such as higher HDL-C and lower levels of total cholesterol, mean arterial pressure and C-reactive protein (CRP) (Loprinzi, 2015). Mora *et al.,* (2007) found that PA lowered the rate of CVD over a 10 year period through it effect on inflammatory biomarkers such as CRP, BP, lipids and body mass index (BMI).

There is now emerging evidence that PA improvements in CVD outcomes can occur independent of their effects on traditional risk factors (Fiuza-Luces et al., 2018; Joyner & Green, 2009). This is due to the fact that several important physiologic and pathologic processes at play in patients with CVD are favourably modulated by PA. Vascular dysfunction is one of the earliest events in the development of atherosclerosis, the most common form of CVD. Damage to the endothelial occurs prior to angiographic detection of the disease. Regular PA through its effect on shear stress, circumferential stress and hydrostatic pressure helps to maintain vascular structure and function across the lifespan (Davignon & Ganz, 2004). In addition, PA results in cardiac remodelling including reduced ventricular stiffness and the development of coronary collaterals, improved autonomic nervous system balance, protection against ischemic-reperfusion injury and stabilization/regression of fibro-fatty plaques (Fiuza-Luces et al., 2018).

Similarly to CVD, there is compelling evidence for the role of PA in the primary prevention of T2DM. A review of prospective studies concluded that a 30% - 50% risk reduction of T2DM is associated with a physically active lifestyle, compared to a sedentary lifestyle (Skerrett & Manson, 2002). Physical inactivity and obesity are the primary non-genetic determinants of T2DM. Even in the absence of weight loss, PA has been shown to decrease the risk of developing T2DM (Tuomilehto et al., 2001). Moreover, the Da Qing IGT and Diabetes Study in China found that exercise significantly decreased the development of T2DM in individuals diagnosed with prediabetes due to impaired glucose tolerance (Pan et al., 1997). Both the Finish Diabetes Prevention Study (Tuomilehto et al., 2001) and the Diabetes Prevention Program (Diabetes Prevention Program Research Group, 2002) found that among individuals with impaired glucose tolerance, leisure time PA is associated with a 58% risk reduction in T2DM. Glucose transportation from the circulation into the cells is primarily mediated by a membrane-bound glucose transport protein – GLUT4. Exercise increases the muscle cell content of GLUT4 allowing more efficient removal of glucose from the circulation, which is independent of insulin action (Stanford & Goodyear, 2014). In addition, exercise improves insulin sensitivity resulting in lower levels of insulin release from the beta cells of the pancreas (Stanford & Goodyear, 2014).

Research investigating the effects of PA in the primary prevention of COPD is limited. In a study of almost 7,000 participants, PA was associated with a decreased risk of COPD development over an 11 year follow-up period (Judith Garcia-Aymerich et al., 2007). Even for active smokers, the prevention fraction of COPD attributable to high levels of PA was 21%. PA can attenuate the

inflammatory effects of smoking, through the enhancement of anti-inflammatory markers and antioxidant mechanisms.

Forced expiratory volume in one second (FEV_1) refers to the maximum volume of air that an individual can forcefully exhale in one sec after maximum inhalation, and is a commonly used measure of lung function (David & Edwards, 2019). Among the general population, PA has been found to be associated with the decline in FEV_1 over approximately 4 years, independent of smoking status (Jakes *et al*., 2002). In a 25 year follow-up study, the mean decline in pulmonary function at the 10, 20 and 25 year follow-up was found to be significantly less in the highest PA tertile compared with the lowest and the beneficial effects of PA on pulmonary function was similar across all smoking categories (Pelkonen et al., 2003). Likewsie, Cheng *et al,.* (2003) found PA to be associated with better respiratory function at baseline (BL) and remaining active was associated with higher FEV_1 and forced vital capacity at follow-up of 24 years.

Cancer is an umbrella term used to describe a large group of diseases characterised by abnormal cell growth (World Health Organization, 2018a). There is a strong evidence base for PA in the prevention of colon and breast cancer, with the relative risk reduction for both men and women estimated to be as high as 30-40% (Hardefeldt et al., 2018; Lee, 2003; Wu et al., 2013). A recent systematic review found that in addition to colon and breast cancer, PA is associated with 10-20% relative risk reduction in endometrium, bladder, stomach, oesophagus and kidney cancer (McTiernan et al., 2019). There is also evidence of a dose-response relation between PA and several cancers (McTiernan et al., 2019). A pooled analysis of prospective studies involving 1.44

million participants found that higher leisure time PA was associated with lowering the risk of 13 cancers (Moore *et al*., 2016).

The mechanisms underlying the association between participation in physical activity and cancer prevention remain unclear. Proposed pathways include reducing inflammation, preventing obesity, reducing the time it takes for food to travel through the digestive system, which decreases exposure of possible carcinogens to the gastrointestinal tract, preventing high levels of insulin, and controlling levels of sex hormones such as estrogen and growth factors that have been associated with cancer development (McTiernan, 2008; National Cancer Institute, 2020). Obesity is an independent risk factor for cancer (Avgerinos et al., 2019) and it is well established the PA can reduce obesity (Jakicic & Davis, 2011), but this link in theory appears to apply to obesity-related cancers only.

Physical Activity in the Secondary Prevention of Chronic Disease

Secondary prevention of CD refers to actions that halt the progression of a disease, prevent complications or reduce the risk of premature mortality (Zafari & Wenger, 1998). Even for those with an established CD, PA has a major role to play in disease management and, in many cases has the potential to be a first-line treatment option (Luan et al., 2019). PA can have simultaneous therapeutic and preventive benefits for individuals with CD. As a therapeutic approach, PA can been used to treat a condition or disease in the same sense as treatment via pharmacotherapy. As a preventive approach, PA can prevent the onset of additional health conditions that otherwise may be inevitable, for example the development of CVD as a result of

hypertension (Hegde & Solomon, 2015; Stamler et al., 1993). Current public health policy recommends that individuals with one or more CD meet the same PA guidelines as a healthy adult (Department of Health & Children & Health Service Executive, 2009) and for those who are unable to achieve this level of PA, to do as much regular PA as abilities allow (US Department of Healt and Human Services, 2018b).

Exercise Rehabilitation

For many CDs, the health benefits of exercise surpass what could be achieved with conventional medications, and PA is now routinely included as part of the medical management plan (Durstine et al., 2013). Structured exercise interventions for individuals with CD have consistently shown to have positive effects on a variety of health outcomes. For people with CD, exercise rehabilitation has the potential to improve physical function, decrease symptoms, enhance QoL, decrease future use of healthcare services and reduce the risk of mortality (Anderson et al., 2016; Dunlay et al., 2014; Houchen-Wolloff et al., 2018; McCarthy et al., 2015; Puhan et al., 2016; Shepherd & While, 2012).

A recent meta-analysis, which included 84 studies, aimed to provide evidence-based knowledge for professionals in exercise medicine in relation to the role of exercise in CD treatment (Pasanen et al., 2017). The main findings of this extensive review were that exercise interventions can improve physical functioning and health-related QoL across a variety of CD groups, including CVD, cancer, COPD, chronic kidney disease, osteoarthritis, rheumatoid arthritis and fibromyalgia, with over half the included studies producing moderate to large effects. Included studies involved

aerobic exercise, resistance exercise and a combination of both, as part of their exercise interventions, with much diversity in the delivery of the exercise components, highlighting that exercise in many forms has the potential to improve health outcomes across numerous CD.

Cardiovascular disease

Physical activity

The mechanisms through which PA can attenuate the progression of CVD have been widely established. PA can lower resting heart rate, systolic BP and increase heart rate reserve, which in turn decreases myocardial oxygen demand, and in patients with CVD reduces the risk of myocardial ischemia (May & Nagle, 1984; Oliveira et al., 2013; Ribeiro et al., 2012). The beneficial effects of PA are thought to expand to neurovascular responses for patients with CVD, with improved functioning in the autonomic nervous system, which promotes a decrease in sympathetic tone and enhanced parasympathetic activity (Ribeiro et al., 2012; Rosenwinkel et al., 2001). Furthermore, PA has been shown to improve myocardial perfusion as a result of the combined effects of improved endothelial function and enhanced coronary circulation (Hambrecht et al., 2003). Endothelial dysfunction is evident during all stages of atherosclerosis. The proposed mechanism by which PA enhances endothelial function is as a response to increases in blood flow-mediated shear stress, which stimulates the endothelial production of nitric oxide, reducing the risk of degradation by reactive oxygen species (Ribeiro et al., 2010).

The anti-inflammatory effect of PA for patients with CVD has also been investigated. Atherosclerosis is considered a condition characterised by chronic low-level inflammation (Hansson, 2005; Liuzzo, 2001; Ross, 1999). Circulating levels of systemic biomarkers of inflammation, namely circulating pro-inflammatory cytokines and CRP are reduced as a result of PA in individuals with CVD (Ribeiro et al., 2010). Arterial stiffness, which is as an independent predictor of cardiovascular and all-cause mortality in individuals with CAD and post-myocardial infarction patients (Vlachopoulos et al., 2010), decreases in response to PA (Oliveira et al., 2015).

Exercise rehabilitation

Cardiac rehabilitation is a multidisciplinary treatment designed to facilitate lifestyle changes, improve exercise capacity, optimize medical treatment, address social and psychological issues and control risk factors following the onset of CVD. It is now a well-established component for the management of various manifestations of CVD (Dalal et al., 2015; McMahon et al., 2017). Exercise training is consistently recognised as a central component of cardiac rehabilitation (Mampuya, 2012). Following a major coronary event, exercise rehabilitation is associated with significant improvements in QoL in the domains of general health, vitality and mental health (Seki et al., 2003). Numerous markers of cardiovascular health have been found to be positively affected by exercise training in a range of CVD patients including BMI, body fat percentage, plasma lipids, markers of inflammation and exercise capacity (Lavie et al., 2009; Lavie & Milani, 1997a; Lavie & Milani, 1997b; Milani et al., 2004). Williams *et al.,* (2006) present evidence for the efficacy of exercise rehabilitation for patients who have experienced myocardial infarction, coronary artery

bypass graft surgery, stable angina, percutaneous coronary intervention, chronic heart failure, cardiac transplant and cardiac valve repair/replacement. The evidence suggests that exercise-based cardiac rehabilitation affects the basic pathophysiology of CVD and the underlying disease processes through mechanisms which include increasing angina threshold, delaying the onset of ischemia and improving endothelial-dependent vasodilation of the coronary arteries. Meta-analysis of cardiac rehabilitation with exercise as a primary component, for patients with CAD, observed a reduction in cardiac mortality ranging from 20% to 32% (Bobbio, 1989; O'Connor et al., 1989; Oldridge et al., 1988; West, 1995). Across the various forms of CVD, such as CAD, heart failure, stroke and PAD, PA is associated with reducing the impact of the disease, slowing the disease progression and preventing recurrences (Darden et al., 2013). A recent systematic review and meta-analysis of over 2,000 patients with CVD, found that aerobic and combined aerobic and resistance exercise can significantly improve atrial stiffness in this cohort (Zhang et al., 2018). In addition to improving physiological health, exercise has also been show to significantly augment psychological health (del Pozo-Cruz et al., 2018). Cochrane reviews on exercise based cardiac rehabilitation for CAD (Heran et al., 2011) and heart failure (Sagar et al., 2015) reported significant improvements in QoL, across a number of validated QoL measures. The benefits of cardiac rehabilitation have also extensively been demonstrated in stroke patients (Han et al., 2017; Pang et al., 2005; Stoller et al., 2012; Tiozzo et al., 2015).

Type 2 Diabetes Mellitus

Physical activity

For individuals with T2DM or prediabetes, the initiation and maintenance of PA is vital for blood glucose management in addition to overall health. CVD mortality is a major cause of premature death in T2DM, and there is strong evidence that PA reduces the risk of CVD mortality in a dose-response manner (Sadarangani et al., 2014; US Department of Health and Human Services, 2018a). Walking at least 2 hours per week has been associated with lower premature mortality in adults with T2DM (Gregg et al., 2003). Current treatment for patients with T2DM is focused on glycemic control and the prevention of microvascular complications including nephropathy, retinopathy and neuropathy, all of which are strongly associated with hyperglycaemia (Stolar, 2010).

Exercise rehabilitation

A number of clinical trials in patients with diabetes have reported improved glycemic control in response to both aerobic and resistance exercise, with potentially greater benefits achieved with resistance training (Agurs-Collins et al., 1997; Cauza et al., 2005; Dunstan et al., 2002, 2005; Holten et al., 2004; Honkola et al., 1997). Blood levels of glycated heamoglobin (HbA_{1c}), reflect average blood glucose levels over the previous 8-12 weeks. A meta-analysis of 14 studies, which included over 500 diabetic participants, found that exercise resulted in statistically and clinically significant reductions in HbA_{1c} (Boulé et al., 2001). Indeed, the effects of exercise on HbA_{1c} are comparable to the effects achieved with insulin therapies (UK Prospective Diabetes

Study Group, 1998). A single bout of exercise has been shown to improve insulin sensitivity in individuals with diabetes for up to 72 h (Devlin et al., 1987) and chronic adaptations in glucose transport and metabolism in response to exercise training can bring blood glucose levels into the normal range (Borghouts & Keizer, 2000).

Other factors associated with cardiometabolic health also improve with exercise in patients with T2DM, including BP, lipid profiles, autonomic regulation, vascular function, inflammation, body composition and cardiorespiratory fitness (CRF) (Chudyk & Petrella, 2011; Després & Lamarche, 1994; Kemps et al., 2019; Loimaala et al., 2003; Rees et al., 2017; Zoppini et al., 2006). Type 2 diabetics who participate in cardiac rehabilitation following a myocardial infraction, have a lower all-cause mortality rates and lower rate of incidents that required revascularization (Jiménez-Navarro et al., 2017).

Chronic Obstructive Pulmonary Disease

Physical activity

Many of the clinical characteristics of patients with COPD, such as disease severity, comorbidities, exacerbations and behavioural factors are related to levels of PA (Henrik Watz et al., 2014). Of clinical importance, device-measured PA shows moderate positive associations with FEV_1, and less exacerbations in patients with COPD (Belza et al., 2001; Pitta et al., 2005; Steele et al., 2000; Walker et al., 2008; Waschki et al., 2012; Watz et al., 2009a, Waschki et al., 2012). The development of MM is common among individuals with documented COPD (Barnes & Celli, 2009;

Nussbaumer-Ochsner & Rabe, 2011; Vanfleteren et al., 2013). However increased levels of PA is associated with a reduced risk of developing systemic inflammation and cardiac dysfunction (Henrik Watz et al., 2008), metabolic syndrome (Henrik Watz et al., 2009b) or T2DM (Garcia-Aymerich et al., 2004). In a cohort of newly diagnosed COPD patients, PA was found to have a stronger association with the presence of comorbidities than airflow obstruction (Van Remoortel et al., 2014). Across a variety of measures of physical fitness, positive correlations between PA and physical fitness are evident in individuals with COPD (Eliason et al., 2011; Pitta et al., 2005; Waschki et al., 2012; Watz et al., 2009a).

Exercise rehabilitation

Compared to the lack of evidence for PA in the primary prevention of COPD, exercise-based pulmonary rehabilitation is established and widely implemented as a secondary prevention strategy (Nici et al., 2006; Ries et al., 2007; Spruit et al., 2013). Participation in exercise can be difficult for patients with COPD, as a result of symptoms that arise with this condition, principally dyspnea or breathlessness. The sensation of breathlessness while exercising can induce anxiety and further exacerbate symptoms (McCarthy et al., 2015). Due to the substantial impact of dyspnea and fatigue on functional capacity and QoL in COPD (May & Li, 2015), the research on exercise rehabilitation has been centred around these outcomes (McCarthy et al., 2015; Puhan et al., 2016; Spruit et al., 2013). In two extensive Cochrane systematic reviews of pulmonary rehabilitation versus usual care (McCarthy et al., 2015) and pulmonary rehabilitation after hospital admission for exacerbations (Puhan et al., 2016), exercise-based pulmonary rehabilitation was

found to improve dyspnea, fatigue, exercise capacity, HRQoL, emotional function, and the patients' sense of control over their condition. More recently, research has found exercise-based pulmonary rehabilitation to be associated with survival rates for patients with COPD (Houchen-Wolloff et al., 2018).

Although the primary pathophysiology of COPD involves airflow obstruction, secondary complications, including skeletal muscle wasting and dysfunction, osteopenia, cardiac dysfunction and depression, are common (Agusti, 2005; Agusti et al., 2003; Nici et al., 2006). Exercise training has the potential to address many of these other clinical manifestations. In fact, adaptations associated with exercise in COPD seem to primarily involve the muscular system and the cardiovascular system, which in turn relieve dependence on ventilation when participating in higher intensity activities (Butcher & Jones, 2006).

Even for patients with severe COPD, an exercise intensity can be achieved to elicit skeletal muscle adaptations (Maltais et al., 1996) including remodelling of both type I and type II muscle fibres to increase their oxidative capacity and increased capillary density (Antonucci et al., 2003). The improvements in skeletal muscle function are associated with enhanced exercise capacity, even in the absence of observed changes in lung function. Furthermore, with improvements in oxidative capacity and efficiency of skeletal muscles, the requirement of alveolar ventilation at a given work rate is reduced. This can potentially reduce dynamic hyperinflation and in turn reduce exertional dyspnea (Nici et al., 2006). Cardiovascular adaptations include increases in blood volume, haemoglobin concentrations, cardiac output, arteriovenous oxygen difference and

potential reductions in BP, all of which can contribute to improvements in endurance capacity for patients with COPD (Maltais et al., 1996).

Cancer

Physical activity

There is evidence to support the therapeutic role of PA at all stages of the cancer journey, from the point of diagnosis, through treatment and into survivorship. PA has been prompted by many organisations and governing bodies, such as The American College of Sports Medicine, The British Association of Sports and Exercise Sciences and The American Cancer Society, to publish specific PA recommendations for individuals with cancer (Campbell et al., 2012; Rock et al., 2012; Schmitz et al., 2010). PA can improve overall health and wellbeing throughout the cancer journey and is associated with reductions in recurrence and mortality (Lahart et al., 2015; Schmid & Leitzmann, 2014). The current recommendations by the American Cancer Society (2020) for cancer patients both during and after cancer treatment are to avoid inactivity and aim to achieve 150 min of exercise per week.

Among postmenopausal women with breast cancer and a BMI < 25 kg/m^2, a 66% reduction in overall mortality was observed in physically active women compared to sedentary (Emaus et al., 2010). Cancer-related fatigue is one of the most frequent and distressing side effects of treatment within this cohort (Jones et al., 2016). Lower rates of fatigue were observed in cancer patients who increased or maintained PA levels after cancer (Matias et al., 2019). Moreover, cancer

patients who are more physically active, have been reported to have lower psychological distresses and greater resilience (Matzka et al., 2016).

Exercise rehabilitation

Exercise can counteract the adverse effects of cancer and its treatment. It is also associated with improvements in patient outcomes and treatment-related side effects along with decreased risk of cancer recurrence and cancer mortality (Ashcraft et al., 2019; Cormie et al., 2018; Haydon et al., 2006; Holmes et al., 2005). The accumulating body of research demonstrating exercise as a safe and effective intervention in individuals living with and beyond cancer has led to recommendations that exercise be embedded into standard cancer care as an adjunct therapy (Cormie et al., 2018).

During cancer treatment, exercise may improve a patient's ability to withstand strenuous medical interventions such as surgery and chemotherapy. Pre-operative exercise training has been shown to improve functional capacity and clinical outcomes for cancer patients (Boereboom et al., 2016; Singh et al., 2013). In lung cancer, pre-operative training has been found to reduce the risk of post-operative complications by 48%, and the length of hospital stay by three days when compared to controls (Steffens et al., 2018a). Evidence of the effect of pre-operative exercise training on post-operative outcomes in other cancer diagnosis has not yet been established but is being investigated (Steffens et al., 2018b; Wallen et al., 2018). Cachexia is commonly associated with cancer and can negatively impact surgical outcomes (Bachmann et al., 2013; Barber et al., 1999; Pausch et al., 2012). In a systematic review by Loughney *et al,.* (2016) pre-operative exercise

training was highly effective in reducing the effects of cachexia while enhancing physical fitness and additionally health-related QoL in breast and rectal cancer patients.

Responses to exercise including increases in blood flow, pH regulation, heat production, sympathetic activation and endocrine effects have the potential to regulate tumor growth kinetics, metastatic potential, tumor metabolism and the immunogenic profile of the tumor (Hojman et al., 2018). The effects of exercise may also enhance the effects of the immune system in infiltrating tumors. Exercise can promote T-cell trafficking by increasing the circulating levels of interlukin 6, a cytokine involved in the upregulation of adhesion molecules located on the tumor vascular endothelium. Moreover, exercise can acutely increase the number and function of natural killer cells, which have a cytotoxic effect on cancer cells (Ashcraft et al., 2019; Bigley et al., 2014; L. Pedersen et al., 2016).

The is evidence that during neoadjuvant chemotherapy, exercise training can positively affect patient symptoms and response to treatment and, potentially alter tumour phenotype (Ashcraft et al., 2019; Jones et al., 2013a). Improvements in vascular function associated with exercise may have implications for the delivery and efficacy of systemic anticancer agents. An increase in the number of functional tumor microvessels, will potentially increase chemotherapy exposure to a larger proportion of tumor cells (Ashcraft et al., 2019). Finally, tumor hypoxia is associated with poor radiotherapy outcomes and increased propensity towards metastasis (Ashcraft et al., 2019). Exercise has been shown to increase tumor radiosensitivity by reducing tumor hypoxia (Ashcraft et al., 2019; Betof et al., 2015; McCullough et al., 2014). A recent

consensus statement by Campbell *et al.,* (2019) highlighted the growing evidence-base supporting exercise prescription in cancer cohorts after diagnosis and during treatment. Their review concludes that there is currently strong evidence for the positive effects of exercise on many common side effects of treatment including anxiety, depressive symptoms, fatigue, the impact on HRQoL and physical functioning. Although Campbell states that gaps still remain with regards to the prescription of exercise in terms of types of cancer and timing of treatment, the current evidence should guide clinicians in advising patients to be active, with a goal of achieving 30 mins of exercise on ≥ 3 days per week. Similarly, in a recent call to action by Schmitz *et al.,* (2019) a step by step approach for clinicians dealing with cancer patients is outline on how they can effectively assess and advise on exercise participation in this cohort. The guidelines for clinicians are as follows;

1. Assess current PA at regular intervals;

2. Advise patients with cancer on their current and desired levels of PA and convey the message that moving matters; and

3. Refer patients to appropriate exercise program or to the appropriate health care professional who can evaluate and refer to exercise.

Improvements in cancer diagnosis and treatment have contributed to increased survival rates for this population (Allemani et al., 2018; Bluethmann et al., 2016). The challenges facing cancer survivors include treatment-related side effects and psychological distress associated with

transitioning to survivorship, particularly with limited supports (Cormie et al., 2018; Kantsiper et al., 2009). Exercise interventions improve body composition, physical functioning, cancer-related fatigue, QoL, self-esteem and reduce anxiety, depression, the risk of cancer reoccurrence, cancer mortality and all-cause mortality in cancer survivors (Fong et al., 2012; Ibrahim & Al-Homaidh, 2011; Meneses-Echávez et al., 2015; Schmitz et al., 2010; Speck et al., 2010; Spence et al., 2010). Indeed, cancer-related fatigue is one of the major causes of distress for cancer survivors (Akechi et al., 1999). Cancer-related fatigue is distinct from the typical fatigue that is experienced as a result of normal daily living. It is disproportional to levels of activity and is not relieved by sleep or rest (Ryan et al., 2007). In a systematic review and meta-analysis by Kessels *et al*., (2018) exercise was found to have a large positive effect on cancer-related fatigue of cancer survivors. Currently, the National Comprehensive Cancer Network (2020) promote the use of exercise as a strategy for reducing cancer-related fatigue. Although exercise has been shown to reduce cancer-related fatigue among patients both during and after cancer treatment, exercise interventions appear to have a greater effect in reducing cancer-related fatigue post treatment (Puetz and Herring, 2012). Exercise is reported to have a palliative effect on cancer-related fatigue in patients undergoing treatment and a restorative effect in patients post treatment.

Exercise Setting

Exercise rehabilitation, delivered primarily through hospital-bsaed outpatient departments, is part of standard care in the majority of cardiac and many pulmonary settings. Uptake and adherence rates to exercise rehabilitation programmes in the hospital setting are

suboptimal. Less than 35% of eligible patients participate in cardiac rehabilitation (Bethell et al., 2008; Mosleh et al., 2015) and non-attendance rates among those referred to pulmonary rehabilitation are between 8-50% (Keating et al., 2011).

Commonly cited barriers to participation in exercise rehabilitation programmes include environmental factors, such as distance to the facility and lack of transport and health system resources (Cox et al., 2017; Keating et al., 2011; Ruano-Ravina et al., 2016). Delivering exercise rehabilitation in non-hospital settings such as the home or community setting has been demonstrated as safe, while also resulting in similar benefits compared to hospital-based programmes (Clark et al., 2015; Man et al., 2004; Neves et al., 2016; Waterhouse et al., 2010). Embedding exercise services within the community may remove many of the barriers associated with poor participation rates in hospital-based rehabilitation programmes.

CBER can be delivered in local fitness centres, gyms and community centres. McNamara *et al*., (2016) conducted semi-structured interviews with individuals who had attended both hospital- and CBER programs. The convenience of accessing the community venue, with close proximity to free parking was a major appealing factor for the CBER programs. Participants expressed how the community venue facilitated a positive rehabilitation experience and promoted a sense of "normality", that exercise was a normal health behaviour as opposed to a treatment for their condition. The community setting enabled participants to gain confidence to explore exercise in different settings in the future. The psychosocial benefits of CBER were identified through focus groups with individuals with COPD (Desveaux et al., 2014b). Participants acknowledged the

importance of the opportunity to integrate into the community and with community members. The experience of social connection with regular gym members provided a sense of feeling socially included and valued. Participants also received social support from the interactions with peers within the exercise group. The interpersonal relationships with the gym instructors contributed to the participants' sense of safety and comfort with the program.

Although an abundance of mainstream exercise programs are available within most communities, programs specific to individuals with CD have certain appealing qualities for this cohort. Cancer patients have described that they are drawn to the condition specific programs as they offer an opportunity for social contact and mutual support within a safe environment and are led by instructors who have specific training to cater for their condition specific requirements (Catt et al., 2018; Moreton et al., 2018). CEBR programmes can operate at a relatively low cost by utilizing available local leisure infrastructure (Mendes et al., 2016). Compared to hospital programs, CBER programs typically have more available space, equipment and staff (Bethell & Mullee, 1990), which results in greater potential for scalability.

Community-based exercise programs for chronic disease

CBER is a safe and effective model of delivering exercise rehabilitation (Desveaux et al., 2014a) with research reporting similar benefits compared to hospital-based programmes (Clark et al., 2015; Neves et al., 2016). Improvements in physical function and health-related quality of life have been reported in a variety of clinical populations following CBER, including cardiac (Mosleh et al., 2015), pulmonary (Beauchamp et al., 2013), cancer (Rajotte et al., 2012; Swartz et al., 2017),

stroke (Desveaux et al., 2014a), osteoarthritis (Kelley et al., 2011), and PAD (Bendermacher et al., 2007). The evidence for CBER in the four major CDs (CVD, COPD, cancer and T2DM) are subsequently presented. CBER is also frequently prescribed for neuromuscular and musculoskeletal conditions and therefore, the evidence for these conditions is also described. A summary of the research on CBER in CD is displayed in table 2.1.

Table 2.1 Studies examining the effects of community-based exercise rehabilitation on chronic disease populations

Author	Disease Cohort	n	Study Design	CBER Intervention	Duration	Results
Bethell & Mellee (1990)	CAD	311	RCT	Group circuit training supervised by GPs in local sports centre	3 m	↑VO_2max and perceived energy levels ↓ Angina pectoris
Kwan *et al*., (2016)	CAD	136	Retrospective database analysis	Supervised group aerobic and resistance exercise	1 yr	↑ aerobic endurance ↓ %body fat, total cholesterol LDL-C, TGs
Taylor *et al*., (2016a)	CAD	670	Retrospective trial of median 14 yr follow-up	Supervised group aerobic and resistance circuit based training	12 wk	↑ fitness ↓ risk of all cause morality in the least fit at baseline
Cramp *et al*., (2010)	Stroke	18	Time series experimental design	Group exercise aerobic and resistance circuits led by fitness instructors	14 wk	↑ lower limb muscle strength, paretic knee extension, walking velocity and balance
Eng *et al*., (2003)	Stroke	25	Single-arm repeated measures	Group exercise classes focused on balance, mobility, functional strength and functional capacity	8 wk	↑ functional capacity, aerobic capacity, balance and satisfaction and perception of physical performance
Harrington *et al*., (2010)	Stroke	243	RCT	Group exercise focused on balance, endurance, strength, flexibility and function	8 wk	↑ physical integration and psychological health
Leroux (2005)	Stroke	20	Single-arm repeated measures	Group exercise classes focused on strength, balance, mobility and co-ordination	8 wk	↑ motor performance
Marsden *et al*., (2016)	Stroke	20	Pilot controlled trial	Individually tailored home- and community-based exercise	12 wk	↑ aerobic endurance
Pang *et al*., (2005)	Stroke	63	RCT	Group progressive aerobic, strength, mobility and balance exercise	19 wk	↑ CRF, paretic leg muscle strength
Bendermacher *et al*., (2007)	PAD	56	Time series experimental design	Individual treadmill walking program	6 m	↑ absolute claudication distance
Kruidenier *et al*., (2009)	PAD	129	Prospective cohort study	Individual treadmill walking program	12 m	↑ functional claudication distance and absolute claudication distance

Table 2.1 continued

Author	Disease Cohort	n	Study Design	CBER Intervention	Duration	Results
Gallé *et al*., (2019)	T2DM	69	Prospective controlled trial	Supervised group aerobic and resistance circuit exercise	9 m	↑ physical functional and physical activity ↓ BMI, HbA_1c, waist circumference
Mendes *et al*., (2016)	T2DM	43	Single-arm repeated measures	Supervised group aerobic, resistance, balance and flexibility exercise	9 m	↑ aerobic endurance, strength, balance and flexibility
Mendes *et al*., (2017)	T2DM	124	Non-randomised controlled trial	Group supervised aerobic, resistance, balance and flexibility exercise	9 m	↑ glycemic control, total cholesterol, LDL-C, HDL-C, TGs, SBP, DBP, BMI, waist circumference and 10-year risk of CAD
Amin *et al*., (2014)	COPD	24	RCT	Aerobic and resistance personal training in local health club	12 wk	↑ aerobic endurance, strength and QoL
Beauchamp *et al*., (2013)	COPD	29	Single-arm longitudinal	Minimally supervised self-conducted aerobic and resistance exercise program	12 m	↑PA levels, endurance, strength and QoL
Effing *et al*., (2011)	COPD	159	RCT	Physiotherapist delivered aerobic and strength exercise program	11 m	↑ maximal exercise capacity and step count ↓ dyspnoea
Godtfredsen *et al*., (2018)	COPD	803	Single-arm repeated measures	Multicentred program with supervised aerobic and strength exercise training	6 – 12 wk	↑ aerobic endurance and QoL
Varas *et al*., (2018)	COPD	33	RCT	Exercise training combined with a walking plan	8 wk	↑ step count, aerobic endurance and self-reported PA ↓ symptoms of COPD
Christopher and Morrow (2004)	Cancer	23	Single-arm repeated measures	Supervised group aerobic, resistance and flexibility exercise	12 wk	↑ psychological health and social wellbeing
Foley and Hasson (2016)	Breast cancer	52	Single-arm repeated measures	Group supervised aerobic, resistance, balance and flexibility training	12 wk	↑ mobility, muscular strength, flexibility and balance ↓ SB and DBPP
Foley *et al*., (2018)	Breast cancer	52	Single-arm repeated measures	Supervised group interval aerobic and musculoskeletal exercise	12 wk	↑ physical function and psychological health
Haas *et al*., (2012)	Cancer	177	Single-arm repeated measures	Individual monitored program of aerobic, resistance and flexibility exercise	24 m	↑ QoL

Table 2.1 continued

Author	Disease Cohort	n	Study Design	CBER Intervention	Duration	Results
Knobf *et al.*, (2014)	Breast Cancer	26	Single-arm repeated measures	Multicentre supervised individual progressive aerobic program on a treadmill	4 – 6 m	↑ QoL
Leach *et al.*, (2015)	Breast cancer	80	Single-arm repeated measures	Supervised group or home-based aerobic, resistance and flexibility exercise	12 wk	↑ BP, waist circumference, WHR, skin folds, ↑ grip strength, flexibility, aerobic fitness and health-related QoL ↑ BMI and RHR
Rajotte *et al.*, (2010)	Cancer	221	Single-arm repeated measures	Group supervised aerobic warm up with resistance exercise	12 wk	↑ aerobic endurance, strength, flexibility and QoL
Santa Mina *et al.*, (2017)	Cancer	224	Prospective cohort study	Group supervised interval aerobic and musculoskeletal exercise	30 wk	↑ aerobic endurance, PA levels, balance cancer-related fatigue, social wellbeing and SBP
Amara *et al.,* (2020)	Parkinson's disease	55	RCT	Supervised one-to-one resistance and mobility exercises	16 wk	Improved sleep efficiency, total sleep time, time spent in slow-wave sleep and wake after sleep onset
Combs *et al.*, (2013)	Parkinson's disease	31	RCT	G1 traditional exercise (stretching, resistance, aerobic and balance) G2 boxing training (stretching, boxing, resistance and aerobic)	12 wk	↑ balance, mobility and quality of life in both groups ↑ gait velocity and endurance in boxing group only
Corcos *et al.*, (2013)	Parkinson's disease	38	RCT	Supervised individual G1 progressive resistance training G2 stretching, balance and strength exercises	24 m	↑ physical function and motor control off medication in both groups ↑ strength and movement speed in progressive resistance training group only
Kelly *et al.,* (2014)	Parkinson's disease	15	Single-arm repeated measures	Supervised one-to-one aerobic, resistance, mobility and balance exercises	16 wk	↑ total body strength, leg power, single leg balance, 6 min walk test, QoL and improved sit to stand motor unit activation and muscle histology (myofiber hypertrophy, shift to less fatigable myofiber type profile and ↑ mitochondrial complex activity

Table 2.1 continued

Lavin *et al.,* (2020)	Parkinson's disease	20	Single-arm repeated measures	Supervised one-to-one aerobic, resistance, mobility and balance exercises	16 wk	Improved muscle mass, neuromuscular function (strength, power and motor unit activation), indices of neuromuscular junction integrity, cognition and well-being
Elsworth *et al*., (2011)	Neurological conditions	99	RCT	Individual gym-based aerobic and resistance exercise	3 m	↑ aerobic endurance, strength and QoL
Poliakoff *et al*., (2013)	Parkinson's disease	32	RCT	Supervised group aerobic, gait and agility exercise	10 - 20 wk	↑ lower body motor functioning and reaction time
Salbach *et al*., (2014)	Neurological conditions	14	Single-arm repeated measures	Group supervised task-oriented circuit exercise	12 wk	↑ aerobic endurance and physical function

Note: CAD = coronary artery disease; T2DM = type 2 diabetes mellitus; PAD = peripheral arterial disease; COPD = chronic obstructive pulmonary disease; RCT = randomised controlled trial; GP = general practitioner; G1 = group 1; G2 = group 2; wk = week; m = months; ↑ = increase ; ↓ = decrease; BMI = body mass index; LDL-C = low density lipoprotein cholesterol; TGs = triglycerides; HDL-C = high density lipoprotein cholesterol; SBP = systolic blood pressure; DBP = diastolic blood pressure; CRF = cardiorespiratory fitness; QoL = Quality of life; BP = blood pressure; WHR = waist to hip ratio; RHR = resting heart rate

Cardiovascular Disease

There is now a substantial body of evidence demonstrating the effectiveness of CBER programs in the secondary prevention of CVD. A 12 week CBER program supervised by general practitioners in a local sports centre was found to be effective in increasing maximal oxygen uptake, perceived energy levels and reduced angina pectoris among 200 patients following an acute myocardial infarction (Bethell & Mullee, 1990). A retrospective analysis of 670 patients with CAD who participated in the 'Heart Watch' CBER program delivered by local council leisure centres found a reduced risk of all-cause mortality at 14 year follow-up (Taylor et al., 2016a). Similarly, a retrospective analysis in 136 participants with CAD who had completed a one-year CBER program found improvements in aerobic endurance, body composition total cholesterol, LDL-C and TG Kwan *et al*., (2016).

Cerebrovascular disease can have disabling effects including weakness, hemiplegia or paralysis (Irish Heart Foundtaion, 2020). Similar to CVD, a number of studies have reported beneficial effects among stroke survivors following their participation in home and community-based exercise rehabilitation programs. A 12-week individually tailored home-based exercise program delivered by a neurological physiotherapist and an exercise scientist to 20 stroke survivors resulted in a significant improvement peak oxygen uptake (VO_{2peak}) and distance covered in a 6 min walk test (6MWT). Pang *et al*., (2005) found significant improvements in both CRF and paretic leg muscle strength in 63 stroke patients who participated in a 19 week supervised group-based exercise rehabilitation. Similarly, other supervised community-based exercise programs in stoke patients have resulted in significant

improvements in functional capacity, aerobic capacity, balance and satisfaction, perception of physical performance (Eng et al., 2003), motor performance (Leroux, 2005) physical integration, psychological health (Harrington et al., 2010), lower limb muscle strength, paretic knee extension, walking velocity and balance (Cramp et al., 2010). CBER has also been found to be an effective approach to rehabilitation among individuals with PAD. Supervised treadmill walking programs undertaken in physiotherapy practices, have been shown to significantly improve absolute and functional claudication distance in patients with PAD (Bendermacher et al., 2007, Kruidenier et al., 2009).

Type 2 diabetes mellitus

In patients with T2DM, a range of improvements have been associated with participation in CBER cohort. Participation in supervised group-based exercise programs located in community sports centres results in significant improvements in aerobic endurance, strength, balance and flexibility, glycemic control, total cholesterol, LDL-C, HDL-C, TG, systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, waist circumference and 10-year risk of CAD in men and women with T2DM (Mendes et al., 2016, Mendes et al., 2017). Recently, Gallé et al., (2019) found significant improvements in PA levels, physical functioning, BMI, HbA_1c and waist circumference in individuals with T2DM following participation in a supervised CBER program.

Chronic Obstructive Pulmonary Disease

COPD patients who attended an 8-week CBER program which combined exercise training with a plan to increase daily step count, had a significant improvement on exercise capacity, and a 45% increase in daily step count (Varas et al., 2018). Similarly, Effing *et al*., (2011) reported an increase in daily step count and maximal exercise capacity in COPD patients attending a CBER program that involved a combination of one to one supervised exercise in a private physiotherapy practice and unsupervised home-based training. Significant improvements in aerobic endurance, strength and QoL, were observed in 24 COPD patients by Amin *et al*., (2014) after 12 weeks of personal training in a local health club. In a longer-term study, Beauchamp et al. (2013), found significant improvements in PA levels, endurance, strength and QoL, in 29 patient with COPD, after 12 months of individual exercise rehabilitation in a local fitness centre, with minimal formal supervision from fitness centre staff. Finally, Godfredsen *et al*., (2019), reported significant improvements in aerobic endurance and QoL among 800 patients following their participation in a supervised community-based pulmonary rehabilitation program.

Cancer

In a comprehensive study by Rajotte *et al*., (2012) with a mixed cohort of 221 cancer survivors, the benefits of a 12 week, supervised group-based exercise program located in community centres, encompassed improvements in SBP, DBP, upper and lower body strength, aerobic endurance, flexibility and overall QoL. In a more recent study involving 52 breast cancer patients, Foley and Hasson (2016) found significant improvements in SBP, DBP,

mobility, strength, flexibility and balance, after a 12 week group-based exercise program supervised by fitness instructors in local community centres. Among 224 cancer survivors, Santa Mina *et al*., (2017) reported significant improvements in cancer-related fatigue, SBP and social wellbeing after 30 weeks of supervised group-based exercise, located in community-based centres.

A reduced health-related QoL is often associated with cancer (Nayak et al., 2017) and there is strong evidence that participation in a CBER program can significantly increase QoL in cancer survivors. Improvements in psychological health and social wellbeing were observed by Christopher and Morrow (2004) in 23 female cancer survivors, who participated in a 12 week, group-based exercise rehabilitation program. Similarly, Foley *et al*., (2018) found significant improvements in physical function and psychological health in 52 breast cancer survivors, after 12 weeks of supervised group-based exercise training in local community centres. Significant improvements in QoL were observed by Knobf *et al*., (2014), in 26 breast cancer survivors after participation in 4 – 6 months of supervised individual exercise training in community fitness centres. In a mixed cancer population, long term improvements in all sub-scales of QoL were found after 24 months of individualized exercise in a community gym (Hass et al., 2012).

The majority of CBER studies in cancer cohorts have focused on survivorship. However Leach *et al*., (2015) demonstrated the feasibility and safety of supervised exercise in a community-based exercise facility and home based exercise for breast cancer patients during treatment. Importantly, the community/home based exercise program was effective

in counteracting the usual declines in physical and psychosocial outcomes that patients experience during chemotherapy and radiotherapy.

Neurological and musculoskeletal disorders

Parkinson's disease is a condition often associated with impaired functioning and may be linked to muscle weakness (Cano-de-la-Cuerda et al., 2010). Significant improvements in physical function and motor control were found in Parkinson's patients (off medication) following a 24 month progressive resistance training program that included stretching and balance exercise and delivered one to one by a personal trainer (Corcos *et al*., 2013). Paliakoff *et al*., (2013) also found significant improvements in lower body motor functioning and reaction time, after 10 – 20 weeks of gym-based group exercise classes in individuals with Parkinson's disease. In addition to improvements in strength, power, motor unit activation, endurance and QoL, Kelly *et al.,* (2014) reported positive adaptations in skeletal muscle histology after 16 wk of exercise training in Parkinson's disease patients. The skeletal muscle adaptations identified included myofiber hypertrophy, a shift to less fatigable myofiber type profiles and increased mitochondrial complex activity. A recent study, which incorporated the same 16 wk exercise training program as Kelly *et al.,* (2014) reported similar improvements in strength, power and motor unit activation while also identifying improvements in indices of neuromuscular junction integrity, cognition and well-being (Lavin et al., 2020). Transcriptome-wide skeletal muscle gene expressions were generate for a sub-sample of 5 participants in this study, to identify transcriptional networks that may underpin the resistance training induced neuromuscular remodelling in Parkinson's Disease. The results

of this novel analysis found that following the program 304 genes were significantly upregulated, which were notably related to remodelling and nervous system / muscle development. In addition, 402 genes, which were primarily associated with negative regulators of muscle adaptations, were downregulated. Sleep disorders affect 74% - 98% of individuals with Parkinson's disease (Lees et al., 1988; Nausieda et al., 1982). In a 16 wk exercise training program by Amara *et al.,* (2020) objective sleep outcomes were improved including sleep efficiency, total sleep time, time spent in slow-wave sleep and wake after sleep onset.

The beneficial effects of CBER in patients with neurological conditions extend beyond Parkinson's disease. In a study cohort that included 99 participants with a range of neurological conditions, three months of individual, gym-based exercise training, delivered by fitness instructors resulted in significant improvements in aerobic endurance, strength and QoL (Elsworth et al., 2011). Similarily, Salbach *et al*., (2014), found significant improvements in aerobic endurance and physical function in 14 participants with a range of neurological conditions following participation in a 12 week, group-based circuit exercise training, delivered by physical therapists and fitness instructors in community centres.

Improvements in measures of mobility were found in mixed cohort of individuals with multiple sclerosis, motor neuron disease, neuro-muscular disorders, Parkinson's disease and cerebral palsy following their participation in community based exercise program (Elsworth et al., 2011). Likewise, Salbach *et al*., (2014), reported that a community-based model of exercise delivery for individuals with stroke, acquired brain injury and multiple sclerosis was as safe and feasible and resulted in physical functioning related benefits, and

Currently the majority of rehabilitation programs available for individuals with a CD are disease specific. However, individuals with CD often experience the same manifestations such as fatigue, decrements in psychological health, peripheral muscular deconditioning and reduced functional capacity. CBEPs that cater for a variety of CDs groups maximizes the utilization of resources and relieves some of the demand on the clinical service.

A recent meta-analysis reported that CBER programs that catered for multiple CDs simultaneously was effective at improving both functional capacity and QoL among CD populations, when compared with standard care (Desveaux et al., 2014a). All CBEPs included in the analysis were well tolerated across all settings. A limitation of this review is that a limited number of CDs were included in the analysis (osteoarthritis, stroke, COPD and T2DM), which reduces the generalizability of the review. Although the results endorse the simultaneous inclusion of multiple CDs in CBEPs, further research which supports these findings across a wider variety of CDs is required.

The benefits and efficacy of CBER for individuals with CD has been widely established. Currently the majority of exercise rehabilitation programs available for individuals with a CD are segregated by disease. A systematic review of the structure and delivery of CBER programmes across CD populations identified that the design and components of programmes were similar, irrespective of CD (Desveaux et al., 2014a). The primary components of > 85% of the programmes included a combination of aerobic and resistance exercise. Such programmes can be easily applied across a range of conditions with minimal disease-specific adjustments. Similarities in the clinical manifestations between CD, such as reduced functional capacity and peripheral muscular deconditioning, and the growing

prevalence of MM, appears to negate the need for separate programmes for SCD. An integrated model is likely to represent a more resource efficient approach however the evidence-base supporting the mixed approach to CBER is limited. The integrated model has potential to widen access for CD patients to CBER while also reducing the burden on overwhelmed clinical-based services for delivering exercise rehabilitation. In addition, the health enhancing effects of CBER on CD cohorts has the potential to reduce future hospital admissions and use of clinical healthcare services. Investigations evaluating the efficacy of the integrated approach to CBER are warranted.

Sedentary Behaviour and Health Status

Relative to the extensive literature on the effects of PA on health, much less is known about the physiological responses and health outcomes associated with SB. The published research to date indicates that there are substantial health hazards associated with excessive SB. Importantly, SB is associated with an increased risk of all-cause and CVD mortality, which appear to be independent of PA (Patterson et al., 2018; Rezende et al., 2014). Furthermore, high levels of SB are associated with the development of a number of CD and the relation appears to be independent of PA and other risk factors, including diet and BMI (Katzmarzyk et al., 2009; Patel et al., 2010; van der Ploeg et al., 2012).

The relative risks associated with prolonged sitting become more pronounced in individuals who are also insufficiently active (Biswas et al., 2015; Bouchard et al., 2015; Ekelund et al., 2016). PA may attenuate some of the risk associated with SB. Ekelund *et al.,* (2016) demonstrated that greater sitting time increased the risk of all-cause mortality, where

the least active individuals were at the greatest risk in their meta-analysis which included data of more than one million individuals. However, the magnitude of increased risk with sitting is mitigated with PA, and completely attenuated when achieving 60 – 75 min of MVPA per day. The level of PA that must be achieved to attenuate the risk associated with SB is of a duration and intensity, that is beyond the abilities of most individuals, particular those with a CD.

In a more recent meta-analysis, Ekelund *et al*., (2019) found a non-linear dose-response relation between high PA levels of any intensity and a reduced risk of all-cause mortality, while accounting for SB. However, the risk of mortality gradually increased with SB > 7.5 h/day. Similarly, Chau *et al*., (2013) estimated that the mortality risk is 34% higher in individuals who sit for > 10 h/day even after taking PA into account.

The associations between SB and mental health have also been explored. Overall sitting time has been associated with depression and anxiety in observational research (Rebar et al., 2014). In a meta-analysis by Zhai *et al.,* (2014), the pooled risk of depression for highest levels of SB compared to occasional SB was 31% greater in cross-sectional studies and 14% greater in longitudinal studies. Similarly, Teychenne et al., (2015) found moderate evidence for a positive relation between overall SB and risk of anxiety. More recent research suggest that the context of SB may influence the association of SB with mental health. Hallgren *et al.,* (2018) found a lower risk of depression for those who participated in mentally-active SB such as office-work and a positive association between depression and passive SB, such as watching TV. More recently, Hallgren *et al.,* (2020a) reported that substituting 30 min per day of passive SB with mentally active SB, the odds of depression symptoms reduced by 5%.

Hallgren et al., (2020b) reported that higher volumes of SB in the leisure context may be associated with frequent symptoms of depression and anxiety.

Self-reported sedentary behaviour

The Canada Fitness Survey of 7278 men and 9735 women used a lifestyle questionnaire to assess the amount of time spent sitting during work, school and housework (Katzmarzyk et al., 2009). At 12-year follow-up, there was a dose-response relation between sitting time and mortality from all causes and CVD. The dose-response relation was independent of leisure time PA, and was similar among non-smokers, former smokers and current smokers and all BMI categories. Self-report of television viewing is commonly used surrogate to measure SB. A study involving 8800 adults found that each one h increment in television viewing per day was associated with an 11% and 18% increased risk of all-cause and CVD mortality, respectively (Dunstan et al., 2010). In addition, greater than 4 h per day watching television increased the risk of all-cause and CVD mortality by 46% and 80%, respectively, when compared to those watching television for ≤ 2 h per day. In a U.S. study of 7,744 male participants, > 10 hours per week riding in a car or > 23 hours per week of combined television viewing and riding in a car were associated with an 82% and 64% higher risk of CVD mortality than men who reported < 4 hours per week or < 11 hours per week, respectively (Warren et al., 2010). Self-report SB has been found to be negatively associated with subjective-well-being, in particular within the subscales of physical well-being, independence, learning and growth and environmental well-being (Ku et al., 2011).

Device-measured sedentary behaviour

Self-report measures of SB usually involve recall, which in some cases can be a highly complex cognitive task, particularly for older adults. SB because of its habitual nature appears even more difficult for older adults to recall than PA (Wullems et al., 2016). Device-measured PA and SB can avoid subjective bias and enable more accurate and robust measures. Accelerometers are the primary tool utilised by researchers to objectively measure SB and PA in free-living conditions over a number of days (Pate et al., 2008). Such devices not only provide the cumulative time spent sedentary but also the time spent in each sedentary bout and the frequency of breaks in SB (Wullems et al., 2016).

The use of devices to assess SB has grown rapidly in recent years. The findings are in agreement self-report studies that SB negatively impacts health, often independent of PA levels. In 2015, a systematic review of accelerometer-measured SB and cardiometabolic biomarkers reported consistent unfavourable associations between SB and insulin sensitivity, independent of PA (Brocklebank et al., 2015). There was also some evidence of unfavourable associations between SB and fasting insulin levels, insulin resistance and TG. A systematic review of biomarkers associated with accelerometer-derived SB in older adults found that most of the biomarkers associated with SB were of a cardiometabolic nature. There was negative impact of SB on markers of body composition, blood lipids, glycemic biomarkers (Wirth et al., 2017). A recent systematic review and meta-analysis by Powell *et al*., (2018) investigated the cross-sectional associations between device-measured SB and cardiometabolic biomarkers in adults. This extensive review, which included 46 studies and a combined sample size of 70,576 participants, found increased SB to have deleterious

associations of clinical significance with fasting glucose, fasting insulin, TG, HDL-C and waist circumference. Moreover, it is suggested that to offset the effect size identified for increased SB on cardiometabolic health, several weeks of aerobic training is required.

Accelerometers are not without limitations, in particular in relation to the thresholding of accelerometer counts. SB is commonly classified as inactive periods of accelerations below a defined threshold, e.g. < 100 counts per min, which is specific to each brand of monitor (Byrom et al., 2016). Such an approach can misclassify standing as SB. Bouts of standing are physiologically distinct from sitting and lying and have been associated with beneficial impacts on physiological processes such as glucose metabolism (Edwardson et al., 2017). Accelerometers that incorporate an inclinometer can determine the posture of the wearer and distinguish between sitting and standing. Powell *et al.,* (2018) examined the influence of the device using when investigating the associations between SB and markers of cardiometabolic health and reported that the activPAL device offers the most precision.

Patterns of Sedentary Behaviour

SB is often described as total daily sedentary time, which has been useful in investigating the health risk associated with this behaviour. The pattern in which SB is accumulated appears to also be of clinical relevance. Prolonged or less fragmented SB is potentially more detrimental to health. A single day of uninterrupted SB in healthy adults was shown to reduce insulin action by 39% (Stephens et al., 2011). Following 5-7 d of uninterrupted bed rest, glucose and TG levels were found to be elevated by 34% and 34.8%, respectively (Hamburg et al., 2007; Zorbas et al., 1999). Although these are extreme examples

of unbroken SB, the immediate negative responses to this behaviour cannot be ignored, in particular with regards to patients with CD where periods of symptom exacerbation may result in similar SB patterns.

A definitive threshold of what is considered a prolonged sedentary bout that induces negative physiological responses is yet to be established. However, sedentary bouts of ≥10 min in duration were shown to be positively associated with waist circumference (Judice et al., 2015). The odds of abdominal obesity were 7%, 11%, 15% and 48% higher for each sedentary bout of 10-20 min, 20-30 min, 30-60 min and > 60 min, respectively.

Breaking up SB can have a beneficial effect on cardiometabolic risk and other indices of health, which may be independent of total sedentary time. Research has reported favourable associations between the number of breaks in sedentary time and measures of adiposity, blood lipids, glucose control and inflammation (Bankoski et al., 2011; Dunstan et al., 2012; Healy et al., 2008a; Healy et al., 2011). In a cross-sectional study of 168 participants, Healy *et al*., (2008a) found the number of breaks in sedentary time, defined as interruptions in sedentary time of > 100 accelerometer counts/min, was inversely associated with waist circumference, BMI, TG and 2 h plasma glucose, independent of total sedentary time, MVPA, and the mean intensity of the breaks.

Among the first experimental studies to investigate the effects of breaking up prolonged sitting, Dunstan *et al*., (2012) compared the effects of seven h uninterrupted sitting and sitting interrupted every 20 min with 2 min of LIPA or MVPA on postprandial glucose and insulin levels in 19 overweight/obese adults. Postprandial glycemic and insulinemic responses

were reduced with sitting interrupted by LIPA and MVPA compared with uninterrupted sitting. The effects were similar irrespective of whether the breaks consisted of LIPA or MVPA. Subsequent acute experimental studies have confirmed the positive effects of breaking up sedentary time on metabolic outcomes. Benatti and Ried-Larsen (2015) found that replacing sitting time with LIPA appears sufficient to counteract the negative effects of prolonged sitting in those who are physically inactive or have T2DM. MVPA may be required obtain such benefits in those who are habitually physically active. Recent evidence reports that reallocating 30 min from sleep sedentary time or standing time to LIPA is associated with significant reductions in BMI, body fat and fat mass (Powell et al., 2020).

The chronic effects of breaking sedentary time has been much less researched. An uncontrolled trial reported significant decreases in waist and hip circumferences, LDL-C, total cholesterol, and glycosylated haemoglobin with the introduction of treadmill desk workstations for nine months in 12 overweight/obese adults (John et al., 2011). In a quasi-experimental trial of 32 non-obese healthy adults, sit-stand workstations were associated with improvements in HDL-C after three months compared with control (Alkhajah et al., 2012). There were no differences in anthropometrics, fasting glucose or other lipid markers.

Breaking up sedentary time has also been found to be associated with functional capacity in cross-sectional studies, including upper and lower body strength and an overall physical functioning score independent of total sedentary time (Sardinha et al., 2015). In older adults, breaks in SB was associated with better lower extremity functioning (Davis et al., 2014) and ability to complete ADL (Chen et al., 2016b), which appear to be independent of MVPA.

Physiological Mechanisms Associated with Sedentary Behaviour

The physiological mechanisms responsible for the unfavourable associations between SB and health are not fully understood. A number of mechanisms have been proposed. One involved the impairment of lipid metabolism due to suppression of lipoprotein lipase (LPL) activity. LPL is the rate-limiting enzyme for the hydrolysis of the triacylglycerol component of circulating lipoproteins. A reduction in LPL activity impairs tissue-specific uptake of lipoprotein-derived fatty acids and abnormalities in LPL function have been found to be associated with a number of pathophysiological conditions, including atherosclerosis, obesity, insulin resistance and diabetes (Mead et al., 2002). LPL may also have a role in regulating inflammation (Ziouzenkova et al., 2003).

The primary physiological regulator of LPL activity in the vasculature of the skeletal muscle is local contractile activity/inactivity. In rodent models of inactivity involving 10 h/day of unloading, almost all of the LPL activity associated with vascular endothelium of oxidative muscle fibers was lost within one day (Bey & Hamilton, 2003). The reduction was localized to the immobilized muscles and the inactivity was also associated with a local reduction of TG uptake into muscle and a decrease in HD-C concentration compared to low intensity ambulatory controls. The decrease in LPL activity occurred in the absence of a change in LPL mRNA concentration. Instead there was a decrease in LPL protein mass, suggesting the possible involvement of the transcriptional inhibitor actinomycin D. The effects of the transcriptional blockage were specific to the inactive group because there was no effect on LPL in standing/ambulatory rat (Hamilton et al., 2007). LPL activity was restored within 4 h of resuming weight bearing and ambulatory activity. There is also some evidence that plasma

lipids can acutely downregulate LPL activity and that this effect is augmented by inactivity (Zderic & Hamilton, 2006).

A second potential mechanism for the detrimental responses to SB is that lower skeletal muscle blood flow resulting from excessive sitting leads to lower shear stress on vascular endothelial cells and, consequently decreased endothelial nitric oxide synthase expression (Stamatakis et al., 2011). Vascular studies have shown that shear rate, flow mediated dilation and brachial artery diameter decrease, while endothelial cell damage and BP increase with increasing SB (Wullems et al., 2016).

SB has been positively associated with increased arterial stiffness, even when controlling for MVPA, resting heart rate, adiposity and metabolic syndrome (Huynh et al., 2014). SB has also been associated with ankle-brachial index, a vascular measure that is an indicator of PAD and predictor of cardiovascular events (Parsons et al., 2016). Every additional 30 min of SB was associated with an OR of 1.19 for a low ankle-brachial index. Considered together, these findings provide preliminary evidence that the mechanisms associated with SB relate to impaired vascular function and structure.

Systemic inflammation has also been implicated in the negative physiological effects of SB. CRP, a low-grade inflammatory marker, was shown to be doubled in individuals who engaged in > 4 hours/day of screen time compared with < 2 hours per day (Stamatakis et al., 2011). More recent research found that MVPA and CRF (when above an estimated median value) attenuated the risk of elevated CRP (Edwards & Loprinzi, 2018). Additionally, continual underloading due to SB may negatively affect muscle-tendon properties, which could lead to

muscle atrophy (Stamatakis et al., 2011). SB may change the balance between bone resorption and deposition, mainly by a rapid increase in bone resorption, without changes in bone formation. This would reduce bone mineral content and increases the risk of osteoporosis.

Finally, poor diet quality and increased caloric intake are behaviours associated with sitting, in particular television watching, suggesting the detrimental effects on health might stem from the dietary intake associated with sitting time, rather than sitting itself (Patterson et al., 2018). However, the association between TV viewing time and cardiometabolic biomarkers remains significant after controlling for dietary intake.

Several hypotheses have been proposed to describe the potential mechanisms underlying the association between SB and mental health. The social withdrawal hypothesis, which proposes that the more frequently people watch television or use computers, the less they engage in social interactions, is suggested as a potential mechanisms (Kraut et al., 1998; Lewinsohn, P., 1974). In contrast, Shaw and Grant (2002) argue that SB while using the internet can involve communication with others (e.g. emailing and chat rooms), and suggest that not all SB are applicable to the social withdrawal hypothesis. A second possible explanation for the positive associations between SB and risk of depression, is that SB may displace potential PA, and PA is strongly associated with reducing the risk of depression (Teychenne et al., 2008; Zhai et al., 2015). The associations between depressive symptoms, SB and inflammatory markers has also been explored. Longitudinal associations between SB and low grade inflammation over a 4 year follow-up was reported by Hamer *et al.,* (2015) and given the associations between inflammatory markers and depressive symptoms (Irwin &

Miller, 2007) it is feasible to hypothesize that the associations between SB and depressive symptoms might partly be explained by underlying inflammatory mechanisms (Hamer and Smith, 2018).

The potential biological pathways between SB and anxiety may include central nervous arousal (Wang et al., 2006), sleep disturbances (Dworak et al., 2007) or poor metabolic health (Mommersteeg et al 2012). On the contrary, Sabiston *et al.*, (2007) suggest that those suffering from anxiety may be more inclined to engage in SB as a means of coping with anxiety.

Recent evidence proposes differential associations of passive and mentally active SB with mental health (Hallgren et al., 2018; Hallgren et al., 2020a). Furthermore, Hallgren *et al.,* (2020b) suggest that SB which occurs during leisure-time (e.g. television-viewing) may be the predominate cause of SB associated depressive symptoms. Prolonged television viewing is often associated with social-isolation, which may limit people opportunities for supportive and mood-enhancing interactions. SB which involves screen-based devices may also contribute to sleep or mood disturbances. Finally, as SB frequently occurs indoors, away from direct sunlight, the potential that SB might reduce vitamin D synthesis has also been suggests.

Physical activity and Sedentary behaviour in individuals with chronic disease

A very small proportion of individuals with CD achieve the recommended daily PA (Bernard et al., 2018; Fox et al., 2015; Loprinzi et al., 2013; Morrato et al., 2007; Serrano-Sanchez et al., 2014). Mean daily MVPA has been reported as 17 min per day in adults with T2DM (Wang et al., 2017), 16.5 – 7.0 min per day in patients with COPD (Bernard et al., 2018;

Eliason et al., 2011), 11.4 min per day in individuals with angina (Evenson et al., 2014), 10 min/day in cancer survivors (Loprinzi et al., 2013), 8.6 min per day among those with heart failure, (Evenson et al., 2014), and 3.7 min per day in breast cancer survivors (Lynch et al., 2010).

Tudor-Locke *et al*., (2009) reported the lowest daily steps count of 2237 steps per day in patients with COPD and the highest number at 8008 steps per day in type 1 diabetes. Other studies in COPD report step count ranges of 4782 steps per day to 7232 step per day, with evidence that step count reduces with increasing disease severity (Bernard et al., 2018; Moy et al., 2012). Daily step counts of between 4,000 and 6,000 have been reported individuals with Parkinson's disease (Benka Wallén et al., 2015; Christiansen et al., 2017; Lord et al., 2013), intermittent claudication (Lauret et al., 2014), impaired glucose tolerance (Yates et al., 2014).

Research comparing PA levels of individuals with CD to their healthy counterparts has produced mixed findings. Among 300,000 adults in the US, individuals with CHD participated in less self-reported PA at the recommended level than those without CHD (Zhao et al., 2008). Adults > 65 years of age with T2DM were found to be less likely to engage in self-reported physical activity than those without T2DM (Zhao et al., 2011). In small scale studies of COPD (Pitta et al., 2005) and intermittent claudication (Lauret et al., 2014), accelerometer-derived PA was significantly less than in healthy controls. The Canadian Health Measures Survey of over 6000 participants found no difference in accelerometer-derived PA levels between individuals with a single CD and those with no CD. However, PA levels were significantly lower in individuals with individuals with MM compared to those with a single

CD and with no CD (Hains-Monfette et al., 2019). COPD patients with moderate to severe disease were found to engage in significantly less MVPA than healthy individuals (Bernard et al., 2018). In contrast, cancer survivors were more likely to report engaging in PA compared to non-cancer participants in analysis of data from the NHANES (Kim et al., 2013).

There are current no guidelines in relation to what is considered excessive SB. There is evidence that individuals with CD engage in more SB than their healthy counterparts. For example, stroke patients were found to accumulate more daily SB in longer uninterrupted bouts than healthy controls (English et al., 2016, Lewis et al., 2016). Similarly, patients with COPD spent more time sedentary than sedentary healthy elderly subjects (Pitta et al., 2005) and spousal carers (Lewis et al., 2016). Participants who completed cardiac rehabilitation and to whom active living had been promoted, spent eight h per day in SB (Prince et al., 2016). In the Canadian Health Measures Survey, individuals with MM had significantly higher levels of SB compared to individuals with a single CD and those with no CD.

The Effect of Exercise Rehabilitation on Physical Activity Levels and Sedentary Behaviour

A substantial amount of research has investigated the effects of exercise rehabilitation on health-related outcomes and compelling evidence supports the beneficial effects of exercise rehabilitation on health-related outcomes such as functional capacity, disease-related symptoms, QoL, mortality and the disease burden on healthcare services, (Anderson et al., 2016; Dunlay et al., 2014; Houchen-Wolloff et al., 2018; McCarthy et al., 2015; Puhan et al., 2016; Shepherd & While, 2012). However, the research to date reports conflicting evidence for the effects of exercise rehabilitation on habitual levels of PA.

A previous systematic review reported that cardiac rehabilitation services are not consistently successful in increasing everyday PA in patients with cardiac disease (Jolliffe & Taylor, 1998). Similarly, Ter Hoeve *et al*., (2015) compared the effectiveness of both centre-based and home-based cardiac rehabilitation studies and found conflicting evidence for their effectiveness in improving PA levels. Centre-based programs did not have an effect, long-term, on PA, however moderate evidence was found that home-based programs were more effective in long term. More recently, Dibben *et al*., (2018) conducted a systematic review and meta-analysis investigating the effects of cardiac rehabilitation on both CAD and heart failure which included 47 studies. Of the 145 cardiac rehabilitation versus control comparisons reported across all studies, 26% of results reported statistically significant improvements in PA with cardiac rehabilitation, demonstrating moderate evidence for the effects of cardiac rehabilitation on PA levels. Pooled meta-analysis results found an increase in mean daily step count of 1423 steps/day (95% CI 757.1 to 2089.4). This is potentially a clinically meaningful improvement as Demeyer *et al.,* (2016) estimated the threshold for a clinically meaningful change in daily step count for COPD to range between 600 to 1100 steps/day. No differences were found between control vs cardiac rehabilitation groups for SB, LIPA or MVPA for pool analyses of these measures. A review of 32 studies that evaluated the effects of pulmonary rehabilitation on PA showed inconsistent result, with 19 studies demonstrating a positive effect and 12 revealing no effect on PA (Shioya et al., 2018). A 12 month hospital based exercise rehabilitation program for cancer patients, found significant improvements in self-reported PA (Midtgaard et al., 2013).

Limited research exists investigating the effects of CBER on PA levels. The evidence available indicates those who are currently participating in CBER or have previously attended CBER, have higher levels of PA and lower levels of SB compared to those have do not (Hernandes et al., 2013; Simoes et al., 2009). Interestingly, median daily step count remained higher, even on days when they did not attend the classes in adults who participated in CBEPs compared to those who do not. On the contrary, Schutzer and Graves (2004) outline evidence suggesting that elderly populations lack the knowledge and the understanding of the role of daily PA for maintaining health. Hence, it is possible that exercise programs may not improve overall activity levels as individuals who participate may reduce activity levels outside of the program, as they could feel satisfied with their exercise participation. Further investigation is required to provide a clearer indication of the role of CBER in increasing PA and reducing SB. Specifically in CD cohorts, research indicates that habitual PA increases with CBER. In patients with T2DM, nine months of CBER resulted in significant improvements in self-reported PA (Gallé et al., 2019). Similarly, self-reported PA increased in individuals with COPD, after a 12 month CBER program (Beauchamp et al., 2013). Device-measured PA shows promising results. Daily step count increased in individuals with COPD after an 11 month CBER program (Effing et al., 2011). Daily steps per day were also found to increase after eight weeks of CBER in a study by. Varas *et al*., (2018) for individuals with COPD.

A focus on increasing PA levels has dominated research in the area of health for decades, however, only in more recent times has the focus started to shift and recognize the role of decreasing SB. It is too often assumed that an increase in MVPA automatically results in a decrease in SB, however increasing PA causes fatigue that, consequently can have the

unintended effect of also increasing SB, resulting the possible offset of the PA related health benefits (Siddique et al., 2018). A systematic review and meta-analysis by Prince *et al*., (2014) provides some supporting evidence that small reductions in SB can result from PA focused interventions. Interventions that target both PA and SB also resulted in modest reductions in daily SB, however SB focused interventions may be the most effective in resulting in large and clinically meaningful reductions in daily SB.

Determinants of Physical Activity

Adherence to health-related behaviours is defined by the WHO as *"the extent to which a person's behaviour corresponds with agreed recommendations from healthcare providers"* (World Health Organization, 2003). In medical research, adherence is generally expressed as a percentage of the prescribed dose of a medical treatment that has been completed across a specific time period (Osterberg & Blaschke, 2005). In the example of CBER adherence can refer to the percentage of classes attended of the recommended dose (Herring et al., 2014). In contrast, compliance to exercise therapies describes the degree to which subjects completed the prescribed exercise intensity (Miller et al., 2014). In the healthcare setting, the term "adherence" is often favoured over "compliance" because it implies an agreement between the patient and healthcare professional on the treatment plan (Osterberg & Blaschke, 2005). Compliance depicts a more one-sided interaction, where a clinician decides on a suitable treatment, which the patient is required to comply to regardless of suitability (Chakrabarti, 2014).

Adherence to these behaviours, of which PA is one, is a complex behavioural process, which has numerous compounding factors (Middleton et al., 2013). Understanding

the factors associated with PA adherence, is an important component to consider in the design and delivery of interventions aimed at increasing PA participation. Tailoring an intervention to target factors that are known to influence PA behaviour in a particular population can contribute to the success of the intervention in increasing and maintaining PA levels. Many cross-sectional studies report significant associations between a range of personal, social and environmental variables and levels of PA. For example, a study may report that socioeconomic status is associated with PA behaviours. Such relations inform correlates of PA, however, do not identify causal inferences. The logic of causality is fundamental to building an understanding of factors associated with increasing the probability of an outcome. The term 'determinant' is most when defining causal factors / predictive relations to behaviours such as PA (Bauman et al. 2002).

In the literature, demographics (e.g. age, gender), psychological factors (e.g. self-efficacy, perceived enjoyment), social factors (social support from family and friends), and physical environment factors (e.g. living/built environment, access to facilities) have been described as determining factors in PA adherence (Brochado et al., 2010). In a recent systematic review, a range of positive and negative environmental factors were reported as determinants of PA for adults and older adults (Carlin et al., 2017). At the neighbourhood level, negative street characteristics, such as lack of sidewalks and street lights were reported as barriers to PA. Street connectivity and availability/access/proximity of public transport were positivity associated with general walking and cycling in adults. Overall socioeconomic status was identified as a significant positive determinant of overall PA and leisure time PA in adults and older adults and a negative determinant of occupational PA in a systematic review by O'Donoghue *et al.,* (2018). In terms of psychological determinants of PA in adults attitude

and belief where positive determinants of PA in a systematic review by Cortis *et al.,* (2017). Barriers to PA, lack of knowledge of PA benefits, pain/fatigue/weakness, fear to go out alone, fear of injuries or falling, lack of support and emotional distress were reported as negative determinants of PA. Behavioural determinants of PA for adults and older adults include positive associations with baseline activity level and negative associations for smoking (Condello et al., 2017). When investigating determinants of PA in CD cohorts, research has primarily focused on physical factors, such as functional capacity or disease severity (Gimeno-Santos et al., 2014; Stewart et al., 2013). This is unlikely to provide a complete understanding of what determines PA levels in this population.

Behaviour change theories can assist in the understanding of the determinants of behaviour, guide the development of interventions to successfully change behaviour and provide insights into the mechanisms underpinning successful behaviour change. The Transtheoretical Model (also known as the Stages of Change Model) received a lot of attention in the exercise domain. The Transtheoretical Model suggest that individuals progress through multiple stages when changing their exercise behaviour, with each stage transition requiring different determinants and possibly different interventions (Courneya et al 2001; Prochaska et al., 1994). The TTM proposes five stages of change that reflect the temporal dimensions of change in health behaviours and describe an individual's motivation or readiness for change (Figure 2.4).

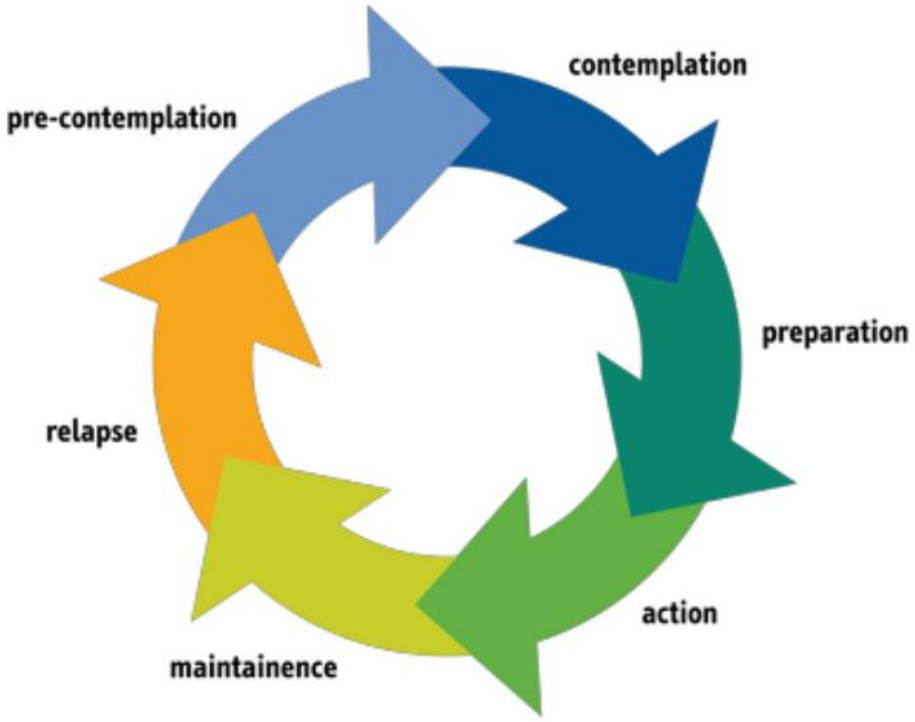

Figure 2.4 The Transtheoretical Model of Behaviour Change
(Prochaska et al., 1994)

Precontemplation: Individuals are not engaged in the recommended health behaviour and have no intention of changing in the foreseeable future.

Contemplation: Individuals have formed an intention to change in the near future but are still not performing the behaviour.

Preparation: Individual intends to take action in the immediate future and may have a detailed plan for taking action or made some small steps towards behaviour change.

Action: The behaviour has been changed to the recommended target level.

Maintenance: The behaviour has been maintained at the target level for at least 6 months.

Other research in the exercise domain have used Ajzen's (1991) Theory of Planned Behaviour to understand and predict the stages of change. The Theory of Planned Behaviour suggests that a person's intention to perform a behaviour is the primary determinant of that behaviour. Three conceptually independent variables (attitude, subjective norms and perceived behavioural control), in turn, determine intentions. Attitudes in this context refer to a positive or negative evaluation of performing the behaviour. Subjective norms represents the perceived social pressure an individual may feel to perform or not perform a certain behaviour. Perceived behavioural control describes the perceived ease or difficulty of performing the behaviour.

The Social Cognitive Theory (SCT) (Bandura, 1998) is one of the most widely used theories in health behaviour research and one of the most effective theories for determining PA behaviour (Taylor et al., 2016b). The theory proposes that learning occurs in a social context with a dynamic and reciprocal interaction between personal, environmental and behavioural factors (figure 2.4). In relation to PA, personal factors can include age, race, gender and cognitive factors such as self-efficacy. Environmental factors include social support, such as modelling from family and friends, support from exercise partners and feedback received from exercise instructors. Behavioural factors which are vital to sustained PA participation predominantly involve self-regulatory behaviours, including the ability to self-monitor and set goals (Anderson-Bill et al., 2011). Although the SCT recognises that environments shape behaviour, the theory focuses on the individual's potential abilities to alter and construct environments to suit personal beliefs (McAlister et al., 2008).

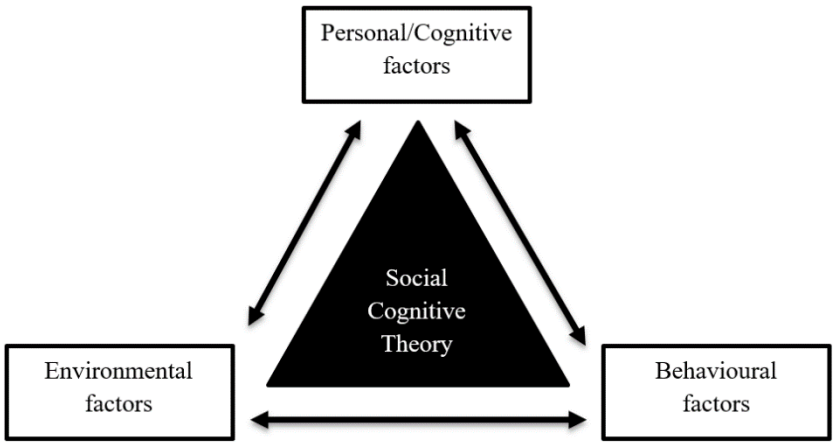

Figure 2.5Social Cognitive Theory
(Bandura, 1998)

The SCT encompasses eight key concepts, namely reciprocal determinism, outcome expectancy, self-efficacy, collective efficacy, observed learning, incentive motivation, facilitation, self-regulation and moral disengagement. These constructs explain 40–70% of the variance in PA behaviours in adults (Anderson-Bill, Winett, & Wojcik 2011; Ayotte et al., 2010; Phillips & McAuley, 2013; Rovniak et al., 2002; White et al., 2012).Self-efficacy, which describes a person's beliefs about their ability to perform behaviours successfully and achieve an intended outcome, plays a pivotal regulative role in the multifaceted causal structure of the SCT. Bandura *et al*., (1999) state that self-efficacy is the single, most necessary motivational element involved in pushing individuals to take actions. Particularly in relation to task orientated behaviours, self-efficacy is a vital component (Bandura, 2004). Self-efficacy is considered a key determinant of PA participation. Self-efficacy for exercise specifically refers to beliefs in one's ability to exercise, even given constraints and impediments such as feeling tired or being busy. It is suggested as the primary determining constraint of achieving health promoting levels of PA (Bandura et al., 1999) and the relationship between exercise beliefs and exercise behaviours is described as reciprocal. Behaviour change can be

determined by other factors, including outcome expectations and sense of controllability (Neupert et al., 2009). An individual can have high self-efficacy for exercise but does not believe beneficial effects can be achieved by engaging in the behaviour. Self-efficacy is not an individual concept, however it is often depicted this way in research. Task self-efficacy describes an individual's confidence in the ability to perform the elemental aspects of a task (e.g. the ability to walk for 30 mins at a moderate intensity), while coping self-efficacy refers to an individual's confidence in their ability to perform tasks under challenging conditions (e.g. confidence in the ability to exercise while in a bad mood) (Rodgers & Sullivan, 2001). In patients who participated in cardiac rehabilitation, maintenance self-efficacy, which refers to beliefs about one's ability to sustain a behaviour regardless of barriers specific to the maintenance period, and recovery self-efficacy, which describes an individual's beliefs about their ability to resume action after relapses, predicted participation in PA eight months after cardiac rehabilitation (Luszczynska & Sutton, 2006).

For those with CD, self-efficacy plays a significant role in exercise adherence. Self-efficacy predicts exercise behaviour in individuals with CVD and cardiac rehabilitation can have a positive effect on exercise self-efficacy in this cohort (Blanchard et al., 2015; Carlson et al., 2001; Lemanski, 1990). A higher self-efficacy has been shown to be independently associated with greater PA levels in patients with COPD (Belza et al., 2001; Hartman et al., 2013; Steele et al., 2000). Self-efficacy was a stronger predictor of attendance to and functional improvement from pulmonary rehabilitation compared to demographics and clinical indicators (Selzler et al., 2016). Exercise behaviours in cancer patients have been shown to be highly associated with exercise-self-efficacy (Pinto et al., 2009; Rodgers et al., 2002; Vallance et al., 2008). A similar association between self-efficacy and PA has been

described among individuals with diabetes (Dutton et al., 2009; Plotnikoff et al., 2000). Dutton *et al*., (2009) investigated the effect of a 1-month print-based PA intervention, which was individually tailored based on theoretical constructs including self-efficacy, on PA levels in individuals with T2DM. After controlling for all potential cofounders, the improvements in PA levels were found to be completely accounted for by the improvements in self-efficacy. In a mixed CD cohort, a cross sectional study of 483 patients reported that PA was positively correlated with self-efficacy (Daniali et al., 2017). Sex, self-efficacy and fatigue explained 87% of the variance of PA. It was suggested that a focus on psychological factors such as self-efficacy has the potential to improve the self-care of CD patients.

Other potential psychosocial factors associated with PA in a mixed CD was explored by Shin *et al*., (2005). Prior exercise experience, perceived health status, exercise benefits and barriers and exercise social support were identified as significant determinants of PA participation. The role of social support and social connectedness in maintaining or initiating behaviour change is well recognised and is a component of many theoretical models of behaviour change, including the SCT (Ajzen, 1991; Bandura, 2004; Bronfenbrenner, 1977; McLeroy et al., 1988; Rosenstock et al., 1988). Key themes have been identified when describing social support, which include social relationships that are reciprocal, accessible and reliable and provide any means of supportive resources (Williams et al., 2004). Social support can include social-emotional support (expressing feelings, values and attitudes), practical support (the provision of the necessary facilities and resources), information support (providing information, recommendations and guidelines) and social belonging (sense and presence of a companion to engage in activity with) (Heaney & Israel, 2008; Uchino, 2004).

Perceived social support is believed to have a direct influence on exercise behaviour (Resnick et al., 2002). It was identified as a primary determinant of PA in community dwelling older adults, especially when social support came from family members (Smith et al., 2017). Social support can influence PA levels and potentially strengthen exercise self-efficacy in patients with CDs, such as CVD and diabetes (Adeniyi et al., 2012; Aliabad et al., 2014; Won & Son, 2017). Social support has also been identified as a positive determinant of PA in cancer survivors (Barber, 2012). Recently, low levels of social support for PA have been found in T2DM (Morowatisharifabad et al., 2019), which are thought to be due to a number of factors such as reduced awareness of individuals and families about the impact of PA on the improvement of patient health, along with cultural perspectives and concerns about PA.

The importance of increasing PA levels for patients with CD is well recognised and understanding and targeting the factors that determine this behaviour is likely to contribute to greater success in this effort. Determinants of PA can guide the investigation of an intervention to identify both how it achieved its desired outcome, or explain why it may not have been successful. Interventions can be refined or tailored based on these discoveries in order to optimally support patients to enhance their PA behaviour. Behaviour change techniques are defined as techniques designed to enable behaviour change by augmenting factors that facilitate behaviour change, or by mitigating factors that inhibit behaviour change (Carey et al., 2019). In the chronic disease population, there is strong evidence that PA interventions can have health enhancing outcomes, however it remains unclear how the efficacy of such interventions could be enhanced. Research has identified strategies to increase self-efficacy for PA in clinical and non-clinical populations. Behaviour change techniques such as “action-planning” where individuals are prompted to form detailed plans

of their behaviour change process where successful in improving exercise self-efficacy (Williams & French, 2011). Behaviour change techniques that facilitate self-regulation (e.g. goal setting or self-monitoring) where identified as important components of physical activity behaviour change in older adults, in a systematic review by Samdal *et al.,* (2017). Behaviour change techniques reported as effective in changing diet and exercise in patients with T2S include 'instructions on how to perform the behaviour', 'behavioural practice/rehearsal', 'action planning' 'feedback and monitoring' and 'demonstration of the behaviour' (Cradock et al., 2017). The optimal combination of an exercise intervention which incorporates successful behaviour change techniques remains unknown, and future research should investigate the efficacy and feasibility of behaviour change techniques to enhance CBER for individuals with CD.

Conclusion

CD is an umbrella term for a range of long-term, medical conditions that can develop in response to genetic, environmental and lifestyle related risk factors. CVD, cancer, T2DM and chronic lung conditions are currently the most prevalent CDs from a global perspective. All CDs have the potential to limit the functional capacity and QoL for the individuals who live with them.

The role of PA in both the primary and secondary prevention of CD is widely established. Despite the evidence, the levels of PA in CD cohort is consistently reported as low and SB as excessive. The majority of previous studies examining the levels of both PA and SB in CD populations have involved primarily single disease cohorts. Currently, there is limited research examining such behaviours in a mixed CD population and frequently individuals with

MM are excluded. Differential methods of measures PA and SB in previous research prevents comparison of the available evidence across disease groups. Consequently, the evidence base regarding PA levels and potential benefits of PA in CD cohorts remain segregated.

There is compelling evidence that CBER is a successful intervention for the secondary prevention of CD. Substantial evidence supports the efficacy of CBER in enhancing physical functioning and QoL for individuals with CD. The effects of CBER on habitual PA levels and SB in CD cohort remains unclear and further investigation is warranted. In line with the current research trends on PA levels in CD cohorts, the current model of CBER delivery is primarily restricted to single disease cohorts. The effectiveness of an integrated model of CBER deliver which caters for individuals with a range of CD diagnosis and those with MM is yet to be established. Research building on the evidence base for an integrated approach to CBER has the potential to inform future delivery of this vital service.

Chapter 3

Methodology

Study Setting

MedEx Wellness is a unique CBER program for individuals with CD in Ireland. As opposed to usual SCD delivery of CBER, MedEx Wellness offers an integrated approach to the delivery of CBER. Individuals with a range CD including CVD, pulmonary disease, T2DM and cancer, and those with MM attend and participate together within the same supervised exercise classes. Patients are referred to the program by hospital consultant physicians and their teams, phase III (outpatient) cardiac rehabilitation teams and general practitioners. The MedEx Wellness Chief Medical Officer provides clinical oversight to the program, which is coordinated by exercise scientists and delivered by exercise instructors certified in cardiac prevention and rehabilitation. The program is not a fixed duration. Participants can attend the program on a continuous basis and are encouraged to establish a lifelong relationship with MedEx Wellness. The program is a user-pay model, with options to pay per class (€7 with a medical card, €8 without) or per month (€50) for leisure centre membership.

This PhD was part of a larger trial, funded by the Health Service Executive (HSE) to determine the effect of the MedEx Wellness program on physical, clinical and psychological health. This research was undertaken at the MedEx Wellness program located at Dublin City University (DCU). The program was coordinated by members of academic staff from the School of Health and Human Performance and the Sports Service department in DCU. The exercise classes were delivered in the campus Sports Centre. The program grew to an offering

of 25 supervised classes per week and there were no restrictions on how often participants could attend. There were approximately 700 participant visits per week to MedEx Wellness. Referral to the service was a rolling process, and weekly inductions were conducted involving approximately 10-15 new participants each week.

Study Design

A quasi-experimental study was conducted. Participants were recruited at induction to the MedEx Wellness program following referral from a healthcare professional and were observed over the course of 12 months of participation in the programme. Outcomes were assessed at BL and 3, 6 and 12 months. Figure 3.1 outlines the study algorithm. As the study setting was within an established programme in the community, withholding service to allow for a controlled trial was not considered ethically appropriate. A cluster-controlled design was not feasible due to the challenge of identifying a matched sample to this diverse disease population.

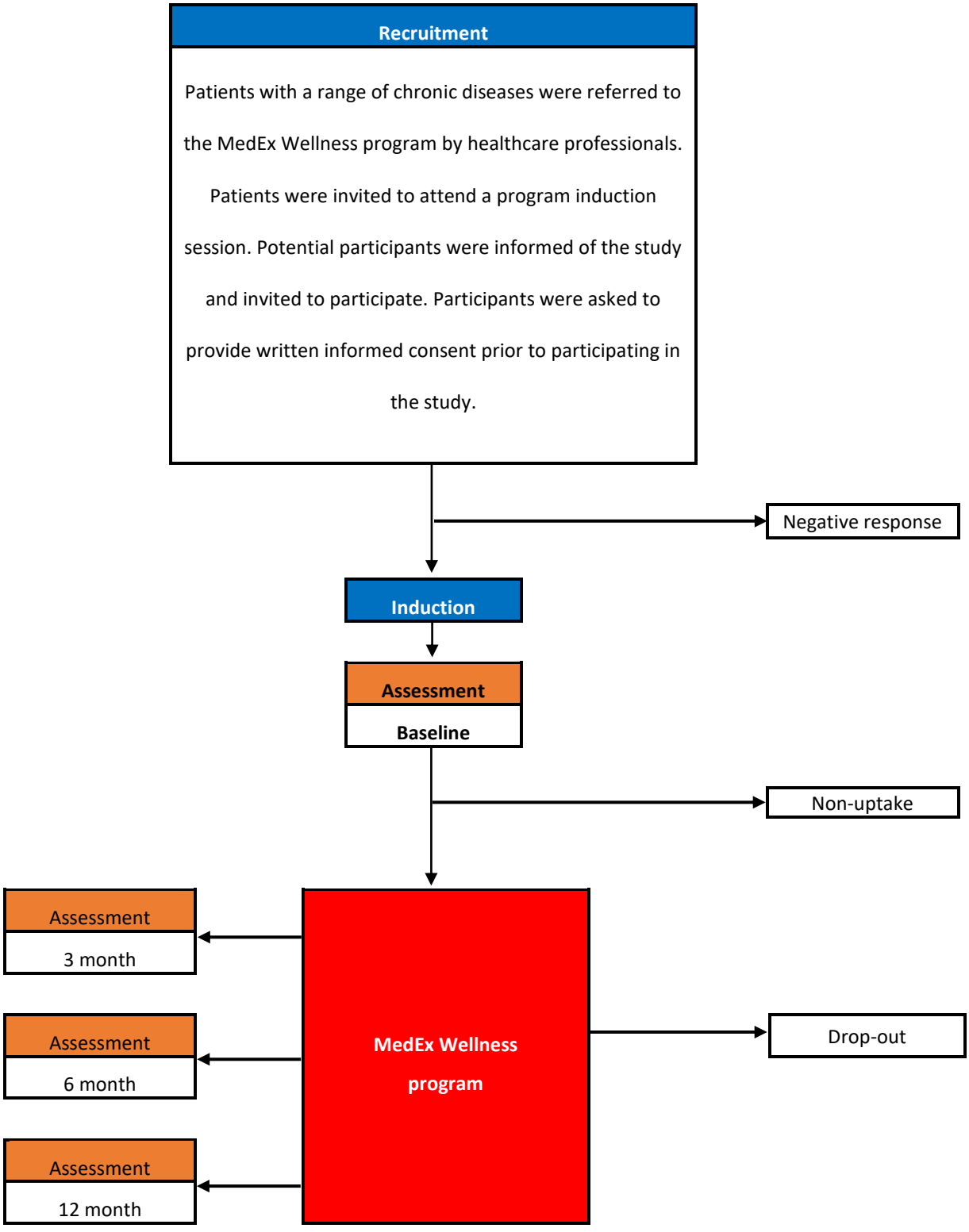

Figure 3.1 Study algorithm

Participants

Men and women (aged > 18 yr) with one or more documented CDs referred to the MedEx Wellness program were recruited. The most common primary diseases were CVD, respiratory disease, metabolic disease (including T2DM and impaired glucose tolerance), cancer, or neuromuscular or musculoskeletal disorders (including arthritis, Parkinson's disease and multiple sclerosis). Exclusion criteria included an uncontrolled CVD condition or a significant musculoskeletal condition, neurological condition, mental illness or intellectual disability that restricted participation in a physical training programme.

Recruitment

Consultant physicians, hospital-based exercise rehabilitation teams and general practitioners issued a referral letter to the MedEx Wellness program for patients with established CD. Upon receipt of the referral letter, patients were invited to attend a program induction session during which they were fully informed of the purpose and design of the study and the experimental procedures. They were provided with a plain language statement (Appendix A) before giving written informed consent (Appendix B) in accordance with the Research Ethics Committee at Dublin City University (DCUREC:2014/227). Rolling recruitment took place from September 2015 to July 2016 at the weekly induction sessions, involving 10-15 individuals per week.

Sample size

The critical determination of the sample size was the standard deviation of the change in 6-min time trial (6MTT) distance from BL to 12 months. The standard deviation

estimate used was 90 m (Polkey et al., 2013). The minimum difference to be detected was 25 m (Holland & Nici, 2013). For a power of 80% and two-sided significance of 5%, a sample size of 104 participants was required. This PhD was part of a larger trial, funded by the Health Service Executive (HSE). The primary outcome for this PhD is the change in physical activity and sedentary behaviour and was not considered as part of the power calculation.

Intervention: MedEx Wellness

Induction

Induction to the MedEx Wellness program involved three visits over an eight day period. Visit one introduced participants to the program and provided information on the program purpose, structure and logistics, such as accessing the facility, car parking, class times and venues. The second visit took place six days later and involved an exercise consultation, (described in detail later). Visit three took place 24 h after the second visit and consisted of a beginner exercise class. The class followed the same format as regular MedEx Wellness classes but involved smaller group sizes and included demonstrations and teachings on the exercise techniques and equipment. The beginner exercise was a component of the MedEx Wellness service which aimed to improve self-efficacy and foster social support to improve programme initiation and adherence.

Exercise classes

Following the three day induction process, participants were advised to attend two supervised group exercise classes per week. Participants were encouraged to attend the

same classes every week in order to promote social-support and habit formation. Classes were 60 min in duration and consisted a 15-min warm up, the main exercise training component and 5-10 min cool down. Exercise involved a combination of moderate intensity aerobic exercises and resistance training using a range of ergometers, weighted machines, free weights and body weighted exercises. Table 2.1 summaries the class structures depending on class size and program.

The warm up involved a combination of aerobic and range of motion exercises. Due to limited availability of equipment (e.g. ergometers and machine weights) and space participants were divided into 2 or 3 groups for the main exercise component of the class. If ≤30 participants were present, the class was divided into two groups that alternated between 20 min of aerobic ergometer exercise and 20 min of resistance exercise. If > 30 participants were present, the class was divided into three groups that rotated between 10 min of aerobic ergometer exercise, 10 min of resistance exercise and 10 min of a combined aerobic and resistance circuit. The reduced main phase component in classes >30 participants, allowed for a 1-2 minute change over period between each group.

The aerobic ergometer exercise involved the use of a range of exercise ergometers depending on participant preference and ability and included treadmills, cycle, rowing and elliptical ergometers. Classes catered for all abilities and participants were encouraged to work at a moderate to vigorous. For aerobic components of the class, the prompts employed by instructors to assist participants in interpreting the prescribed intensity was to work at an intensity at which they "feel moderately breathless, have a read face and sweat" or "moderately breathless but can still hold a conversation". To prompt participants on how to achieve a moderate intensity level during the resistance component of the circuit, instructors

advised participants to work at a slow, controlled pace, using a weight or resistance in which the participant could complete 10 – 15 repetitions at a comfortable intensity. Compliance with the prescribed exercise intensity during the classes has previously been established (Hurley et al., 2017). This research indicated that participants exercised at at an exercise intensity corresponding to 61.3 ± 9.2 %VO_2peak and 76.9 ± 9.5% HRpeak, and concluded that participants could effectively self-regulate participation at a moderate intensity during the MedEx Wellness classes.

The cool down consisted of aerobic exercises that gradually decreased in intensity, range of motion exercises and stretching. A social area was set up after class where participants were offered tea or coffee.

MedEx Wellness classes were ongoing, allowing participants to engage in the program on an open ended basis. With one exception, all classes included mixed CD groups. The stand-alone 12-week 'Move On' program was limited to individuals recovering from cancer related treatment. Shorter term programs are common in cancer survivorship rehabilitation (Christopher & Morrow, 2004; Foley & Hasson, 2016; Leach et al., 2015). The general characteristic of the cancer survivors cohort, warranted a program design focused on aiding participants to "Move On" from cancer treatment back to general public habits of exercise participation. On completion of the program, participants were encouraged to maintain exercise participation in general public exercise classes in local gyms. Two 12-week cycles of the Move On program were included in this study. The functional capacity and general health of the participants attending the Move On program allowed for a more flexible approach to the exercise content, as abilities tending to be higher in this program.

Classes were led by DCU sports complex employees. A ratio of 1:15 instructor to participant ratio was adhered to while conducting classes. At least one instructor in every class has British Association for Cardiovascular Prevention and Rehabilitation Specialist Exercise Instructor Level 4 qualification.

Table 3.1 Exercise prescription of MedEx Wellness classes

	≤ 30 participants	**≥ 30 participants**	**Move On**
Warm up	15 min aerobic and range or motion exercises	15 min aerobic and range or motion exercises	15 min aerobic and range of motion exercises
Main Phase	Aerobic: 20 min continuous on a treadmill, stationary bike or cross-trainer Resistance: 20 min circuit based using a combination of machine weights or free weight. 1 min work/20-30 s rest	Aerobic: 10 min continuous on a treadmill, stationary bike or cross-trainer Resistance: 10 min circuit based using a combination of machine weights or free weight. 1 min work/20-30 s rest Combination: 10 min interval body weight resistance exercises and aerobic (e.g. jumping jacks, high knees) 30 – 1 min work / 10 – 30 s rest	The main phase of this program varied each class. A combination of the following was included: Aerobic: continuous or interval on a treadmill, stationary bike or cross-trainer Resistance: circuit based using a combination of machine weights or free weight. 1 min work/20-30 s rest Instructor lead: step aerobics, combination of aerobic and resistance circuits, spinning, Pilates and total body resistance (TRX) suspension training
Cool down	5 – 10 min low intensity aerobics, range of motion exercises and stretching	5 – 10 min low intensity aerobics, range of motion exercises and stretching	5 – 10 min low intensity aerobics, range of motion exercises and stretching

Note: min = minutes; s = seconds

Exercise consultations

An exercise consultation was delivered to participants during the induction process and was repeated at 1, 3 and 6 months. The purpose of the consultation was to use behaviour change techniques to improve exercise adherence. Previous research was conducted in the MedEx Wellness service, to identify factors associated with uptake and adherence to the program (O'Leary E, 2019). Self-efficacy to exercise, intentions for exercise and social support to exercise were found to be significantly different between individuals who never attended the program following induction (non-uptake) and those initiated the program (attend at least one class following induction)

The exercise consultation was delivered in a group setting, which has previously been reported to promote peer social support and allow for group problem solving with specific focus on barriers identified during decisional balance work. The exercise consultations were designed by an academic in PA and behaviour change. The delivery of exercise consultations were led by an academic with expertise in applied psychology and researchers trained in exercise consultation delivery. The researchers adhered to a motivational interviewing style, where the approach was client-centred, emphasised personal choice and incorporated negotiating strategies between the participants and researches. Behaviour change techniques included in the exercise consultations were goal setting, problem solving, action planning, pros and cons, instructions on how to perform the behaviour, review of behaviour goals, feedback on behaviours and focus on past success. During the exercise consultations at 1, 3 and 6 months, participants were given the opportunity to review previously set behavioural goals and provided with feedback on progress, which consisted of a feedback

report (Appendix C) that outlined results from physical function tests at BL and subsequent assessments.

Outcomes

Outcomes were assessed at BL and 3, 6 and 12 months. Assessments at each time point were conducted over 2 days, separated by 6 days. BL assessments were integrated with the induction process to the MedEx Wellness program, as outlined in Figure 3.2. During the first visit a fasting blood sample was taken, body composition, strength and flexibility were assessed and participants completed a questionnaires to obtain demographic information (at BL only), barriers to self-efficacy for exercise, intentions for exercise and family support for PA (Appendix D). Selected participants were provided with an accelerometer to wear for 6 days and a take home questionnaire to assess HRQoL, self-regulatory self-efficacy for exercise and friend support for PA (Appendix E). Participants were encouraged to complete questionnaires independently but where required, a member of the research team or a family member or friend provided assistance. Visit 2 involved an assessment of CRF. Table 2.2 outlines the test battery for the study.

Table 3.2 Test battery

Domain	Subsections	Variables
Participant characteristics	Demographics	• Age • Gender • Median household income • Educational status • Marital status • Working status • Smoking status
	Chronic disease	• Primary CD diagnosis • SCD or MM
Physical activity		• Accelerometer
Physical Function	Aerobic capacity	• 6MTT
	Strength	• Sit-to-stand test • Handgrip test
	Flexibility	• Sit-and-reach test
Body composition		• Height and weight • Body mass index • Waist circumference • Hip circumference • Waist to hip ratio
Biomarkers	Blood sample	• Fasting glucose • Lipids • hsCRP
Quality of Life	Symptoms of depression	• PHQ8
	Self-rated health	• EQ-VAS
	Satisfaction with life	• SWLS
	Positive mental health	• SWEMWBS
Determinants of physical activity		• Barriers self-efficacy • Self-regulatory self-efficacy • Intention for exercise • Social support for exercise

Note: CD = chronic disease; SCD = single chronic disease; MM = multimorbidity; hsCRP = high sensitivity C-reactive protein; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQoL Visual Analogue Scale; SWLS = satisfaction with life scale; SWEMWBS = The Short Warwick Edinburgh Mental Wellbeing Scale

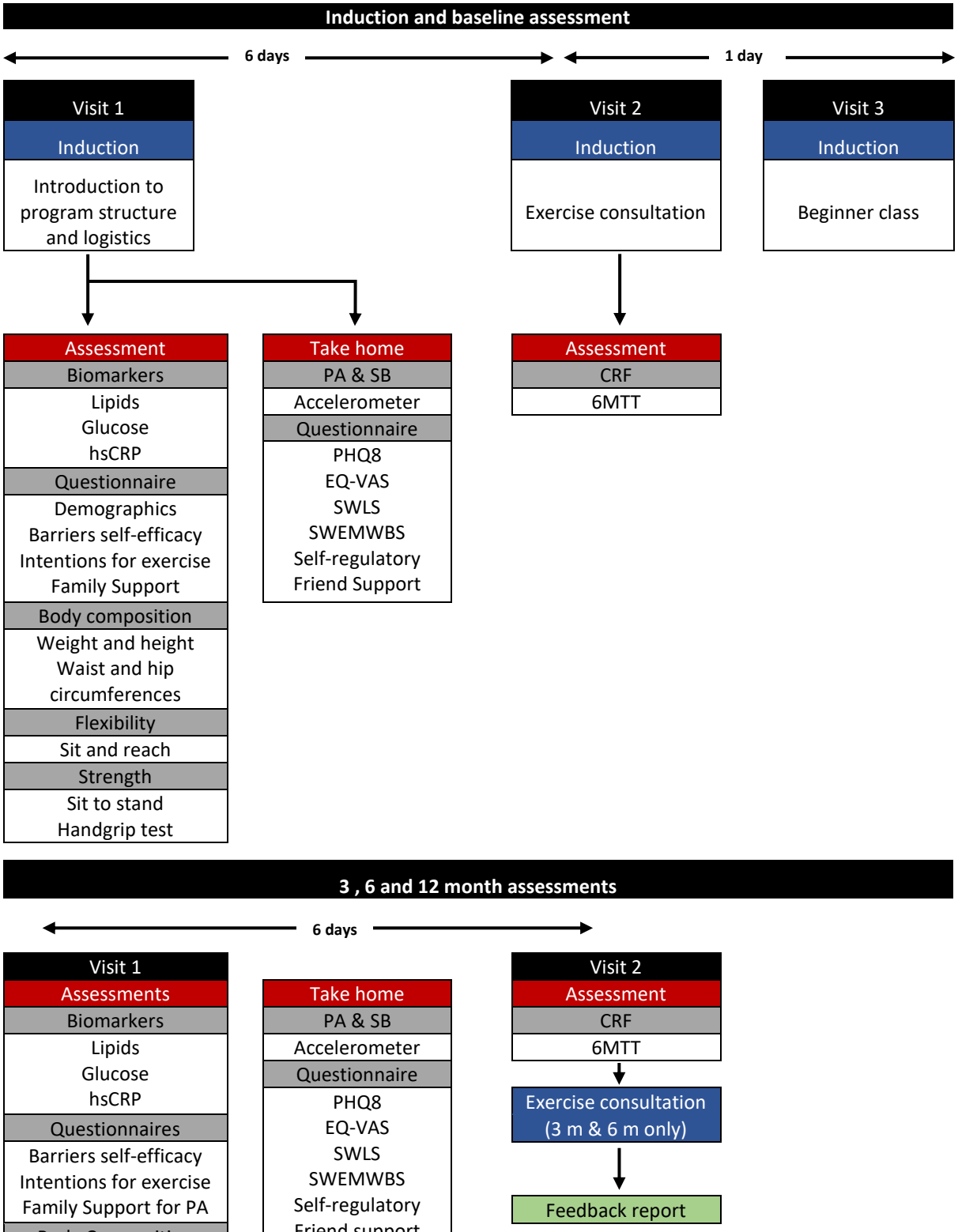

Figure 3.2 Overview of program induction and outcome assessments

Note: CRP = c-reactive protein; PA & SB = physical activity & sedentary behaviour; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQoL Visual Analogue Scale; SWLS = Satisfaction with Life Scale; SWEMWBS = The Short Warwick Edinburgh Mental Wellbeing Scale; CRF = cardiorespiratory fitness; 6MTT = 6 min time trial

Demographics

Participants completed a self-report questionnaire at BL to provide information on age, sex, residential locality, and educational, marital, employment and smoking status. Residential address was used to estimate median household income based on the geographical profiles of income in Ireland (Central Statistics Office, 2019).

Chronic Disease

Participants' primary CD diagnosis and co-morbidities, to indicate whether the participant had a SCD or MM, were obtained (with participant consent) from the patient referral letter provided to the MedEx Wellness program by the referring healthcare professional.

Physical Activity and Sedentary Behaviour

The activPAL^3 micro (PAL Technologies Ltd. Glasgow, Scotland) was used to quantify free-living activity behaviours. Device-based measures of PA and SB have demonstrated higher validity and reliability relative to self-report measures (Chastin et al., 2018; Healy et al., 2011; Sylvia et al., 2014) A limited number of devices were available and a sub-sample of randomly selected participants were issued an accelerometer. The device measures bodily accelerations using a triaxial accelerometer sampling at 20 Hz for 15 s epochs. An inbuilt inclinometer measures thigh inclination and detects the postural orientation of the wearer. The device was worn on the midpoint of the anterior aspect of the right thigh. It was covered with a water-resistant nitrile sleeve and attached to the skin using a 3M Tegaderm^{TM} Film

(Kooperationspartner Wundversorgung, Germany) adhesive dressing. Participants were instructed to wear the device continuously, 24 h per day, for 6 consecutive days, except during water immersion activities, i.e., swimming and bathing.

Accelerometer Data Processing

Raw acceleration data were processed and stored in a range on file formats, including csv files or 15 s epoch summary files. Proprietary algorithms classified activities into sitting/lying time, standing time, stepping time, step count and activity counts. Tudor-Locke *et al*., (2011a) defined 100 steps/minute as the threshold for MVPA in older adults. Based off this threshold, MVPA was classified as ≥25 steps within a 15 sec epoch. Trost *et al*. (2005) suggest a minimum of 3 to 5 days is required to reliably estimate the outcome variables measures with accelerometery. Only datasets that provided ≥ 4 valid days of activity data, including one weekend day, were processed for analysis. A valid day was defined as ≥ 600 min of recording during daytime hours, i.e., 7 am to 11 pm (Trost et al., 2005). Non-wear time was defined as ≥ 60 min of consecutive zero accelerometer counts (Dowd et al., 2012).

SB characteristics were examined using a customized MATLAB® (version 7.0.1, The Mathworks Inc, Natick, MA, USA) software programme (Dowd et al., 2012). The MATLAB® program examined the sedentary output file of the activPAL^3 micro accelerometer epoch-by-epoch. Initially, the program binary coded each epoch (15 s) using the following sequence: a sedentary epoch, defined as an epoch spent entirely in sedentary activity, (i.e., sitting or lying) was coded as 1. A non-sedentary epoch, defined as an epoch containing more than zero s of standing or stepping, (an epoch with less than 15 s spent in sedentary activity), was coded as 0. The program examined the sequence of each sedentary period to identify the start and

the end time for each one in hh:mm:ss format. Sleep time for each participant was manually identified by examination of the sedentary epoch Microsoft Excel output produced by MATLAB®. The first break in a SB after 6am each day was selected as the rise time. The last registered non-sedentary epoch of the day, which was followed by a prolonged, uninterrupted sedentary period (> 2 h) was selected as the time the subject went to bed. This method allowed for the differentiation between sleep time and daily SB. The number and duration of day time sedentary bouts per day was calculated. Sedentary bouts were categorized by specific durations, namely < 10 min, 11-30 min, 31-60 min and > 60 min. The number of sedentary bouts and the total duration in sedentary bouts in each category were calculated.

Physical Function

Cardiorespiratory Fitness*:* was assessed using 6MTT (Ayán-Pérez et al., 2017; Bergmann et al., 2014). The 6MTT demonstrates high reliability (interclass correlation coefficient: 0.97; 95% CI: 0.96-0.99) (Ayán-Pérez et al.,2017). The test was undertaken with 5-6 participants at a time. No warm-up was permitted before the 6MTT. Participants were instructed to cover as much distance as possible in 6 min while walking and/or running between two cones placed 20 m apart on a flat 20 m indoor course. They received a standard set of instructions and standard encouragement according to the ATS guidelines for the 6MWT (Enright, 2003). The total distance was calculated to the nearest meter by adding the distance covered in the last lap to total number of completed laps.

Muscle Strength*:* Lower body strength was assessed using a 10 repetition sit to stand test from a seat height of 43-45 cm (Csuka & McCarty, 1985). High test-retest reliability has been demonstrated for the 10 repetition sit to stand test in individuals undergoing haemodialysis (interclass correlation coefficient: 0.88; 95% CI: 0.79-0.94) (Segura-Ortí & Martínez, 2011). From a starting position with their arms crossed, feet placed flat on the floor pointing parallel to each other and approximately shoulder width apart, participants were instructed to stand up and sit down 10 times as fast as possible. Legs had to be fully extended and hips had to touch off the chair during the squat descent for the repetition to be valid. Participants were not allowed bounce from the chair when transferring from a seated to standing position. The time taken to complete 10 repetitions was measured using a stopwatch. Each participant performed two trials separated by 2 min. To control for the risk of a learning effect between the two trials, the best score was recorded.

Handgrip strength was measured in the dominant arm using a hand dynamometer (Takei 5401 Hand Grip Dynamometer (Digital)). High test-retest reliability has been demonstrated for the handgrip strength test for both the left (interclass correlation coefficient: 0.95; 95% CI: 0.89-0.98) and right (interclass correlation coefficient: 0.91; 95% CI: 0.80-0.96) hands in community-dwelling older adults (Bohannon & Scheubert, 2005). The test was administered in a standing position with the upper arm held tight at the trunk and forearm at a right angle to upper arm. The gripping handle was adjusted to ensure the middle of their four fingers was resting on the handle. The handle was squeezed at maximum force and held for approximately 3 s. Three trials separated ≥ 15 s were performed and the best

score was recorded. Mathiowetz *et al.,* (1984) suggest that the mean of three trail is a more accurate measure than one trail of even the highest score of three trails.

Flexibility*:* was assessed using a sit and reach test (Baumgartner & Jackson, 1995),. Participants sat on the bench with their legs fully extended and feet flat against a sit and reach box (Eveque Leisure Equipment Ltd, Cheshire, UK). The sit and reach test demonstrates high reliability (interclass correlation coefficient: 0.92; 95% CI: 0.88-0.95)(Ayala et al., 2012). They were instructed to flex forward, with arms fully extended and one hand on top of the other and to reach their fingertips as far as possible along the measurement scale while keeping the legs fully extended. The distance reached on the box was recorded (cm). Rest interval between trials was at the participants discretion (approximately 10 – 20 s). To control for the risk of a learning effect between the three trials, the best score was recorded.

Body Composition

Height and body mass were measured using a stadiometer and electronic scale (model 707 balance scales (Seca GmbH, Hamburg, Germany). Footwear and any heavy clothing were removed prior to the measurements. Height was recorded to the nearest 0.01 cm and body mass was measured to the nearest 0.1 kg. BMI was calculated as body mass in kilograms divided by squared height in metres.

Waist and hip circumferences were measured in cm by a trained researcher using a tape measure. Participants removed any bulky clothing and were instructed to stand with feet together, arms by their side and to breathe normally. Measurements were taken over one thin layer of clothing at the end of normal expiration in. Hip circumference was measured

at the narrowest point as viewed from the front of the body. The hip circumference was taken around the widest portion of the buttocks. The tape was snug to the body during both measurements. Waist to hip ratio (WHR) was derived by dividing the waist measurement by the hip.

Biomarkers

Venous blood samples were taken following an overnight fast. Serum vacutainers were allowed to stand for 30 min before centrifugation at 3000 rpm (1600 g) for 15 min at 4°C. Serum plasma was aliquoted into collection tubes, labelled and stored in a freezer at -80°C. Before analysis samples were defrosted. Serum triglycerides, total cholesterol, HDL-C, LDL-C, high sensitivity C-reactive protein (hsCRP) and fasting glucose were determined using spectrophotometric assays, performed on an automated bench-top clinical chemistry system (ACE®, Alfa Wassermann B.V., Netherlands) using the appropriate reagents, calibrators and controls (Randox Laboratories, UK).

Psychological Health

Depressive Symptoms*:* were measured using the 8-item Patient Health Questionnaire Depression Scale (PHQ8), a validated diagnostic and severity measure of depression in the general population (Kurt Kroenke et al., 2009). Satisfactory validity and reliability (Cronbach α=0.82) has also been demonstrated in individuals with chronic heart failure (Pressler et al., 2011). Participants indicated how frequently they had experienced symptoms of depression, for example "*Little interest or pleasure in doing things*" on a 4-level

Likert scale that ranged from "*Not at all*" to "*Nearly every day*". A higher score indicated greater severity of symptoms of depression in the PHQ8 scale.

Self-rated Health*:* was measured using the EuroQoL Visual Analogue Scale (EQ-VAS) (Dyer et al., 2010). Evidence of high validity and reliability of the EQ-VAS in a range of CD cohorts has been established (interclass correlation coefficient: 0.78; 95% CI: 0.75-0.82) (Sakthong et al., 2015). Participants rated their health on a vertical visual analogue scale ranging from 0 – 100, where the endpoints are labelled 'best imaginable health state' (100) and 'worst imaginable health state' (0).

Satisfaction with Life*:* was measured using the Satisfaction with Life Scale (SWLS), a valid and reliable 5-item scale designed to measure global cognitive judgments of one's life satisfaction (Pavot et al., 1991). Additional evidence supports the use of the SWLS in adults over the age of 50 y (Cronbach α=0.74) (López-Ortega et al., 2016). Participants indicated how much they agreed or disagreed with each of the statements for example, "*In most ways my life is close to ideal*", using a 7-point scale, where 1 means "*strongly disagree*" and 7 means "*strongly agree*". A higher score on the SWLS indicated greater satisfaction with life.

Positive Mental Health*:* was measured using The Short Warwick Edinburgh Mental Wellbeing Scale (SWEMWBS), a validated 7-item positively worded mental health scale that captures a range of concepts including affective-emotional aspects, cognitive-evaluation dimensions and psychological functioning (Tennant et al., 2007). In a large population sample ranging from ages 16 – 95 y high internal consistency has been demonstrated from the SWEMWBS (Cronbach α=0.88) (Koushede et al., 2019). Participants indicated their response

on a 5-level Likert scale ranging from "*None of the time*" to "*All of the time*" for statements such as "*I've been feeling optimistic about the future",* with a higher score indicating greater positive mental health.

Psychosocial Determinants for Physical Activity

Barrier self-efficacy*:* was assessed using a validated 13-item scale (E. McAuley, 1992). Participants were asked to rate their confidence in their capability to be physically active in the presence of common barriers, for example bad weather or exercising alone. Participants indicated their response on a Likert scale from 0 (not confident at all) to 100 (very confident).

Self-regulatory self-efficacy for exercise*:* was assessed using a modified 11-item scale (Luszczynska & Sutton, 2006). Task, scheduling and recovery self-efficacy were also assessed within the scale. Questions began with the stem "*How confident are you that you can…*" and were followed by statements such as "*plan exercise session that will be at least moderately difficult (e.g. have you breathing a little hard, your heart rate increases)?*" or "*Schedule exercise session into your weekly routine so that you get at least 30 minutes of exercise a day, 3 times per week?*". Participants rated their confidence on a Likert scale which ranged from 0 (not confident at all) to 10 (very confident).

Intentions for exercise*:* was assessed using a modified 6-item measure, which investigated intentions for exercise in general, along with intentions to attend the CBER (Sniehotta et al., 2005). Questions began with the stem "*I intend to…*" and were followed by statements including "*exercise several times a week*" and "*attend MedEx at least once a*

week". Participant responses were recorded on a Likert scale from 1 (completely disagree) to 4 (totally agree), with a higher score indicating greater intentions.

Social support for physical activity from family and friends*:* was assessed using a validated 10-item questionnaire (Sallis et al., 1987). Participants were required to indicate on a Likert scale of 1-5, how frequently over the past three months "*a family member offered to exercise with me*", or "*gave me encouragement to stick with my exercise plan*" for example. Higher scores represented greater social support.

Attendance

During induction participants were assigned a personal fob wristband which they were required to scan each time they entered the facility. Attendance to the program was monitored via the number of scanned entrances to the facility.

Program initiation: Initiation of the program was defined as participants who attended at least one exercise class following induction to the program. Those who never attended following induction were defined as 'non-uptakers'.

Drop-out: Individuals who initiated the program, but stopped attending before the 12 month assessment were defined as 'drop-outs'. Participants were contacted via phone call to confirm attendance to each assessment and if participant confirmed during the call that they were no longer attending, the reason for drop-out was requested.

Completers: Participants who attending ≥ 1 sessions between BL and 12 months and also completed a 12 month assessment.

Adherence: Adherence to the program was based on the recommendation that participants attend at least 2 MedEx Wellness classes per week. MedEx Wellness offered classes on 46 weeks of the year, with a three week break in service both during the summer and at Christmas. Adherence was defined as the percentage of the 92 classes attended. Attendance recorded at 92 classes or more between BL and 12 months was defined as 100% adherence.

Safety

Any adverse events where recorded and reported to the MedEx Wellness Chief Medical Officer and an incident report was filled with the DCU Sports Complex. Adverse events included training-related accidents or injuries or any other adverse event that interrupted participation in the program. Serious adverse events were defined as all-cause mortality or hospitalization for medical complications. If deemed necessary by the Chief Medical Officer or management within DCU sport, participants were required to provide medical clearance to return to the program following an adverse event.

Data Analysis

Procedures for data checking and entering

Measures of physical function where manually recorded during assessment by researchers on individual data collection sheets assigned to each participant (Appendix F). Hardcopy questionnaires were completed by participants. To minimise data entry error, a double data entry and cleaning process was employed while entering data to encrypted excel spreadsheets.

Statistical Analysis

A diagram representing the timepoints included in the analysis for each study is present in figure 3.3. All analysis was conducted using IBM SPSS statistics software (version 25). Data cleaning was conducted by checking each variable for outliers. Outliers identified as a possible error were checked against original data collection files including paper files or original activPAL downloaded file. Data was checked for normal distribution using Komolgorov-Smirnoff test of normality. A significant ($p \leq 0.05$) Komolgorov-Smirnoff value was identified for many of the variables, indicating deviations from normal distribution. Ghasemi and Zahediasl (2012) suggest that when a sample size is large than 30 participants, it is still appropriate to use parametric procedures for analysis. As the sample size for this study was > 30 for all analysis, parametric procedures were employed. Specific statistical analysis procedures for each study are described in each chapter.

Study 1 (Chapter 4) describes a cross-sectional analysis of the BL data. The purpose of this study was to describe the daily PA and SB of a diverse CD population with SCDs and MM and investigate the association between PA and SB with indices of health.

Study 2 (Chapter 5) describes the quasi-experimental study trial. The primary aim of this study was to investigate the effects of a mixed CBER program on PA levels and SB of a diverse CD population with SCDs and MM. The secondary aim of this study was to investigate effects of the mixed CBER program on physical, psychological and clinical measures of health.

Study 3 (Chapter 6) investigates factors associated with an effective response to participation in a CBER, in terms of a measurable change, in men and women with SCD and MM. A secondary aim was to establish the minimum attendance at a CBER needed to achieve clinically meaningful changes in primary indices of health.

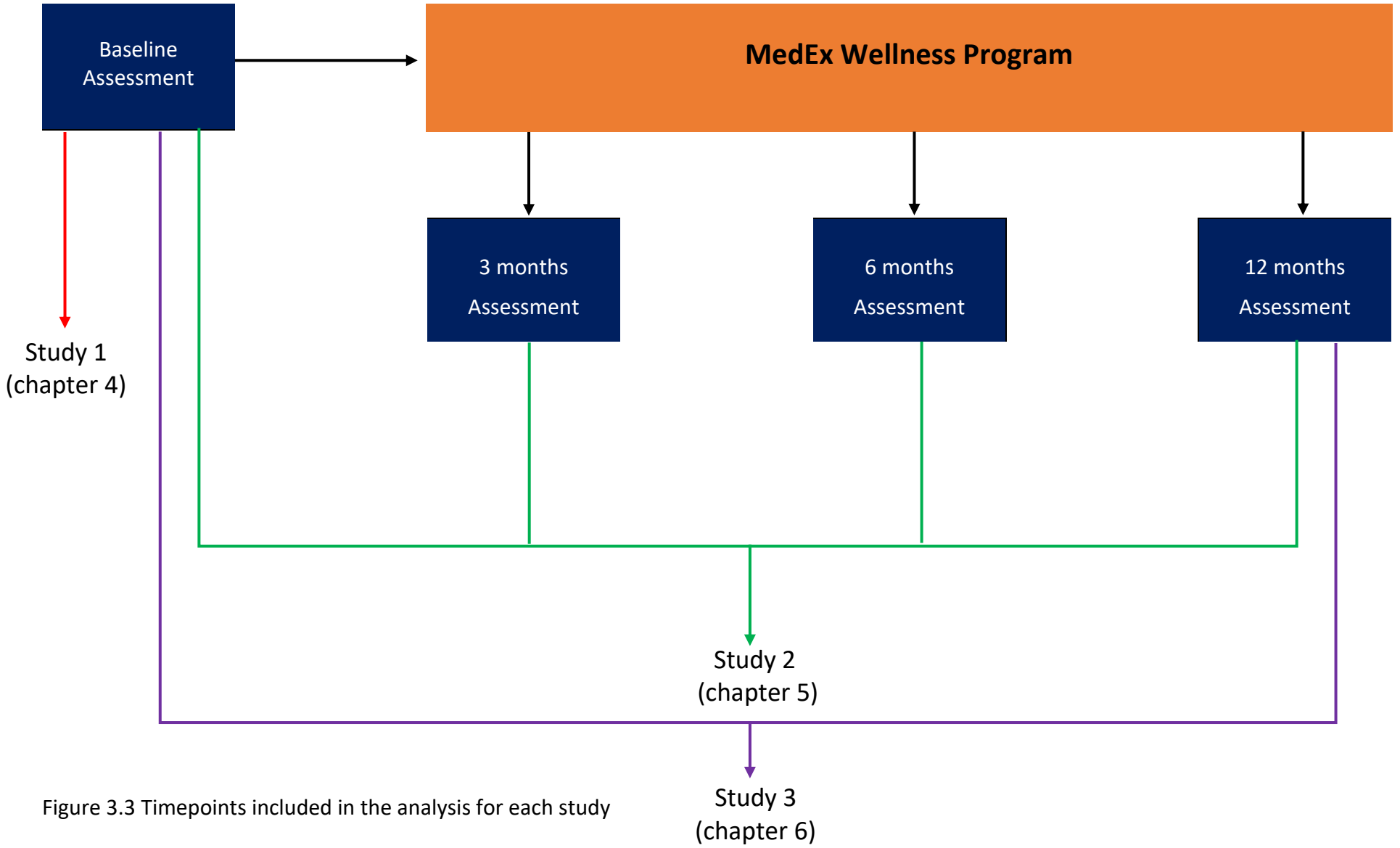

Figure 3.3 Timepoints included in the analysis for each study

Chapter 4

Study I

Exploring Daily Step Count and Sedentary Behaviour in a Diverse Chronic Disease Population

Introduction

CD are conditions lasting at least 1 year in duration, require continuous medical attention and can limit ADL (Moorman et al., 2007). The burden of CD on the Irish health care system is substantial with almost 30% of the total adult population in Ireland living with one or more CDs (Department of Health, 2019). MM refers to the coexistence of two or more long-term medical conditions or diseases and is associated with advancing age and a higher risk of premature death, hospital admission, reduced functional capacity and QoL compared to those with a SCD. (Bayliss et al., 2004; Fortin et al., 2004; Smith & O'Dowd, 2007; Wallace et al., 2015). Currently, over 70% of Irish older adults have MM (Hernández et al., 2019). The ongoing management of MM patients is challenging due to their complex care needs and the involvement of multiple healthcare professionals (Kuipers et al., 2020). Patients with MM are at higher risk of safety issues related to poor integration of health care, diagnostic errors, inappropriate prescription, poor medication adherence, adverse drug events, advanced age, cognitive impairment, limited health literacy and comorbidity of depression or anxiety (Phillips et al., 2004).

Several of the biological risk factors including hypertension, obesity, insulin resistance, hyperglycemia, dyslipidemia and chronic inflammation that are shared across CD groups are positively impacted by PA (Koene et al., 2016; Nesto, 2019; Warburton et al., 2006; World Health Organization, 2005b). Indeed, there are exceptionally few CDs in which the burden of the disease, comorbidities related to the disease, or HRQoL are not improved with PA (Desveaux et al., 2014a; Kelley et al., 2011; Pasanen et al., 2017).

To attain optimal health-related benefits for the secondary prevention of CD it is recommended that CD patients undertake 150 min/week of MVPA (US Department of Healt and Human Services, 2018b). Unfortunately, a very small proportion of CD patients achieve the daily recommended dose of PA. Bernard *et al.,* (2018) reported individuals with COPD to participate in significantly less MVPA than health controls (6.7 min/day vs 11.7 min/day). Morrato *et al.,* (2007) found 39% of adults with CD to meet the guidelines for MVPA compared to 58% of health controls. In a large population sample the proportion of the population completing no MVPA was 46% for those with no CD, 49% for one CD, 59% for 2 MM and 61% for those with three or more MM (Serrano-Sanchez et al., 2014). This may be due in part to the fact that many individuals with a SCD or MM have a low functional capacity secondary to their sedentary lifestyle and/or a disease related limitation that limits their ability to undertake MVPA (Brown & Flood, 2013; Kujala et al., 2019; Welmer et al., 2013).

SB is defined as any waking behaviour characterized by an energy expenditure ≤ 1.5 metabolic equivalents of task (METs), while in a seated, reclined or lying posture (Tremblay et al., 2017). It is distinct from physical inactivity, where an individual does not perform the recommended amount of MVPA. Epidemiological investigations and meta-analysis (Chau et al., 2013; Sun et al., 2015) have consistently found a strong dose-response relation between

SB and CVD and all-cause mortality. Furthermore, high levels of PA (≥ 35.5 MET-hour per week or 60-75 min of daily MVPA) appear to attenuate the negative cardiovascular consequences of SB (Ekelund et al., 2016). However such levels of PA are typically unattainable for individuals with CD.

LIPA characterized by an energy expenditure ranging from 1.5 to 3.0 METs may be central to improving or maintaining health-related outcomes, particularly among individuals with one or more CDs and reduced functional capacity. Research has indicated that increasing LIPA can have beneficial effects in obesity, markers of lipid and glucose metabolism and mortality (Fuezeki et al., 2017a). Specifically in CD patients, increases in LIPA are significantly associated with reduced hospitalizations, a lower risk of mortality and improvements in lipid profiles (Beddhu et al., 2015; Donaire-Gonzalez et al., 2015; Li et al., 2019). Breaking up prolonged bouts of sitting with 2 min bouts in LIPA every 20 min has a positive impact on metabolic health (Dunstan et al., 2012). Longitudinal data also suggest that replacing sedentary time with LIPA is significantly associated with a reduced risk of all-cause and CVD mortality (Dohrn et al., 2018).

Reallocation of SB with either MVPA or LIPA is associated with immediate health benefits, primarily by increasing energy expenditure (Biswas et al., 2018). Therefore, "*moving more at any intensity*" has the potential to be an effective public health message (Stamatakis et al., 2019). The number of steps taken per day is an all-encompassing measure of ambulatory activity. Step count has been described as a means of bridging the gap between research and clinical practice, where research has the opportunity to have real word application (Tudor-Locke et al., 2012). Step count is an understandable common metric which can be easily communicated to practitioners and patients alike. A 10,000 step/d guidelines

has been highlighted in both popular press and academic literature (Bassett & Tudor-Locke, 2004). However more recent evidence revealed that as few as approximately 4400 steps/d was significantly associated with lower mortality rates (49% risk reduction) when compared to approximately 2700 step/d. With more steps, mortality rates continued to decrease, however no additional risk reduction was achieved above 7500 step/d in older women (Lee et al., 2019). Moreover, stepping intensity was not clearly associated with lower levels of mortality when accounting for total daily steps per day. The possible role of step count guidelines in eliciting increased PA participation over MVPA guidelines was demonstrated by Samuels *et al.,* (2011). Participants in this study received PA counselling advising participants to increase daily PA by increasing daily step count or achieving 30 min of MVPA daily. The 10,000 step/d guidelines resulted in the greatest increase in PA in terms of both daily step count achieved and MVPA. In terms of public health application, the evidence suggest that advise on daily step count may have greater efficacy in increasing PA participation while also inducing health enhancing effects.

Recent advancements in movement senor technologies have allowed for the development of devices which objectively measure both SB and PA, however limitations still exist with the classification of SB using device-measurements. The characterization of SB as < 100 - 200 accelerometer counts per min (Matthews et al., 2008; Mitchell et al., 2012; Ridgers et al., 2012) often fails to distinguish between standing and sitting. The ActivPAL™ PA monitor (PAL Techologies Ltd, Glasgow, UK) is equipped with an inbuilt inclinometer that detects postural orientation and allows for direct measurement of SB.

The majority of previous studies examining the levels of both PA and SB in CD populations have involved primarily single disease cohorts. Currently, there is limited

research examining such behaviours in a mixed CD population and frequently individuals with MM are excluded. Differential methods of measures PA and SB in previous research prevents comparison of the available evidence across disease groups. Consequently, the evidence base regarding PA levels and potential benefits of PA in CD cohorts remain segregated. The purpose of this study was to describe the daily PA and SB of a diverse CD population with single and MM and investigate the association between PA and SB with selected indices of health. It was hypothesized that total daily PA will be low, SB will be high and will be accumulated in prolonged bouts in men and women with CD and MM and higher PA and lower SB will be associated with more favourable measures of physical, clinical and psychological health.

Methods

A cross-sectional design was employed and the detailed methodology is described in Chapter 3. In summary, individuals with one or more CDs were recruited at induction to the MedEx Wellness program following referral from a healthcare professional. Participants primary CD diagnosis, namely CVD, respiratory disease, cancer, metabolic disease or neuromuscular/musculoskeletal disorders (neuro/MSK), and information on whether that participant had a SCD or MM was obtained from the referral letter provided by the referring healthcare professional. Data collection was conducted over two visits separated by 6 d (figure 4.1). PA and SB were assessed for 6 d using the activPAL ™ PA monitor (PAL Techologies Ltd, Glasgow, UK). Physical function was assessed using a 6-min time trial (6MTT); sit to stand test, grip strength, and sit and reach test. Body composition was assessed with measures of BMI and waist and hip circumference. A fasting blood sample was taken to measure fasting glucose, triglycerides, total, HDL and LDL cholesterol and CRP. Indices of psychological health were evaluated with measures of depressive symptoms, self-rated health, satisfaction with life and positive mental health. Finally psychosocial determinants of PA including, barriers to self-efficacy for exercise, self-regulatory self-efficacy for exercise, intentions for exercise and social support for PA were assessed.

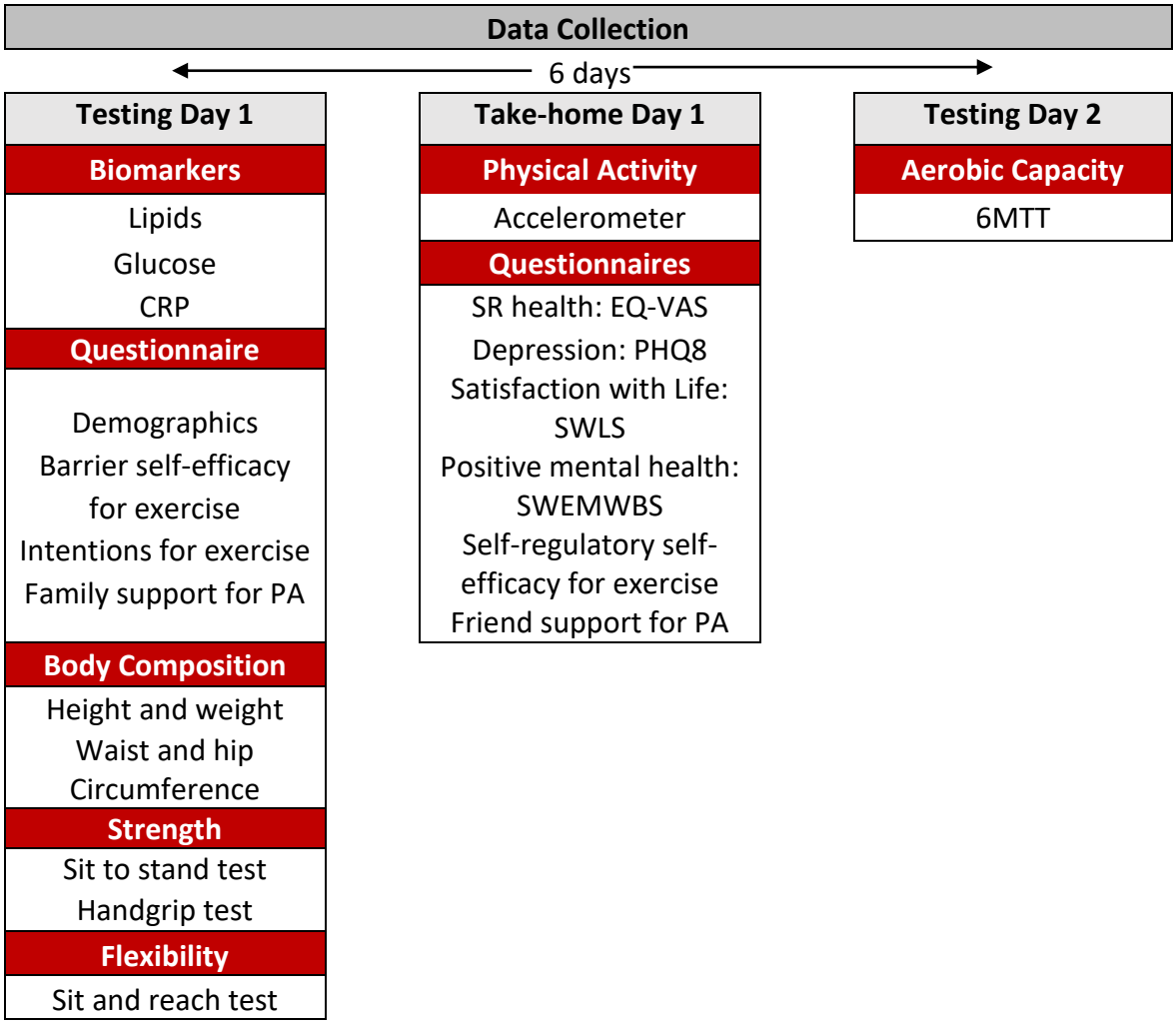

Figure 4.1 Outline of data collection procedures

Note: PA = physical activity; SR health = self-rated health; EQ-VAS = EuroQoL Visual Analogue Scale; PHQ8 = 8-item Patient Health Questionnaire; SWLS = Satisfaction with Life Scale; SWEMWBS = The Short Warwick Edinburgh Mental Wellbeing Scale; 6MTT = 6 minute time trial

Statistical Analysis

Participants demographics, PA and SB, health-related outcomes and psychosocial determinant of PA were reported using mean ± standard deviations (SD) or frequencies and percentages. Participants were categorized by i) primary CD diagnosis and ii) SCD or MM. Differences in participant demographics between primary CD diagnosis and between those with SCD of MM were assessed using Chi-square tests. Adjusted residual values were examined and computed to p-values to identify specific group differences. In addition, differences in age between primary CD diagnosis and between those with SCD of MM were assessed using a univariate analysis of covariance (ANCOVA). The ANCOVA controlled for sex, median household income, educational status, marital status, current work status and smoking status.

Preliminary analysis revealed a high degree of correlation among many of the variables derived from the activPAL ™ monitor. To control for type 1 error further analysis included only measures of step count and sedentary time. Participants were also categorized as ≥ MVPA guidelines or <MVPA guidelines. Differences in step count and sedentary time between primary CD diagnosis and between SCD and MM was assessed using a multivariable analysis of covariance (MANCOVA) controlling for participant demographics. Bonferroni-adjusted post hoc analysis was conducted to investigate pairwise comparison between groups where a significant main effect was present.

Preliminary analysis identified a high degree of correlation among the measured health-related outcomes body composition, physical function, blood biomarkers, psychological health, and also psychosocial determinants of PA. To reduce the risk of making

a type 1 error while using these health-related outcomes and psychosocial determinants of PA in further analysis, two statistical analyses approaches were conducted.

The first approach involved using all health-related measures and psychosocial determinants of PA as dependent variables in general linear models to assess their association with step count, sedentary time and category for achieving the guidelines of MVPA (independent variable). Guidelines recommended by Pallant (2013) for the suitability of dependent variables for either ANCOVA or MANCOVA include; if there is a bivariate correlation coefficient ≥ 0.6 between any two dependent variables, one of the variables should be excluded. Dependent variables within a bivariate correlation coefficient ranging from 0.30 to 0.59 are suitable for MANCOVA and dependent variables with a bivariate correlation coefficient ≤ 0.29 are suitable for ANCOVA.

Person's correlation coefficient matrix was examined for all health-related variables and psychosocial determinants of PA. Dependent variables suitable for ANCOVA ($r \leq 0.29$) were sit and reach, handgrip strength, fasting glucose, triglycerides, HDL-C, LDL-C and hsCRP. Sit to stand and 6MTT had a degree of correlation suitable for dependent variables on a MANCOVA. Measures of BMI and waist to hip ratio (WHR) were highly correlated ($r \geq 0.6$) with waist and hip circumference measures. BMI and WHR are well established as primary descriptors of body composition and were included in the MANCOVA as their correlation coefficient was between 0.30 to 0.59 (Esmaillzadeh et al., 2004; World Health Organization, 2011b). SWEMWBS was highly correlated ($r \geq 0.6$) with all other measures of health-related wellbeing and excluded from further analysis. With the exception of self-efficacy, the correlation coefficients between psychosocial determinants of PA were ≥ 0.60. PHQ8, SWLS, self-rated health and self-efficacy met the criteria for MANCOVA.

All ANCOVA and MANCOVA models included health-related variables and psychosocial determinants of PA as dependent variables, with step count and sedentary time as independent variables. In a separate model category for achieving the guidelines of MVPA was included as an independent variable in place of step count and sedentary time. ANCOVA and MANCOVA controlled for participant demographics primary CD diagnosis and SCD or MM. Bonferroni-adjusted post hoc analysis was undertaken to investigate mean differences for health-related variables and psychosocial determinants of PA.

The second statistical approach used principal component analysis (PCA) on the health-related variables and psychosocial determinants of PA to reduce the risk of committing a type 1 error. To ensure factors derived from the PCA were orthogonal, varimax rotation was used and minimum eigenvalue for extracted was set as 1. Factors produced from the PCA were included in a series of ANCOVAs as dependent variables. Step count and sedentary time were included as independent variables. A separate model included category for achieving the guidelines of MVPA as an independent variable. All models were controlled for participant demographics, primary CD diagnosis, SCD and MM. Bonferroni-adjusted post hoc analysis was undertaken to investigate mean differences for health-related variables and psychosocial determinants of PA.

Partial eta squared was used to interpreted effect sizes. A value of ≥0.01 was defined as small, >0.01-0.06 as medium and ≥0.14 as large (Pallant, 2013).

Results

Participant Characteristics

A total of 403 participants were recruited. Table 4.1 and 4.2 summarizes the participant demographics, health-related outcomes and psychosocial determinants of PA. The mean (± SD) age was 62.98 ± 10.99 yr and 50.6% were men. More than one-third (37.7%) of participants had a primary CD diagnosis of CVD which included CAD, PAD, hypertension, and stroke, 18.6% respiratory disease which included COPD, chronic bronchitis asthma and pulmonary hypertension, 22.8% cancer including breast, colorectal and prostate, 11.2% metabolic disease including type 1 and 2 diabetes and impaired glucose tolerance, 6.7% neuro/MSK disorders including arthritis, Parkinson's disease and multiple sclerosis and the primary CD of 6.0% of participants was not specified. The proportion of participants with a SCD and MM was 52.4% and 47.6%, respectively. Due to limitations with available accelerometers, a subsample of 283 participants were issued ActivPAL activity monitors, with 237 providing valid ActivPAL datasets for analysis. Reasons for missing datasets included non-wear time (n=29) and technical error with the accelerometer or software (n=17).

Table 4.1 Participant demographics for the entire cohort, primary chronic disease, single chronic disease and multimorbidity

		Primary Chronic Disease						Number of Chronic Diseases	
Variable	**All n=403**	**CVD n=140**	**Respiratory n=75**	**Cancer n=92**	**Metabolic n=45**	**Neuro or MK n=27**	**Unspecified n=24**	**SCD n=204**	**MM n=185**
Age (years)	62.98 ± 11	66.52 ± 8.1	64.94 ± 9.5	57.54 ± 11.2	58.49 ± 11.3	67.33 ± 12.9	60.75 ± 14.9	61.8 ± 11.3	64.3 ± 10.4
Sex (men)	204 (50.6)	103 (72.9)	32 (42.7)	28 (30.4)	23 (51.1)	8 (29.6)	11 (45.8)	107 (52.5)	93 (50.3)
Income (€)									
64,393 – 105,943	82 (21.2)	23 (16.9)	11 (15.7)	24 (27.3)	10 (22.2)	6 (32.1)	8 (38.1)	42 (21.5)	36 (20.2)
51,535 – 64,278	163 (42.2)	62 (45.6)	25 (35.7)	33 (37.5)	25 (55.6)	11 (42.3)	7 (33.3)	81 (41.5)	77 (43.3)
42,309 – 51,517	97 (25.1)	39 (28.7)	21 (30.0)	23 (26.1)	4 (8.9)	5 (19.2)	5 (23.8)	51 (26.2)	43 (24.2)
< 33, 493	44 (11.4)	12 (8.8)	13 (18.6)	8 (9.1)	6 (13.3)	4 (15.4)	1 (4.8)	21 (10.8)	22 (12.4)
Educational status									
Some primary	45 (11.8)	18 (13.3)	15 (22.4)	2 (2.2)	2 (4.4)	5 (20.0)	3 (13.6)	23 (11.7)	22 (12.7)
Junior cert or equiv.	81 (21.1)	32 (23.7)	19 (28.4)	9 (10.0)	11 (25.6)	5 (20.0)	5 (22.7)	36 (18.3)	42 (24.3)
Leaving cert or equiv.	79 (20.7)	28 (20.7)	12 (17.9)	22 (24.4)	9 (20.9)	5 (20.0)	3 (13.6)	40 (20.3)	36 (20.8)
Diploma or cert	81 (21.2)	25 (18.5)	7 (10.4)	27 (30.0)	13 (30.2)	4 (16.0)	5 (22.7)	52 (26.4)	28 (16.2)
Degree or post grad	96 (25.1)	32 (23.7)	14 (20.9)	30 (33.3)	8 (18.6)	6 (24.0)	6 (27.3)	46 (23.4)	45 (16.2)
Marital status									
Married / partner	258 (67.7)	101 (74.8)	39 (57.4)	63 (70.8)	24 (55.8)	17 (68.0)	14 (66.7)	144 (72.7)	106 (62.4)
Divorced or widowed	64 (16.8)	20 (14.8)	19 (27.9)	11 (12.4)	6 (14.0)	4 (16.0)	4 (19.0)	26 (13.1)	36 (21.2)
Single	59 (15.5)	14 (10.4)	10 (14.7)	15 (16.9)	13 (30.2)	4 (16.0)	3 (14.3)	28 (14.1)	28 (16.5)
Working status									
Working or studying	106 (29.3)	36 (27.5)	8 (12.1)	35 (44.9)	20 (46.5)	4 (16.0)	3 (15.8)	66 (35.3)	38 (23.3)
Unemployed	88 (24.3)	19 (14.5)	29 (43.9)	18 (23.1)	9 (20.9)	8 (32.0)	5 (26.3	37 (19.8)	45 (27.6)
Retired	168 (46.4)	79 (58.0)	29 (43.9)	25 (32.1)	14 (32.6)	13 (52.0)	11 (57.9)	84 (44.9)	80 (49.1)
Smoking status									
Current or past smoker	224 (59.1)	92 (70.2)	52 (73.2)	38 (43.2)	20 (48.8)	9 (36.0)	13 (56.5)	88 (45.1)	61 (35.5)
Never smoked	155 (40.9)	39 (29.8)	19 (26.8)	50 (56.8)	21 (51.2)	16 (64.0)	10 (43.5)	107 (54.9)	111 (64.5)
Number of CDs									
SCD	204 (52.4)	70 (50.7)	28 (38.4)	61 (67)	14 (32.6)	17 (68)	14 (73.7)		
MM	185 (47.6)	68 (49.3)	45 (61.6)	30 (33)	29 (67.4)	8 (32)	5 (26.3)		

Continuous variables are displayed as mean ± SD. Categorical variables are presented as n (%)

Note: CVD = cardiovascular disease; neuro/MK = neuromuscular/musculoskeletal disorders; SCD = single chronic disease; MM = multimorbidity; Equiv. = equivalent

Table 4.2 Health-related measures for the entire cohort, primary chronic disease, single chronic disease and multimorbidity

			Primary Chronic Disease						Number of Chronic Diseases	
Variable	**n**	**All**	**CVD**	**Respiratory**	**Cancer**	**Metabolic**	**Neuro or MK**	**Unspecified**	**SCD**	**MM**
Physical Function										
6MTT (m)	384	468 ± 136	470 ± 145	391 ± 126	556 ± 98.7	447 ± 107	442 ± 105	429 ± 147	498 ± 141	438 ± 126
Sit to stand (sec)	400	22.8 ± 8.7	21.9 ± 7.0	26.2 ± 8.1	19.7 ± 5.5	23.4 ± 9	25.7 ± 12.7	25.7 ± 15.8	21.8 ± 8.3	23.7 ± 8.7
Handgrip (kg)	401	26.1 ± 9.0	28.7 ± 9.5	23.6 ± 7.9	25.7 ± 9.1	26 ± 7.6	21.8 ± 8.0	25.0 ± 8.5	26.6 ± 9.4	25.7 ± 8.6
Sit and reach (cm)	392	7.1 ± 9.4	6.0 ± 9.2	7.1 ± 8.2	9.9 ± 9.7	4.0 ± 10.1	6.9 ± 10.2	7.8 ± 8.1	7.7 ± 9.2	6.5 ± 9.5
Body Composition										
Weight (kg)	402	83.5 ± 20.5	85.6 ± 17.3	78.5 ± 21.1	79.3 ± 18	95.2 ± 27	76.8 ± 16.6	88.9 ± 23.6	80.9 ± 20.5	86.2 ± 20.3
BMI (kg/m^2)	400	30.0 ± 6.7	29.9 ± 5.4	29.0 ± 7.6	28.3 ± 5.7	34.3 ± 8.9	29.0 ± 5.3	32.2 ± 6.8	28.8 ± 5.8	31.1 ± 7.2
Waist circumference (cm)	403	100.9 ± 17.1	103.5 ± 14.4	99.2 ± 17.5	94.8 ± 15	110.9 ± 21.2	93.3 ± 13.1	104.7 ± 20.7	97.8 ± 16.0	104.2 ± 17.4
Hip Circumference (cm)	401	108.0 ± 13.5	106.9 ± 10.6	106.0 ± 16	107 ± 10.1	115.5± 21.5	107.5 ± 10.1	110.5 ± 11.0	105.5 ± 11.7	110.4 ± 14.7
Waist to hip ratio	401	0.9 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Blood biomarkers (mmol/L)										
Fasting glucose	304	6.6 ± 2.2	6.5 ± 1.8	6.3 ± 1.6	5.8 ± 1.0	9.2 ± 4.0	5.5 ± 0.7	5.9 ± 1.0	6.1 ± 1.5	7.0 ± 2.7
Triglycerides	336	1.2 ± 0.6	1.2 ± 0.7	1.2 ± 0.5	1.1 ± 0.7	1.3 ± 0.6	1.1 ± 0.4	1.2 ± 0.6	1.1 ± 0.6	1.2 ± 0.6
Total cholesterol	335	4.6 ± 1.2	4.1 ± 1.2	5.1 ± 1.2	5.0 ± 1.1	4.2 ± 1.0	5.3 ± 0.9	4.9 ± 1.3	4.7 ± 1.2	4.5 ± 1.3
HDL cholesterol	333	1.4 ± 0.5	1.2 ± 0.4	1.6 ± 0.5	1.4 ± 0.5	1.1 ± 0.3	1.6 ± 0.4	1.3 ± 0.5	1.4 ± 0.5	1.3 ± 0.5
LDL cholesterol	333	2.4 ± 1.1	2.1 ± 1.0	2.7 ± 1.1	2.6 ± 1.1	2.2 ± 1.1	2.6 ± 0.9	2.5 ± 1.0	2.5 ± 1.0	2.3 ± 1.1
hsCRP	282	6.9 ± 13.0	4.9 ± 5.0	12.5 ± 25.6	5.3 ± 6.1	8.9 ± 8.0	2.8 ± 1.9	5.2 ± 4.9	6.8 ± 16.4	7.0 ± 8.6
Psychological health										
PHQ8	310	5.3 ± 5.0	4.5 ± 4.2	7.1 ± 5.7	5.7 ± 5.2	5.2 ± 5.0	4.0 ± 4.6	7.0 ± 5.7	4.9 ± 4.9	5.7 ± 5.0
EQ-VAS	332	65.2 ± 18.4	68.1 ± 16.7	55 ± 18.9	68.1 ± 17	64.9 ± 17.6	66.9 ± 19.8	64.3 ± 23.2	67.4 ± 18.5	63.1 ± 18.3
SWLS	325	23.7 ± 6.9	24.7 ± 6.1	21.0 ± 6.9	23.8 ± 7.5	24.2 ± 6.5	26.1 ± 6.6	20.2 ± 8.2	23.8 ± 7.0	23.7 ± 7.0
SWEMWBS	324	26.6 ± 4.6	27.2 ± 4.4	26.3 ± 4.9	26.1 ± 4.5	26.4 ± 3.9	26.8 ± 4.6	25.3 ± 6.7	27.1 ± 4.4	26.1 ± 4.7
Psychosocial determinants										
Barriers self-efficacy	343	60.6 ± 21.0	64.5 ± 22.2	52.5 ± 19.4	60.1 ± 19.8	58.7 ± 18.9	59.4 ± 18.3	64.8 ± 23.4	63.3 ± 20.9	57.6 ± 20.2
Self-regulatory self-efficacy	252	76.3 ± 19.0	76.5 ± 17.9	64.8 ± 23.2	81.2 ± 15.0	74.1 ± 20.5	79.5 ± 17.3	69.4 ± 29.2	78.9 ± 17.8	73.6 ± 19.7
Intentions for exercise	358	3.4 ± 0.5	3.4 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	3.4 ± 0.4	3.2 ± 0.6	3.4 ± 0.7	3.5 ± 0.5	3.4 ± 0.5
Family support	363	2.4 ± 1.2	2.4 ± 1.2	2.1 ± 1.0	2.5 ± 1.2	2.3 ± 1.2	2.2 ± 0.9	2.6 ± 1.4	2.4 ± 1.1	2.3 ± 1.2
Friend support	277	2.1 ± 1.1	2.1 ± 1.2	2.0 ± 1.0	2.2 ± 1.0	2.2 ± 1.2	2.0 ± 0.8	2.3 ± 1.3	2.2 ± 1.1	2.1 ± 1.2

Variables are displayed as mean ± SD

Note: CVD = cardiovascular disease; neuro/MK = neuromuscular/musculoskeletal disorder; SCD = single chronic disease; MM = multimorbidity; 6MTT = 6 minute time trial; BMI = body mass index; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQol Visual Analogue Scale; SWLS = Satisfaction with Life Scale; SWEMWBS = The Short Warwick Edinburgh Mental Well-being Scale; HDL = high density lipoprotein; LDL = low density lipoprotein; hsCRP = high sensitive C-reactive protein .

Participant demographics and chronic diseases

There was a significant main effect for primary CD diagnosis ($f_{(5,285)}$=4.04, p=0.001, partial eta squared =0.066) and whether participants had a SCD or MM ($f_{(1,285)}$=4.15, p=0.043, partial eta squared =0.014) on age. Participants with CVD were significantly older (estimated marginal means ± standard error (SE); 62.88 ± 61.13 yr) than those with metabolic disease (estimated marginal means ± SE; 57.42 ± 1.29 yr). No other primary CD diagnosis were significantly different in age. Participants with MM were significantly older (estimated marginal means ± SE; 61.98 ± 0.85 yr) than those with a single CD (estimated marginal means ± SE; 60.15 ± 0.60 yr).

Chi square analysis found a significant difference between primary CD diagnosis and sex (X^2 (5) = 49.57, p=0.000), educational status (X^2 (20) = 39.36, p=0.006), working status (X^2 (10) = 46.68, p=0.000), smoking status (X^2 (5) = 29.20, p=0.000) and whether participants had a SCD or MM (X^2 (5) = 26.42, p=0.000). A higher proportion (p < 0.000) of men (72.9%) than women (27.1%) had CVD. There were no other statistically significant differences in sex proportions across primary CD diagnosis. Examination of adjusted residual values did not find any significant differences between primary CD diagnosis on educational status, work status, smoking status or those with SCD or MM.

There was a significant difference in working status between SCD and MM (X^2 (2) = 6.80, p=0.033). However, examination of adjusted residual values did not indicate any specific group differences. There were no other statistically significant differences in participant demographics between SCD and MM.

Health-related outcomes and psychosocial determinants of physical activity and chronic diseases

Summary of main effects for primary CD diagnosis and SCD or MM on health-related measures are presented in table 4.3. The estimated marginal means ± SE generated for post hoc analysis are presented in the subsequent text. Appendix G presents results of main effects for participant demographics on health related outcomes and psychosocial determinants of PA.

There was a significant main effect for primary CD diagnosis on 6MTT (p=0.001), sit to stand (p=0.000), BMI (p=0.041), WHR (p=0.012), and fasting blood glucose level (p=0.000). Distance achieved in the 6MTT was significantly higher in participants with cancer (507.40 ± 13.93 m) than in those with respiratory disease (440.14 ± 17.68 m) (p=0.035) and neuro/MSK disorders (426.01 ± 24.89 m) (p=0.038). Time to complete the sit to stand test was significantly slower in the unspecified condition (38.60 ± 4.64 s) than CVD (20.93 ± 1.23 s; p=0.003), cancer (21.99 ± 1.26; p=0.008) and metabolic disease (23.55 ± 1.88; p=0.045). BMI was significantly higher among participants with metabolic disease (33.93 ± 1.48 $kg \cdot m^2$) than cancer (28.59 ± 0.98 $kg \cdot m^2$) (p=0.022). WHR was significantly higher among participants with metabolic disease (0.98 ± 0.02) than those with cancer (0.91 ± 0.01; p=0.029) and a neuro/MSK disorder(0.88 ± 0.02; p=0.020). Fasting blood glucose was significantly higher in participants with metabolic disease (8.97 ± 0.41 $mmol \cdot L^{-1}$) compared to CVD (6.21 ± 0.27 $mmol \cdot L^{-1}$; p=0.000), respiratory disease (6.03 ± 0.35 $mmol \cdot L^{-1}$; p=0.000), cancer (5.81 ± 0.30 $mmol \cdot L^{-1}$; p=0.000) and neuro/MSK disorders (5.96 ± 0.45 $mmol \cdot L^{-1}$;p=0.000).

There was a significant main effect for SCD or MM on 6MTT and BMI. Distance achieved in the 6MTT was significantly higher (p=0.031) in individuals with a SCD (463.01 ± 13.74m) than MM (433.56 ± 14.43 m). BMI was significantly higher (p=0.006) among participants with MM (31.61 ± 1.03 kg·m^2) than SCD (28.93 ± 0.98 kg·m^2) (p=0.006).

Table 4.3 Summary main effects for primary chronic diseases diagnosis and SCD or MM on health-related measures and psychosocial determinants of physical activity.

		Primary CD Diagnosis				**SCD or MM**			
Variables	n	df	*F*	sig	η_p^2	df	*F*	sig	η_p^2
Physical function									
6MTT	186	(5, 163)	4.4	**.001**	.118	(1, 163)	4.7	**.031**	.028
Sit to stand	186	(5, 163)	5.1	**.000**	.135	(1, 163)	1.1	.301	.007
Handgrip	188	(5, 165)	0.6	.670	.019	(1, 165)	1.6	.209	.010
Sit and reach	185	(5, 162)	1.1	.359	.033	(1, 165)	0.0	.935	.000
Body composition									
BMI	188	(5, 165)	2.4	**.041**	.067	(1, 165)	7.8	**.006**	.045
Waist to hip ratio	188	(5, 165)	3.0	**.012**	.084	(1, 165)	0.9	.349	.005
Blood biomarkers									
Fasting glucose	139	(5, 116)	10.6	**.000**	.313	(1, 116)	0.8	.387	.006
Triglycerides	155	(5, 132)	1.3	.275	.046	(1, 123)	2.0	.161	.015
LDL cholesterol	154	(5, 131)	0.7	.615	.026	(1, 131)	0.7	.405	.005
HDL cholesterol	154	(5, 131)	2.2	.059	.077	(1, 131)	0.2	.647	.002
hsCRP	124	(5, 101)	1.6	.175	.072	(1, 101)	0.1	.791	.001
Health-related wellbeing									
PHQ8	132	(5, 109)	1.9	.103	.079	(1, 109)	1.0	.311	.019
EQ-VAS	132	(5, 109)	0.5	.811	.020	(1, 109)	0.4	.527	.009
SWLS	132	(5, 109)	0.5	.755	.024	(1, 109)	3.5	.064	.067
Psychosocial determinants									
Barriers to self-efficacy for exercise	132	(5, 109)	1.6	.163	.069	(1, 109)	2.9	.092	.013

Note: CD = chronic disease; SCD = single chronic disease; MM = multimorbidity; 6MTT = 6 mIn time trial; BMI = body mass index; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQol Visual Analogue Scale; SWLS = Satisfaction with Life Scale; LDL = low density lipoprotein; HDL = high density lipoprotein; hsCRP = high sensitivity C-reactive protein
Number in **BOLD** indicates p ≤ 0.05

Physical Activity and Sedentary Behaviour

Among all participants, 9.5 ± 1.9 h of the waking day was spent sedentary. On average participants spent 4.1 ± 1.6 h·day^{-1} standing, 1.4 ± 6 h·day^{-1} stepping, 1.1 ± 0.4 h·day^{-1} in LIPA and 0.3 ± 0.3 h·day^{-1} in MVPA. The mean (±SD) daily step count was 6713.3 ± 3143.2 steps. A total of 63.7% of participants did not meet the recommended 150 min of MVPA per week. Figure 4.2 summarizes the PA and sedentary time for all participants and individuals with SCD and MM. Figure 4.3 outlines the PA and sedentary time for each primary CD diagnosis. Figure 4.4 illustrates the mean number of sedentary bouts and the total time accumulated in each sedentary bout duration. Participants accumulated 45.27 ± 14.73 sedentary bouts per day. Of the total waking sedentary time, 15.47% ± 7.31% was accumulated in bouts < 10 min in duration, 27.05% ± 8.36% was in sedentary bouts 11-30 min, 25.41% ± 7.06% was in sedentary bouts 31-60 min and 32.07% ± 14.45% was in sedentary bouts > 60 min. A high degree of correlation was identified among PA variables and SB. To control for type 1 error further analysis included only measures of step count and sedentary time.

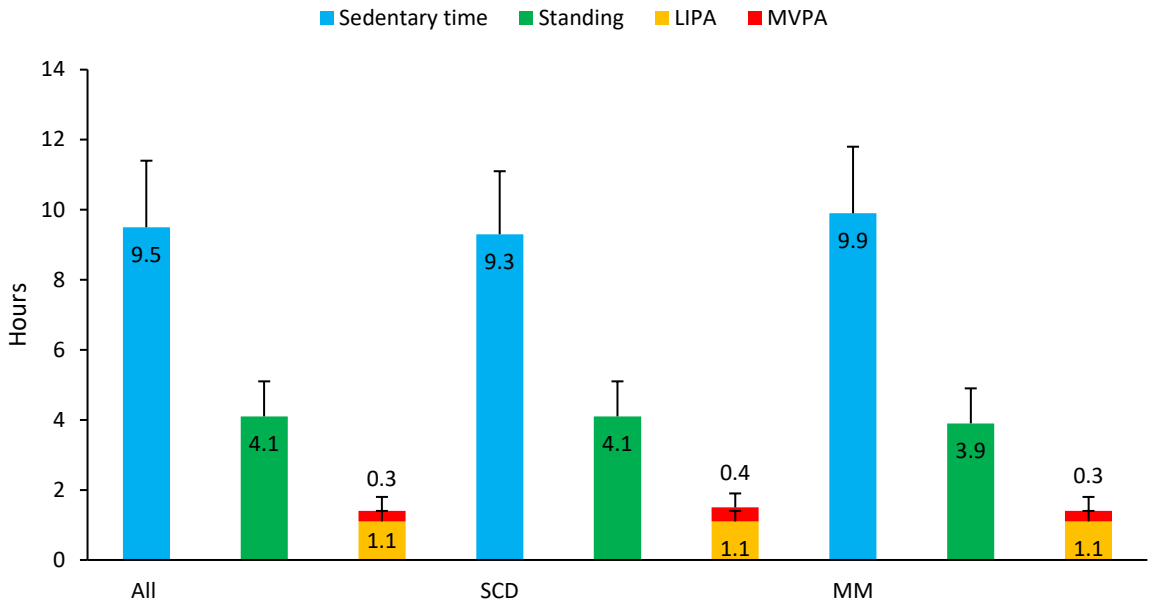

Figure 4.2 Physical activity and sedentary time for all participants and individuals with a single chronic disease and multimorbidity

Data presented as means and standard deviations

Note; LIPA = light intensity physical activity; MVPA = moderate to vigorous physical activity; SCD = single chronic disease; MM = multimorbidity

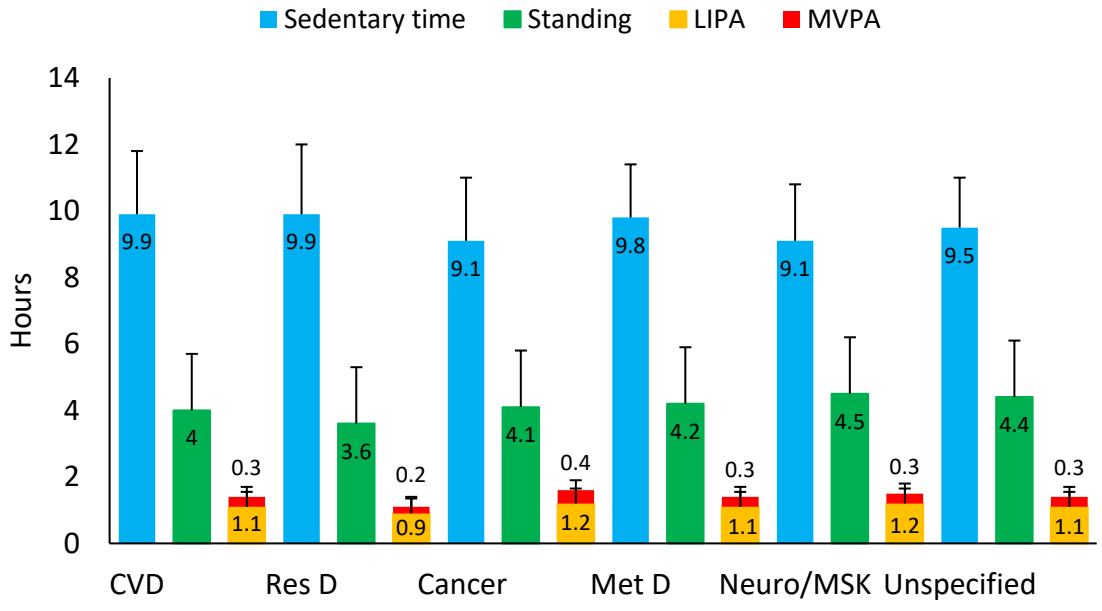

Figure 4.3 Physical activity and sedentary time for all participants and primary chronic disease

Data presented as means and standard deviations
Note: LIPA = light intensity physical activity; MVPA = moderate to vigorous physical activity; CVD = cardiovascular disease; Res D = respiratory disease; Met D = metabolic disease; Neuro/MSK = neuromuscular/musculoskeletal disorders.

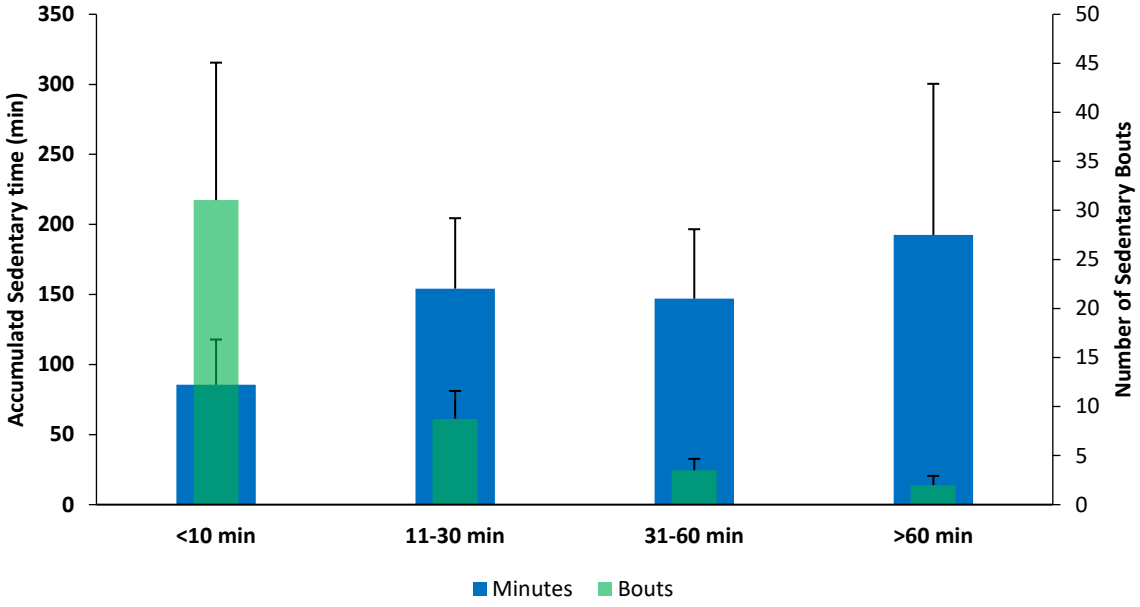

Figure 4.4 Patterns of sedentary behaviour
Data presented as means and standard deviations

Step count and sedentary time, participants demographics and chronic diseases

There were no significant differences in daily step count or sedentary time between primary CD, SCD or MM, age, sex, median household income, educational status, marital status and current work status. There was a significant main effect of smoking status on step count ($f_{(1,168)}$=6.73, p=0.010, partial eta squared =0.039). Daily step count was significantly higher (p=0.010) in non-smokers than current/past smokers (estimates marginal mean ± SE; 6769 ± 532 vs5562 ± 497 steps·day^{-1}).

Associations of step count and sedentary time with health-related measures

Step count was positively associated with 6MTT (p=0.000) and self-rated health (p=0.031) and inversely associated with BMI (p=0.003) and WHR (p=0.045). Sedentary time was positively associated with performance in the sit to stand test (p=0.012), where an increase in the sit to stand score, indicated poorer lower body strength, and inversely associated with LDL-C (p=0.003) and PHQ8 score (p=0.016). An increase in PHQ8 results indicates worsening symptoms of depression. Results presented in table 4.4.

Differences between individuals above and below the guidelines of MVPA for health related outcomes.

Individuals who participated in MVPA at or above the recommended level had significantly more favourable measures for the 6MTT (p=0.000), BMI (p=0.001), WHR (p=0.015) and the EQ-VAS (p=0.018). Results are presented in table 4.5.

Table 4.4 Relation of step count and sedentary time with health related outcomes

Health-related outcomes		Step count				Sedentary time			
	n	df	*F*	sig	η_p^2	df	*F*	sig	η_p^2
Physical function									
6MTT	186	(1, 163)	49.7	**.000**	.234	(1, 163)	0.0	.893	.000
Sit to stand	186	(1, 163)	2.8	.097	.017	(1, 163)	6.4	**.012**	.038
Handgrip	188	(1, 165)	2.3	.129	.014	(1, 165)	0.6	.445	.004
Sit and reach	185	(1, 162)	0.4	.524	.003	(1, 162)	0.9	.358	.005
Body composition									
BMI	188	(1, 165)	9.4	**.003**	.054	(1, 165)	3.2	.075	.019
Waist to hip ratio	188	(1, 165)	4.1	**.045**	.024	(1, 165)	0.1	.801	.000
Blood biomarkers									
Fasting glucose	139	(1, 116)	0.9	.335	.008	(1,116)	3.7	.057	.031
Triglycerides	155	(1, 132)	3.2	.074	.024	(1, 132)	0.0	.901	.000
LDL-C	154	(1, 131)	0.5	.477	.004	(1, 131)	8.9	**.003**	.064
HDL-C	154	(1, 131)	1.4	.240	.011	(1, 131)	0.5	.475	.004
hsCRP	124	(1, 101)	1.9	.172	.018	(1, 101)	0.1	.758	.001
Psychological health									
PHQ8	132	(1, 109)	0.5	.497	.004	(1, 109)	6.0	**.016**	.052
EQ-VAS	132	(1, 109)	4.8	**.031**	.042	(1, 109)	0.5	.480	.005
SWLS	132	(1, 109)	1.6	.206	.015	(1, 109)	2.2	.145	.019
Psychosocial determinants									
Barriers to self-efficacy for exercise	132	(1, 109)	0.1	.888	.000	(1, 109)	3.2	.078	.028

Note: 6MTT = 6 minute time trial; BMI = body mass index; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQol Visual Analogue Scale; SWLS = Satisfaction with Life Scale; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein.
Number in **BOLD** indicates $p \leq 0.05$

Table 4.5. Differences between individuals above and below the guidelines of MVPA for health related outcomes

Health-related outcomes	≥MVPA guidelines		<MVPA guidelines					
	n	m±SE	n	m±SE	df	*F*	sig	η_p^2
Physical function								
6MTT (m)	68	490±12	118	413±14	(1, 164)	23.8	**.000**	.127
Sit to stand (s)	68	25.9±1.5	118	27.4±1.2	(1, 164)	1.1	.294	.007
Handgrip (kg)	69	25.2±1.2	119	24.5±1.0	(1,166)	0.4	.545	.002
Sit and reach (cm)	69	6.8±1.8	116	8.7±1.6	(1, 163)	1.6	.212	.010
Body composition								
BMI (kg/m^2)	69	28.2±1.1	119	31.6±0.9	(1, 166)	10.5	**.001**	.060
Waist to hip ratio	69	0.90±0.01	119	0.93±0.01	(1, 166)	6.0	**.015**	.035
Blood biomarkers (mmol/L)								
Fasting glucose	50	6.6±0.3	89	6.7±0.3	(1, 117)	0.4	.552	.003
Triglycerides	52	1.3±0.1	103	1.3±0.1	(1, 133)	0.4	.530	.113
LDL-C	52	2.4±0.2	102	2.4±0.2	(1, 132)	0.0	.860	.000
HDL-C	52	1.5±0.1	102	1.4±0.1	(1, 132)	0.3	.607	.002
hsCRP	39	5.6±1.7	85	6.8±1.3	(1, 102)	0.6	.428	.006
Psychological health								
PHQ8	49	5.5±0.9	83	5.9±0.8	(1, 110)	0.2	.661	.002
EQ-VAS	49	70.0±3.9	83	61.8±3.4	(1, 110)	5.7	**.018**	.050
SWLS	49	22.6±1.5	83	21.5±1.3	(1, 110)	0.7	.384	.007
Psychosocial determinants								
Barriers to self-efficacy for exercise	49	59.9±4.2	83	60.1±3.6	(1, 110)	0.0	.953	.000

Note: m±SE = mean ± standard error; 6MTT = 6 minute time trial; BMI = body mass index; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQol Visual Analogue Scale; SWLS = Satisfaction with Life Scale; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein.
Number in **BOLD** indicates $p \leq 0.05$

Principal component analysis of health-related measures

The PCA performed on the health-related measures produced seven distinct factors that accounted for 72.1% of the total variance in measures. Item loading with values ≥ 0.30 were used for interpretation of factors (Pallant, 2013). Kaiser-Mayer measures of sampling adequacy for variables included in PCA was 0.630. Factors were interpreted to represent measures of psychological health, body composition, functional capacity and self-efficacy to be active, metabolic health, social support to be active, cholesterol and lipid profile. Table 4.5 outlines the factor characteristics with item loading on which interpretation of factors was based.

Table 4.6 Factor derived from principal component analysis of health-related measures

	Factor 1 Psychological health	**Factor 2** Body composition	**Factor 3** Functional capacity & self-efficacy	**Factor 4** Metabolic health	**Factor 5** Social support	**Factor 6** Cholesterol	**Factor 7** Lipid profile
BMI		.947					
Waist Circumference		.810		.510			
Hip Circumference		.946					
WHR				.785			
6MTT			.735				
Sit to stand			-.801				
Handgrip			.525	.520			
Sit and reach		-.326	.419	-.316			
PHQ8	-.850						
EQ-VAS	.842						
SWLS	.835						
SWEMBS	.883						
Fasting glucose				.594			
Triglycerides							.905
HDL cholesterol				-.470		.567	-.351
LDL cholesterol						.834	
hsCRP		.619					.353
Barriers self-efficacy			.312	.479		.392	
Self-regulatory self-efficacy	.591		.489				
Intentions for exercise			.653				
Family support					.812		
Friend support					.888		

Extraction method: principal component analysis

Rotation method: varimax with kaiser normalization. Rotated component matrix with factor loading. Values < 0.30 are not displayed.

Note: BMI = body mass index; 6MTT = 6-minute time trial; PHQ8 = 8-Item Patient Health Questionnaire; SWLS = Satisfaction with Life Scale; SWEMWBS = The Short Warwick Edinburgh Mental Well-Being Scale; HDL = high-density lipoprotein; LDL = low-density lipoprotein; hsCRP = high sensitivity c-reactive protein

The relation of PCA derived factors with demographics, chronic disease, physical activity and sedentary behaviour

The sample size was reduced to 52 as a result of excluding cases listwise during both the PCA analysis and ANCOVA. Table 4.6 presents the main effects for participant demographics, disease status, physical activity and sedentary time on factors derived from PCA. Results presented in the subsequent text are PCA factor scores and the estimated marginal means ± standard error generated for post hoc analysis.

Participant demographics

There was a significant main effect for sex on functional capacity and self-efficacy to be active (p=0.014), metabolic health (p=0.007), social support (p=0.031) and lipid profile (p-0.021). The score for functional capacity and self-efficacy to be active was significantly higher (p=0.014) for men than women (0.43 ± 0.24 vs.0.17 ± 0.19) indicating better functional capacity and self-efficacy to be active among men. Metabolic health (p=0.007), social support to be active (p=0.031) and lipid profile (p=0.021) were significantly better in women than men participants. There was a significant main effect of current work status on lipid profile (p=0.037), however pairwise comparison did not indicate any significant group differences for current working status.

Chronic disease

There was a significant main effect of primary CD diagnosis on functional capacity and self-efficacy to be active (p=0.024). Pairwise comparisons did not indicate any significant group differences for primary CD diagnosis and functional capacity & self-efficacy to be active.

Physical activity and sedentary behaviour

Sedentary time was significantly inversely associated with functional capacity & self-efficacy to be active (p=0.041) and cholesterol (p=0.030).

Table 4.7 ANCOVA main effects for participant demographics, disease status, physical activity and sedentary time on factors derived from principal component analysis

	Psychological health				Body composition				Functional capacity & SE				Metabolic health				Social support				Cholesterol				Lipid profile			
	df	*F*	sig	η_p^2	df	*F*	sig	η_p^2	df	*F*	sig	η_p^2	df	*F*	sig	η_p^2	df	*F*	sig	η_p^2	df	*F*	sig	η_p^2	df	*F*	sig	η_p^2
Demographics																												
Age	(1, 29)	3.8	.062	.115	(1, 29)	0.4	.618	.014	(1, 29)	1.7	.207	.054	(1, 29)	0.3	.569	.011	(1, 29)	0.4	.549	.013	(1, 29)	0.1	.711	.005	(1, 29)	3.9	.058	.119
Sex	(1, 29)	0.6	.451	.020	(1, 29)	2.0	.165	.065	(1, 29)	2.3	**.014**	.190	(1, 29)	8.6	**.007**	.228	(1, 29)	5.2	**.031**	.151	(1, 29)	4.0	.054	.122	(1, 29)	5.9	**.021**	.170
Income	(3, 29)	1.4	.276	.123	(3, 29)	2.0	.140	.169	(3, 29)	0.2	.861	.025	(3, 29)	1.1	.378	.100	(3, 29)	1.5	.226	.137	(3, 29)	1.3	.289	.120	(3, 29)	0.5	.679	.050
Education st.	(4, 29)	0.6	.661	.007	(4, 29)	0.1	.996	.006	(4, 29)	0.6	.689	.072	(4, 29)	0.3	.906	.034	(4, 29)	0.8	.545	.097	(4, 29)	0.6	.683	.074	(4, 29)	1.3	.301	.150
Marital st.	(2, 29)	0.2	.788	.016	(2, 29)	0.7	.525	.043	(2, 29)	0.2	.789	.016	(2, 29)	2.1	.135	.129	(2, 29)	2.6	.088	.154	(2, 29)	1.1	.360	.068	(2, 29)	0.4	.687	.026
Working st.	(2, 29)	0.5	.629	.031	(2, 29)	0.02	.985	.001	(2, 29)	0.9	.405	.061	(2, 29)	0.003	.997	.000	(2, 29)	0.4	.664	.028	(2, 29)	0.6	.360	.037	(2, 29)	3.7	**.037**	.204
Smoking st,	(1, 29)	2.6	.116	.083	(1, 29)	0.3	.567	.001	(1, 29)	1.2	.275	.041	(1, 29)	3.0	.096	.092	(1, 29)	0.1	.893	.001	(1, 29)	0.2	.675	.006	(1, 29)	0.1	.788	.003
Disease status																												
Primary CD	(5, 29)	0.2	.961	.033	(5, 29)	1.9	.121	.249	(5, 29)	3.1	**.024**	.346	(5, 29)	1.0	.811	.148	(5, 29)	1.7	.167	.226	(5, 29)	0.6	.686	.096	(5, 29)	0.4	.873	.058
SCD/MM	(1, 29)	2.1	.159	.067	(1, 29)	1.7	.205	.055	(1, 29)	0.3	.599	.010	(1, 29)	0.4	.540	.013	(1, 29)	0.1	.883	.001	(1, 29)	0.3	.565	.012	(1, 29)	0.1	.913	.000
PA & SB																												
SB	(1, 29)	0.2	.632	.008	(1, 29)	0.3	.618	.009	(1, 29)	4.6	**.041**	.136	(1, 29)	0.5	.465	.019	(1, 29)	0.6	.446	.020	(1, 29)	5.2	**.030**	.152	(1, 29)	2.8	.103	.089
Step count	(1, 29)	0.02	.881	.001	(1, 29)	0.5	.465	.019	(1, 29)	0.7	.419	.023	(1, 29)	0.1	.727	.004	(1, 29)	0.1	.785	.003	(1, 29)	3.7	.063	.114	(1, 29)	2.5	.128	.078
MVPA gl.	(1,30)	0.3	.605	.009	(1, 30)	0.1	.823	.002	(1, 30)	0.9	.340	.030	(1, 30)	0.1	.757	.003	(1, 30)	0.1	.831	.002	(1, 30)	0.01	.612	.009	(1, 30)	3.3	.078	.100

Note: Functional capacity & SE = functional capacity & self-efficacy to be active; Education st. = educational status; Marital st. = marital status; Working st. = working status; smoking st. = smoking status; Primary CD = primary chronic disease; SCD/MM = single chronic disease or multimorbidity; SB = sedentary behaviour; MVPA gl. =moderate to vigorous physical activity guidelines.
Number in **BOLD** indicates $p \leq 0.05$

Discussion

Significant differences exist across the diverse CD population between participant demographics and health-related measures. There were no significant differences between primary CDs or SCD and MM for PA or SB. Participants took on average 6,700 steps per day. Participants spent 9.5 $h \cdot day^{-1}$, 4.1 $h \cdot day^{-1}$, 1.4 $h \cdot day^{-1}$, and 0.3 $h \cdot day^{-1}$ sedentary, standing, in LIPA or MVPA observed, respectively. The majority of sedentary time was accumulated in bouts lasting 30 min or more. A higher daily step count was associated with more favourable measures of body composition, aerobic fitness and self-rated health, with medium, large and medium effect sizes, respectively. Those achieving the recommended guidelines of MVPA had more favourable measures of aerobic fitness and body composition with a large effect size and self-rated health with a medium effect size. More sedentary time was associated with less favourable lower body strength, however the effect size of this association was small. In contrast, more SB was also associated with more favourable measures of LDL-C and depressive symptoms, both with a medium effect size observed.

Low levels of PA are consistently reported in CD cohorts (Bernard et al., 2018; Christiansen et al., 2017; Eliason et al., 2011; Evenson et al., 2014; Lauret et al., 2014; Lynch et al., 2013; Wang et al., 2017). According to the classifications by Tudor-Locke *et al.,* (2008), the mean daily step count of 6,700 steps in the present CD cohort is low. On average, the study participants failed to meet the recommended levels of 150 min MVPA per week. Similarly, the high levels of SB in the present study has been reported in a number of previous investigations involving CD populations (English et al., 2016; Lewis et al., 2016; Pitta at al., 2005; Prince et al., 2016). It is important to note however, that the majority of previous studies examining the impact of exercise in CD populations have involved primarily single

disease cohorts. The current findings indicate that the levels of daily PA are low and SB high among individuals with either SCD or MM. There is a need for public health services to provide an integrated strategy to promote the engagement in PA and reductions in SB across all individuals living with SCD or MM.

Chapter 5

Study II

Effect of a Community-based Exercise Rehabilitation Program on Physical Activity Levels, Sedentary Behaviour and Health Outcomes in a Diverse Chronic Disease Population

Introduction

The beneficial effect of PA and reduced SB in the secondary prevention of multiple CDs is well documented (Anderson et al., 2016; Houchen-Wolloff et al., 2018; Jefferis et al., 2015; Judice et al., 2015; McCarthy et al., 2015; Puhan et al., 2016; Sardinha et al., 2015). Regular PA and reduced SB mitigates many of the established risk factors that are associated with the development of a range CDs. These include hypertension, dyslipidemia, hyperglycemia, hyperinsulinemia and obesity (Koene et al., 2016; Nesto, 2019; Warburton et al., 2006; World Health Organization, 2005b). However, in CVD patients, the positive impact of PA and reduced SB on established risk factors accounts for only 50% of the reduction in morbidity and mortality in these patients. There is now emerging evidence that PA and reduced SB induces improvements in CVD outcomes that can occur independent of their effects on traditional risk factors (Fiuza-Luces et al., 2018; Joyner & Green, 2009). This is due to the fact that several important physiologic and pathologic processes at play in patients with CVD are favourably modulated by PA and reduced SB. These include myocardial repair, positive vascular remodelling, coronary plaque stabilization and/or regression, development of coronary collateral blood vessels, improved autonomic nervous system balance, cardio-

protection against ischemia–reperfusion injury and improvement in myocardial calcium sensitivity and contractility (Fiuza-Luces et al., 2018; Hambrecht et al., 2003; Nickolay et al., 2019; Ribeiro et al., 2010, 2012; Vlachopoulos et al., 2010; Zhang et al., 2018). Although well established in CVD, it is likely that similar physiologic and pathological processes are associated with other CDs and are therefore positively affected by PA and reduced SB.

In addition to the positive effects on physiologic and pathological processes, regular PA improves functional capacity and QoL in patients with CD (Arne et al., 2009; Han et al., 2017; Sagar et al., 2015; Varas et al., 2018). All CDs have the potential to limit the functional capacity of the people who live with them (Harris & Wallace, 2012) and decrease functional independence, which can significantly impair QoL (Nihtilä et al., 2008). The benefits of PA for CD cohorts extend beyond what could be achieved by any other single treatment.

The growing burden of CD mandates the development and delivery of exercise rehabilitation services for patients with CD and MM. Community-based programmes are a safe and effective mode of delivery for CD rehabilitation (Desveaux et al., 2014b) and allow for increased accessibility and scalability through a public health approach (Kelley et al., 2011). CBER programs allow for much of the burden in the delivery of PA programs to patients with CD to be removed from the healthcare system into the community.

Poor long-term compliance to exercise following cardiac rehabilitation is a major problem with over 50% of patients returning to pre-rehabilitation levels of PA within 3 months of completing the program (Bock et al., 1997). Egan et al., (2012) found no significant changes in habitual PA levels after seven weeks of pulmonary rehabilitation, and at a one year follow-up, none of the physical function improvements observed immediately following the program

had been sustained. Patients have reported a preference towards CBER programs compared to hospital-based exercise rehabilitation (McNamara et al., 2016). Patients expressed how CBER promoted a sense of 'normality' within the rehabilitation experience, distinguishing exercise as a normal behaviour as opposed to a treatment for their condition. The community model may improve adherence by allowing for longer term or continual service provision or support.

CBER programmes have historically accommodated specific individual CDs (Anderson et al., 2016; Kelley et al., 2011; Mccarthy et al., 2015; Swartz et al., 2017). However, it is well recognised that these programmes have similar structures and components, irrespective of the disease (Desveaux et al., 2014b) and therefore, there appears to be no compelling evidence to indicate that community-based programmes need to be disease-specific (Kelley et al., 2011). Considering the growing prevalence of MM (Violan et al., 2014), an integrated approach to community-based exercise for CD management represents a more resource efficient strategy. Recent studies have found that CBER programs are an effective model for exercise rehabilitation across numerous CD groups (Gallé et al., 2019; Marsden et al., 2016; Pang et al., 2005; Santa Mina et al., 2017; Varas et al., 2018). Increases in daily PA levels with CBER have been reported in CD cohorts (Moreton et al., 2018; Varas et al., 2018).

There is compelling evidence that CBER is a successful intervention for the secondary prevention of CD. Substantial evidence supports the efficacy of CBER in enhancing physical functioning and QoL for individuals with CD. The effects of CBER on habitual PA levels and SB in CD cohort remains unclear, a further investigation is warranted. In line with the current research trends on PA levels in CD cohorts, the current model of CBER delivery is primarily restricted to single disease cohorts. The effectiveness of an integrated model of CBER deliver

which caters for individuals with a range of CD diagnosis and those with MM is yet to be established.

MedEx Wellness is a novel CBER programme for CD in Ireland. Participants with a range of CD, including CVD, pulmonary disease, diabetes, and cancer, are referred to the programme by hospital physicians and their teams and general practitioners. With medical oversight, MedEx Wellness offers a common CD programme of supervised group exercise classes. The programme is not fixed in duration and participants can attend on a continuous basis. Participants are encouraged to establish a lifelong relationship with MedEx Wellness, which supports the development of habitual exercise participation, and fosters the maintenance of active living.

The purpose of this study was to determine the effect of a CBER program (MedEx Wellness) on PA levels and SB in a diverse CD population and to assess its effect on selected health indices. It was hypothesized that participation in a CBER program will result in significant improvements in PA, SB, physical, clinical and psychological health.

Methods

The study used a quasi-experimental study design. Detailed methodology is described in Chapter 3. Briefly, participants with one or more established CD recruited from patients referred by healthcare professionals to a CBER programme (MedEx Wellness) were observed over 12-month period. Participants underwent an induction to the MedEx Wellness programme, which i) provided information on the programme structure and logistics; ii) involved a group exercise consultation and iii) a beginner exercise class. Group exercise consultations were repeated at 1, 3, and 6 months. Following induction, participants were recommended to attend 2 supervised group exercise classes per week. The classes were 60 min in duration consisting of a combination of aerobic and resistance exercise. Outcomes were assessed at baseline and 3, 6 and 12 months. Figure 5.1 outlines the intervention and data collection timepoints.

The primary outcome measures were PA and SB measured using the ActivPAL^3 micro (PAL Technologies Ltd. Glasgow, Scotland). Specifically, time spent in SB, standing, LIPA and MVPA; bouts of uninterrupted SB and mean daily step count were measured. Secondary outcome measures were physical function, body composition, blood biomarkers, psychological health and psychosocial determinants of PA.

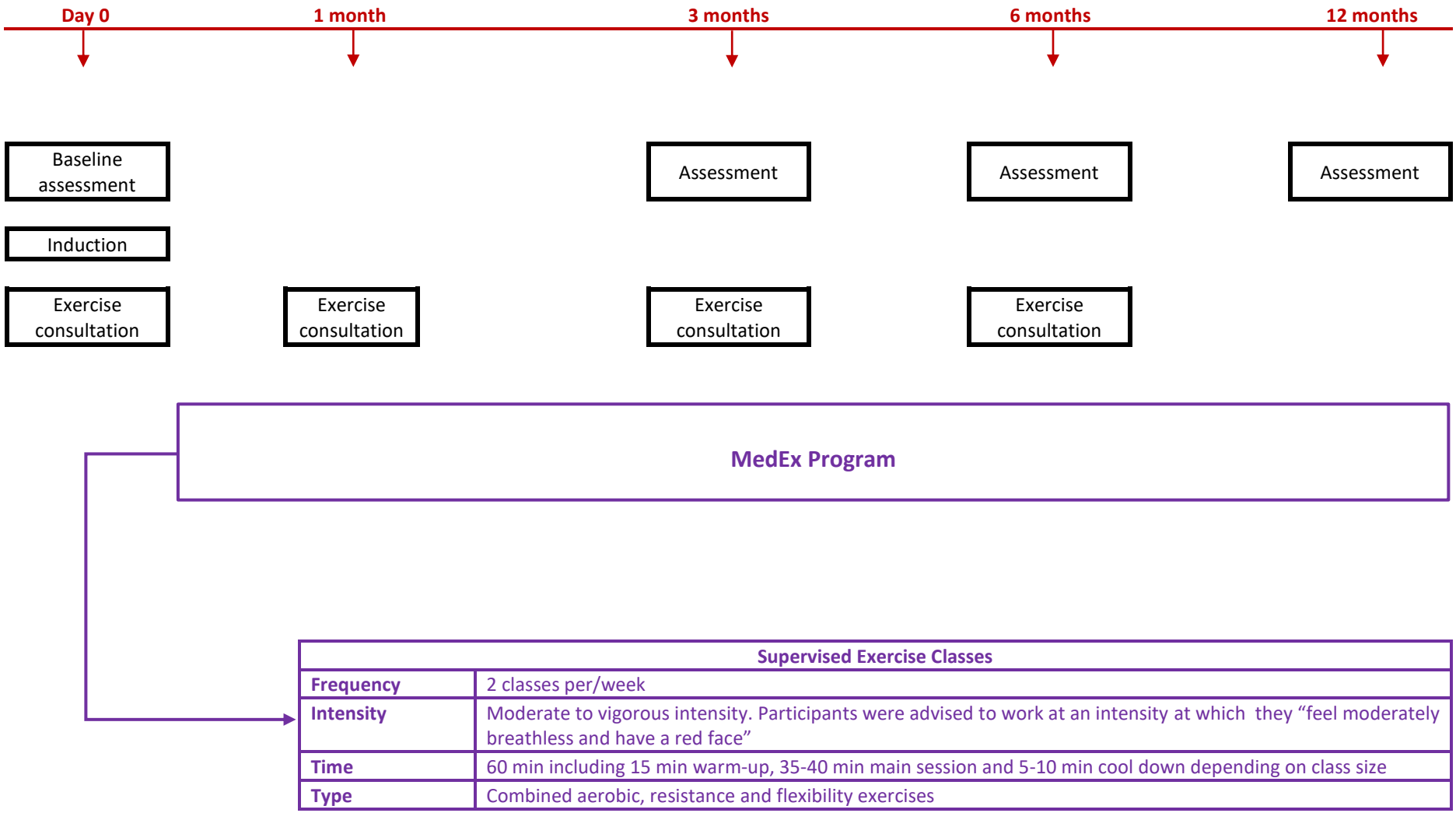

Figure 5.1 The MedEx Wellness program and data collection timepoints

Statistical Analysis

Patterns of attendance to the program for all participants, completers and dropouts were presented using descriptive statistics. Independent t-tests and Chi Square analyses were used to compare differences between drop-outs and those who completed the program. Adjusted residual values were examined and computed to p-values, to identify group differences.

A linear mixed model analysis (MMA) was used to assess longitudinal changes. A MMA is a suitable approach to modelling time series data which contains repeated measures for several subjects (Haapalainen et al., 2008). The MMA does not require complete data sets and does not exclude participants with missing data (Armstrong, 2017; Howell, 2015). Furthermore, MMA has less stringent assumptions than other repeated measures models (such as analysis of variance) and also exhibits increased power to detect treatment effects. In addition, MMA accommodates longitudinal designs where data collection does not have to take place at equally spaced intervals, e.g. 3, 6 and 12 months (Armstrong, 2017).

The model was analysed for autoregressive, compound symmetry, diagonal, toeplitz and unstructured variance structures. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used as a metric to identify the best-fit model. Time was treated as repeated measures and also incorporated as a fixed effect in the model. Categorical variables of primary CD diagnosis and SCD or MM were also included as fixed effects. Total number of classes attended was included as a covariate. The main effects for time and attendance and the interaction effects for time*primary CD diagnosis and time*SCD

or MM were investigated. To control for heterogeneity within the population, models were adjusted for baseline principal health-related variables.

For primary outcome measures, models were adjusted for baseline measures of mean daily step count, 6MTT and BMI. For secondary outcome measures, models were adjusted for baseline measures of 6MTT and BMI. Daily step count was not controlled for in secondary outcome measures as this resulted in a significant decrease in sample size for these variables. To determine the timepoints at which intervention effects occurred between baseline (BL), 3 months (3 m), 6 months (6 m) and 12 months (12 m), Bonferroni-adjusted post-hoc stratified analysis comparing estimated marginal means at each timepoint were performed for primary and secondary outcome measures that indicated a significant main effect for time. To decompose significant interaction effects, a Bonferroni-adjusted simple effects analysis was used. Cohen's D was calculated. A value of ≥0.2 was defined as a small effect size, >0.2-0.5 as medium and ≥0.8 as large (Pallant, 2013).

Finally, Pearson's correlation was used to investigate the relation between change in measures of physical activity between BL and 12 months and changes in psychosocial determinants of PA.

Results

Participants

Four hundred and three participants (mean age 62.98 ± 11.00 yr; 50.6% men) were recruited. Forty-nine percent of participants were referred to the MedEx Wellness programme by hospital consultants and a further 14% from hospital-based phase IV cardiac rehabilitation. GPs were responsible for 26% of referrals. Participant demographics are described in Chapter 4.

Uptake and Adherence

Rates of programme initiation and drop-out and reasons for drop-out are summarised in figure 5.2. Thirty participants (7.5%) did not attend an exercise class following induction to the programme and were classified as non-uptakers. A total of 167 (41.4%) participants initiated the exercise classes but dropped out at a later stage. The dropout rate was 26.3% (n=106) between BL - 3 m, 5.0% (n=20) between 3 m - 6 m and 8.9% (n=36) between 6 m - 12 m. Time of drop out could not be determined for 5 participants as attendance data was not obtained

Attendance results are presented in table 5.1. Participants attended a mean of 22.97 classes during the 12 months, with large fluctuations in mean attendance evident throughout the program. Based on the recommendation of attending two exercise classes per week, and the program operating on 46 weeks of the year, adherence to the program over 12 months was estimated at 26%.

Program completers and dropouts had a mean attendance rate over the 12 months of 31.85 and 12.05 classes, respectively, with the highest mean attendance recorded in the first 3 months for both. Adherence for completers was estimated at 36%. There was a significant difference for number of sessions attended between completers and drop-outs at all time-points ($p \leq 0.000$).

Table 5.1 Number of classes attended for all participants, completers and drop-outs across all timepoints

Timepoint	All participants	Completers	Drop-outs
BL – 3 m	10.82 ± 6.81	12.66 ± 6.5*	8.54 ± 6.52*
3 m – 6 m	5.06 ± 6.99	7.54 ± 7.8*	2.01 ± 4.14*
6 m – 12 m	7.06 ± 12.22	11.57 ± 14.56*	1.50 ± 4.08*
BL – 12 m	22.97 ± 21.91	31.85 ± 24.26*	12.05 ± 11.5*

* Indicts significant difference between groups ($p \leq 0.000$)
Note: BL = baseline; 3 m = 3 months; 6 m = 6 months; 12 m = 12 months

BL participant demographics along with measures of physical, clinical, psychological and psychosocial characteristics for completers and drop-outs are presented in tables 5.2 – 5.4. Drop-outs were significantly younger (p=0.020, Cohen's D=0.23) than completers. Compared to completers a lower proportion of drop-outs were male (p=0.033, Cramer's V (V)=0.11), retired (p=0.006, V=0.19) and a higher proportion were unemployed (p=0.009, V=0.19). There was a higher proportion of completers with CVD (p=0.000, V=0.25). There were no significant differences between completers and drop-outs for PA levels at BL. Compared to drop-outs, completers had a greater number (p=0.013, Cohen's D=0.33) and greater accumulated time (p=0.025, Cohen's D=0.29) in sedentary bouts that lasted between 31 – 60 min. Drop-outs had significantly less favourable measures of BMI (p=0.016, Cohen's D=0.24), hip circumference (p=0.004, Cohen's D=0.30), triglycerides (p=0.048, Cohen's D=0.22), total cholesterol (p=0.000, Cohen's D=0.40), LDL-C (p=0.005, Cohen's D=0.31) and family support for PA (p=0.005, Cohen's D=0.29) than completers.

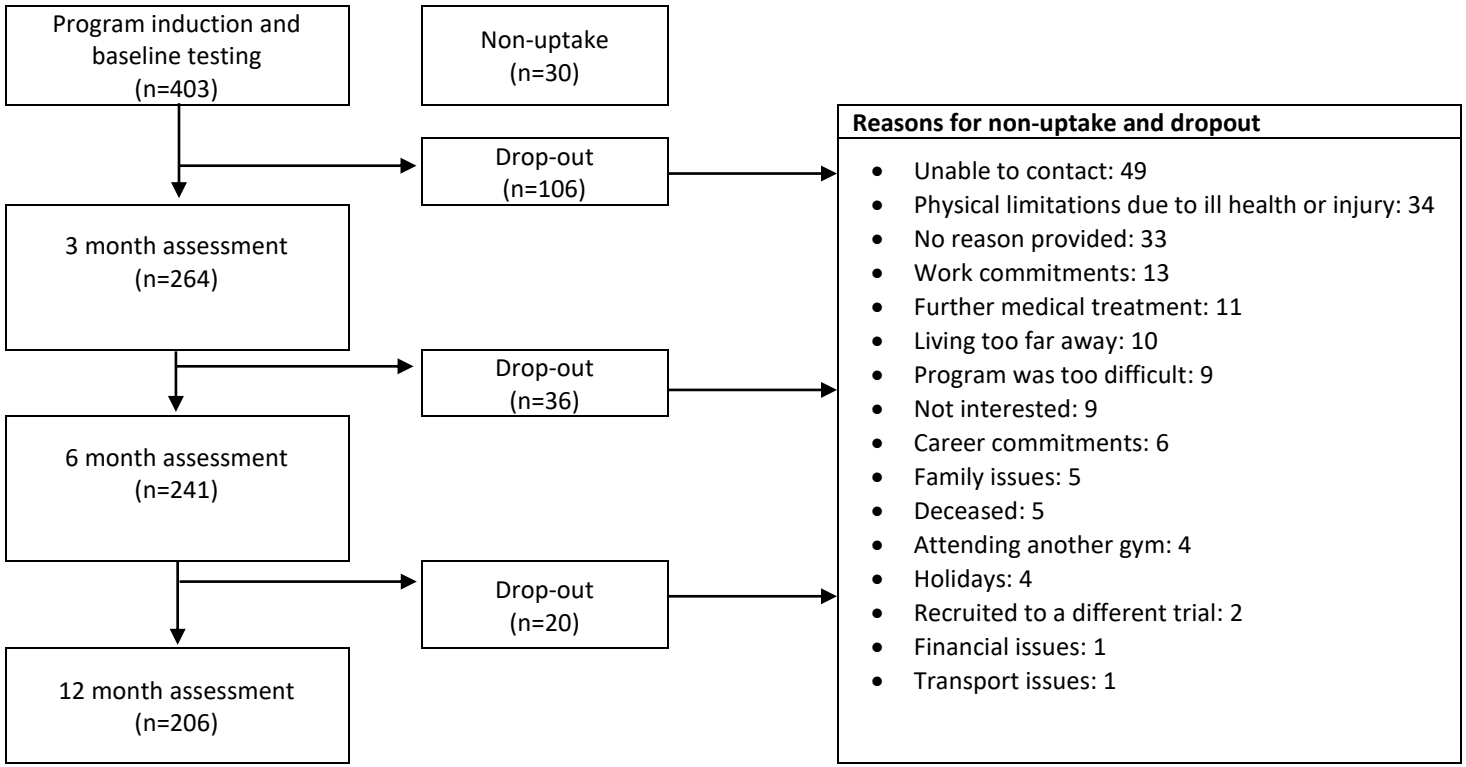

Figure 5.2 Program completion and dropout flow chart

Note: Attendance data was not obtained for 5 participants who dropped out and time of drop-out was not identified

Table 5.2 Demographics for completers and drop-outs

Variable	Completers n=206	Drop-outs n=196	p value	Effect size
Age (years)	64.22 ± 10.45	61.67 ± 11.40	**.020**	0.23
Gender (male)	115 (55.8)	89(45.2)	**.033**	0.11
Income (€)				0.14
64,393 – 105,943	42 (21.1)	40 (21.4)	1.00	
51,535 – 64,278	85 (42.7)	78 (41.7)	.998	
42,309 – 51,517	49 (24.6)	48 (25.7)	.997	
< 33, 493	23 (11.6)	21 (11.2)	1.00	
Educational status				0.16
Some primary	23 (11.7)	22 (11.9)	1.00	
Junior cert or equiv.	44 (22.3)	37 (20.0)	.989	
Leaving cert or equiv.	29 (14.7)	50 (27.0)	.066	
3Diploma or cert	44 (22.3)	37 (20.0)	.987	
Degree or post grad	57 (28.9)	39 (21.1)	.537	
Marital status				0.05
Married / partner	136 (69.7)	122 (65.6)	.687	
Divorced or widowed	30 (15.4)	34 (18.3)	.751	
Single	29 (14.9)	30 (16.1)	.944	
Working status				0.19
Working or studying	52 (27.8)	54 (30.9)	.816	
Unemployed	33 (17.6)*	55 (31.4)	**.009**	
Retired	102 (54.5)	66 (37.7)	**.006**	
Smoking status				0.05
Current or past smoker	75 (38.7)	80 (43.2)	.364	
Never smoked	119 (61.3)	105 (56.8)	.364	
Primary CD diagnosis				0.25
CVD	95 (46.1)	45 (22.8)	**.000**	
Respiratory disease	35 (17.0)	40 (20.3)	.981	
Cancer	36 (17.5)	56 (28.4)	.232	
Metabolic disease	20 (9.7)	25 (12.7)	.970	
Neuro/MSK	12 (5.8)	15 (7.6)	.665	
Unspecified	8 (3.9)	16 (8.1)	.992	
SCD or MM				0.04
SCD	110 (54.5)	94 (50.3)	.409	
MM	92 (45.5)	93 (49.7)	.409	

Continuous variables are displayed as mean ± standard deviation. Categorical variables are presented as n (%)
Numbers in **BOLD** indicate $p \leq 0.05$.
Note: Equiv. = equivalent ; CVD = cardiovascular disease; neuro/MSK = neuromuscular/musculoskeletal disorders; SCD = single chronic disease; MM = multimorbidity
Note: effect size reported for age = Cohen's D; effect size reported for all other variables = Cramer's V

Table 5.3 Baseline physical activity and sedentary behaviour for completers and drop-outs

Variable	Completers n=126	Drop-outs n=111	p value	Cohen's D
Sedentary Time (hr)	9.58±1.88	9.49±1.90	.716	0.05
Standing Time (hr)	4.05±1.38	4.06±1.74	.957	0.01
LIPA (hr)	1.14±0.41	1.07±0.43	.243	0.15
MVPA (hr)	0.34±0.28	0.30±0.28	.277	0.14
Step Count (steps/day)	6979±3189	6411±3077	.166	0.18
Number of SedB < 10 min	32.05±15.04	29.92±12.73	.244	0.15
Time SedB < 10 min (min)	88.14±32.45	82.61±32.01	.189	0.17
Number of SedB 11-30 min	8.86±2.79	8.62±2.89	.526	0.08
Time SedB 11-30 min (min)	156.71±49.84	151.24±50.86	.406	0.11
Number of SedB 31-60 min	3.67±1.20	3.30±1.11	**.013**	0.33
Time SedB 31-60 min (min)	153.81±51.33	139.33±46.41	**.025**	0.29
Number of SedB > 60 min	1.94±0.95	2.04±0.93	.418	0.11
Time SedB > 60 min (min)	183.50±100.26	202.75±115.64	.172	0.18
Total number of. SedB	46.52±15.64	43.87±13.54	.169	0.18

Variables are displayed as mean ± standard deviation
Numbers in **BOLD** indicate $p \leq 0.05$
Note: LIPA = light intensity physical activity; MVPA = moderate to vigorous intensity physical activity; SedB = sedentary bouts

Table 5.4 Baseline physical, clinical and psychological characteristics for completers and drop-outs

Variable	n (completers/dropouts)	Completers	Drop-outs	p value	Cohen's D
Physical Function					
6MTT (m)	202, 184	475.16±124.18	460.52±148.72	.294	0.11
Sit to stand (sec)	204, 196	22.05±7.15	23.66±7.15	.066	0.19
Handgrip (kg)	205, 196	26.59±9.23	25.55±8.81	.252	0.11
Sit and reach (cm)	203, 189	7.42±9.43	6.66±9.30	.425	0.08
Body Composition					
Weight (kg)	205, 197	81.72±18.51	85.39±22.25	.073	0.18
BMI (kg/m^2)	205, 195	29.16±5.62	30.78±7.53	**.016**	0.24
Waist (cm)	206, 197	99.79±15.49	102.13±18.52	.171	0.14
Hip (cm)	205, 196	106.09±10.98	110.03±15.42	**.004**	0.30
Waist to hip ratio	205, 196	0.94±0.11	0.93±0.10	.216	0.12
Blood biomarkers (mmol/L)					
Fasting glucose	157, 147	6.35±1.47	6.77±2.77	.100	0.19
Triglycerides	173, 163	1.11±0.54	1.24±0.67	**.048**	0.22
Total cholesterol	172, 163	4.36±1.26	4.86±1.17	**.000**	0.40
HDL cholesterol	170, 163	1.31±0.47	1.39±0.47	.143	0.16
LDL cholesterol	171, 142	2.21±1.01	2.53±1.07	**.005**	0.31
hsCRP	145, 137	6.28±8.72	7.64±16.32	.379	0.10
Psychological health					
PHQ8	179, 140	4.96±4.74	5.81±5.20	.134	0.17
EQ-VAS	179, 153	66.58±18.90	63.64±17.78	.148	0.16
SWLS	179, 146	24.35±6.75	22.94±7.09	.068	0.20
SWEMWBS	175, 149	26.85±4.67	26.23±4.54	.231	0.13
Psychosocial determinants of PA					
Barriers self-efficacy for exercise	179, 164	61.66±20.64	59.36±21.30	.311	0.11
Self-regulatory self-efficacy for exercise	157, 95	76.87±18.50	75.40±19.95	.555	0.08
Intentions for exercise	189, 169	3.39±0.50	3.45±0.53	.348	0.10
Family support for physical activity	186, 177	2.52±1.09	2.18±1.19	**.005**	0.29
Friend support for physical activity	151, 126	2.11±1.07	2.19±1.18	.566	0.07

N is displayed as completers, dropouts

Variables are displayed as mean ± standard deviation

Numbers in **BOLD** indicate p ≤ 0.05

Note: 6MTT = 6 minute time trial; BMI = body mass index; hsCRP = high sensitivity c-reactive protein; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQoL Visual Analogue Scale; SWLS = Satisfaction with Life Scale; SWEMWBS = The Short Warwick Edinburgh Mental Wellbeing Scale; PA = physical activity

Adverse events

There was one fatality during the trial, that resulted from a cardiac arrest following participation in a MedEx Wellness class. The participant was a male of 62 yr with a primary diagnosis of CVD and no MM. He had been participating in the study for 10 months and had attended 52 classes.

Outcomes

Of the 403 participants who completed BL assessment, 264 (65.5%), 240 (59.6%) and 206 (51.1%) participants completed repeat assessments at 3 months, 6 months and 12 months, respectively.

Primary Outcome: Physical Activity and Sedentary Behaviour

Results of mixed model analyses on PA and SB variables are displayed in table 5.5. Statistically significant main effects for time were found for LIPA (p=0.016, Cohen's D=0.14), number of sedentary bouts between 11-30 min (p=0.040, Cohen's D=0.10), time in sedentary bouts of 11-30 mins (p=0.037, Cohen's D=0.11) and total number of sedentary bouts (p=0.040, Cohen's D=0.09). The post-hoc analysis indicated that there was a significant improvements in LIPA between BL - 6 m (p=0.014, Cohen's D=0.06) (figure 5.3), but did not find a significant differences at any time point for the number of and time spent in bouts of 11-30 min or total number of sedentary bouts (Figure 5.4). A summary table of pairwise comparisons on primary outcome variables with a significant main effect for time is included in Appendix H.

A significant positive association was found between attendance and LIPA (p=0.006), MVPA (p=0.010) and step count (p=0.002). There was a significant inverse association between attendance and time spent in sedentary bouts > 60 min (p=0.050). There were no significant interaction effects for time*primary CD diagnosis or time*SCD or MM.

Table 5.5 Type III analysis of time, attendance, time*primary chronic disease and time*SCD or MM effects for primary outcomes

Primary outcome variables n=224	BL	3 m	6 m	12 m	Time			Attendance			Time* Primary CD diagnosis			Time* SCD or MM		
					df	F	sig	df	F	sig	df	F	sig	df	F	sig
Sedentary Time (hr)	9.4±0.2	9.6±0.2	9.6±0.2	9.7±0.3	(3, 114)	0.3	.886	(1, 202)	1.0	.323	(15, 121)	1.2	.246	(3, 119)	0.6	.616
Standing Time (hr)	4.2±0.1	4.1±0.2	4.2±0.2	4.3±0.2	(3, 117)	0.4	.787	(1, 192)	0.3	.568	(15, 127)	1.5	.124	(3, 125)	0.6	.699
LIPA (hr)	1.1±0.04	1.2±0.05	1.3±0.1	1.2±0.1	(3, 119)	3.7	**.016**	(1, 206)	7.6	**.006**	(15, 134)	1.2	.305	(3, 124)	0.4	.726
MVPA (hr)	0.33±0.03	0.38±0.03	0.36±0.03	0.36±0.05	(3, 116)	1.2	.310	(1, 217)	6.8	**.010**	(15, 134)	0.8	.669	(3, 123)	0.1	.989
Step Count (steps/day)	6885±273	7535±360	7671±397	7380±494	(3, 115)	2.4	.076	(1, 217)	9.4	**.002**	(15, 123)	1.2	.261	(3, 121)	0.2	.869
No. SedB < 10 min	29.72±1.3	31.62±1.5	32.59±1.5	32.6±1.7	(3, 132)	2.2	.088	(1, 206)	0.1	.718	(15, 142)	0.9	.614	(3, 140)	0.6	.594
Time SedB < 10 min (min)	82.6±2.9	88.4±3.3	89.8±3.6	90.9±4.6	(3, 118)	2.6	.054	(1, 195)	0.5	.475	(15, 125)	1.0	.440	(3, 123)	2.2	.090
No. SedB 11-30 min	8.5±0.3	9.3±0.3	9.3±0.4	9.3±0.4	(3, 120)	2.9	**.040**	(1, 110)	0.1	.875	(15, 125)	0.8	.714	(3, 123)	0.1	.982
Time SedB 11-30 min (min)	149.8±4.5	163.1±5.1	163.8±6.3	163.1±7.9	(3, 120)	2.9	**.037**	(1, 209)	.01	.945	(15, 122)	0.8	.665	(3, 123)	.03	.994
No. SedB 31-60 min	3.5±0.1	3.5±0.2	3.5±0.2	3.4±0.2	(3, 125)	0.1	.968	(1, 202)	2.5	.117	(15, 141)	0.6	.859	(3, 133)	0.4	.737
Time SedB 31-60 min (min)	148.1±4.5	146.3±7.3	148.9±7.4	143.1±8.1	(3, 126)	0.2	.923	(1, 200)	1.9	.175	(15, 138)	0.8	.698	(3, 133)	0.3	.805
No. SedB > 60 min	2.0±0.1	1.9±0.1	1.9±0.1	2.0±0.1	(3, 122)	0.8	.488	(1, 174)	3.7	.056	(15, 128)	1.1	.402	(3, 128)	1.2	.307
Time SedB > 60 min (min)	194.8±9.5	179.6±10.1	177.4±13.1	191.9±15.5	(3, 118)	1.0	.405	(1, 171)	3.9	**.050**	(15, 123)	0.9	.572	(3, 123)	1.3	.274
Total No. SedB	44.3±1.4	46.8±1.6	47.8±1.6	47.6±1.8	(3, 125)	2.9	**.040**	(1, 211)	0.1	.716	(15, 134)	1.1	.346	(3, 135)	0.2	.919

Data at each timepoint presented as estimated marginal means ± standard error.

Note: CD = chronic disease; SCD = single chronic disease; MM = multimorbidity; LIPA = light intensity physical activity; MVPA = moderate to vigorous intensity physical activity; No. SedB = number of sedentary bouts; Time SedB = time in sedentary bouts. Numbers in **BOLD** indicate $p \leq 0.05$.

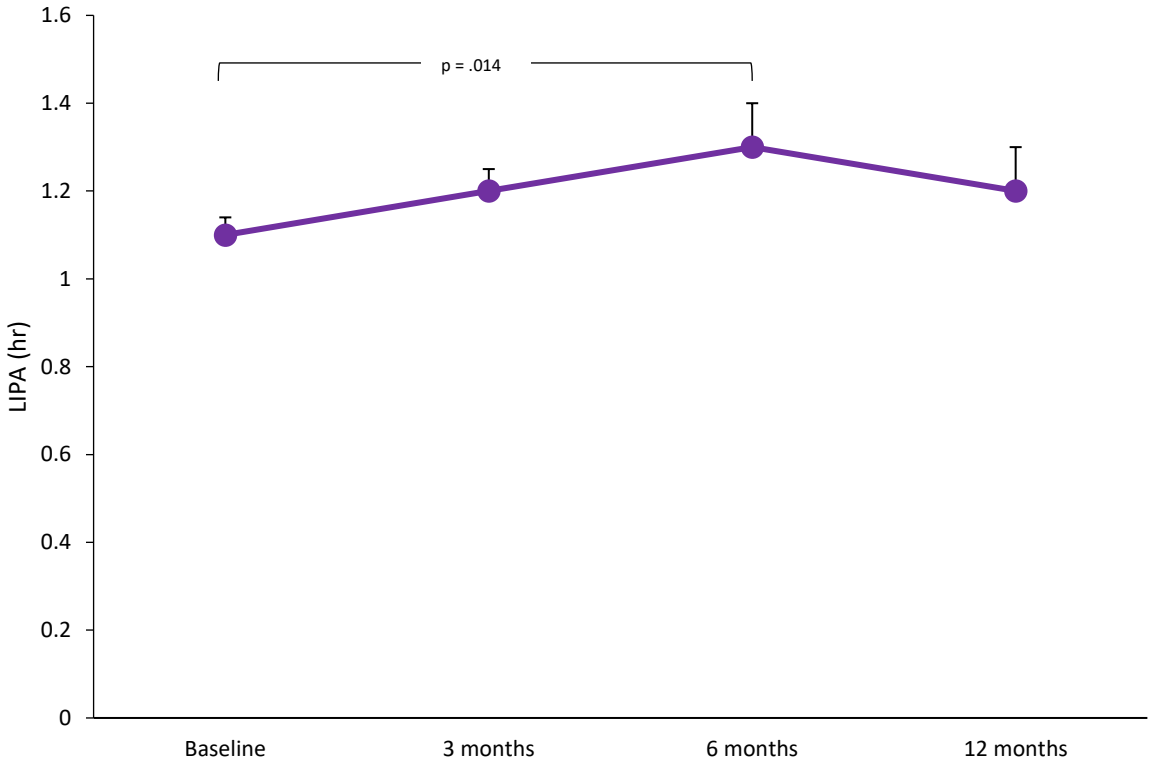

Figure 5.3 LIPA (BL-12m) pairwise comparisons

Data presented as estimated marginal means and standard error

(┌──────┐) indicates significant change between two timepoints ($p < 0.05$)

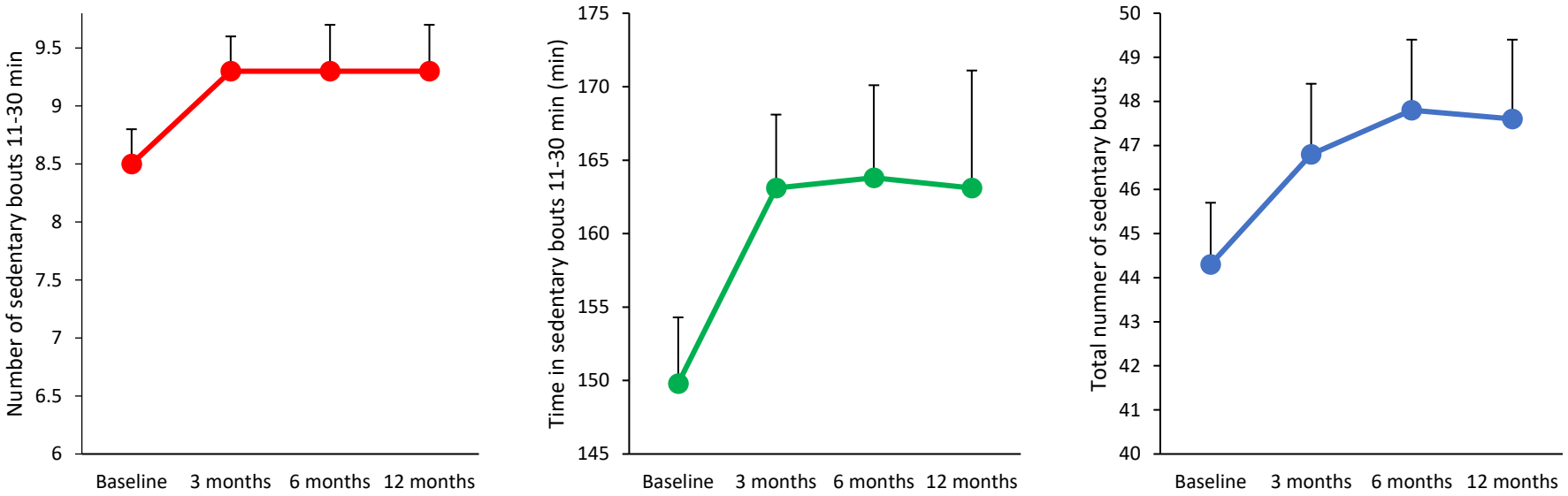

Figure 5.4 Number of and time spent in sedentary bouts of 11-30 min duration and total number of sedentary bouts (BL-12m) pairwise comparisons

Data presented as estimated marginal means and standard error

Secondary Outcomes

A summary of results for secondary outcomes are in table 5.6. Results with a significant main effect for time were subjected to pairwise comparisons. Results are summarized in table 5.7.

Table 5.6 Type III analysis of time, attendance, time*primary chronic disease and time*SCD or MM effects for secondary outcomes

Secondary variables	outcome	n	BL	3 m	6 m	12 m	Time			Attendance			Time* Primary CD diagnosis			Time* SCD or MM		
							df	F	sig	df	F	sig	df	F	sig	df	F	sig
Physical function																		
	6MTT (m)	369	457.2 ± 8.6	508.6±10.4	522.7±11.3	532.1±12.2	(2, 221)	37.0	**.000**	(1, 361)	2.0	.157	(15, 222)	4.0	**.000**	(3, 220)	0.5	.673
	Sit to stand (secs)	369	23.1±0.5	20.4±0.5	19.9±0.6	20.4±0.6	(3, 231)	17.6	**.000**	(1, 317)	3.4	.067	(15, 240)	1.7	.052	(3, 227)	0.2	.873
	Handgrip (kg)	369	25.1±0.6	25.4±0.6	25.9±0.6	26.3±0.7	(3, 228)	3.8	**.011**	(1, 360)	.004	.952	(15, 227)	0.9	.515	(3, 225)	1.2	.294
	Sit and reach (cm)	263	6.80±0.7	7.3±0.8	8.2±0.8	8.1±0.9	(3, 191)	2.6	.054	(1, 345)	3.3	.069	(15, 192)	0.6	.886	(3, 191)	3.8	**.011**
Body composition																		
	Weight (kg)	369	83.5±1.4	83.2±1.4	83.2±1.3	82.8±1.3	(3, 218)	1.0	.407	(1, 333)	4.2	**.041**	(15, 218)	1.7	.055	(3, 216)	1.3	.271
	BMI (kg/m^2)	369	30.2±0.4	30.1±0.4	30.1±0.4	30.0±0.4	(3, 215)	0.7	.575	(1, 336)	4.2	**.041**	(15, 215)	1.7	.057	(3, 213)	1.2	.295
	Waist cir (cm)	369	100.7±1.1	99.0±1.1	99.2±1.1	97.9±1.1	(3, 230)	9.1	**.000**	(1, 324)	2.5	.112	(15, 231)	1.0	.412	(3, 229)	1.8	.142
	Hip cir (cm)	369	108.3±0.9	107.2±0.9	107.3±0.9	105.9±0.9	(3, 218)	14.4	**.000**	(1, 333)	6.0	**.015**	(15, 219)	1.1	.331	(3, 216)	2.3	.076
	Waist to hip ratio	369	0.93±0.01	0.92±0.01	0.92±0.01	0.92±0.01	(3, 229)	1.2	.314	(1, 344)	0.5	.483	(15, 228)	1.1	.382	(3, 225)	1.5	.208
Blood biomarkers (mmol/L)																		
	Fasting glucose	324	6.5±0.1	6.6±0.2	6.6±0.2	6.3±0.2	(3, 134)	2.3	.081	(1, 224)	1.8	.201	(15, 152)	0.8	.704	(3, 138)	0.5	.716
	Triglycerides	337	1.2±0.04	1.2±0.1	1.2±0.1	1.2±0.1	(3, 181)	0.4	.738	(1, 303)	1.2	.279	(15, 182)	0.7	.804	(3, 183)	1.1	.357
	HDL cholesterol	337	1.4±0.03	1.4±0.04	1.4±0.03	1.5±0.05	(3, 198)	1.9	.131	(1, 311)	0.2	.654	(15, 199)	1.0	.424	(3, 197)	0.8	.514
	LDL cholesterol	337	2.4±0.1	2.3±0.1	2.4±0.1	2.6±0.1	(3, 189)	3.7	**.012**	(1, 307)	0.04	.836	(15, 194)	1.1	.353	(3, 192)	1.5	.225
	Total cholesterol	337	4.8±0.1	4.8±0.1	4.8±0.1	4.8±0.1	(3, 193)	0.1	.964	(1, 323)	0.2	.661	(15, 212)	1.5	.141	(3, 194)	0.5	.663
	hsC-reactive protein	317	6.2±1.0	5.8±0.8	4.5±0.7	4.1±0.7	(3, 138)	2.2	.085	(1, 157)	0.6	.433	(15, 151)	0.8	.694	(3, 138)	2.0	.111

Table 5.6 Continued

Secondary outcome variables	n	BL	3 m	6 m	12 m	Time			Attendance			Time* Primary CD diagnosis			Time* SCD or MM		
						df	F	sig	df	F	sig	df	F	sig	df	F	sig
Psychological health																	
PHQ8	337	5.3±0.4	4.4±0.4	4.0±0.4	4.1±0.4	(3, 176)	5.9	**.001**	(1, 287)	15.8	**.000**	(15, 172)	1.8	**.038**	(3, 168)	0.4	.767
EQ-VAS	346	65.8±1.3	69.7±1.4	72.3±1.5	72.3±1.6	(3, 204)	9.1	**.000**	(1, 281)	11.9	**.001**	(15, 196)	0.9	.546	(3, 188)	0.4	.750
SWLS	338	23.7±0.5	24.5±0.5	25.2±0.5	24.5±0.6	(3, 186)	4.1	**.008**	(1, 294)	18.4	**.000**	(15, 185)	1.7	**.049**	(3, 176)	1.5	.225
SWEMWBS	338	26.6±0.3	26.7±0.4	26.5±0.4	27.0±0.5	(3, 168)	0.4	.762	(1, 312)	5.9	**.015**	(15, 172)	2.4	**.004**	(3, 161)	2.8	**.043**
Psychosocial determinants of PA																	
Barriers self-efficacy for exercise	347	60.6±1.5	55.0±2.1	54.9±2.2	56.0±2.4	(3, 186)	2.8	**.042**	(1, 301)	7.3	**.007**	(15, 182)	0.9	.568	(3, 172)	0.4	.568
Self-regulatory self-efficacy for exercise	299	77.1±1.5	74.8±1.7	71.2±1.8	72.2±2.2	(3, 179)	3.9	**.009**	(1, 269)	17.6	**.000**	(15, 173)	0.8	.727	(3, 164)	1.6	.184
Intentions for exercise	347	3.4±0.04	3.3±0.04	3.2±0.05	3.2±0.06	(3, 195)	5.8	**.001**	(1, 301)	10.6	**.001**	(15, 192)	1.6	.068	(3, 188)	0.4	.778
Family support for physical activity	356	2.4±0.1	2.5±0.1	2.4±0.1	2.3±0.1	(3, 197)	1.4	.235	(1, 317)	2.6	.108	(15, 206)	1.4	.143	(3, 195)	0.5	.684
Friend support for physical activity	324	2.2±0.1	2.4±0.1	2.2±0.1	2.4±0.1	(3, 213)	1.7	.158	(1, 292)	0.6	.434	(15, 208)	0.6	.864	(3, 185)	0.2	.884

Results are presented as estimated marginal means ± standard error.

Numbers in **BOLD** indicate $p < 0.05$.

Note: BL = baseline; 3 m = 3 months; 6 m = 6 months; 12 m = 12 months; BMI = body mass index; cir = circumference; 6MTT = 6 minute time trial; HDL = high density lipoprotein; LDL = low density lipoprotein; hsC-reactive protein = high sensitivity c-reactive protein; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQoL Visual Analogue Scale; SWLS = Satisfaction with Life Scale; SWEMWBS = The Short Warwick Edinburgh Mental Wellbeing Scale; PA = physical activity

Table 5.7 Summary of pairwise comparisons on secondary outcome variables with a significant main effect for time

Health-related measure	Timepoint	P	Standard error	df	C.I	Cohen's D
6MTT	BL – 3 m	**.000**	5.67	264.03	(-66.53, -36.39)	1.33
	BL – 6 m	**.000**	7.10	255.47	(-84.45, -46.71)	1.54
	BL – 12 m	**.000**	8.39	245.78	(-97.25, -52.63)	1.65
	3 m – 6 m	.058	5.41	216.24	(-28.52, 0.29)	0.41
	3 m – 12 m	**.009**	7.33	209.86	(-43.00, -3.95)	0.60
	6 m – 12 m	.822	6.27	170.85	(-26.09, 7.36)	0.29
Sit to stand	BL – 3 m	**.000**	.439	289.06	(1.55, 3.88)	0.24
	BL – 6 m	**.000**	.483	260.01	(1.93, 4,49)	0.29
	BL – 12 m	**.000**	.513	271.51	(1.38, 4.10)	0.23
	3 m – 6 m	1.00	.430	232.16	(-0.65, 1.64)	0.05
	3 m – 12 m	1.00	.419	199.14	(-1.09, 1.15)	0.00
	6 m – 12 m	1.00	.409	176.12	(-1.56, 0.62)	0.06
Handgrip	BL – 3 m	1.00	.355	274.37	(-1.24, 0.65)	0.03
	BL – 6 m	.108	.339	248.95	(-1.71, 0.09)	0.09
	BL – 12 m	**.024**	.400	220.42	(-2.23, -0.10)	0.12
	3 m – 6 m	.761	.334	233.27	(-1.40, 0.38)	0.06
	3 m – 12 m	.132	.376	212.90	(-1.87, 0.13)	0.10
	6 m – 12 m	1.00	.384	200.23	(-1.38, 1.40)	0.04
Waist circumference	BL – 3 m	**.000**	.408	257.87	(0.55, 2.72)	0.16
	BL – 6 m	**.003**	.422	252.29	(0.39, 2.63)	0.15
	BL – 12 m	**.000**	.586	233.74	(1.21, 4.33)	0.24
	3 m – 6 m	1.00	.379	224.43	(-1.14, 0.88)	0.01
	3 m – 12 m	.248	.553	223.31	(-0.34, 2.61)	0.10
	6 m – 12 m	.080	.508	200.74	(-0.09, 1.14)	0.13
Hip circumference	BL – 3 m	**.001**	.282	262.45	(0.37, 1.88)	0.13
	BL – 6 m	**.006**	.300	236.56	(0.21, 1.80)	0.12
	BL – 12 m	**.000**	.406	221.65	(1.40, 3.56)	0.26
	3 m – 6 m	1.00	.300	209.44	(-0.92, 0.68)	0.02
	3 m – 12 m	**.010**	.423	220.87	(0.23, 2.48)	0.14
	6 m – 12 m	**.000**	.362	162.79	(0.50, 2.44)	0.19
LDL cholesterol	BL – 3 m	.505	.091	209.73	(-0.08, 0.40)	0.04
	BL – 6 m	1.00	.088	218.01	(-0.18, 0.28)	0.01
	BL – 12 m	.452	.095	197.82	(-0.42, 0.08)	0.04
	3 m – 6 m	1.00	.097	202.93	(-0.37, 0.15)	0.02
	3 m – 12 m	**.008**	.100	176.80	(-0.40, -0.06)	0.08
	6 m – 12 m	.144	.096	176.11	(-0.48, 0.04)	0.05
PHQ8	BL – 3 m	**.015**	.312	215.00	(0.12, 1.79)	0.12
	BL – 6 m	**.001**	.328	222.62	(0.41, 2.15)	0.15
	BL – 12 m	**.012**	.384	204.84	(0.18, 1.23)	0.14
	3 m – 6 m	1.00	.301	160.65	(-0.48, 1.13)	0.05
	3 m – 12 m	1.00	.359	151.64	(-0.71, 1.21)	0.03
	6 m – 12 m	1.00	.359	166.34	(-1.03, 0.88)	0.01

Table 5.7 continued

Health-related measure	Timepoint	p	Standard error	df	C.I	Cohen's D
EQ-VAS	BL – 3 m	**.009**	1.23	240.44	(-7.23, -0.68)	0.23
	BL – 6 m	**.000**	1.47	222.23	(-10.52, -2.67)	0.36
	BL – 12 m	**.000**	1.57	212.76	(-10.75, -2.39)	0.36
	3 m – 6 m	.453	1.48	225.91	(-6.56, 1.29)	0.14
	3 m – 12 m	.627	1.48	200.51	(-6.88, 1.66)	0.15
	6 m – 12 m	1.00	1.64	203.38	(-4.35, 4.40)	0.00
SWLS	BL – 3 m	.356	.421	226.08	(-1.92, 0.32)	0.08
	BL – 6 m	**.003**	.437	213.09	(-2.69, -0.36)	0.16
	BL – 12 m	.883	.548	175.93	(-2.26, 0.67)	0.08
	3 m – 6 m	.585	.439	213.86	(-1.90, 0.44)	0.08
	3 m – 12 m	1.00	.524	144.73	(-1.45, 1.45)	0.00
	6 m – 12 m	1.00	.550	161.68	(-0.74, 2.20)	0.08
Barriers self-efficacy for exercise	BL – 3 m	.066	2.19	253.08	(-0.21, 11.42)	0.24
	BL – 6 m	.086	2.28	232.95	(-0.44, 11.67)	0.24
	BL – 12 m	.446	2.54	204.66	(-2.21, 11.30)	0.20
	3 m – 6 m	1.00	2.20	180.17	(-5.86, 5.88)	0.00
	3 m – 12 m	1.00	2.37	157.55	(-7.39, 5.28)	0.05
	6 m – 12 m	1.00	2.21	144.61	(-6.98, 4.84)	0.06
Self-regulatory self-efficacy for exercise	BL – 3 m	.801	1.54	227.18	(-1.78, 6.43)	0.12
	BL – 6 m	**.007**	1.80	224.99	(1.13, 10.71)	0.29
	BL – 12 m	.137	2.13	163.49	(-0.80, 10.60)	0.26
	3 m – 6 m	.163	1.62	195.85	(-0.71, 7.90)	0.20
	3 m – 12 m	.973	1.84	142.71	(-2.33, 7.49)	0.16
	6 m – 12 m	1.00	1.99	147.49	(-6.33, 4.30)	0.06
Intentions for exercise	BL – 3 m	.232	.051	280.45	(-0.03, 0.24)	0.03
	BL – 6 m	**.001**	.054	228.38	(0.07, 0.36)	0.06
	BL – 12 m	**.011**	.065	209.62	(0.03, 0.38)	0.06
	3 m – 6 m	.325	.056	198.75	(-0.04, 0.26)	0.03
	3 m – 12 m	.644	.060	157.15	(-0.06, 0.26)	0.03
	6 m – 12 m	.100	.060	157.39	(-0.17, 0.15)	0.00

Numbers in **BOLD** indicate $p < 0.05$.

Note: BL = baseline; 3m = 3 months; 6m = 6 months; 12m = 12 months; 6MTT = 6 minute time trial; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQoL Visual Analogue Scale; SWLS = Satisfaction with Life Scale; LDL = Low density lipoprotein

Physical Function

There was a significant main effect for time on 6MTT (p=0.000, Cohen's D=0.17), sit to stand (p=0.00, Cohen's D=0.14), and handgrip (p=0.011, Cohen's D=0.04). Performance in the 6MTT significantly improved between BL - 3 m (p=0.000, Cohen's D=1.33), BL - 6 (p=0.000, Cohen's D=1.54), BL - 12 m (p=0.000, Cohen's D=1.65) and 3 m - 12 m (p=0.009, Cohen's D=0.60). Sit to stand significantly improved between BL - 3 m (p=0.000, Cohen's D=0.24), BL - 6 m (p=0.000, Cohen's D=0.29) and BL - 12 m (p=0.000, Cohen's D=0.23). Handgrip significantly improved between BL - 12 m (p=0.024, Cohen's D=0.12). There were no significant associations between measures of physical function and attendance. There was a significant interaction effect for time*primary CD diagnosis on 6MTT (p=0.000, Cohen's D=0.57) (figure 5.5) and for time*SCD or MM on sit and reach (p=0.011, Cohen's D=0.08) (figure 5.6).

Individuals with cancer had a significantly higher 6MTT distance compared to all other primary CD diagnosis at BL, 3 m and 6 m ($p < 0.05$) and those with CVD (p=0.001) and respiratory disease (p=0.000) at 12 m. In addition, individuals with respiratory disease had a significantly lower 6MTT than those with CVD (p=0.001) at BL and those with CVD and metabolic disease at 3 m, 6 m and 12 m ($p < 0.05$) (Appendix I).

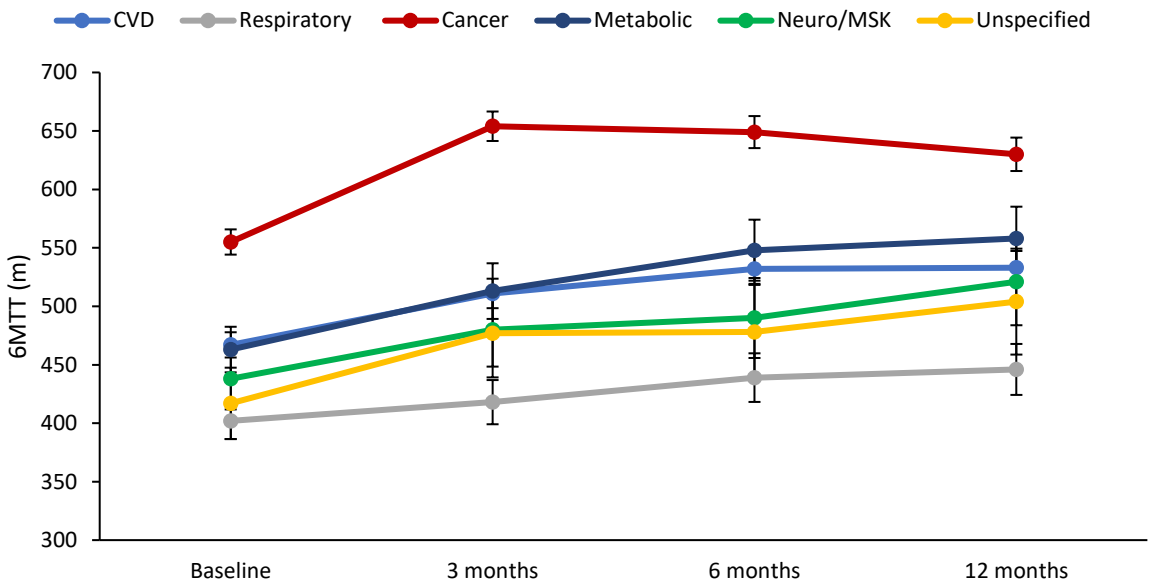

Figure 5.5 BL – 12m for primary chronic diseases diagnosis
Dates presented as estimated marginal means and SEM
Note: CVD = cardiovascular disease; Neuro/MSK = neuromuscular/musculoskeletal; m = meters

There were no significant differences between SCD and MM for the sit and reach test within the simple effects analysis.

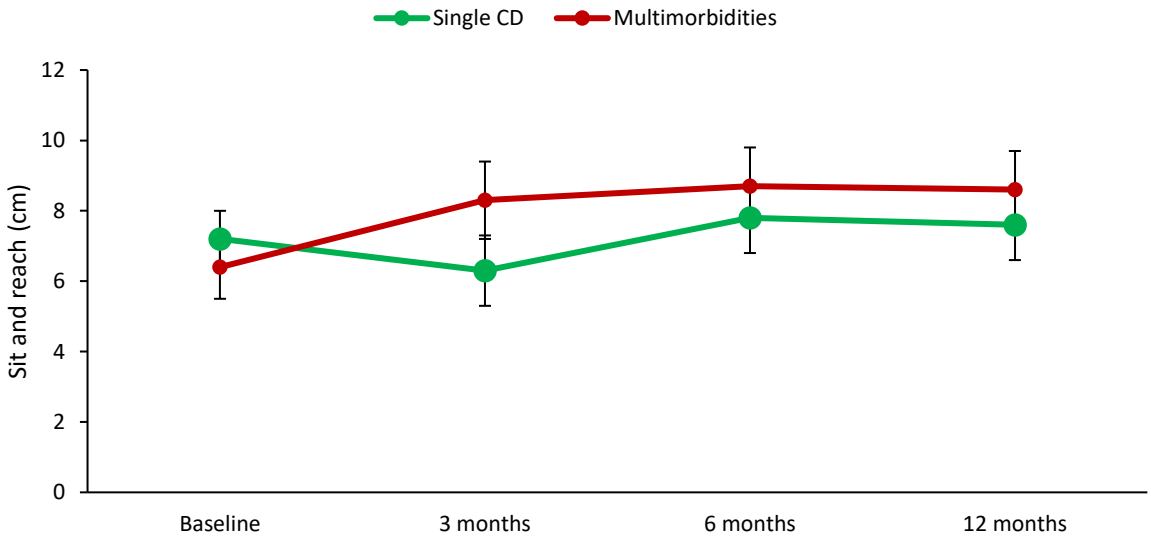

Figure 5.6 Sit and reach BL – 12m for single chronic disease and multimorbidity
Dates presented as estimated marginal means and SEM
Note: CD = chronic disease

Body Composition

There was a significant time main effect for waist circumference (p=0.000, Cohen's D=0.06) and hip circumference (p=0.000, Cohen's D=0.06). Waist circumference significantly decreased between BL - 3 months (p=0.000, Cohen's D=0.16), BL - 6 m (p=0.003, Cohen's D=0.15) and BL - 12 m (p=0.000, Cohen's D=0.24). Hip circumference significantly decreased between BL - 3 m (p=0.001, Cohen's D=0.13), BL - 6 m (p=0.006, Cohen's D=0.12), BL - 12 m (p=0.000, Cohen's D=0.26), 3m - 12 m (p=0.010, Cohen's D=0.14) and 6m - 12 m (p=0.000, Cohen's D=0.19). There was a significant inverse association between attendance and weight (p=0.041), BMI (p=0.041) and hip circumference (p=0.015).

Blood Biomarkers

There was a significant main effect for time on LDL (p=0.012, Cohen's D=0.02). LDL significantly worsened between 3 m - 12 m (p=0.008, Cohen's D=0.08).

Psychological Health

There was a significant main effect for time on PHQ8 (p=0.001, Cohen's D=0.09), EQ-VAS (p=0.000, Cohen's D=0.15) and SWLS (p=0.008, Cohen's D=0.08). PHQ8 improved between BL - 3 m (p=0.015, Cohen's D=0.12), BL - 6 m (p=0.001, Cohen's D=0.15) and BL - 12 m (p=0.012, Cohen's D=0.14). EQ-VAS improved between BL - 3 m (p=0.009, Cohen's D=0.23), BL - 6 m (p=0.000, Cohen's D=0.36) and BL - 12 m (p=0.000, Cohen's D=0.36). SWLS improved between BL - 6 m (p=0.003, Cohen's D=0.16). The was a significant inverse association between attendance and PHQ8 (p=0.000), and a significant positive association between attendance and EQ-VAS (p=0.001), SWLS (p=0.000) and SWEMWBS (p=0.015).

There was a significant interaction effect for time*primary CD diagnosis for PHQ8 (p=0.038, Cohen's D0.35) (figure 5.7), SWLS (p=0.049, Cohen's D=0.37) (figure 5.8) and SWEMWBS (p=0.005, Cohen's D=0.31) (figure 5.9). There was a significant interaction effect for time*SCD or MM on SWEMWBS (p=0.043, Cohen's D=0.08) (figure 5.10).

Individuals with respiratory disease had significantly higher PHQ8 score than those with cancer (p=0.043) at 3 m, CVD (p=0.022) and metabolic disease (p=0.025) at 6 m and those with CVD (p=0.000), metabolic disease (p=0.015) and cancer (p=0.000) at 12 m (Appendix J).

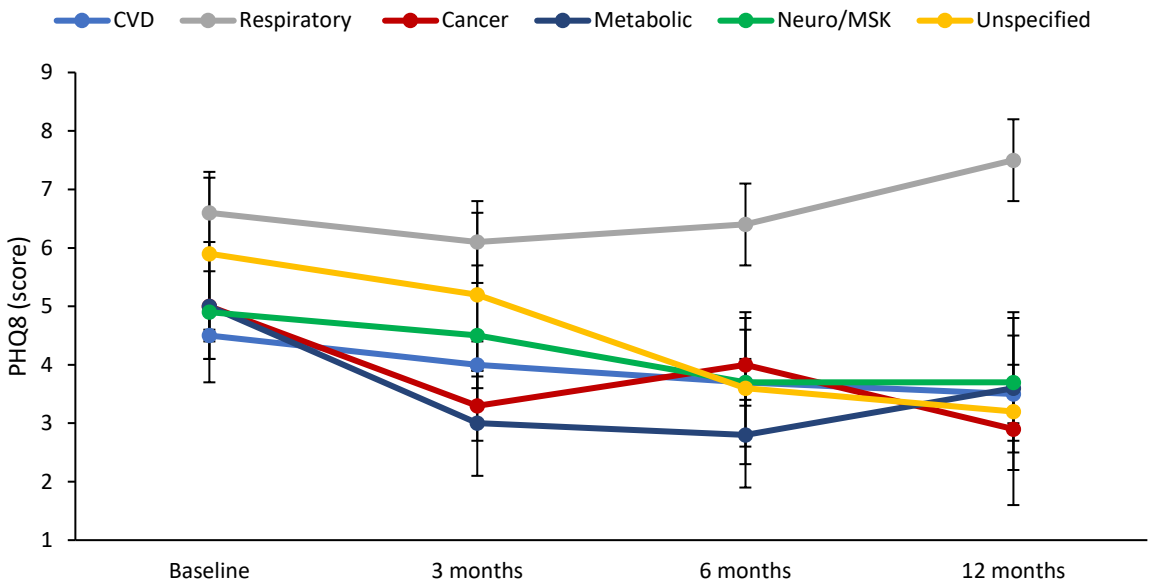

Figure 5.7 8-item Patient Health Questionnaire BL – 12m for primary chronic disease diagnosis
Dates presented as estimated marginal means and SEM
Note: CVD = cardiovascular disease; Neuro/MSK = neuromuscular/musculoskeletal; PHQ8 = 8-item Patient Health Questionnaire

Individuals with respiratory disease had significantly lower SWL scores than those with cancer ($p < 0.05$) at BL and 6 m, and those with CVD ($p=0.049$) and cancer ($p=0.000$) at 12 m (Appendix K).

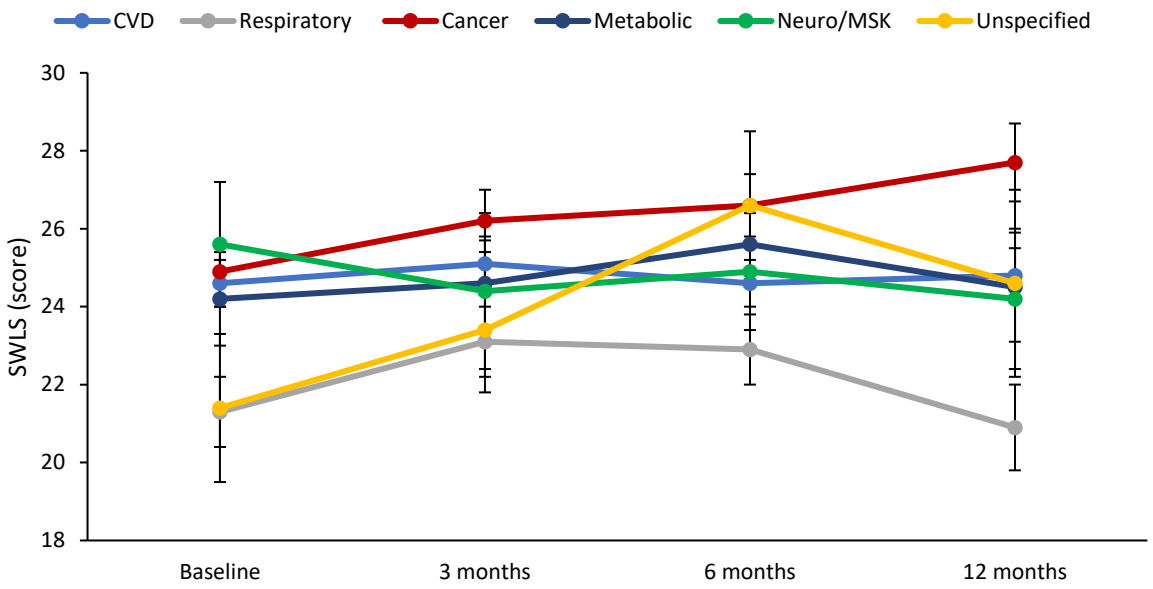

Figure 5.8 Satisfaction with Life Scale BL – 12m for primary chronic disease diagnosis
Dates presented as estimated marginal means and SEM
Note: CVD = cardiovascular disease; Neuro/MSK = neuromuscular/musculoskeletal disorders; PHQ8 = 8-item Patient Health Questionnaire

Individuals with respiratory disease had significantly lower SWEMWBS scores than those CVD (p = 0.008) and cancer (p = 0.001) at 12 m (Appendix L).

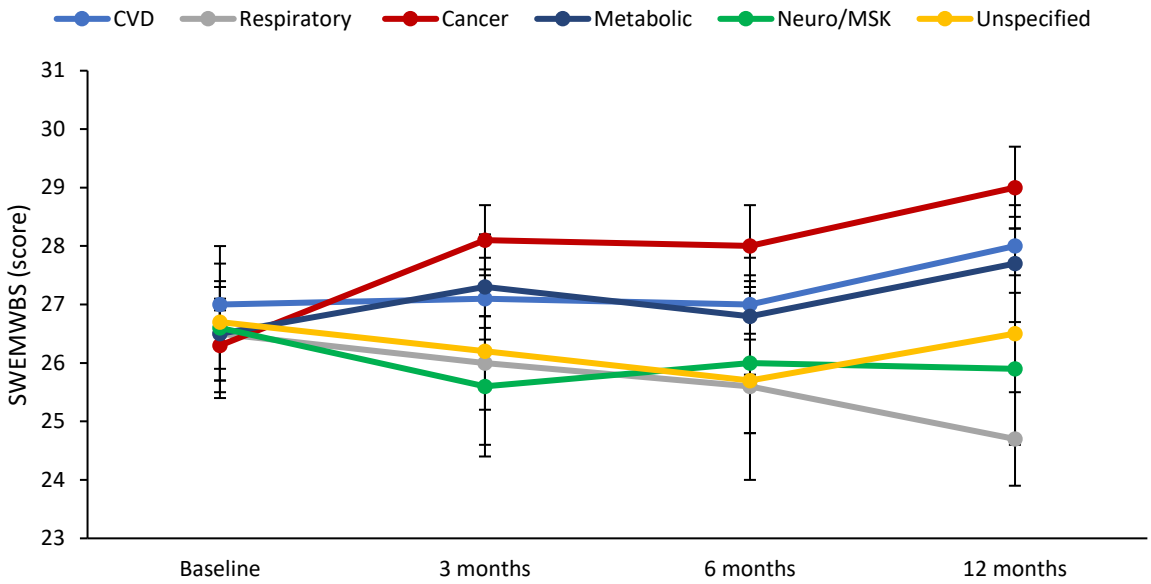

Figure 5.9 The Short Warwick Edinburgh Mental Wellbeing Scale BL – 12m for primary chronic disease diagnosis

Dates presented as estimated marginal means and SEM

Note: CVD = cardiovascular disease; Neuro/MSK = neuromuscular/musculoskeletal disorders; SWEMWBS = The Short Warwick Edinburgh Mental Wellbeing Scale

There were no significant differences identified between those with SCD and MM for the SWEMWBS within the simple effects analysis.

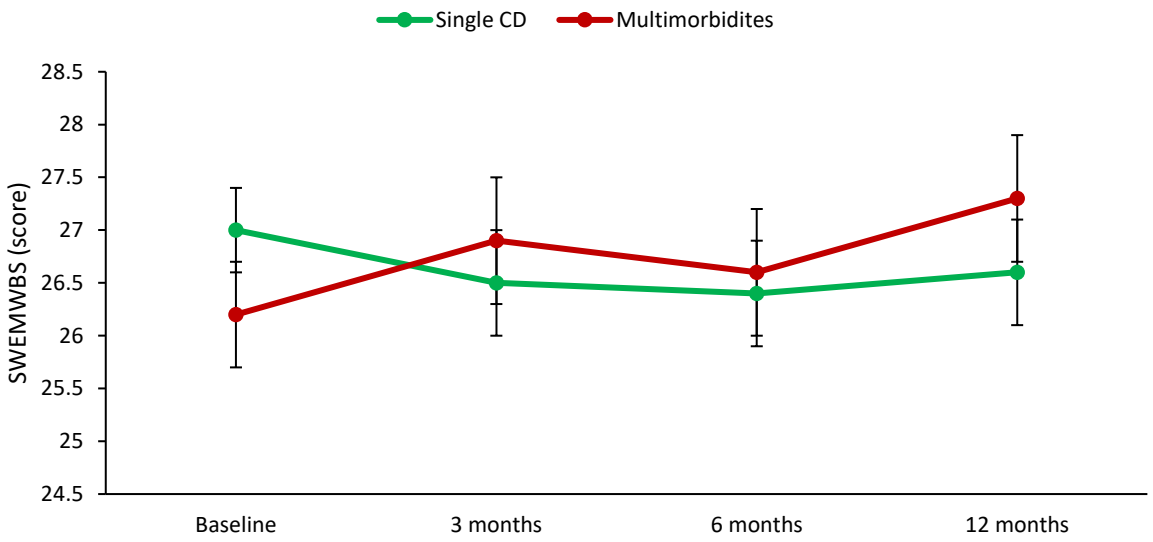

Figure 5.10 The Short Warwick Edinburgh Mental Wellbeing Scale BL – 12m single chronic disease and multimorbidity
Dates presented as estimated marginal means and SEM
Note: CD = chronic disease; SWEMWBS = The Short Warwick Edinburgh Mental Wellbeing Scale

Psychosocial Determinants of Physical Activity

There was a significant main effect for time on barrier self-efficacy for exercise (p=0.042, Cohen's D=0.10), self-regulatory self-efficacy for exercise (p=0.009, Cohen's D=0.11) and intentions for exercise (p=0.001, Cohen's D0.17). Self-regulatory self-efficacy for exercise decreased between BL - 6 m (p=0.007, Cohen's D=0.29) and intentions for exercise significantly decreased between BL - 6 m (p=0.001, Cohen's D=0.06) and BL - 12 m (p=0.011, Cohen's D=0.06). Post hoc analysis did not indicate any significant differences in timepoints for barrier self-efficacy for exercise. There was significant positive association between attendance and barrier self-efficacy (p=0.007), self-regulatory self-efficacy (p=0.000) and intentions for exercise (p=0.001).

Psychosocial determinants of physical activity

Change in MVPA was positively correlated with both change in self-regulatory self-efficacy for exercise (*r* = 0.264, p=0.030) and the change in intentions for exercise (*r* = 0.321 p=0.003). Change in step count was significant correlated with the change in self-regulatory self-efficacy for exercise (*r* = 0.252, p=0.026) and the change in intentions for exercise (*r* = 0.319 p=0.003). Results are displayed in table 5.8.

Table 5.8 Correlation between change in measures of physical activity and psychosocial determinants of physical activity between baseline - 12 months

	LIPA		**MVPA**		**Step count**	
Psychosocial determents of physical activity	***r***	**p**	***r***	**p**	***r***	**p**
Barriers to self-efficacy for exercise	.063	.570	.202	.068	.177	.110
Self-regulatory self-efficacy for exercise	.100	.385	.246	**.030**	.252	**.026**
Intentions for exercise	.204	.065	.321	**.003**	.319	**.003**
Family support for physical activity	.069	.650	.177	.238	.178	.238
Friend support for physical activity	.124	.554	.202	.333	.195	.349

Note: LIPA = light intensity physical activity, MVPA = moderate to vigorous physical activity
Note: Results are not adjusted for multiple testing

Discussion

Participation in the MedEx Wellness CBER program was associated with a significant increase in LIPA, number and time spent in sedentary bouts of 11-30 min and total number of sedentary bouts. The observed effect size for all changes in PA and SB was small. Greater attendance to the program was associated with improvements in LIPA, MVPA, step count, time in sedentary bouts > 60 min. Significant improvements were also observed in measures of physical function, body composition and psychological health. Again all observed effect sizes where small, apart from CRF were a large effect size was identified for the change in this measures. With the exception of an increase in LDL-C, there was no significant change in any other of the other measured biomarkers. In addition, significant decreases in psychosocial determinants of PA were observed. Greater attendance was associated with improvements in body composition, all measures of psychological health, barrier self-efficacy for exercise, self-regulatory self-efficacy for exercise and intentions for exercise. Improvements occurred within 3 to 6 months of participation and were maintained at 12 months of participation. Significant interaction effects for time*primary CD diagnosis were observed for the CRF, symptoms of depression, satisfaction with life and positive mental health. The cancer cohort had higher CRF fitness across all timepoints, while those with respiratory disease were had significantly lower. Moreover, those with respiratory disease had less favourable measures of satisfaction with life and positive mental health. Significant interaction effects for time*SCD or MM were found for flexibility and positive mental health, however simple effects analyses did not indicate and differences between these groups.

The findings from this study provide evidence that an integrated delivery model of CBER is an effective approach to increasing PA levels, reducing SB and improving physical

functioning, body composition and positive mental health for individuals with a range of CDs and MM. Improvements in health-related outcomes as a result of CBER has been well documented in SCD cohorts (Gallé et al., 2019; Mendes et al., 2016, 2017; Bethell & Mullee, 1990; Cramp et al., 2010; Kwan et al., 2016; Marsden et al., 2016; Taylor et al., 2016a; Amin et al., 2014; Beauchamp et al., 2013; Godtfredsen et al., 2019; Varas et al., 2018; Foley & Hasson, 2016; Foley et al., 2018; Knobf et al., 2014; Leach et al., 2015; Rajotte et al., 2012; Santa Mina et al., 2017). Surprisingly, relatively few studies have investigated the effects of CBER on habitual levels of PA and SB. The current findings indicate that CBER has the potential to positively impact both PA and SB. LIPA improved significantly, however whether the improvements are clinically meaningful is worth noting as the mean daily increase in LIPA between BL and 12 m was approximately 6 min. Furthermore, the findings provide preliminary evidence for the efficacy of a shared delivery model of CBER as a viable strategy in the secondary prevention of CD for those with both SCD and MM. Future studies should focus on optimising the various components of the MedEx Wellness shared CD model in order to inform best practice for CBER.

Chapter 6

Study III

Factors Associated with Inter-Individual Variability in Response to Community-Based Exercise in a Diverse Chronic Disease Population

Introduction

PA and CRF are major indicators of health status and risk of mortality for healthy populations and those with CD (Bossenbroek et al., 2011; Laukkanen et al., 2002; Warburton et al., 2006). Despite the strong evidence for PA and CRF, individuals with CD are reported to participate in low levels of PA (Hains-Monfette et al., 2019; Lauret et al., 2014; Lewis et al., 2016; Pitta et al., 2005; Segura-Jiménez et al., 2015).

CBER has been shown as an effective approach in increasing PA and CRF among individuals with CD (Gallé et al., 2019; Marsden et al., 2016; Pang et al., 2005; Santa Mina et al., 2017; Varas et al., 2018). Results from studies examining the health-related changes in CD populations in response to PA interventions are normally presented as average statistics. However, there is normally large inter-individual variability in the measured outcomes in response to these programs. In pulmonary rehabilitation research, approximately 25-30% of patients may be considered non-responders, where non improvements are observed in terms of health status and exercise tolerance (Garrod et al., 2006; Stoilkova-Hartmann et al., 2015). To date, there is currently a limited understanding of the factors that may predispose individuals with CD at an increased risk of non-response to CBER.

The term non-responder can be defined as the lack of a clinically meaningful change or the lack of a measurable change (Pickering & Kiely, 2019). Of greatest concern for healthcare professionals are adverse responses to exercise rehabilitation. Adverse training responses have been reported during exercise rehabilitation studies. In a review article of 6 exercise interventions, Bouchard *et al*., (2012), found that 31% of participants had at least one adverse response, 6.0% had two and 0.8% showed ≥ 3 adverse responses. In a 14 week CBER program for individuals with metabolic syndrome, where mean waist circumference, fasting glucose, HDL-C, TG and BP all significantly improved post intervention, the prevalence of an adverse cardiometabolic response was between 3.6% - 6.0% (Dalleck et al., 2015). This is considered low, and the general consensus is that severe adverse events are very rare in exercise rehabilitation programs that follow evidence-based practice.

Further research is warranted to identify factors within a CD population associated with response to CBER. Understanding both the genetic and non-genetic factors associated with inter-individual variability in response to exercise based rehabilitation programs will inform potential measure that could be deployed to reduce the number of non-responders. Non-genetic factors that could help to explain the inter-individual variability in response to exercise based rehabilitation include body weight, BL fitness, training history, training program, exercise prescription, nutritional status and mental health (Pickering & Kiely, 2019). Mann *et al*., (2014) undertook a detailed review on the phenomenon of 'high-responders' and 'low-responders' and suggested a better understanding of non-genetic training determinants of training responses would allow for the more individually tailored approach that would ensure optimal outcomes for all participants. Establishing the non-genetic factors associated with non-response to CBER could inform screening procedures that could be

implemented into such programs. This would allow for high risk participants of non-response to be identified from the onset and allow for strategies to be put in place which could reduce the risk of non-response. The current evidence base on the factors associated with non-response however, remains under developed.

The minimum clinically meaningful change, refers to changes in health-related outcomes as a result of treatment or intervention, which are meaningful to a CD patient or have importance in the clinical management for the patient (Cook, 2008; Sedaghat, 2019). It is not uncommon for statistically significant changes to have little clinical significance for patient cohorts (Jaeschke et al., 1989). Minimum clinically meaningful changes provide healthcare professionals with a systematic approach to interpreting certain treatment effects. A responder is the term used to describe a patient who has achieved a clinically meaningful improvement in a given health-related outcome (Copay et al., 2007).

For patients with CD, the mediating role of PA in optimizing health is also of clinical importance. From a functional prospective, regular PA promotes mobility and reduces the risk for falls and fractures, which is vital in prevented dependency and institutionalisation in old age (Paterson & Warburton, 2010). For individuals with CD, maintaining independent living and preserving functional capacity, has direct implications on QoL and psychological health (Maresova et al., 2019). In addition, PA can attenuate the risk of developing MM, for those with an already established CD (Dhalwani et al., 2016). In terms of a PA intervention for CD, results which indicate no change, and therefore maintenance of health status also could be considered a positive result.

A recent study found that only 50% of CD patients attending exercise rehabilitation achieved clinically meaningful changes in 6MWT distances, at the end of the program (Barker *et al*., 2018). In addition, this study reported significant improvements in ability to perform activities of daily living, however only one third of participants improved to a level established as clinically meaningful in this measure. Although a third of participants achieving a clinically meaningful improvement as a result of an intervention may be considered an effective intervention, there is a need to understand why certain participants attain a beneficial response while others do not. The translation of evidence based interventions into clinical practice is a major challenge within clinical research. Developing strategies that optimes the patient response to interventions will assist in bridging this gap. To date, little information is available regarding the inter-individual responses to exercise rehabilitation programs involving patients with more than one CD. Although shared exercise rehabilitation offers numerous benefits, identifying factors associated with meaningful biological and behavioural responses could assist in program design and delivery.

The primary aim of this study was to identify factors associated with an effective response to participation in a CBER, in terms of a measurable improvement, in men and women with SCD and MM. A secondary aim was to establish the minimum attendance at CBER needed to achieve measurable/clinically meaningful changes in selected indices of health. It was hypothesized that inter-individual variability in physical (activity behaviours and physical functioning), clinical or psychological health between men and women with SCD and MM will predict response to CBER.

Methods

The study used a quasi-experimental study. Detailed methodology is described in Chapter 3. In summary, individuals with one or more established CDs, primarily CVD, respiratory disease, metabolic disease, cancer or neuro/MSK disorders, were recruited at induction to the MedEx Wellness programme following referral from healthcare professionals. Following induction, participants were recommended to attend 2 supervised group exercise classes per week. The classes were 60 min in duration and consisted of a combination of aerobic and resistance exercise. Outcome measures that included PA, SB, physical function, blood biomarkers, mental health and psychosocial determinants of PA were assessed at BL and 3, 6 and 12 months.

Health related outcomes that improved significantly in response to participation in a CBER program (chapter 5), were selected as dependent variables and used to explore predictors of achieving a measurable improvement. The health related outcomes included were LIPA, CRF, lower body strength, upper body strength, waist circumference, hip circumference, number and time spent in sedentary bouts 11 to 30 min in duration, total number of sedentary bouts, symptoms of depression, self-rated health and satisfaction with life (Appendix M). Outcome variables that changed significantly, but unfavourably were not explored in further analysis. These included LDL-C, barriers to self-efficacy for exercise, self-regulatory self-efficacy for exercise and intentions for exercise showed. The statistical analysis in chapter 5 indicated that there was a significant time main effect for the number of classes attended and time spent in sedentary bouts 11 to 30 min in duration and the total

number of sedentary bouts. However, as the post hoc analysis did not identify specific time points of significant chances, these variables were not included in further analysis.

In study 2 (chapter 5) a significant association was found between total number of classes attended between BL and 12 months and LIPA, MVPA, step count, time spent in sedentary bouts < 60 min, weight, BMI, hip circumference, symptoms of depression, self-rated health, satisfaction with life, positive mental health, barriers to self-efficacy for exercise, self-regulatory self-efficacy for exercise and intentions for exercise (appendix N). These variables were selected to estimate the approximate number of attendance to MedEx Wellness classes requires to achieve a measurable change and a clinically meaningful change in each individual outcome measure. Defining a clinically meaningful change in barriers to self-efficacy for exercise, self-regulatory self-efficacy for exercise and intentions for exercise was deemed inappropriate and these variables were analysed in terms of a measurable change only.

A measurable change was defined as an improvement in a health-related outcome of ≥0.01. A clinically meaningful change was defined as an improvement identified to have a meaningful impact on a participants health status, functional capacity and/or QoL. A non-responder referred to participants who did not change from BL or regressed between BL and 12m.

Minimum clinically meaningful change

Evidence based publications were reviewed to establish a threshold which could be used to represent a minimum clinically meaningful improvement for each outcome variable.

Physical activity and sedentary behaviour

Light intensity physical activity

The volume of LIPA required to elicit health benefits is not yet known, and recommendations do not yet exist on the clinically meaningful change in LIPA for healthy populations or CD cohorts. There is however, accumulating evidence to indicate that health-related benefits of increasing LIPA are possibly independent to the amount of MVPA performed. Khoja *et al*., (2016) found independent associations between LIPA and a variety of cardiometabolic health markers in patients with rheumatoid arthritis. Each additional min of LIPA per day was associated with improvements in BMI, BP, insulin sensitivity, HDL-C and disability. The PA and SB patterns of this cohort (9.8 h/d sedentary, 3.5 h/d in very low intensity activity, 2.1 h/d in LIPA and 36 min/d in MVAP) were comparable to the PA and SB reported of the mixed chronic disease cohort of the current study (results chapter 4, study 1). Furthermore, each one min increase in LIPA/h during the waking day, was found to decrease the risk of mortality in healthy population and those with chronic kidney disease (Beddhu *et al*., 2015). Based on these findings, an increase in LIPA of ≥ 16 min/d was used as a threshold for a clinically meaningful change in LIPA.

Moderate to vigorous physical activity

Strong evidence supports that even small increases in MVPA can confer significant health-benefits for individuals with CD (Warburton & Bredin, 2016). A generalized minimum clinically meaningful change has yet to be established for MVPA. Hur *et al*., (2019) recently estimated that an increase in MVPA of 26 min/week as the minimally important clinically

meaningful difference for patients with interstitial lung disease. An increase of ≥ 26 min/week in MVPA between BL and 12 months was used as a threshold for a clinically meaningful change in MVPA.

Step count

Estimations of clinically meaningful changes in step count are limited, particularly in CD. A study in COPD estimated the minimal clinically important change for COPD to range between 600 to 1100 steps/day (Demeyer et al., 2016). An increase in daily step count of ≥ 1100 was used as a threshold for a clinically meaningful change in MVPA.

Time in sedentary bouts > 60 min

Guidelines recommending changes in SB are yet to be established. A recommendation of reducing total SB by 60 min a day has been proposed (Dempsey et al., 2016). As there are no specific evidence based recommendations applicable to time spent in sedentary bouts > 60 mins, only a measurable change in this variable was analysed.

Physical function

Six minute timed trial

Self-paced walk run tests have been established as valid tool for estimating CRF (Mayorga-Vega et al., 2016). The current study used a modified version of the 6 min walk test, in which participants where allow to run, walk or a combination of both to complete the test.

Numerous studies have established a clinically meaningful change in the 6 min walk test across a variety of disease groups. There estimations range from 34.3 m to 82 m in studies including Alzheimer's disease, geriatric participants, stroke, osteoporosis, Parkinson's disease and pulmonary diseases (Eng et al., 2004; Flansbjer et al., 2005; Kennedy et al., 2005; Perera et al., 2006; Rasekaba et al., 2009; Redelmeier et al., 1997; Ries et al., 2007; Steffen & Seney, 2008). More recently, in a systematic review by Bohannon and Crouch (2017) the minimal clinical change for 6MWT was estimated as between 14 – 30.5 m across multiple patient groups.

Based on the Bohannon and Crouch's most recent research, incorporating a mixed CD cohort, which is a useful comparison to the current study, an improvement of ≥ 30.5 m was used as a threshold for a clinically meaningful change in 6MTT. Caution with the interpretation of this analysis is considered as the current estimate is based on the walk only test.

Sit to stand

The present study used a 10-repatition protocol for the sit to stand test. Based on the 5 repetition sit to stand test, minimal clinical different ranges from -1.7 s to 3.1 s (Jones et al., 2013b; Vaidya et al., 2017). A decrease in time of ≥ 3.1 s was used as a threshold for a clinically meaningful change in sit to stand. Similar to the 6MTT, caution with the interpretation of this analysis is considered as the current estimate is based on the 5 repetition sit to stand test.

Handgrip

Clinically meaningful changes in handgrip strength using a handgrip dynameter have been estimated to range from 5.0 kg – 6.2 kg in healthy populations and those with CD (Bohannon, 2019; Lang et al., 2008; Nitschke et al., 1999). A threshold improvement of ≥ 5.0 kg was used as a threshold for a clinically meaningful change in handgrip.

Body composition

Weight

A 5% reduction in weight from a BL measures has been defined as clinically significant and is associated with significant improvements cardiometabolic health (Donnelly et al., 2009; Williamson et al., 2015). A threshold of ≥ 5% reduction in weight was as a threshold for a clinically meaningful change in weight.

Note: Changes in BMI between BL and 12 m in the present study will be fundamentally the product of changes in weight as BMI is a composite score which includes weight as a primary component. BMI was not included in further analysis.

Waist Circumference

Verweij *et al*., (2013) suggest that a clinically meaningful change in waist circumference lies within the range of 3.0 cm and 6.8 cm. Cerhan *et al*., (2014) found in a pooled analysis of 650,000 adults, that for each 5 cm increment in waist circumference the risk of mortality in men and women increased by 7% and 9% respectively, independent of

BMI. A decrease in waist circumference of 5 cm was used as a threshold for a clinically meaningful change in waist circumference.

Hip Circumference

The focus on changes in body composition, with regards to waist and hip measurements, have primarily focused on waist circumference and WHR (World Health Organization, 2011b). Hip circumference alone does not effectively represent body composition (Mbanya et al., 2015), and was therefore not included in further analysis.

Psychological health

8-item Patient Health Questionnaire

The PHQ8 categorizes individuals by severity of depression ranging from none/minimal to severe. A 5 point decrease indicates an improvement in severity category (Kroenke & Spitzer, 2010). A decrease in score of ≥ 5 was used as a threshold for a clinically meaningful change in PHQ8.

EuroQoL-Visual Analogue Scale

Zanini *et al*., (2015) estimated a minimal clinically important change in EQ-VAS scores, for patients with COPD as an increase of eight points. Similarly, Chen *et al*., (2016a) a minimal clinically important different in stroke patients as 8.6 to 10.8 points. An increase in score of ≥ 10 points was used as a threshold for a clinically meaningful change in EQ-VAS.

Satisfaction with Life Scale

The satisfaction with life scale is a measurement tool of the life satisfaction component of subjective wellbeing. Total scores are accumulated and results range from "extremely satisfied" to "extremely dissatisfied". An increase in score ≥ 5 results in an improvement in overall life satisfaction (Diener, 2006). An increase in score of ≥ 5 was used as a threshold for a clinically meaningful change in SWLS.

The Short - Warwick Edinburgh Mental Wellbeing Scale

The SWEMWBS is a tool used to monitor positive mental health. The minimal detectable change in the SWEMWBS is estimated as a change in score by ≥ 3 points (Warwick Medical School, 2019). An increase in score of ≥ 3 points was used as a threshold for a clinically meaningful change in SWEMWBS.

Statistical analysis

Health-related outcomes where a significant main effect for time was identified in study 2 (chapter 5) were used to classify participants in groups representing response category, based on absolute change achieved. The absolute change between BL and 12 months for measures of 6MTT, sit to stand, handgrip, waist circumference, PHQ8 and EQ-VAS, and between BL and 6 months for measures of LIPA and SWLS was computed on IMB SPSS statistics software (version 25). Participants were classified into three groups for descriptive analysis: i) non-responder = no change in measure variables or a negative change, ii) measurable change = any observed improvement in measured variable iii) clinically

meaningful change = an improvement equal to or above the identified clinically meaningful value in the measured variable.

Binary logistic regression models were used to assess factors associated with achieving a measurable change in health-related outcomes where a significant main effect for time was found in study 2 (chapter 5). Based on the absolute change of each health-related measure, participants where stratified into 2 groups: 0 = non-responder; 1 = measurable change achieved. The dichotomous variables representing non-response or measurable change achieved were used as dependent variables in binary logistic regression. Age, sex, primary CD diagnosis, SCD or MM, smoking status and BL measures of the specific dependent variable were included as independent variables. Contingency table results were used to estimate the accuracy of the predictive model, based on the percentage of cases correctly classified. The model discrimination was assed using relative operating characteristics (ROC) curves. The area under the curve (AUC) was generated using the predicted probabilities values (test variable) and non-response or measurable change achieved (state variable) (Chan, 2004). The ROC analysis results were interpreted as follows: AUC ≥ 0.60 indicated poor discriminatory ability, AUC = 0.61 – 0.70 fair discriminatory ability and AUC > 0.70 = good discriminatory ability (Mandrekar, 2010). P-values reported were not adjusted for multiple testing.

Health-related variables where a significant main effect for attendance was identified in study 2 (chapter 5), were investigated to assess if a corresponding attendance value could be estimated which is associated with achieving a measurable change and a clinically meaningful change. The absolute change between BL and 12 months for LIPA, MVPA,

step count, weight, BMI, PHQ8, EQ-VAS, SWLS, WEMWBS, Barriers to Self-Efficacy for Exercise Scale, Self-Regulatory Self-Efficacy for exercise and Intentions for Exercise were computed using SPSS statistical package v25. Based on the absolute change of each health-related measures and psychosocial determinant of PA, participants where stratified into 2 groups representing non-response (0 = non-responder) and achieving a measurable change (1 = measurable change achieved). In addition, based on the absolute change of each health-related measures, participants were stratified in to 2 groups representing non-response (0 = non-responder) and achieving a clinically meaningful change (1 = clinically meaningful change achieved). Dichotomous variables were used in binary logistic regression models as dependent variables. Number of sessions attended between BL and 12 months were used as independent variables. The intercept value for each model was divided by the parameter estimate to calculate the point in attendance that corresponds to a change from non-response to both achieving a measurable change and a clinically meaningful change. Only models with a $p > 0.05$ were interpreted to estimate number of attendance required for achieving a measurable change or a clinically meaningful change. P-values reported were not adjusted for multiple testing.

Results

A total of 403 participants were recruited for this study with 206 participants completing the trial. Participant characteristics are presented in the results section of chapter 4 and reasons for drop out are presented in the results section of chapter 5. In summary, the mean age was 62.98 ± 11.00 years and 50.6% were male. The prevalence of achieving a positive measurable change in ≥1 health-related variable was 92.2%. In addition, 86.4% of participants achieved a measurable change in ≥ 1 health-related variable while also being categorized as a non-responder in another.

Predictors of achieving a measurable change

Light Intensity Physical Activity

A total of 121 participants had valid BL and 6 months LIPA data, with 38.0% classified as non-responders (a decrease in LIPA ≥ 0 hr) and 62.0% achieving a measurable change (an increase in LIPA ≥ 0.01 hr) (figure 6.1). A clinically meaningful improvement in LIPA was achieved by 25.6% of participants (an increase in LIPA ≥ 0.26 hr).

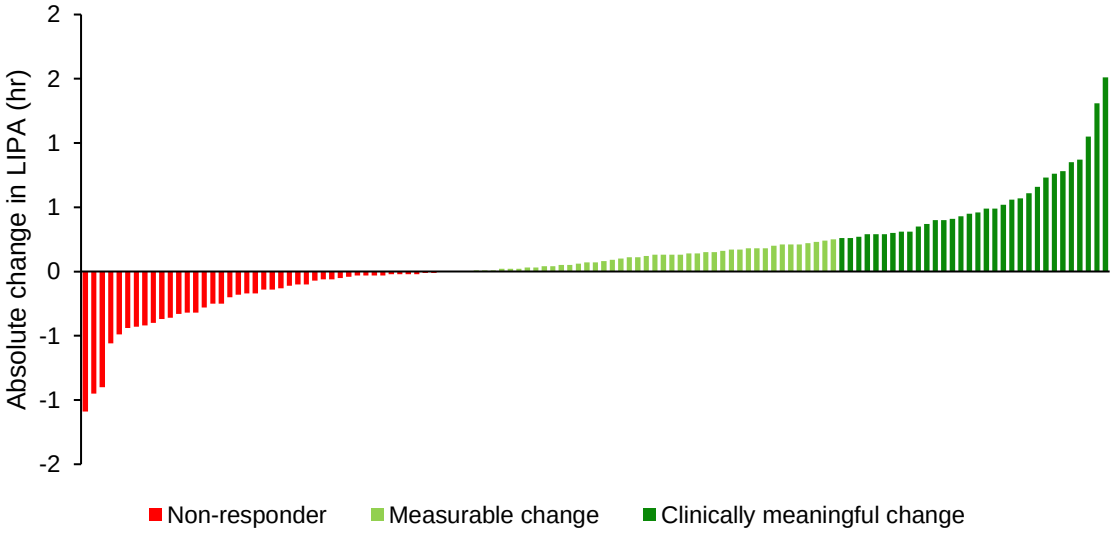

Figure 6.1 Inter-individual variability for change in light intensity physical activity between baseline and 6 months
Note: LIPA = light intensity physical activity; hr = hours

The logistic regression was statistically significant $X^2(11) = 27.51$, p=0.004. The model correctly classified 68.7% of cases. The AUC for predicted probabilities was 0.76 (SE 0.05, p=0.000, 95% CI 0.67 – 0.85). A lower BL LIPA increased the likelihood of achieving a measurable increases in LIPA (ß=-1.65, OR 0.19, 95% CI 0.06 – 0.60, p=0.005). In addition, a primary CD diagnosis of metabolic disease decreased the likelihood of achieving a measurable change in LIPA (ß=-2.73 OR 0.07, 95% CI 0.01 – 0.73, p=0.027).

6 minute timed trial

A total of 198 participants completed the 6MTT at BL and 12 months, with 19.2% classified as non-responders (a decrease in 6MTT ≥ 0 m) and 80.8% achieving a measurable change (an increase in 6MTT ≥ 0.01 m) (figure 6.2). A clinically meaningful change in 6MTT was achieved by 65.7% of participants (an increase in 6MTT ≥ 30.5 m).

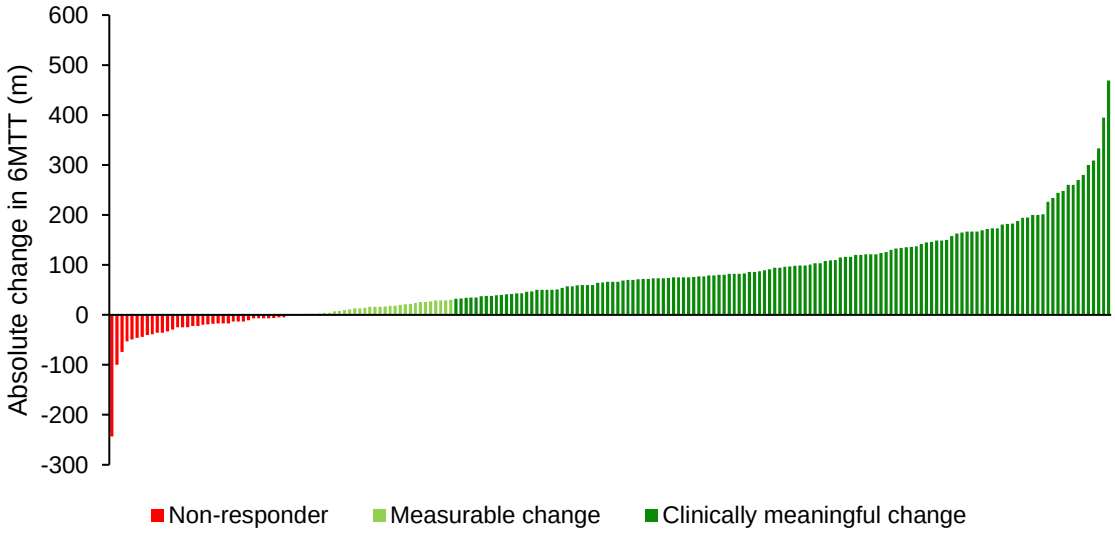

Figure 6.2 Inter-individual variability for change in six minute timed trial between baseline - 12 months
Note: 6MTT = 6 minute timed trial; m = metres

The logistic regression was statistically significant $X^2(11) = 24.97$, p=0.009. The model correctly classified 81.8% of cases. The AUC for predicted probabilities was 0.76 (SE 0.05, p=0.000, 95% CI 0.68 – 0.84). Increasing age reduced likelihood of achieving a measurable change in 6MTT (ß=-0.08, OR 0.93, 95% CI 0.87 – 0.98, p=0.008) and lower 6MTT at BL reduced likelihood of achieving a measurable change (ß=0.01, OR 1.01, 95% CI 1.00 – 1.04, p=0.022).

Sit to stand

A total of 201 participants completed sit to stand at BL and 12 months, with 20.9% classified as non-responders (an increase in STS ≥ 0 sec) and 79.1% achieving a measurable change (a decrease in STS ≥ 0.01 sec) (figure 6.3). A clinically meaningful change in sit to stand was achieved by 54.7% of participants (a decrease in STS ≥ 3.1 sec).

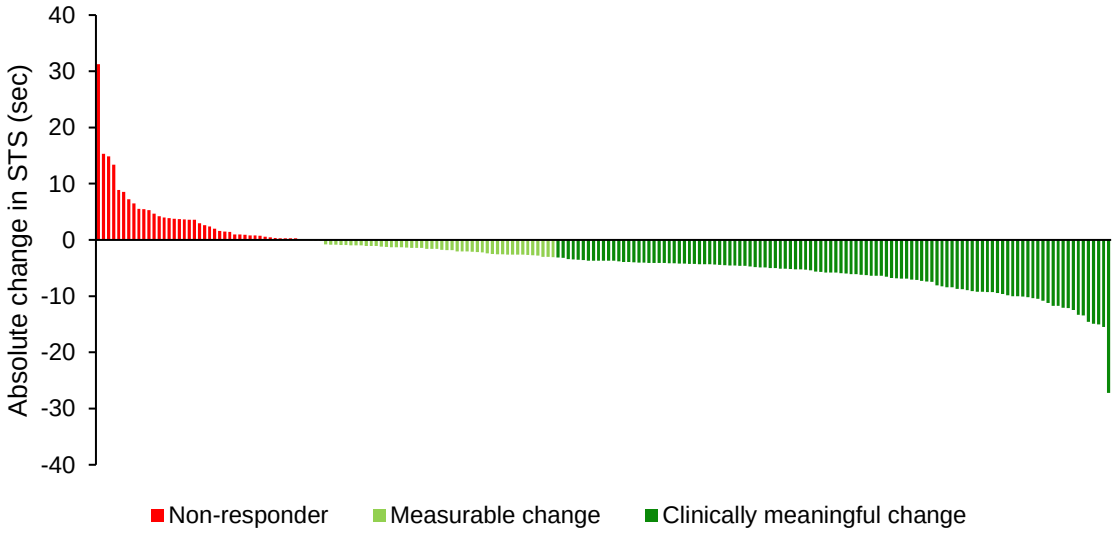

Figure 6.3 Inter-individual variability for change in sit to stand between baseline - 12 months
Note: STS = sit to stand; sec = seconds

The logistic regression was statistically significant $X^2(11) = 25.19$, p=0.009. The model correctly classified 81.5% of cases. The AUC for predicted probabilities was 0.74 (SE 0.04, p=0.000, 95% CI 0.66 – 0.83). A higher BL sit to stand score, an indication of decreasing lower body strength, increased likelihood of achieving a measurable change in sit to stand (ß=0.12, OR 1.13, 95% CI 1.04 – 1.23, p=0.006). In additional, a primary CD diagnosis of cancer increased the likelihood of achieving a measurable change in sit to stand (ß=2.10, OR 8.17, 95% CI 1.14 – 58.37, p=0.036).

Handgrip

A total of 205 participants completed handgrip at BL and 12 months, with 42.9% classified as non-responders (a decrease in HG ≥ 0 kg) and 57.1% achieving a measurable change (an increase in HG ≥ 0.01 kg) (figure 6.4). A clinically meaningful change in handgrip was achieved by 17.6% of participants (an increase in HG ≥ 5 kg).

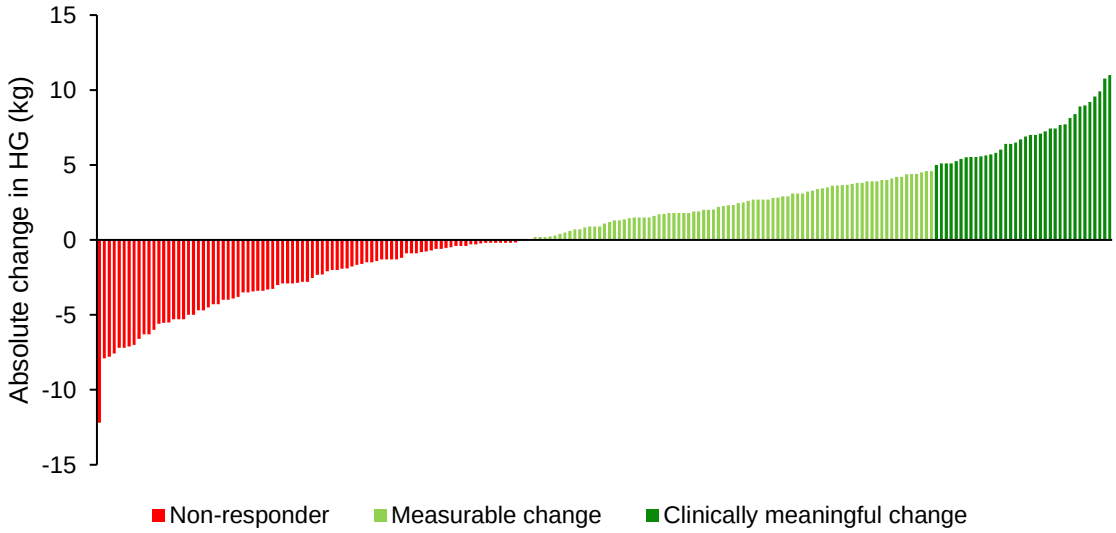

Figure 6.4 Inter-individual variability for change in handgrip between baseline - 12 months
Note: HG = handgrip; kg = kilograms

The logistic regression was statistically significant $X^2(11) = 23.99$, p=0.013. The model correctly classified 63.6% of cases. The AUC for predicted probabilities was 0.70 (SE 0.04, p=0.000, 95% CI 0.62 – 0.77). Increasing age reduced the likelihood of achieving a measurable change in handgrip (ß=-0.05, OR 0.95, 95% CI 0.92 – 0.99, p=0.011) whereas a poor handgrip score at BL increased the likelihood of achieving a measurable change (ß=-0.11, OR 0.90, 95% CI 0.85 – 0.95, p=0.000). Finally, women were less likely to achieve a measurable change in handgrip (ß=-1.73, OR 0.18, 95% CI 0.07 – 0.48, p=0.001).

Waist circumference

A total of 203 participants completed waist measurements at BL and 12 months, with 23.3% classified as non-responders (an increase in waist circumference ≥ 0 cm) and 76.8% achieving a measurable change (a decrease in waist circumference ≥ 0.01 cm) (figure 6.5). A clinically meaningful change in waist circumference was achieved by 42.6% of participants (a decrease in waist circumference ≥ 5 cm).

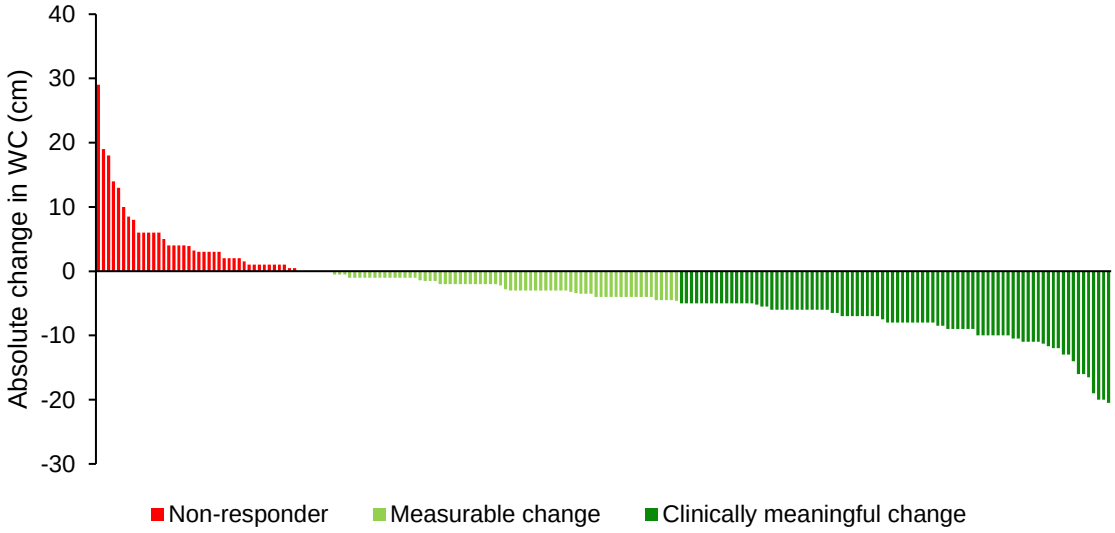

Figure 6.5 Inter-individual variability for change in waist circumference between baseline - 12 months
Note: WC = waist circumference; cm = centimetres

The logistic regression was statistically significant $X^2(11) = 33.51$, p=0.000. The model correctly classified 79.3% of cases. The AUC for predicted probabilities was 0.78 (SE 0.04, p=0.000, 95% CI 0.70 – 0.86). A higher waist circumference at BL increased the likelihood of achieving a measurable change in waist circumference (ß=0.04, OR 1.04, 95% CI 1.01 – 1.08, p=0.025). Current or past smokers were less likely to achieve a measurable change in waist circumference compared to those who never smoked (ß=-1.09, OR 0.34, 95% CI 0.13 – 0.83, p=0.019).

8-item Patient Health Questionnaire

A total of 139 participants completed PHQ8 at BL and 12 months, with 47.5% classified as non-responders (an increase in PHQ8 score > 0) and 52.5% achieving a measurable change (a decrease in PHQ8 score ≤ 0.01) (figure 6.6). A clinically meaningful change in PHQ8 was achieved by 13.7% of participants (a decrease in PHQ8 score ≥ 5).

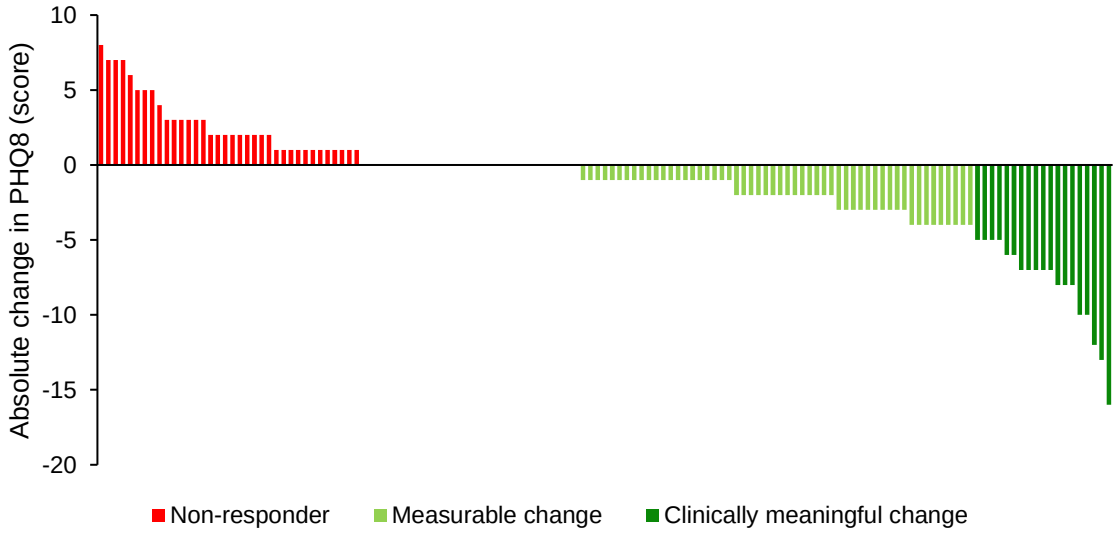

Figure 6.6 Inter-individual variability for change in 8-item Patient Health Questionnaire between baseline - 12 months
Note: PHQ8 = 8-item Patient Health Questionnaire

The logistic regression was statistically significant $X^2(11) = 36.71$, p=0.000. The model correctly classified 77.6% of cases. The AUC for predicted probabilities was 0.81 (SE 0.04, p=0.000, 95% CI 0.73 – 0.89). A high PHQ8 score at BL, indicating increased symptoms of depression, increased the likelihood of achieving a measurable change in PHQ8 (ß=0.31, OR 1.37, 95% CI 1.18 – 1.59, p=0.000).

EuroQoL Visual Analogue Scale

A total of 149 participants completed EQ-VAS at BL and 12 months, with 44.3% classified as non-responders (a decrease in EQ-VAS score ≤ 0) and 57.7% achieving a measurable change (an increase in EQ-VAS score ≥ 0.01) (figure 6.7). A clinically meaningful change in EQ-VAS was achieved by 39.6% of participants (an increase in EQ-VAS score ≥ 10).

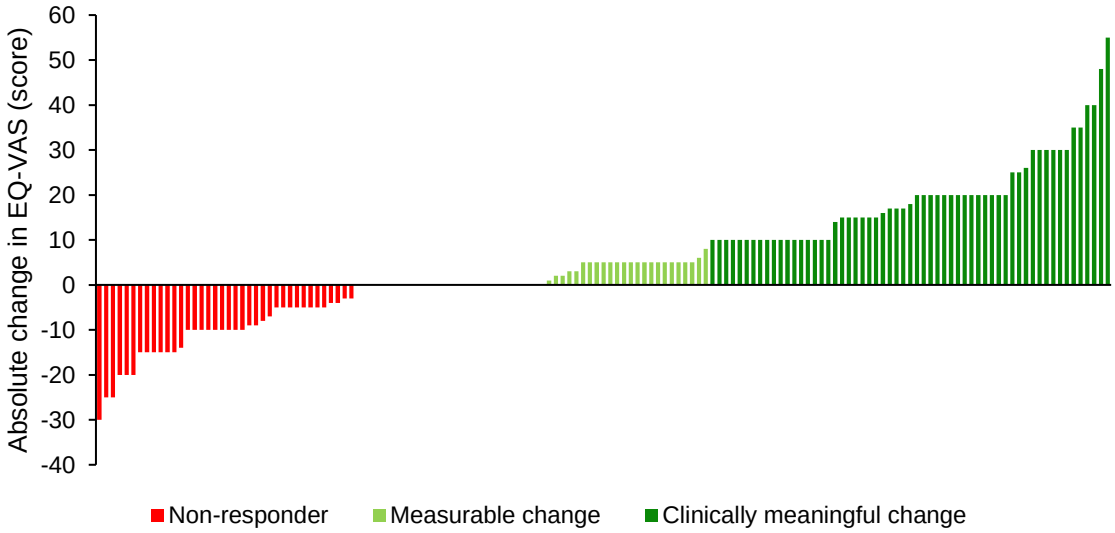

Figure 6.7 Inter-individual variability for change in EuroQoL Visual Analogue Scale between baseline - 12 months
Note: EQ-VAS = EuroQoL Visual Analogue Scale

The logistic regression was statistically significant $X^2(11) = 49.77$, p=0.000. The model correctly classified 74.5% of cases. The AUC for predicted probabilities was 0.83 (SE 0.04, p=0.000, 95% CI 0.66 – 0.90). Increasing age reduced the likelihood of achieving a measurable change in EQ-VAS (ß=-0.06, OR 0.94 95% CI 0.89 – 0.99, p=0.028). A primary CD diagnosis of a respiratory disease reduced the likelihood of achieving a measurable change in EQ-VAS (ß=-4.33,OR 0.01 95% CI 0.001 – 0.20, p=0.002).

Satisfaction with Life Scale

A total of 176 participants completed SWLS at BL and 6 months, with 53.4% classified as non-responders (a decrease in SWLS score ≤ 0) and 46.6% achieving a measurable change (an increase in SWLS score ≥ 0.01) (figure 6.8). A clinically meaningful change in SWLS was achieved by 17.6% of participants (an increase in SWLS score ≥ 5).

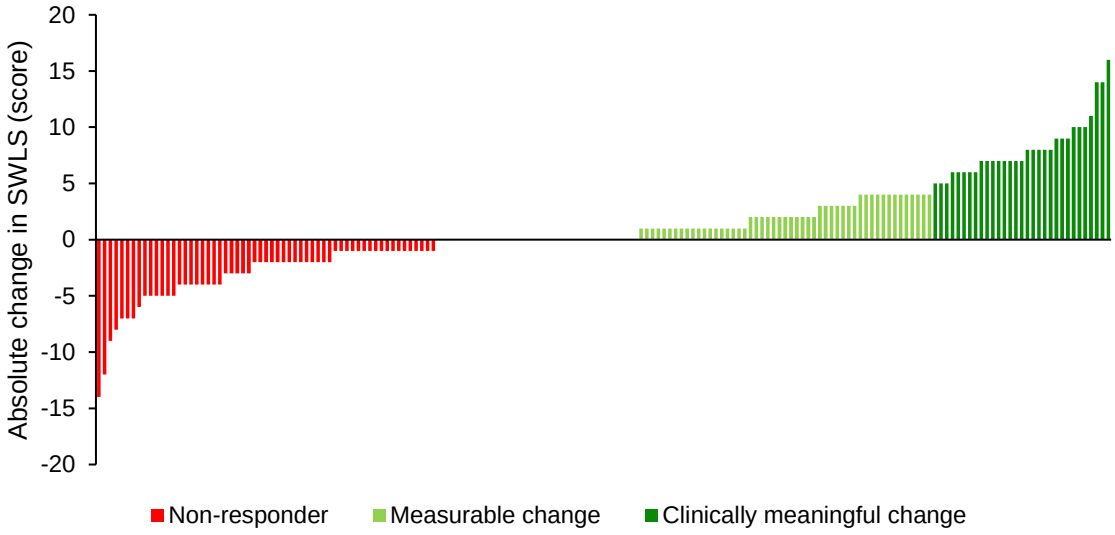

Figure 6.8 Inter-individual variability for change in Satisfaction with Life Scale between baseline and 6 months
Note: SWLS = Satisfaction with Life Scale

The logistic regression was statistically significant $X^2(11) = 38.27$, p=0.000. The model correctly classified 66.5% of cases. The AUC for predicted probabilities was 0.77 (SE 0.04, p=0.000, 95% CI 0.70 – 0.84). A lower SWLS at BL, increased the likelihood of achieving a measurable change in the SWLS (ß=-0.11, OR 0.89, 95% CI 0.84 – 0.95, p=0.000).

Estimated number of classes attended to achieve measurable/clinically meaningful improvements.

Significant binary logistic regression models ($p \leq 0.05$) for LIPA, barriers to self-efficacy for exercise and, intentions for exercise were identified and used to estimate the number of attended classes required to achieve a measurable change in each of the three variables. It was estimated that attending a mean of 13.3 classes was required to achieve a measurable change in LIPA, attending a mean of 41.3 classes was required to achieve a measurable change in Barriers to Self-Efficacy for Exercise and attending a mean of 51.8 classes was required to achieve a measurable change in Intentions for Exercise. Results displayed in table 6.1

Significant binary logistic regression models ($p \leq 0.05$) for step count and weight were found and used to estimate number of attended classes required to achieve a clinically meaningful change in each variable. It was estimated that attending a mean of 70.5 classes was required to achieve a clinically meaningful change in step count and attending a mean of 146.8 classes was required to achieve a clinically meaningful change in weight. Results displayed in table 6.1.

Table 6.1 Binary logistic regression results used to estimate required number of attendance for achieving a measurable change and clinically meaningful change in health related measures and psychosocial determinants of physical activity

	Measurable change				Clinically meaningful change			
Variable	**β ± SE**	**Intercept**	**No of attendance**	**p**	**β ± SE**	**Intercept**	**No of attendance**	**p**
LIPA	.017 ± .008	-.226	**13.3**	**.036**	.007 ± .008	-1.354	193.4	.425
MVPA	.004 ± .007	-.028	7.0	.608	.002 ± .008	-.698	349.0	.797
Step count	.012 ± .008	-.172	14.3	.117	.017 ± .008	-1.199	**70.5**	**.029**
Time spent in bouts > 60 min	.008 ± .007	-.307	38.4	.283			-	
Weight	.011 ± .006	.057	5.2	.065	.015 ± .007	-2.202	**146.8**	**.042**
PHQ8	.006 ± .007	-.089	14.8	.405	.002 ± .010	-1.905	952.5	.842
EQ-VAS	.003 ± .007	.113	37.7	.657	.003 ± .007	-.538	179.3	.679
SWLS	-.004 ± .007	.232	58.0	.534	-.011 ± .010	-1.263	114.8	.250
SWEMWBS	-.005 ± .007	.055	11.0	.491	-.002 ± .007	-.820	410.0	.779
Barriers to self-efficacy for exercise	.029 ± .008	-1.198	**41.3**	**.000**			-	
Self-regulatory self-efficacy for exercise	.011 ± .007	-.997	90.6	.142			-	
Intentions for exercise	.041 ± .009	-2.125	**51.8**	**.000**			-	

Numbers in **BOLD** indicate $p \leq 0.05$

Note: LIPA = light intensity physical activity; MVPA = moderate to vigorous intensity physical activity; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQoL Visual Analogue Scale; SWLS = Satisfaction with Life Scale; SWEMWBS = The Short - Warwick Edinburgh Mental Wellbeing Scale

Note: Within 12 months if participants attended: 2 classes/wk, total available classes = 96; 3 classes/wk, total available classes = 138; 5 classes/wk, total available classes = 230; 6 classes/wk (which is the maximum available) = total available classes = 276

Discussion

Almost all participants (92.2%) achieved a measurable improvement in at least one health related measures after participation in the MedEx Wellness CBER program. For measures of LIPA (OR=0.19), lower-body strength (OR=1.04), upper-body strength (OR=0.90), waist circumference (OR=1.04), symptoms of depression (OR=1.37) and satisfaction with life (OR=0.89), a worse result at BL, increased likelihood of achieving a measurable change. In contrast, a better measure at BL of CRF increased likelihood of achieving a measurable change in this measures (OR=1.01). Older participants were less likely to improve CRF (OR=0.93), handgrip (OR=0.95) and self-rated health (OR=0.94). Women were less likely to improve upper-body strength (OR=0.18). Individuals with a primary diagnosis of metabolic disease and respiratory diseases were less likely to improve on measures of LIPA (OR=0.07) and self-rated health (OR=0.01), respectively. Individuals with cancer were more likely to improve lower-body strength (OR=8.17).

It was estimated that attending 13.3 classes, 41.3 classes and 51.8 classes was required to achieve a measurable improvement in LIPA, barriers to self-efficacy for exercise and intentions for exercise, respectively. In addition it was estimated that attending 70.5 classes, 146.8 classes and 66.3 classes was required to achieve a clinically meaningful improvement in step count, weight and barriers to self-efficacy for exercise, respectively.

A consistent finding of the present study was the large inter-individual variability in response to CBER among a diverse CD population. A lower levels of BL PA, strength, body composition and psychological health was associated with an increased likelihood of improving health related outcomes. Bouchard and Rankinen (2001) found that age, sex and

ethnic origin had a minimal effect on the training response, but that pretraining submaximal HR and BP were associated with a positive response to exercise. Surprisingly, a lower level of BL CRF decreased the likelihood of achieving an improvement in this measure in the current study. It is possible that participants with low CRF were limited in their ability to exercise at an intensity required to elicit positive CRF related adaptations. This is supported by Kaminsky *et al.,* (2013) who found that low CRF levels may limit participation in MVPA. There is currently a need to expand our understanding of the factors associated with non-response to exercise rehabilitation in order to identify non-responders and to tailor programs to minimise the number of participants failing to achieve a positive response.

Chapter 7

Discussion

Overview

Currently, almost half of the world's adult population suffers from at least one CD, with steadily increasing numbers living with MM (Hernández et al., 2019; Kingston et al., 2018). The implications of this epidemic are far-reaching (Booth et al., 2011; Suhrcke et al., 2006). In particular, CD places an overwhelming strain on healthcare resources (Cronin et al., 2017; Smyth, 2017) and a considerable burden on patients, including limiting ADL and impacting QoL (Harris & Wallace, 2012; Moorman et al., 2007). MM is associated with an even higher risk of premature death, hospital admission, reduced functional capacity and QoL compared to those with a SCD (Bayliss et al., 2004; Fortin et al., 2005; Smith & O'Dowd, 2007; Wallace et al., 2015).

A series of studies were undertaken to: i) determine the levels of PA and SB in a mixed CD cohort and to investigate the associations of PA and SB with selected indices of health; ii) evaluate the effects of CBER on PA levels, SB and selected indices of health in a mixed CD cohort and iii) investigate factors associated with a favourable response to CBER in a mixed CD cohort.

Limited research to date has investigated levels of PA and SB in a mixed CD cohort which also includes individuals with MM. In addition a range of methods have been employed to measure PA and SB in specific CD groups, and this has prevented comparison between groups in previous research. The current research has established that levels of PA and SB do

not differ between specific CD cohort or between those with a SCD and MM. This evidence suggest a need to move away from segregated interventions for improving PA and SB levels within the CD cohort and employing an integrated approach.

This research provides evidence that an integrated delivery model of CBER is an effective approach to increasing PA levels, reducing SB and improving physical functioning, body composition and positive mental health for individuals with a range of CDs and MM. The evidence supporting this novel approach to CBER delivery has immense implications for practical application within the healthcare setting.

The final study of this thesis highlighted the inter-individual variability to exists in the response of individuals with CD to CBER. Notably, specific CD diagnosis or the presence of MM has little impact on response to CBER. BL measures of fitness were identified as primary factors determining response to the program. Such findings provide evidence for the ability to create a profile of individuals as risk of non-response, identify these individuals at BL and implement strategies to reduce the risk of non-response for CD patients attending CBER.

Study 1

According to the current WHO guidelines, individuals with CD should accumulate a minimum of 150 min of MVPA per week (World Health Organization, 2010) and/or at least 10,000 steps per day to optimise health status (Tudor-Locke et al., 2011a). The community-dwelling CD population in the present study fall short of both PA recommendations, with a mean MVPA and daily step count of 126 min per week (18 min·day^{-1}) and 6700 steps per day, respectively. Low levels of MVPA are consistently reported in the CD population. Mean daily

MVPA has been described as 17 min per day in adults with T2DM (Wang et al., 2017), 7.0 to 16.5 min per day in patients with COPD (Bernard et al., 2018; Eliason et al., 2011), 8.6 min per day among those with heart failure, 11.4 min per day in individuals with angina (Evenson et al., 2014), 10 min per day in cancer survivors (Loprinzi et al., 2013), and 3.7 min per day in breast cancer survivors (Lynch et al., 2010). Of the participants in this study 36.3% were found to meet the PA guidelines for MVPA. This is lower than what has previously been reported in healthy adult populations. Recent evidence in the US and Ireland reported that 45% and 48% of adults populations meeting the guidelines for MVPA, respectively (Mc Dowell et al., 2020; Zenko et al., 2019). For participants that were meeting or above the recommended levels of MVPA significantly more favourable measures of aerobic fitness and body composition with large effect sizes and self-rated health with a medium effect size were observed.

Historically, PA guidelines have focused primarily on MVPA. There is now increasing awareness of the importance of LIPA for maintaining and enhancing health. A worrying find from the current study is the mean levels of LIPA (1.1 h per day). This is lower than what has previously been reported in CD populations. Mean daily LIPA has been described as 4.5 h per day in LIPA in individuals with a history of breast cancer (Lynch et al., 2010), 5.5 h per day in individuals with rheumatoid arthritis (Khoja et al., 2016) and 5.8 h per day in patients with T2DM (Healy et al., 2007). More comparable findings have been reported individuals with intermittent claudication at one h per day of walking and 21 min per day shuffling (Lauret et al., 2014).

There is accumulating evidence that significant health-related benefits are associated with LIPA and standing. Beddhu *et al*., (2015) found that an increase of 2 min per h of LIPA was associated with a lower risk of mortality in individuals with chronic kidney

disease. LIPA has also been associated with a reduced risk of hospitalization, waist circumference and blood glucose levels in individuals with COPD (Donaire-Gonzalez et al., 2015; Park & Larson, 2014); cholesterol, waist circumference and risk of visual impairments in diabetics (Loprinzi et al., 2014; Loprinzi & Pariser, 2013); and HDL-C and total cholesterol in individuals with MM (Li et al., 2019). Recent evidence has demonstrated that reallocating 30 min of sleep, sedentary time or standing with LIPA is associated with marked improvements in BMI, body fat and fat mass in older adults (Powell et al., 2020). Increasing LIPA may be a more attainable goal among individuals with CD who are unable to achieve the daily recommended min of MVPA due to a reduced functional capacity. The current study promotes that targeting LIPA within CD populations is warranted, as low levels of LIPA within this population are established. Moreover, no differences in LIPA were found between different CD diagnosis or those with SCD and MM. Emphasising the message that *'some activity is better than none*' (US Department of Health and Human Services, 2018a) should be considered as an target for intervention, with potential to elicit substantial health benefits. Research is required to establish feasible and scalable interventions which increase PA participation of any intensity within CD populations.

Daily step count is a useful means of capturing daily PA behaviour as it measures all locomotion across the day encompassing both LIPA and MVPA (Tudor-Locke et al., 2011b). Furthermore, step count can be easily translated into guidelines and simplifies the exercise prescription procedure for both practitioners and patients (Dasgupta et al., 2014). A threshold of 10,000 steps per day is currently recommended for optimal health benefits (Choi et al., 2007; Wattanapisit & Thanamee, 2017).

The total daily step count of the CD population in the present study was 6713 steps per day. This is in the typical range for CD cohorts and is categorised as 'low active' (Tudor-Locke *et al*., 2008). The currenting findings are in line with the mean daily step count reported in previous research. Parkinson's disease patients were found to have a daily step count ranging from 4,765 to 5,423 steps per day (Benka Wallén et al., 2015; Christiansen et al., 2017; Lord et al., 2013). Yates et al., (2014) reported a daily step count of 6,245 steps per day in almost 10,000 individual with impaired glucose tolerance while Lauret *et al.,* (2014), reported a lower daily step count of 5,212 steps per day among patients with intermittent claudication. Among COPD patients, daily step count ranges from 4,782 to 7,232 steps per day, with increasing daily step count associated with a reduction in disease severity (Bernard et al., 2018; Moy et al., 2012).

An important finding in the present study was the significant association between step count and body composition, CRF and self-rated health indicating that a higher step count among individuals with a CD may positively impacts functional capacity, body composition and perception of health status. Effect sizes for these associations ranged from medium to large. Although the current evidence is correlational, research advocates the PA is the behaviours that impacts health outcomes (Blair, 2001). Among individuals with impaired glucose tolerance, each 2000 steps per day increment was associated with a 10% reduction in risk for a cardiovascular event (HR 0.9; 95% CI 0.81 to 1.01) (Yates et al., 2014). A increase in daily step count is associated favourable changes in BP, BMI, waist circumference and HbA1c in women with T2DM (Manjoo et al., 2012; Manjoo et al., 2010). Specifically, each standard deviation increase in daily step count was associated with clinically

significant reductions in waist circumference (-4.6cm; 95% CI -6.4 to -2.8 cm) and BMI (-1.6 kg/m^2; 95% CI -2.4 to -0.8 kg/m^2) and a decline in HbA1c of 0.16% (95% CI 0.35% to 0,04%) (Manjoo et al., 2012). A 1000 daily step count increment was associated with a -2.6mmHg (95% CI; -4.1 to -1.1 mmHg) and a -1.4 mmHg (95% CI; -2.2 to -0.6 mmHg) change in systolic and diastolic BP, respectively (Manjoo et al., 2010). Severity of airflow obstruction and markers of systematic inflammation are associated with daily step counts among COPD patients (Moy et al., 2014; Saunders et al., 2016). A recent longitudinal study in 16,741 women (mean age 72.0 y) revealed that increasing daily step count evoked a steady decline in mortality rates, which appeared to reach a plateau at 7,500 steps per day (Lee *et al*., 2019). Per increase in daily step count quartiles from lowest to highest the corresponding HR were 0.54 (95% CI 0.43 to 0.69), 0.47 (95% CI 0.35 to 0.62) and 0.34 (95% CI 0.24 to 0.48), respectively. Notably, the reduce risk of mortality among the women who increased their daily step count from 2,700 to 4,400 steps per day was approximately 46%. These findings provide strong encouragement for individuals restricted in their ability to achieve 10,000 steps/day and those in the lowest quartile of daily step count.

Compared to healthy populations, the CD cohort are markedly less physically active. In a population based study, the prevalence of self-reported low PA, classified as “mostly sitting down during leisure time”, was highest in COPD (84.2%), followed by rheumatoid arthritis (74.4%), diabetes mellitus (72.5%) and finally healthy subjects (60.2%) (Arne et al., 2009). Similarly, Brawner *et al*., (2016) found lower levels of self-reported leisure time PA across all CD categories compared to healthy comparisons, with the lowest levels found in individuals following a myocardial infarction, diabetes, kidney disease, stroke and COPD. Patients with COPD have reported mean daily walking time of almost half that of healthy age

matched controls (Pitta et al., 2005). In the present study , there was no significant difference in PA or SB between different primary CD diagnosis or between those with SCD or MM. A recent Canadian National Health Survey, also reported no difference in PA or SB between individuals with 1, 2 or ≥ 3 CDs (Hains-Monfette et al., 2019). Efforts to increase PA and reduce SB can apply to all individuals with a CD diagnosis, regardless of condition or severity.

The fact that participants in the current study spent on average 9.5 h of the waking day sedentary is alarming considering that SB is associated with increased BMI, waist circumference and TG, and decreased HDL-C and VO_2peak (Prince et al., 2016). A recent meta-analysis found a positive dose-response relation between sitting time and CVD, and between cancer and all-cause mortality (Zhao et al., 2020). Not surprisingly, an increased risk of MM is associated with SB (Vancampfort et al., 2017). Zhao *et al*., (2020) found that the risk of mortality associated with SB was amplified in participants with T2DM and hypertension, suggesting that SB in combination with CD is more likely to have a damaging impact on health. High levels of MVPA can attenuate the negative effects of prolonged SB (Ekelund et al., 2016) however, individuals with CD are limited in their ability to achieve the required levels. A definitive threshold of too much SB is yet to be established and current recommendations on the daily amount of SB remain vague. The inverse association between SB and the factor representing functional capacity and self-efficacy for exercise is a novel findings and is worthy of further investigation. Moreover the effect size of this association was interpreted as large. This finding suggest that increasing SB may not only limit an individual's functional capability to be active, but can also reduce their exercise self-efficacy. Hence a vicious cycles onsets. The relation between self-efficacy to be active and SB has yet to be established. A recent

meta-analysis reported preliminary evidence that there is a significant inverse association between individual's SB and their self-efficacy to reduce it (Szczuka et al., 2019).

The pattern in which sedentary time is accumulated is also of clinical relevance. Prolonged and less fragmented SB has been associated with less favourable cardiometabolic and inflammatory biomarkers, poorer physical function, increased risk of abdominal obesity, greater BMI and increased risk of developing CD and depression (Dunstan et al., 2012; Healy et al., 2011; Jefferis et al., 2015; Judice et al., 2015; Sardinha et al., 2015). Among participants in the present study, the majority of SB was accumulated in bouts lasting > 30 min, with approximately one third of SB accumulated in bouts > 60 min. Increasing breaks in SB is associated with favourable measures of BMI, waist circumference, HDL-C, triglycerides, and glucose control, independent of total sedentary time (Bankoski et al., 2011; Dunstan et al., 2012; Healy et al., 2008a). Dorhn *et al*., (2018) recently reported that breaks in SB involving LIPA was associated with reduced risk of all-cause and cardiovascular mortality.

Similar to step count, a specific target for total SB or bout length of sedentary behaviour has not yet been identified. In conjunction with increasing PA levels, current guidelines in the US are now promoting the reduction of SB and prolonged bout of SB (US Department of Health and Human Services, 2018a). Other current public health messages regarding SB include statements such as "*break up long periods of sitting as often as possible*" (Australian Department of Health, 2019) or "*adults and older adults should avoid long periods of sitting*" (Fuezeki et al., 2017b).

An unexpected finding was the inverse relation between SB and LDL-C and SB and the PCA factor representing cholesterol, suggesting that longer bouts of SB is associated with

a worsening cholesterol profile. The "active couch potato phenomenon" represents individuals who are highly sedentary however also meet the recommended guidelines of MVPA (Owen et al., 2010). This pattern of PA and SB among participants could explain result in the observed association between SB and LDL-C. However, it is unlikely that this is the case given the low levels of PA also reported within the population. A possible explanation for this finding may be related to HMG CoA reductase inhibitor (statins) induced muscle myopathy. Statins are routinely prescribed to lower cholesterol in patients with CVD (Ziaeian & Fonarow, 2017). One of the most common side effects of statin therapy is muscle myopathy that can severely limited PA (Parker & Thompson, 2012). Lee *et al*., (2014) also reported that older men taking statins had significantly more SB than those who were not on the medication. Although there was no information provided on medication use, more than one third (37.7%) of participants had CVD and were therefore likely to be taking statins as per standard guidelines.

Limitations of Study 1

Participants were recruited from individuals who were referred to and attended induction to a CBER program. Not all patients referred to the program attended the induction session. It is possible that those who did attend may have been more physically active and not representative of the general CD population giving rise to selection bias. Additionally, registering for an exercise rehabilitation program and/or attending induction may motivate participants to become more active. As no ActivPAL threshold currently exists for MVPA in a chronic disease population, MVPA was classified as ≥ 25 steps per 15 sec epoch, based off recommendations by Tudor-Locke et al., (2011a). This stepping frequency may not represent

MVPA in frail and deconditioned participants. Participant use medication was not collected which is a significant limitation of this research. Household income was estimated using the median household income assigned to the area of each participants address. As this is a proxy measure of gross household income it is a limitation when interpreting findings related to income. A major limitation of the research design is that exposure and outcomes are simultaneously assessed, which prevents the identification of causation or the analysis of behaviour over a period of time. Although, accelerometers, particularly those with an inbuilt inclinometer are the most accurate devise currently available to measure PA and SB, they have limitations. Participants may temporarily change their behaviour due to awareness of being monitored (Hawthorn effect) (Wickström & Bendix, 2000). In addition, the device has to be removed for water-based activities such as swimming or aqua aerobics.

Finally, as there was a large number of health-related outcome measures that were used as dependent variable in analysis, there was an increased risk of a type 1 error (Knudson & Lindsey, 2014). Data was subjected to principal component analysis (PCA) as an approach to reducing type 1 error. However, missing data significantly impacted the sample size included within factors.

Conclusion

The aim of this study was to describe the levels of PA and SB in a mixed CD population and to investigate the association of PA and SB with selected indices of health. The findings suggest that individuals with a CD, regardless of condition, participate in low levels of daily PA as measured by daily step count, LIPA and MVPA. Moreover, a high proportion of the day is spent in SB. A higher daily step count was associated with more favourable measures of

body composition, aerobic fitness and self-rated health, with medium, large and medium effect sizes, respectively. More sedentary time was associated with less favourable lower body strength, however the effect size of this association was small. In contrast, more SB was also associated with more favourable measures of LDL-C and depressive symptoms, both with a medium effect size observed.

Whether individuals with CD become less active as a result of worsening health or whether the health of an individual with CD deteriorates as a result of decreased PA levels and/or increasing SB is unclear. Regardless, it is likely that a deleterious cycle exists, where sustained physical inactivity induces dysfunction and disease progression, further limiting PA engagement and increasing SB (Booth et al., 2017). There is a need for public health services to promote the beneficial effects of both increasing PA, including participation in LIPA, and reducing SB. For the CD population, a simple message of "move more, sit less" very much encompasses the action needed to enhance health through PA.

Study 2

Exercise rehabilitation programs offer a means of increasing PA engagement for individuals with CD. CBER programs can shift the resource burden from the healthcare system and remove many of the accessibility barriers associated with participation in hospital-based programmes. MedEx Wellness is a novel CBER program, that takes an integrated approach to CD rehabilitation by delivering a shared program across multiple CD. Study 2 evaluated the effect of 12 months of participation in the MedEx Wellness program in men and women with a diverse range of both SCD and MM. There were significant improvements in LIPA and patterns of SB, physical function, body composition and psychological health. In addition, a

higher rate of attendance was associated with improvements in LIPA, MVPA, step count, patterns of SB, body composition, psychological health and psychosocial determinants of PA. There were largely no differences identified between those with a range of SCD and MM in terms of their response to the integrated CBER program. The results of this study strongly advocate the a mixed CBER model can be efficacious.

The rates of uptake and drop-out to the programme compared favourably to similar exercise rehabilitation programs. Uptake, defined as attending at least one exercise class following induction, was 92.6%. In a systematic review of exercise referral schemes in the UK, the pooled levels of uptake was 66% (Pavey et al., 2012). Of those individuals who initiated the MedEx Wellness program, 41.4% dropped-out within the 12-month period. Drop-out rates of 50% and 58% have been previously been reported for short-term (6 - 8 weeks) cardiac rehabilitation (Cannon & O'Gara, 2007; Mikkelsen et al., 2014; Turk-Adawi et al., 2013) and pulmonary rehabilitation programs (Royal College of Physicians, 2016). Including individuals who never initiated the program, total drop-out was 49%. The highest rate of dropout in the current study occurred in the first 3 months, which is a consistent trend in CD exercise rehabilitation programs (Carmody et al., 1980; Nam et al., 2012; Yohannes et al., 2007). The findings indicate that if patients can be encouraged to attend a CD program for 3 months, there is a much higher likelihood of retention at 12 months.

The primary reason for dropout was physical limitations due to ill-health or injury. Courneya *et al*., (2014) found a similar trend in cancer patients, where adherence to an exercise program was worse in patients with more physical limitations. A negative perception of health is an established barrier to PA among CD patients (Forechi et al., 2018). A perception of poor health may represent a robust negative psychological influence on exercise

engagement in this patient cohort. Obesity and/or BMI have also been identified as determinants of adherence in cardiac rehabilitation (Forhan et al., 2013) and exercise rehabilitation for cancer (Courneya et al., 2014). Dropouts from MedEx Wellness program had significantly less favourable measures of BMI, hip circumference, triglycerides and LDL-C.

Dropouts had significantly less social support for exercise, which is believed to have a direct influence on exercise behaviour (Resnick et al., 2002) and is a primary psychosocial determinant of exercise adherence in CD (Hartman et al., 2013). In patients with CVD, T2DM and cancer, social support has been identified as a strong predictor of PA engagement (Adeniyi et al., 2012; Aliabad et al., 2014; Ormel et al., 2018; Won & Son, 2017). Individuals with CVD were more likely to remain in the MedEx Wellness program compared to other CD cohorts. This may be explained in part by the fact that many of the CVD participants were referred directly from a phase III cardiac rehabilitation program and it is possible that participating in a CBER program may have provided an opportunity to continue their exercise program. It is also likely that having a significant acute health event, such as a myocardial infarction, may intrinsically motivate someone to exercise (Seifert et al., 2012).

There were significant differences in age and employment status between drop-outs and completers. Dropouts were younger and more likely to be unemployed. Selzler *et al*., (2012) reported age to be the strongest predictor of dropout from pulmonary rehabilitation with younger patients at a greater risk of dropping out. Similarly, older adults are more likely to uptake and adhere to exercise referral schemes compared to younger adults (Campbell et al., 2015; Pavey et al., 2011). It is possible that employment is the mediating factor because younger participants are on average, below the retirement age. Unemployment has previously been reported as a predictor of poor adherence to exercise. The mechanisms

linking unemployment and an increased risk of dropout however, remain unclear (Leung et al., 2017). Developing a profile of dropouts could assist in identifing participants at high risk of dropout and guide the support structures required to maintain participation. The current study provides evidence that the characteristics of an individual more likely to dropout from CBER include younger, unemployed, non-retired or overweight individuals. Whether these characteristics occur independently or concurrent has yet to be established, however it is likely that exercise adherence is dependent on a range of factors. As drop-out rates remain sub-optimal, there is a need for a more proactive approach to prevent the loss of vulnerable participants prematurely from CBER programs. For example, the current findings propose that individuals who are retired are less likely to drop out, suggesting that time constraints is a possible barriers resulting in dropout in the younger, non-retired cohort. This information could inform the delivery of CBER services to assist individuals to overcome this barrier. A possible offering of shorter classes (45 min rather than one hr) or classes outside of general working hours (early morning or evening) could have an impact on drop-out rates. Adherence strategies that can be translated into the real-world delivery of CBER requires further research. Interestingly, sex was not associated with uptake or adherence to the MedEx Wellness program, as previous research has reported that women are more likely to uptake exercise referral schemes compared to men, whereas men are more likely to adhere to the programs (Gidlow et al., 2005; Pavey et al., 2011).

Few participants attended the recommended 2 classes per week. Despite the low adherence rate, there were significant improvements in a number of health indices. Previous research has shown some efficacy for low exercise dose interventions (Paw et al., 2008; Theou et al., 2011). Importantly, a higher attendance was associated with greater overall health

benefits. A recent intervention study reported non-significant improvements in HRQoL in older adults participating in a low-dose exercise program (2 exercise session/wk), however those participating in a high-dose exercise program (three exercise classes/wk) demonstrated significant improvements in each HRQoL dimension measured (Kaushal et al., 2019). The evidence advocates that although health related benefits can be attained with minimal attendance, greater benefits are likely to be achieved when attendance is increased. The role of intensity of exercise, in favour of greater intensities, for eliciting positive health-related has been widely accepted (Warburton & Bredin, 2017). However manipulation of total weekly exercise time has yet to has not yet been established.

Home-based exercise programs have shown to be as effective as centre-based in cardiac rehabilitation in terms of mortality risk, cardiac events, exercise capacity, a range of modifiable risk factors and QoL (Dalal et al., 2010) However, adherence to home-based exercise was reported as superior. Home-based rehabilitation provides an opportunity to widen access to exercise rehabilitation and thereby may be associated with greater adherence. Hardcastle & Cohen, (2017) suggest that attending centre-based rehabilitation programs may require a high level of motivation which can result in reduced adoption of these services. Similarly, in cancer survivors, research has reported a preference for home-based PA rather than centre-based (Hardcastle et al., 2017). It is possible that the optimal approach to exercise rehabilitation delivery is to offer a choice between centre-based or home-based. Differing preferences for both home and centre based rehabilitation was explored by Wingham *et al.,* (2006) in cardiac patients. Those showing preference for home-based rehabilitation believed that their rehabilitation should fit in with their lives rather than their lives fitting in with the rehabilitation. In contrast, those with preference for centre-based

rehabilitation placed emphasis on supervision during exercise and the need for the camaraderie of a group. Home-based exercise programs do not provide opportunity for peer support and role modelling. It is possible that a hybrid model of rehabilitation delivery which includes both centre-based and home-based elements may be a suitable alternative to CBER to provide wider access and efficacy of the service.

MVPA and step count did not change significantly in the present study but both were positively associated with attendance. Although MVPA is recommended for optimal health benefits, emerging evidence suggests that LIPA improves health. Participation in the MedEx CBER program was associated with a significant improvement in LIPA. The clinical implications of the observed improvement are questionable as the average daily increase overserved in LIPA between BL and 12 m is approximately 6 min. Conversely, no threshold has yet been identified that must be exceeded before beneficial effects onset as a result of increasing PA levels.

It is well established that psychosocial factors, including self-efficacy for exercise, are important determining factors for PA participation in individuals with CD (Bauman et al., 2012; Dutton et al., 2009; Hartman et al., 2013; Plotnikoff et al., 2000; Selzler et al., 2012). A regression in barriers to self-efficacy for exercise, self-regulatory self-efficacy for exercise and intentions for exercise was observed over the course of this study. This is an unexpected outcome as previous research reports that participation in exercise alone can increase exercise self-efficacy (Fletcher, 2012). In addition, the incorporation of exercise consultations which included a review of participant goals, provided with feedback on progress and strategies to overcome barriers was expected to impact exercise self-efficacy. This finding could account for the minimal changes that occurred in MVPA and step count. Moreover, the

relation between changes in psychosocial determinants for PA and changes in PA were weak, which could indicate the absolute change in both variables was minimal and relations could not be identified.

Program attendance was positively associated with improved self-efficacy for PA, self-regulatory self-efficacy for PA and intentions to exercise, in addition to MVPA and step count. It is probable many of the participants with low attendance did not gain experience or develop confidence in their abilities to be independently physically active or overcome barriers for physical activity. It is likely that participants may have had great intentions to becoming PA at induction to the program, following initial referral from a healthcare professional. The study findings indicate that these intentions were not maintained after the initial stages of joining the program. Several behaviour change techniques such as goal-setting, self-monitoring, prompts, graded tasks, non-specific rewards and social rewards, have been found to enhancing intentions for exercise, self-efficacy and overall PA levels (Finne et al, 2018; Samdal et al., 2017). Further research is required to investigate how to effectively incorporating evidence based behaviour change techniques feasibly into CBER. This knowledge could inform services on how to evoke improvements in exercise self-efficacy and further improve engagement with the program and PA outside of the program.

Increasing the number of interruptions in SB is associated with more favourable measures of BMI, waist circumference, HDL-C, TG, blood glucose control and markers of chronic inflammation (Bankoski et al., 2011; Dunstan et al., 2012; Healy et al., 2008b; Henson, et al., 2013a). For individuals who fail to meet the recommended levels of PA, reducing time spent in prolonged sedentary bouts may be a possible approach to initiating health enhancing behaviours. The evidence from both study 1 and study 2 support this theory. In the cross-

sectional analysis of study 1 less SB was associated with more favourable lower body strength. In study 2, changes in patterns of SB, where SB was accumulated in shorter bouts was observed. In addition a range of improvements in physical functioning, body composition and psychological health were found. No changes in MVPA were found, and minimal changes in LIPA were demonstrated. The current analysis did not identify the mechanisms which led to the positive changes in health outcomes. In line with previous evidence promoting the beneficial effects of more fragmented SB, it is possible that this change in SB may have had a role to play.

There is currently no published data evaluating the impact of CBER as an approach to reducing SB in CD cohorts. However, available evidence indicates those who are current participating in CBER or have previously attended CBER, have lower levels of SB compared to those have do not (Hernandes et al., 2013; Simoes et al., 2009). Although there was no significant change in total sedentary time, there was a change in the pattern of SB. An increase in the total number of sedentary bouts and more time spent in sedentary bouts of 11-30 min in duration, may imply there was greater interruption in SB and SB was accumulated in less prolonged bouts. In addition, attendance was inversely associated with time spent in sedentary bouts > 60 min. Although the threshold for a prolonged bout of SB has yet to be established, research has found that each additional sedentary bout ≥ 10 min was positively associated with waist circumference. Indeed, sedentary bouts of ≥ 60 min are associated with a 48% increased risk of abdominal obesity (Judice et al., 2015).

By participants engaging in the CBER program is was assumed that this would have a knock on effect on SB. However increasing PA causes fatigue that, consequently can have

the unintended effect of also increasing SB, resulting the possible offset of the PA related health benefits (Siddique et al., 2018). A systematic review and meta-analysis by Prince *et al*., (2014) provides some supporting evidence that small reductions in SB can result from PA focused interventions. Interventions that target both PA and SB also resulted in modest reductions in daily SB, however SB focused interventions may be the most effective in resulting in large and clinically meaningful reductions in daily SB. Incorporating SB targeted interventions within the CBER model may have a greater impact on changing SB in this cohort.

It has been well documented that participation in exercise rehabilitation can improve health-related outcomes in individuals with CD, including indices of physical, clinical and psychological health (Anderson et al., 2016; Dunlay et al., 2014; Houchen-Wolloff et al., 2018; McCarthy et al., 2015; Puhan et al., 2016; Shepherd & While, 2012). Much of the research has focused on exercise in a clinical setting but similar improvements have been reported following participation in CBER programs. The effectiveness of CBER in improving health-related outcomes has been demonstrated in patients with diabetes (Gallé et al., 2019; Mendes et al., 2016, 2017), CVD (Bethell & Mullee, 1990; Cramp et al., 2010; Kwan et al., 2016; Marsden et al., 2016; Taylor et al., 2016a), COPD (Amin et al., 2014; Beauchamp et al., 2013; Godtfredsen et al., 2019; Varas et al., 2018), cancer (Foley & Hasson, 2016; Foley et al., 2018; Knobf et al., 2014; Leach et al., 2015; Rajotte et al., 2012; Santa Mina et al., 2017) and neurological conditions (Combs et al., 2013; Corcos et al., 2013; Elsworth et al., 2011; Poliakoff et al., 2013; Salbach et al., 2014).

The research to date is limited to specific CD populations and often excludes individuals with MM. A systematic review of CBER across chronic disease populations identified that the design and components of programmes were similar, irrespective of

disease (Desveaux et al., 2014a). The current study adopted a novel approach by integrating individuals with diverse CD diagnosis and MM into the same CBER program. The findings indicate that a shared approach to CBER is viable for the management of CD and offers a more resource efficient and potentially scalable rehabilitation strategy.

CRF reflects the integrative functioning of the respiratory, cardiovascular and skeletal muscle systems and is an independent predictor of overall health and mortality (Church et al., 2001; McAuley et al., 2009; Steell et al., 2019; Sui et al., 2010). Performance in 6MTT, an indicator of CRF improved at each time point in the present study. This is an important finding because even small improvements in CRF are associated with significant health consequences. For example, a one MET increase in CRF is associated with a 13% reduction in all-cause mortality (Kodama et al., 2009). A significant interaction effect between time and primary CD diagnosis was identified for 6MTT. Individuals with a primary diagnosis of cancer had a significantly higher CRF across all timepoints, suggesting that on average individuals with cancer have greater levels of CRF compared to other disease cohorts. Not surprisingly, those with respiratory disease had significantly lower CRF compared to CVD and metabolic disease across all timepoints. The specific symptoms of COPD make engagement in PA unpleasant as a result of air trapping and increased hyperinflation of the lungs, leading to breathlessness (O'Donnell, 2007). Increased breathlessness provokes anxiety towards PA, which inevitably leads to exacerbations of COPD. A vicious cycle is likely to develop whereby PA is avoided and further deconditioning onsets (Bourbeau, 2007).

The cancer cohort appear to display a distinct pattern of change in CRF compared to all other CD groups (figure 5.5). There was a large improvement 6MTT performance between BL and 3 months, followed by a slight decline. Interestingly, the participants with cancer were

the only group to receive a fixed 12 week program, as opposed to a continuous service. They were assessed at BL and 3 months, in line with other participants and retested at 6 and 12 months. Shorter term programs are common in cancer survivorship rehabilitation (Christopher & Morrow, 2004; Foley & Hasson, 2016; Leach et al., 2015). Once in survivorship, there is a greater emphasis for individuals with cancer to return to general public exercise services (Dennett et al., 2019; Penttinen et al., 2019). Similarly, the MedEx Wellness service catering for cancer survivors, entitled "Move On", worked in 12 week cycles with an emphasis on patients transferring back to previous gym facilities or exercise routines. In addition, the exercise content of the Move On program varied slightly in comparison to the general MedEx Wellness classes. Instructors incorporated spinning, circuits, Pilates and TRX training into classes on a regular basis within the 12 weeks. It is possible that those within the Move On program received a higher intensity exercise prescription during the program, resulting in substantial improvements in CRF. However, once out of the service, the findings from the present study suggest that CRF levels may start to decline, whereas other CD cohorts that remained in the program continued to improve beyond the 3 month timepoint.

Musculoskeletal fitness is associated with functional capacity including ability to carry out ACL, maintaining independence, risk of fracture, QoL and cognitive function (Kell et al., 2001; Pate et al., 2012; Warburton et al., 2001; Warburton & Bredin, 2016) and is predictive of premature mortality (Fujita et al., 1995; Katzmarzyk & Craig, 2002). Muscular strength improved over the course of the program. Improvements in musculoskeletal fitness, have widespread effects for individuals with CD, particularly improved functional capacity and the ability to perform ADL. The current guidelines for resistance training are 8-10 exercises, of at least a moderate intensity for 8-12 repetitions, which targets all major muscle groups on

2 or more days a week (Australian Department of Health, 2019; Chodzko-Zajko et al., 2009; Department of Health & Children & Health Service Executive, 2009; Tremblay et al., 2011; US Department of Health and Human Services, 2018b). The minimum recommended attendance in the MedEx Wellness program of 2 class per week, would ensure participants were meeting these guidelines. Improved muscle strength reduces the reliance on family and society for personal care, delays in disease progression, reduced obesity, and improves glucose metabolism, bone health and psychological health (Hessert et al., 2005; Warburton et al., 2001).

Maintaining flexibility is associated with important health implications including QoL and independent living (Katzmarzyk & Craig, 2002). Interestingly, individuals with MM had less favourable measures for sit and reach values at BL, but appeared to achieve greater improvements across all time points compared to those with SCD. Compared to individuals with SCD those with MM have a significantly greater reduction in functional capacity (Bayliss et al., 2004; Smith & O'Dowd, 2007; Wallace et al., 2015) but also achieve substantial improvements following participation in a regular physical activity program. (Pate et al., 1995).

Favourable changes in body composition were observed over the course of this study, with improvements in both waist and hip circumferences. There was inverse relation between attendance with both BMI and weight. Abdominal obesity is strongly and positively related to all-cause, CVD and cancer mortality, independent of BMI, with elevated waist circumference significantly associated with CVD mortality even among normal weight individuals (Zhang et al., 2008). In addition, obesity is a significant contributor to morbidity and mortality from CVD, diabetes, cancer, osteoarthritis, liver and kidney disease and

depression (Pi-Sunyer, 2009). Exercise training is effective in counteracting the metabolic complications associated with abdominal obesity, both directly through fat loss and through favourable effects on insulin sensitivity, plasma lipoprotein profile and improve fibrinolytic activity (Buemann & Tremblay, 1996).

An unexpected finding was the significant increase in LDL-C over the 12 month period. Although information on prescribed medication was not attained from participants, it is likely that many participants were prescribed statins to lower cholesterol. Research has suggested that 40% of CVD patients reduce adherence to statin therapies within the first year of prescription, due primarily to muscle myopathy (Thornley et al., 2012). There is potential that some of the participants, reduced adherence to statin therapies over the course of the study leading to an increase in LDL-C levels. It is also a possibility that the dose of PA which participants engaged in throughout the study, was not sufficient enough to elicit beneficial effects on LDL-C. The fact that levels of MVPA did not change, suggests the potential of this theory. Finally, there was no data collected on the dietary habits of participants during the study, but it also may be possible that participants changed dietary habits over the 12 m and this may have had an impact on measured LDL-C.

Living with a CD is associated with a significant psychological burden and increased levels of depression, anxiety and decreased satisfaction with life are common in many CD cohorts (Chapman et al., 2008; Hébert, 1997; Mhaoláin et al., 2012; Rajput et al., 2016; Restorick Roberts et al., 2017). Improvements in psychological health are associated with better physical health (Boehm & Kubzansky, 2012; Pressman et al., 2019; Trudel-Fitzgerald et al., 2019). Ideally, treatment strategies for CD should target both the physical and psychological burden of the disease.

There is a substantial body of evidence linking CBER to improved measures of psychological health (Amin et al., 2014; Beauchamp et al., 2013; Christopher & Morrow, 2004; Elsworth et al., 2011; Foley et al., 2018; Godtfredsen et al., 2019; Haas et al., 2012; Harrington et al., 2010; Knobf et al., 2014; Rajotte et al., 2012). Participation in the MedEx Wellness CBER program improved symptoms of depression, self-rated health and satisfaction with life. The largest improvements in psychological health were in participants with the highest attendance.

With the exception of patients with a primary diagnosis of respiratory disease, all other CD groups had a significant improvement in symptoms of depression, satisfaction with life and positive mental health throughout the program. Individuals with respiratory disease had evidence of worsening psychological health scores (figures 5.6 – 5.8). Respiratory disease has been strongly associated with a negative psychological health (Hynninen et al., 2005) and the rates of both anxiety and depression are more prevalent in COPD sufferers compared to other CDs (Solano et al., 2006). The negative impact of respiratory disease on QoL could not be counteracted with CBER, despite significant improvements in other health indices. This may be due in part to the clinical sequelae (fibrosis) and severe functional impairment associated with respiratory disease.

A significant interaction effect was found between time and SCD or MM for positive mental health. Simple effects analysis did not indicate and difference between those with SCD or MM across timepoints. However, lower measures of psychological health were apparent in those with MM at BL compared to individuals with a SCD. Participants with MM achieved greater improvements across all time points than SCD (figure 5.10). MM is associated with a greater impact on QoL compared to SCD (Fortin et al., 2005; Smith & O'Dowd, 2007; Wallace

et al., 2015) and it is likely that those at poorer initial psychological health had more to gain from engagement in the CBER program.

Although group interaction was relatively low as participants attended a mean of 23 – 32 sessions in 12 m (all participants and completers, respectively), it is possible that the group-based setting of the MedEx Wellness classes had an impact on the improvements observed in the various measures of psychological health. Social isolation is commonly observed among individuals with CD (Biordi & Nicholson, 2013) and the group exercise classes offered an opportunity for social interaction and engagement. Although no significant changes in measures of social support were found in this study, it is worth noting that greater attendance was associated with improvements in this measure. In a qualitative study of CBER involving COPD, the psychosocial benefits were believed to mediated in part from the interpersonal relationships with the gym instructors and the support received from peers within the exercise group (Desveaux et al., 2014b). Participants highlighted the importance of the opportunity to integrate into the community and with community members. The experience of social connection with regular gym members provided a sense of feeling socially included and valued.

Limitations of Study 2

The primary limitation of this study is the lack of a usual care control group. As the study setting was within an established program in the community, withholding the service to allow for a controlled trial was not considered ethically appropriate. A clustered controlled trial was not feasible due to the challenge of identifying a control group matched to the diverse CD population included and due to resource limitations. The lack of a comparison

group limits the ability to infer cause and effect. Similar to study 1, there is a risk of selection bias as participants were recruited from those who attended induction to the CBER program and no data was collected on those that were not referred or declined to attend. Additionally, study uptake rates were not recorded, although very few patients attending programme induction declined to participate. The method used to monitor attendance (scanned entry to the gym using individual fobs) could not differentiate between scanner entry for a class or scanned entry to the gym for personal use. Although the use of the gym facility outside of class times was not regularly availed of by participants, there is possibility that some attendance records include personal gym use also. Participant use medication was not collected which is a significant limitation of this research. Given the population studied, maturation may threaten the validity of the findings, as changes in health status may have occurred over the 12-month period. The MedEx Wellness program closes for three weeks during the Summer and three weeks at Christmas, which may have compromised outcome results due to a detraining effect and impacted attrition. Finally the researches were not blinded to the outcome measures.

Conclusion

PA can have a profound effect on the treatment and management of CD (Warburton et al., 2006). Exercise rehabilitation programs provide an opportunity for individuals with CD to increase PA engagement. Delivering such programs in the community can improve accessibility, “normalise” or “demedicalise” exercise, and support individuals to incorporate PA into their daily or weekly routine. This study has shown that adopting a common CD model of CBER delivery can be successful in increasing LIPA levels and improving patterns of SB,

however the observed effect size was small. Moreover CBER is effective in enhancing physical functioning, body composition and psychological health outcomes. Observed effect sizes were small, with the exception of CRF where a large effect size was found. Largely no differences were found between different primary CD diagnosis or between those with a SCD and MM when participating in CBER, advocating for an integrated model approach.

Study 3

The results from Study 2 indicate that participation in the MedEx Wellness CBER program is associated with significant improvements in LIPA, SB, physical function and psychological health in men and women with a range of CDs. However, statistically significant improvements in health outcomes expressed as mean values often mask large inter-individual variability in measurable improvements in the response to lifestyle interventions. The present study identified factors associated with a measurable improvement in physical and psychological outcomes in men and women with SCD and MM in response to participation in a CBER program.

Although a measurable improvement in at least one health related outcome was achieved by 92.2% of participants, the prevalence of non-response (no change or a decrease) ranged from 19.2% for CRF to 53.4% for satisfaction with life. The findings indicate that participants attending a CBER program do not achieve positive improvements across all health-related measures. Both genetic and environmental factors and their interaction determine the individual response to lifestyle interventions. It is well established that BL measures of fitness and health are important determinants of how individuals respond to lifestyle interventions (Mann et al., 2014). Understanding how participants characteristics

determine measurable individual responses to exercise training would greatly assist allied health professionals in the design and deliver of future services. Specifically, individuals with more favourable BL measures of fitness and health are more likely to have a lower response to exercise training than those with less favourable BL measures (Bouchard & Rankinen, 2001). This can be explained by the 'ceiling effect' where further improvements in indices of fitness and health are limited beyond a certain threshold.

In the present study, a less favourable BL measure of PA levels (LIPA), functional capacity (lower- and upper- body strength), body composition (waist circumference), and psychological health (symptoms of depression and satisfaction with life) was found to increase the likelihood of achieving a measurable improvement. In contrast, lower BL CRF and increasing age reduced the likelihood of achieving a measurable change in the CRF. The 6MTT is a commonly used field-based measure of CRF. Low levels of CRF are associated with a small functional reserve and, can therefore severely limit the capacity to undertake moderate intensity exercise (Kaminsky et al., 2013). It is possible that study participants with low CRF levels were unable to exercise at an appropriate intensity level required to improve oxygen uptake, even when the exercise program was modified to account for their low functional capacity. From a clinical perspective, the identification of an age-adjusted, minimum 6MTT performance for entry to CBER would help to identify participants with a minimal functional capacity to ensure sufficient engagement with the program. Individuals below the minimum 6MTT threshold could be prescribed a remedial one-on-one exercise program to increase CRF levels prior to engaging in a group based exercise program.

For a number of health related outcomes, achieving a measurable change was predicted by primary CD diagnosis. A primary diagnosis of metabolic disease decreased the

likelihood of improving LIPA. This has important clinical implications, as low levels of PA are commonly associated with the presence of metabolic diseases (Egede & Zheng, 2002; Loprinzi et al., 2014; Loprinzi & Pariser, 2013; Nelson et al., 2002) and increasing levels of PA is challenging in this sedentary cohort (Cradock et al., 2017). Studies consistently report that participation in MVPA is suboptimal in patients with metabolic diseases and based on the findings in this study increasing efforts to promote LIPA among this patient cohort are warranted.

A primary CD diagnosis of cancer was associated with an increased likelihood of achieving a measurable improvement in the lower-body strength, which was used to assed lower body muscular endurance. Many cancer patients report a substantial decrease in PA levels after diagnosis (Irwin et al., 2011). Cancer therapies including chemotherapy, radiotherapy and hormonal therapy may result in loss of muscle mass and muscle weakness (Daly et al., 2018; Sturgeon et al., 2019) exercise has been shown to reverse the deleterious effect of cancer treatment on muscle function.

A primary diagnosis of respiratory disease was found to reduce the likelihood of improving self-rated health. Psychological health decreased in the respiratory cohort over the duration of the 12-month MedEx Wellness program as described in study 2. An individual's perception of physical exertion during exercise is highly correlated with pulmonary ventilation and respiratory rate (Robertson & Noble, 1997). For individuals with COPD, the experience of inspiratory difficulty can be overwhelming (Hanania & O'Donnell, 2019). In addition, the increased motor command output and contractile muscle efforts associated with exercise induces heavier breathing in both healthy individuals and those with COPD (Burton et al., 2004). Importantly, the anticipation of dyspnea itself can have

considerable negative psychological impact and has been found to be a mediator of anxiety (Janssens et al., 2011). Although PA is important for improving patient outcomes in COPD, experiences of dyspnea, even in patients with a mild diagnosis of COPD, can significant impact health-related QoL (Miravitlles & Ribera, 2017).

A secondary aim of study 3 was to identify the minimum CBER attendance required to achieve measurable/clinically meaningful changes in selected health indices. However, due the fact that statistical model did not control for extraneous variables and the low attendance to the program, the estimations of required number of classes attended to achieve improvements are likely to be imprecise. Notwithstanding these limitation, it was found that almost 5 months attendance (two classes a week) was associated with achieving a measurable change for any of the psychosocial determinants. Indeed, research has consistently demonstrated the link between psychosocial factors and PA participation (Bauman et al., 2012; Dutton et al., 2009; Hartman et al., 2013; Plotnikoff et al., 2000; Selzler et al., 2012), suggesting that one cannot change without the other (i.e. to induce changes in PA, psychosocial factors must also be addressed). The considerable duration of attendance required to achieve improvements in psychosocial determinants of PA, could help to explain the small changes in PA levels over the course of the program.

Maintaining optimal clinical, psychological and physical health and preventing disease progression are outcomes of exercise rehabilitation (Agency for Clinical Innovation, 2017; World Health Organization, 2019a). In this study, individuals who had no change in the selected indices of health or a regression, were classified as non-responders. However, for some of the participants maintaining health status or slowing the rate of disease progression was a positive outcome.

Genotype variations are significant determinants of training response phenotypes. In recent years, a greater number of specific gene variations associated with such responses have been identified. It is well established that approximately 50% of the variance in VO_{2max} response to training is explained by 21 single nucleotide polymorphisms (Bouchard et al., 2011). A significant genetic role has also been identified in the response of muscle performance and body composition to resistance training (Clarkson et al., 2005; Harmon et al., 2010; Van Deveire et al., 2012; Walsh et al., 2012; Walsh et al., 2009). However our understanding of genomic predictions particular, in relation to gene-environmental interactions is only in its infancy and, is currently of little real value in maximizing participants response to CBER.

The current research investigated inter-individual responses to CBER in terms of phenotypic traits including measures of physical function, CD diagnosis and sex. Identifying phenotypic predictors of responders and non-response has practical application in the CBER setting. There is a still lack of understanding of the individual characteristics associated with non-response to CBER. When limiting the number of measures assessed to determine response, it is likely that many positive response mechanisms are missed. (Pickering & Kiely, 2019). Exercise has wide varying implications that it is almost impossible to capture all within the one study. Furthermore, in addition to the established physiological benefits, the psychological and community benefits should also be appreciated.

The findings from this study indicates that individuals with CD attending CBER do not achieve positive improvements across all health-related outcomes. However, there is a predominate pattern whereby those with less favourable BL measures of LIPA, strength, body composition and mental health are more likely to improve with CBER. It is possible that a

cluster exist, where the same individual has less favourable BL measures across all health-outcomes. What is notably from this research is that those initiating the CBER program at the lower end of the spectrum in terms of health related measures, are found to be the most likely to benefit. This further advocates for the role of CBER in the secondary prevention of CD, as it essentially may primarily benefit those who need it most. Moreover, primary CD diagnosis or the presence of MM largely was not associated with response to the program.

Limitations of study 3

The thresholds used to classify clinically meaningful changes require caution with interpretation. For many of the health-related measures, evidence-based clinically meaningful changes do not exist or they are based on a single disease group and may not be generalizable across the range of disease included in this study. Secondly, the analysis used did not differentiate between participants who had healthy measured of certain outcomes at BL and those who did not. For instance, individuals with healthy measured of weight and waist circumference, ideally would remain unchanged, however in this analysis such individuals were considered non-responders. Thirdly, grouping all participants who achieved a measurable change or more may not effectively represent those who achieved a positive change to the program, as large variation exists within this category. For example, there would be substantial difference in an individual who increased their LIPA by ≥ 0.01 min/day and those who increased it by > 30 min or more. Currently both types of individuals are represented within the one group for analysis. Furthermore, training responses can be detected in a myriad of outcome measures and interpreting inter-individual training response on a measurement-by-measurement basis, leads to reduced generalizability of the predictive

outcomes identified. For instance, increasing age was a predictor of non-response to improving handgrip. Although the current evidence suggests that older individuals are less likely to improve handgrip strength, it cannot necessarily be assumed that older individuals will not respond positively in other outcome measures. Moreover, the selected indices of health used to investigate inter-individual responses, do not account for all putative components, which could be impacted by participating in a CBER program. In addition, participant use medication was not collected which is a significant limitation of this research. Finally, the analysis on estimated attendance required to achieve measurable and clinically meaningful improvements is not robust, and specific values revealed from required attendance must be interpreted with caution. Inter-individual variability exists in the required attendance to achieve a measurable change, and the current analysis technique did not account for this variability.

Conclusion

This study found that inter-individual variability exists among participants attending a CBER program. These findings suggest that individuals with lower PA levels, strength and psychological health are more likely to response positively to the program. In contrast, a lower level of CRF is an indicator of non-response. Future research could provide the evidence-base used to predict responders to exercise rehabilitation by identifying the factors or cluster of factors which predispose participants to a greater risk of non-response. Assessing the effectiveness of strategies, such as an introductory individualised program for those identified as at risk of non-response, would enhance the delivery of CBER and maximise the potential of this secondary preventative service in CD.

Strengths of this research

The clinical conditions which fall under the umbrella term of CD, although diverse in many ways, are associated with a similar impact on functional capacity and QoL. The mixed CD population which included individuals with both a SCD and MM is a key strength of this research. Research studies which focus on individual disease cohorts limits the generalizability of findings beyond that of the specific condition in question.

Study 1 (chapter 4) demonstrated that, regardless of disease, PA levels are low and excessive levels of SB exist within Cd population. Integrating a range of CDs within one study, including those with SCD and MM is current a novel approach in this field of research. The findings advocate that increasing PA levels and reducing SB within this cohort, has the potential to significantly impact disease progression, physical function and QoL.

The research was undertaken in the MedEx Wellness program, a CBER program that has been operating since 2007. A major finding of study 2 was that participation in the MedEx Wellness CBER program resulted in significant improvements in LIPA, patterns of SB, physical function and psychological health. Levels of MVPA were not found to significantly change, however a significant improvement in CRF was observed, with a large effect size. This finding suggest that although frequency of MVPA may not have changed, it is possible the intensity of MVPA bouts did while participating in MedEx Wellness classes. This change in MVPA participation was possibly enough to onset improvements in CRF. CRF is a vital predictor of health status (Warburton & Bredin, 2016; Blair et al., 2001; Myers et al., 2004; Williams, 2001). Hence, the effectiveness of the CBER program in eliciting changes in CRF, further advocates for its role in the secondary prevention of CD. The viability of the program has

been clearly demonstrated through its growth as a company, currently operating in a number locations in Ireland. The current research findings provide empirical evidence regarding the effectiveness of the service.

The study sample size would be considered relatively large. There are a limited number of interventional exercise studies involving individuals with CD, meeting the sample size of the current research. The inclusion of a number assessments throughout the study allowed for analysis of temporal changes.

An additional strength to this research is the incorporation of a wide variety of outcome measures, which were related to levels of PA, SB, physical function, clinical health, psychological health and psychosocial determinants of PA. This large data collection series provides a holistic insight into the potential benefits achieved through participation in the MedEx Wellness program. CD, in many cases, is a lifelong condition, and the management of the condition should ideally focus well beyond the immediate disease manifestations. This research highlights the potential of CBER as a comprehensive rehabilitation service which can simultaneously positively impact a number of CDs disease, while also enhancing additional components of health and wellbeing.

Impact of this research

It is likely that a futile cycle is prevalent among individuals with CD, whereby decreased PA participation and increased SB is associated with decreased functional capacity, QoL and accelerated disease progression (figure 7.1). The current findings advocate for an integrated approach to increasing PA participation and reducing SB across CD populations.

The heterogeneity of the population in this research, enhances the external validity of the findings.

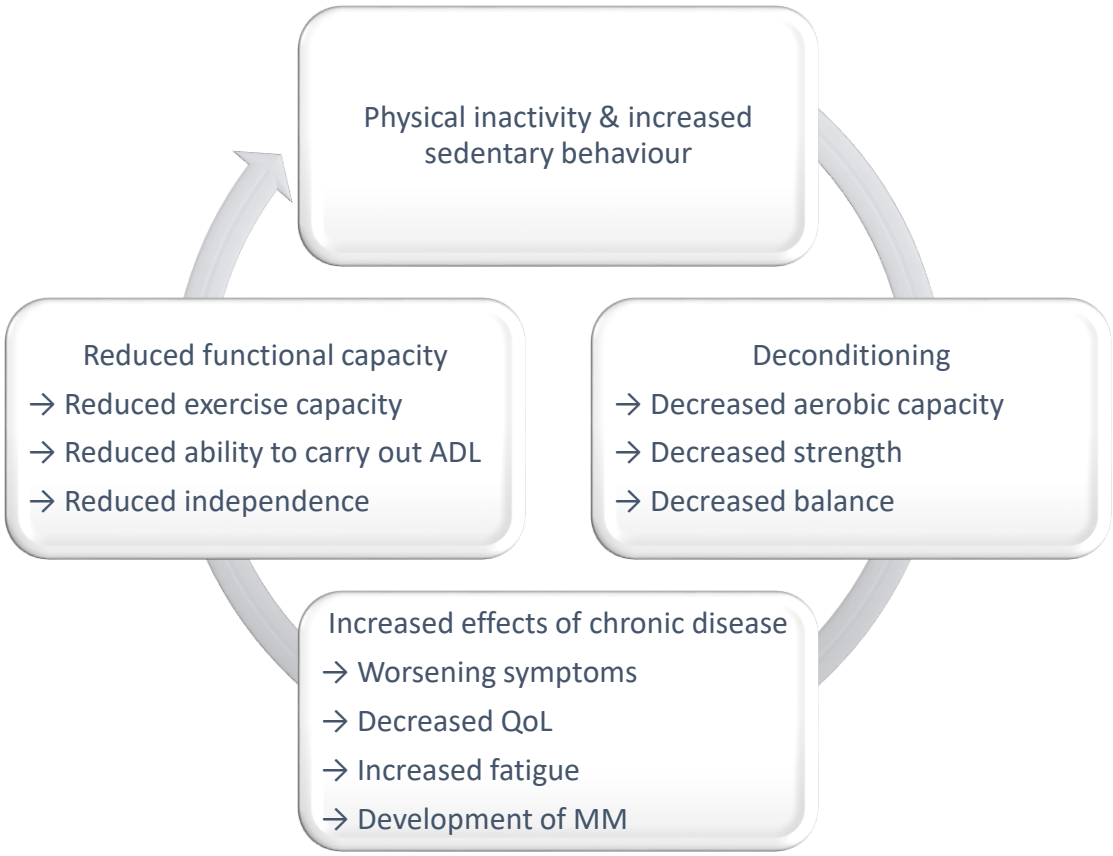

Figure 7.1 Cycle of physical inactivity associated with chronic disease
Note: QoL = quality of life; MM = multimorbidity, ADL = activities of daily living

The current shift in distribution of population age and increased life expectancy make it more likely that the prevalence of CD will continue to remain a substantial burden to society. PA/exercise is well established an adjunctive therapy in the secondary prevention of CD.

Exercise rehabilitation remains an under-utilized therapy within in the treatment of CD. The major findings from the current research are twofold. Firstly, the research provides

evidence for the efficacy of CBER as a secondary preventative therapy. Secondly, the research advocates for the novel integrated approach to CBER delivery for those with SCD and MM. CBER programs have enormous potential to widen access for CD populations to supervised exercise and reduce reliance on overwhelmed clinically based services. Not only does the CBER model remove some of the burden of rehabilitation from the hospitals where resources are sparse, it also has the potential to reduce future hospital admission and use of clinical healthcare systems. Future research is recommended to further enhance CBER design and delivery. For example, the optimal exercise dose remains unknown (optimal frequency of classes, duration and intensity). Although gaps still remain, referral to CBER should become part of standard care for the growing CD cohort.

The current global COVID-19 pandemic has further heightened interest in the delivery of non-essential health services in the community. In response to COVID-19, hospital-based exercise rehabilitation services have ceased, and staff reassigned to intensive care.

National recommendations of social-distancing and cocooning have created an environment less conducive to PA and more likely to promote SB (Pinto et al., 2020). The MedEx Wellness CBER program facilitated continuation of their services through a home-based online delivery platform, demonstrating the adaptability of CBER programs over more traditional hospital-based programs. It is likely that CBER programs will evolve to a blended centre and online model of delivery. Commercial devices are now available to monitor the electrical activity of the heart, respiratory rate and oxygen saturation during exercise (Fourth Frontier, 2020; Gilgen-Ammann et al., 2019). The adoption of these technologies has the potential to allow low to moderate risk CD patients undertake a 'supervised' combined home-

CBER program. This will facilitate the continued access for high risk patients to hospital-based program that will be running at a much lower capacity.

Although it was recommended that participants in the current study attend two classes per week, the MedEx Wellness model of delivery encouraged a flexible approach to attendance. For certain outcome variables, for example 6MTT, continuous significant improvements were observed at each time point, indicating that greater improvements were gained with longer engagement, and suggest that up to 12 months there is no significant plateau effect.

Creating a profile to identify individuals at risk of non-response to CBER has substantial implications for the future of CBER delivery. Inter-individual variability in response to CBER is inevitable, especially in a highly heterogeneous cohort. Notably, the current study found minimal differences in the response to CBER across different CD and between those with SCD or MM. Response was primarily based on BL levels of measurable health outcomes. Although the current consensus supports the theory that those with lower levels of PA, fitness and health at BL are generally the most susceptible to exercise rehabilitation, the current study provides evidence that low levels of CRF may contradict this. Low levels of CRF appear to prevent individuals for effectively responding to the MedEx Wellness program. Establishing a profile of those at risk of non-response, could inform strategies to reduce this risk from the onset, further enhancing the efficacy of CBER.

Recommendations for future research

- Research establishing a threshold for "too much sitting" in terms of the total accumulated amount of sitting per day and the length of a single uninterrupted sedentary bout are paramount in the development of the public health guidelines for this behaviour.
- Future studies should expand on various components of the MedEx Wellness shared CD model that could inform best practice for CBER. Areas in which research is particularly warranted include the following:

  i) Factors associated with uptake and adherence to CBER, which currently remain sub-optimal

  ii) Optimal exercise prescription in terms exercise intensity and total exercise dose

  iii) Compliance of participants to the recommended exercise intensity within the group based setting

  iv) Randomised controlled trials investigating the impact of different models of delivery that provide greater or less flexibility in relation to attendance to determine most effective prescription approach to CBER

  v) Optimal program design to cater for low, moderate and high risk CD patients in order to ensure the most efficient use of resources in both the clinical setting and in the community

  vi) Effect of behaviour change techniques to enhance the impact of CBER on habitual PA and SB. Research should investigate feasible behaviour change techniques that could be incorporated into the service, which focus on deceasing SB and

increasing habitual PA participation outside of class times/days. Specifically, increasing LIPA outside of the classes is recommended.

vii) Strategies to overcome the risk of non-response in order to maximise engagement with CBER for all referred participants

- Research establishing the factors and mechanisms that contribute to response to CBER is warranted. Defining the range of biopsychosocial factors associated with non-response could be used to create a profile of those at risk of non-response. Identifying individuals at BL who are at risk of non-response and implementing strategies to overcome the risk would inform the overall effectiveness of the service in practical application.
- An integrated clinical and community healthcare delivery model has significant potential for enhancing the management of patients with CD. Healthcare delivery systems are beginning to move away from segregated management of SCD to a multidisciplinary approach. Future research should focus on developing an evidence-base to support the new model of delivery
- An economic impact analysis of the CBER shared model is integral to inform future policy development.

Recommendations for future practice

MedEx Wellness, which has been recently renamed ExWell Medical, is a growing company and service. Since its debut in 2006, the program has expanded and is now operating in 3 community-based locations in Dublin and varies additional locations in Ireland, including programs led in University of Limerick, Waterford Institute of Technology, Sligo

institute of Technology, and a University of Pittsburgh Medical Centre supported branch in Kilkenny. All centres have adopted the integrated model to CBER. The evidence provided by this thesis supports commencement of a national roll out of this service. The current research has highlight aspects of the program design and delivery that could be altered to further enhance the service. Attendance was suboptimal, with few participants attaining the recommended levels of twice a week or more. More emphasis on attendance from the medical director during induction to the program could improve this component. Incorporating behaviour change techniques focused on reducing SB and improving habitual PA outside of classes could enhance the holistic impact of this program. Finally, offering a beginners/lower intensity program or one to one service for individuals with very low CRF at baseline may enhance the ability of such participants to engage in the standard group exercise effectively.

There is an imperative need to embed PA into healthcare for the secondary prevention of CD. The current evidence supports an integrated CBER service for those with SCD and MM as an effective health intervention. Government collaboration is recommended to support the provision of CBER nationwide. Resources in terms of trained personnel and support for suitable centres could be incorporated in the government healthcare agenda. In addition, standard procedures for exercise referral should be put in place to promote exercise referral among primary care healthcare professionals. A National Exercise Referral Framework (NERF) for Ireland was published in 2016 (Woods, et al., 2016). The development of NERF was commissioned by the HSE. The framework recommends exercise referral to CBER for those with CD to. The design of the NERF community centres was based off a MedEx Wellness CBER model, however this framework has yet to be funded. The current research

provides the evidence base to advocate for the implementation of the NERF in Ireland. Developing a national registry of appropriate facilities with qualified personnel to deliver CBER and establishing links between local healthcare practitioners and CBER services is the steps the need to be taken to allow for nationwide implementation of CBER.

Ireland's National Centre for Exercise is Medicine® (EIM) was launched in February 2020. Increasing PA assessment, prescription and referral to NERF centres by physicians and allied health professionals has been stated as a primary aim within the current EIM initiative in Ireland (EIM Ireland, 2020). The implementation of an integrated pathway that standardizes the referral of CD patients to evidence based, safe and effective CBER services is recommended.

Conclusion

Despite the beneficial effects of PA in the secondary prevention of CD, only a small proportion of CD patients in this study meet the current PA recommendations. Furthermore, time spent in SB was excessive, potentially accelerating the rate of disease progression. Recent PA guidelines for the general population and those with CD, recommend that individuals who engage in little or no PA, should replace SB with LIPA, as there is no threshold to be exceeded before health benefits are observed (US Department of Healt and Human Services, 2018b). The current thesis findings support these recommendations. A shared CBER model across CD populations was found to be an effective approach to increasing PA engagement and habitual levels of LIPA in this cohort. The model of delivery improved physical function and psychological health. With the growing global burden of CD and the

associated health care costs, there is an urgent need to identify effective approaches to implementing evidence-based exercise rehabilitation services.

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Appendices

Appendix A. Plain language statement

Plain Language Statement

DUBLIN CITY UNIVERSITY

An evaluation of the effects of the MedEx programme on physical, clinical and psychosocial outcomes and an examination of determinants of adherence to MedEx

School of Health and Human Performance, DCU

Dr. Catherine Woods (catherine.woods@dcu.ie), **Dr. Noel McCaffrey** (noel.mccaffrey@dcu.ie) and **Ms Fiona Skelly** (fiona.skelly2@mail.dcu.ie)

Details of what involvement in the Research Study will require

Participation in this study will involve you attending DCU for 2 days of testing, before you start the MedEx programme. Each visit will last approximately 90 minutes and be separated by at least 1 week. On day 1 you will be asked to complete a questionnaire and perform some physical tests, including a simple strength test, and flexibility test. You will also have your height, weight, waist and hip circumference, measured. On this day you will also be asked to give a blood sample. Before you leave on day 1, a device will be given to you to wear for 1 week. This device is an ActivPal Accelerometer and will measure your activity levels throughout the week. A second questionnaire will also be given to fill out at home.

On testing day 2 you will be perform a simple walk test. Along with this you will perform two brain function tasks. One measuring memory and the second measuring attention. As part of the induction process, on day 2, a group exercise consultation will be conducted. This will be repeated at 4 weeks and then at 3 month intervals going forward.

A second questionnaire is also give out to fill out at home. Before you leave on day 2 you will be given a 24 hour blood pressure monitor to wear from for 24 hours.

During your first class participants with claudication will conduct a treadmill walking test, participants with lung conditions will be assess on lung function and also participants identified as at risk of falls will perform a simple balance test.

Every 3 months you will be asked to repeat the induction measures in order to monitor your progress.

Potential risks to participants from involvement in the Research Study (if greater than that encountered in everyday life)

Exercise and exercise testing carries with it a very small risk of abnormal heart rhythms, heart attack or death in less than one in 30,000 people. There may also be a risk of anginal symptoms such as an increased blood pressure or arrhythmias. With all exercise sessions, there is a risk of delayed onset of muscle soreness. Participants will be advised that they may experience muscle soreness. All individuals will be advised and given training to exercise at their own level of intensity and to increase progressively to help minimize any discomfort. Participants may also experience some discomfort due to the effects of exercise, such as increased respiration and sweating. Drawing blood may cause a slight pain where the needle is inserted and can leave a bruise. A person trained to take blood will be used to decrease these risks. The amount of blood drawn is not harmful.

Benefits (direct or indirect) to participants from involvement in the Research Study

Besides the benefits associated with regular exercise which participants will be receiving as part of the MedEx service, benefit to participants will include increased knowledge regarding recommended levels of physical activity for people living with chronic conditions and methods of achieving these recommendations Participants will also benefit from meeting other people in similar situations to themselves and will be provided with a supportive and safe environment in which they can exercise in a supportive safe environment.

Advice as to arrangements to be made to protect confidentiality of data, including that confidentiality of information provided is subject to legal limitations

Confidentiality is an important issue during data collection. Participant's identity, or other personal information, will not be revealed or published. All raw data will only be available to the DCU research team who shall not have any means of accessing the identity of any participants. All responses are anonymous and will be dealt with on a strictly confidential basis. The investigators alone will have access to the data. In accordance with DCU policy all data will be kept on-site in DCU in a locked secure area.

Advice as to whether or not data is to be destroyed after a minimum period

After a 5 year period, if participants do not wish to have their data returned, or do not contact the investigators, all data will be destroyed in accordance with DCU policy.

Statement that involvement in the Research Study is voluntary

If at any point during your participation in the study you feel as if you wish to leave, this is not a problem. You are under no obligation to stay involved if you do not wish too.

If you are willing to do so please contact the investigators if you are unable or unwilling to continue in the project so as we can address an issues within the project.

If participants have concerns about this study and wish to contact an independent person, please contact:

The Secretary, Dublin City University Research Ethics Committee, c/o Research and Innovation Support, Dublin City University, Dublin 9. Tel 01-7008000

Appendix B. Informed Consent

Informed Consent

DUBLIN CITY UNIVERSITY

An evaluation of the effects of the MedEx programme on physical, clinical and psychosocial outcomes and an examination of determinants of adherence to MedEx

Principal Investigator: Dr. Catherine Woods, School of Health and Human Performance, Dr Noel McCaffrey School of Health and Human Performance

Other Investigators: Ms. Fiona Skelly School of Health and Human Performance

The purpose of this study is to evaluate the MedEx programme on participant physical and psychological health, as well as investigating the factors associated with uptake, adherence, relapse, and dropout of a community based chronic illness rehabilitation programme.

This study requires you to participate in physical fitness testing (walk test, lower body strength test, grip strength test, flexibility test, and body composition measure) at induction and at 3 month intervals, and completion of questionnaires at induction, also at 3 month intervals. Finally participants will be asked to give a blood sample at baseline and at 3 month intervals.

As part of the induction process a group exercise consultation will be conducted. This will be repeated at 4 weeks and then at 3 month intervals going forward.

Finally, you are asked to wear two devices. The first is an ActivPal Accelerometer. This is a small device attached to the right leg and worn for one week. The second is a 24-hour blood pressure monitor. This consists of a blood pressure cuff around the left and kept on for 24 hours.

Participant – please complete the following (Circle Yes or No for each question)

I have read the Plain Language Statement (or had it read to me) ***Yes/No***

I understand the information provided ***Yes/No***

I have had an opportunity to ask questions and discuss this study ***Yes/No***

I have received satisfactory answers to all my questions ***Yes/No***

If at any point during your participation in the study, you feel as if you wish to leave this is not a problem. You are under no obligation to stay involved if you do not wish to. Please make sure to contact the investigators if you are unable or unwilling to continue in the project so as we can address any issues within the project.

Dublin City University will protect all the information about me, and my part in this study. I will be assigned a unique ID number under which all my personal information will be stored securely and saved in a password protected file in a computer at DCU. My identity or personal information will not be revealed or published. All records associated with my participation in the study will be subject to the usual confidentiality standards applicable to medical records. All contact information will be securely stored in Dublin City University and will not be revealed to any third party. In addition, the study findings may be presented at scientific meetings and published in a scientific journal but my identity will not be divulged and only presented as part of a group. I am aware that the confidentiality of information provided can only be protected within the limitations of the law. It is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

If I have questions about the research project, I am free to call Dr. Catherine Woods at 01-7008008 or Brona Furlong at 01 7006442

I have read and understood the information in this form. My questions and concerns have been answered by the researchers, and I have a copy of this consent form. Therefore, I consent to take part in this research project:

Participants Signature: _____

Name in Block Capitals: _____

Witness: _____

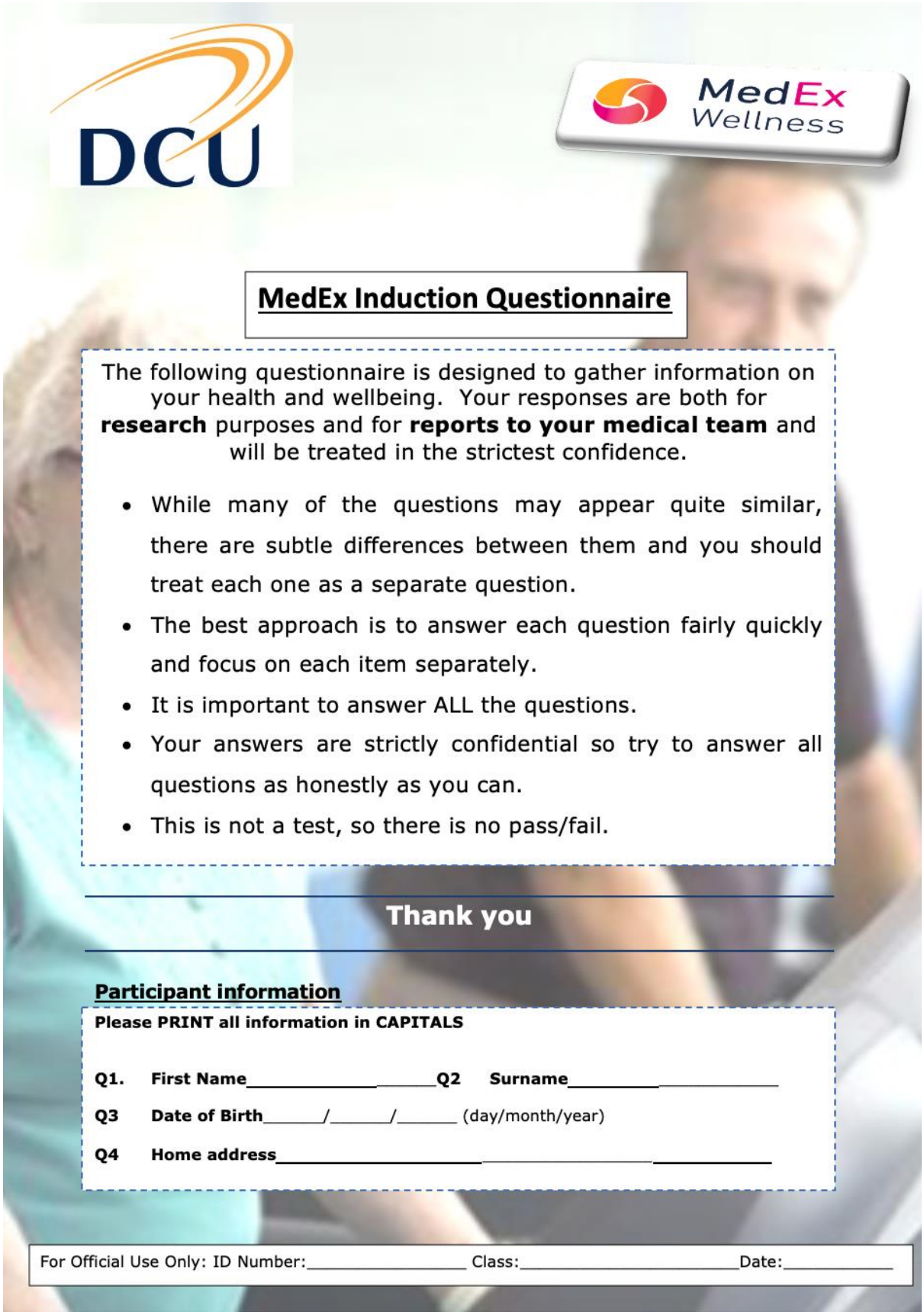
Date: _____

6 MONTH ASSESSMANT

Name :	BS Date:	3 Month date:	6 Month date:

Test	Baseline	3 Months	6 Months
BMI			
Waist			
Hip			
Sit to Stand			
Sit and Reach			
Handgrip			
6 Minute walk test			

Appendix D. Questionnaire competed during visit 1



DCU

MedEx Wellness

MedEx Induction Questionnaire

The following questionnaire is designed to gather information on your health and wellbeing. Your responses are both for **research** purposes and for **reports to your medical team** and will be treated in the strictest confidence.

- While many of the questions may appear quite similar, there are subtle differences between them and you should treat each one as a separate question.
- The best approach is to answer each question fairly quickly and focus on each item separately.
- It is important to answer ALL the questions.
- Your answers are strictly confidential so try to answer all questions as honestly as you can.
- This is not a test, so there is no pass/fail.

Thank you

Participant information

Please PRINT all information in CAPITALS

Q1. **First Name**_____ **Q2** **Surname**_____

Q3 **Date of Birth**_____/_____/_____ (day/month/year)

Q4 **Home address**_____

For Official Use Only: ID Number:_____ Class:_____ Date:_____

Q5 **Gender** (Please tick (✓) one box): Male ☐ 1 Female ☐ 2

Q6 What is your marital status
(Use "✓" to indicate your answer)

Married ..... ☐ 1
Living with partner ..... ☐ 2
Single (never married) ..... ☐ 3
Separated ..... ☐ 4
Divorced ..... ☐ 5
Widowed ..... ☐ 6

Q7 What is the highest level of education you have completed? (Use "✓" to indicate your answer)

Some primary (not completed)..... ☐ 1
Intermediate/junior/group certificate or equivalent... ☐ 2
Leaving certificate or equivalent..... ☐ 3
Diploma/certificate..... ☐ 4
Primary degree..... ☐ 5
Postgraduate/ higher degree ..... ☐ 6
None..... ☐ 7
Don't know ..... ☐ 8

Q8 How would you describe your present principle status? (Use "✓" to indicate your answer)

Working for payment or profit..... ☐ 1
Looking for first regular job..... ☐ 2
Unemployed..... ☐ 3
Student or pupil..... ☐ 4
Looking after home or family..... ☐ 5
Retired from employment..... ☐ 6
Unable to work due to permanent sickness or disability..... ☐ 7
Other..... ☐ 8

Q9 What is (was) your occupation in your main job?

Write in your main occupation? _____

Q10 Sometime in the future we may want to contact you to follow up on this research.
Would that be OK? (Please tick (✓) one box): Yes ☐ 1 No ☐ 2

SECTION 1

Q1. Who referred you to MedEx?

(Use "✓" to indicate your answer)

Hospital Consultant
Please list:_____ 1☐

General practitioner (GP)
Please list:_____ 2☐

Phase III Cardiac Rehab (Beaumont) 3☐

Phase III Cardiac Rehab (Mater) 4☐

Other
Please list:_____ 5☐

SECTION 2

Q1. Please indicate which chronic condition(s) you have (tick all that apply).

None	☐ 1
Heart Disease *Type of heart disease* _____	☐ 2
Peripheral arterial disease/claudication.....	☐ 3
Chronic bronchitis, emphysema or COPD.....	☐ 4
Asthma.....	☐ 5
Other lung disease *Type of lung disease*_____	☐ 6
Cancer *Specify type*_____	☐ 7
Type 2 diabetes.....	☐ 8
Type 1 diabetes.....	☐ 9
Depression.....	☐ 10
Anxiety or other emotional mental health condition.....	☐ 11
Arthritis or other rheumatic disease *Specify type*_____	☐ 12
Other chronic condition *Please specify*_____	☐ 13

Section 3

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

Q1a During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling? Please circle one number.

0 days 1 2 3 4 5 6 7 days

Q1b How much time did you usually spend on one of those days doing **vigorous** physical activities?
_____hours_____minutes **per day**

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

Q2a. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking. Please circle one number.

0 days 1 2 3 4 5 6 7 days

Q2b How much time did you usually spend on one of those days doing **moderate** physical activities?
_____hours_____minutes ***per day***

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

Q3a During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time? Please circle one number.

0 days 1 2 3 4 5 6 7 days

Q3b How much time did you usually spend **walking** on one of those days?
_____hours_____minutes ***per day***

Q3c Which of the following best describes your usual **walking pace?**

A slow pace	A steady average pace	A fairly brisk pace	A fast pace (at least 4mph)
1☐	2☐	3☐	4☐

TIME SPENT SITTING

Q4 During the **last 7 days**, how much of the time did you usually spend **sitting** on **one** week day? (Includes time spent at a desk, visiting friends, reading, travelling, or sitting or lying down to watch television).

_____hours_____minutes ***per day***

SECTION 4

The following items reflect situations that are listed as common reasons for preventing individuals from participating in exercise sessions or, in some cases, dropping out. Using the scales below please indicate how confident you are that you could exercise in the event that any of the following circumstances were to occur.

Please indicate the degree to which you are confident that you could exercise in the event that any of the following circumstances were to occur by ticking the appropriate %. Select the response that most closely matches your own, remembering that there are no right or wrong answers.

FOR EXAMPLE: In question #1 if you have complete confidence that you could exercise even if "the weather was very bad," you would tick 100%. If however, you had no confidence at all that you could exercise (that is, confidence you would not exercise), you would circle 0%.

I believe that I could exercise 3 times per week for the next 3 months if:

1. The weather was very bad (hot, humid, rainy, cold).

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
0% 10 20 30 40 50 60 70 80 90 **100%**
Moderately Confident

2. I was bored by the program or activity.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
Confident **0%** 10 20 30 40 50 60 70 80 90 **100%**
Moderately Confident

3. I was on vacation.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

4. I was not interested in the activity.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
Confident 0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

5. I felt pain or discomfort when exercising.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

6. I had to exercise alone.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
Confident 0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

7. It was not fun or enjoyable.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

8. It became difficult to get to the exercise location.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
Confident 0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

9. I didn't like the particular activity program that I was involved in.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

10. My schedule conflicted with my exercise session.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
Confident 0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

11. I felt self-conscious about my appearance when I exercised.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

12. An instructor does not offer me any encouragement.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
Confident 0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

13. I was under personal stress of some kind.

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Highly Confident
0% 10 20 30 40 50 60 70 80 90 100%
Moderately Confident

Please continue to the next page

SECTION 5

The following items reflect activities surrounding exercise, physical activity and MedEx class attendance. Please indicate the degree to which you intend to do the following items by ticking the appropriate box. Select the response that most closely matches your own. Remember there are no right or wrong answers.

I intend to... (Use "✓" to indicate your answer)	**Completely disagree** 1	**Disagree** 2	**Agree** 3	**Totally agree** 4
Q1. Exercise several times a week	1☐	2☐	3☐	4☐
Q2. Work up a sweat regularly	1☐	2☐	3☐	4☐
Q3. Exercise regularly	1☐	2☐	3☐	4☐
Q4. Be physically active regularly for a minimum of 30 minutes 3 times a week	1☐	2☐	3☐	4☐
Q5. To increase my leisure time activity	1☐	2☐	3☐	4☐
Q6. To adhere to the exercise regimen prescribed to me	1☐	2☐	3☐	4☐
Q7. Attend MedEx classes at least once a week	1☐	2☐	3☐	4☐
Q8. To stick to MedEx classes	1☐	2☐	3☐	4☐

Section 6

Q1 Have you fallen in the last 12 months?

Yes 1☐ No 2☐

Q2 In total, about how many times have you fallen in the last 12 months?

_____

Don't know 1☐

Q3 Are you afraid of falling?

Yes 1☐ No 2☐

Q4 Do you have any problems with your walking or balance?

Yes 1☐ No 2☐

SECTION 7

This section is about exercise support from FAMILY. Please use a "✓" to indicate how much of the time the following statements relate. If these statements do not relate to family please tick "none" instead of leaving it blank.

How much of the time during the past three months, my family (or members of my household)…		None	Rarely	A few times	Often	Very often	Does Not Apply
		1	**2**	**3**	**4**	**5**	**6**
Q1. Exercised with me	**Family**	1☐	2☐	3☐	4☐	5☐	6☐
Q2. Offered to exercise with me	**Family**	1☐	2☐	3☐	4☐	5☐	6☐
Q3. Gave me helpful reminders to exercise ("Are you going to exercise tonight?")	**Family**	1☐	2☐	3☐	4☐	5☐	6☐
Q4. Gave me encouragement to stick with my exercise program	**Family**	1☐	2☐	3☐	4☐	5☐	6☐
Q5. Changed their schedule so we could exercise together	**Family**	1☐	2☐	3☐	4☐	5☐	6☐
Q6. Discussed exercise with me	**Family**	1☐	2☐	3☐	4☐	5☐	6☐
Q7. Planned for exercise on recreational outings	**Family**	1☐	2☐	3☐	4☐	5☐	6☐
Q8. Helped me plan activities around my exercise	**Family**	1☐	2☐	3☐	4☐	5☐	6☐

Please continue to the next page

SECTION 8

Please answer the following questions in relation to smoking, alcohol consumption and diet.

Q1. On how many days during a typical week did you usually drink alcohol, on average?

Number of Days.....

Q.2 On the days that you drank alcohol, how many drinks did you have on average?

A drink is: a half pint/glass of beer, lager, stout or cider
a single measure of spirits (whiskey, rum, vodka, gin)
a single glass of wine, sherry, port

Number of drinks.....

Q.3 Do you smoke cigarettes now?

- ☐ No → Go to Question 6
- ☐ Yes, regularly
- ☐ Yes, occasionally (usually less than 1 per day)

Q.4 In a day, how many of the following do you usually smoke? (Please write a number)

..... branded cigarettes
..... hand rolled cigarettes

Q.5 How long have you been a cigarette smoker for?

..... years

Q.6 Did you ever smoke cigarettes in the past?

- ☐ No, never
- ☐ Current smoker
- ☐ Occasionally (usually less than 1 cigarette per day)
- ☐ Yes, regularly

Q.7 How often do you eat convenience food (i.e. fast food or 'take-aways': e.g. Chinese, Indian, pizza, burgers, chips, etc.)

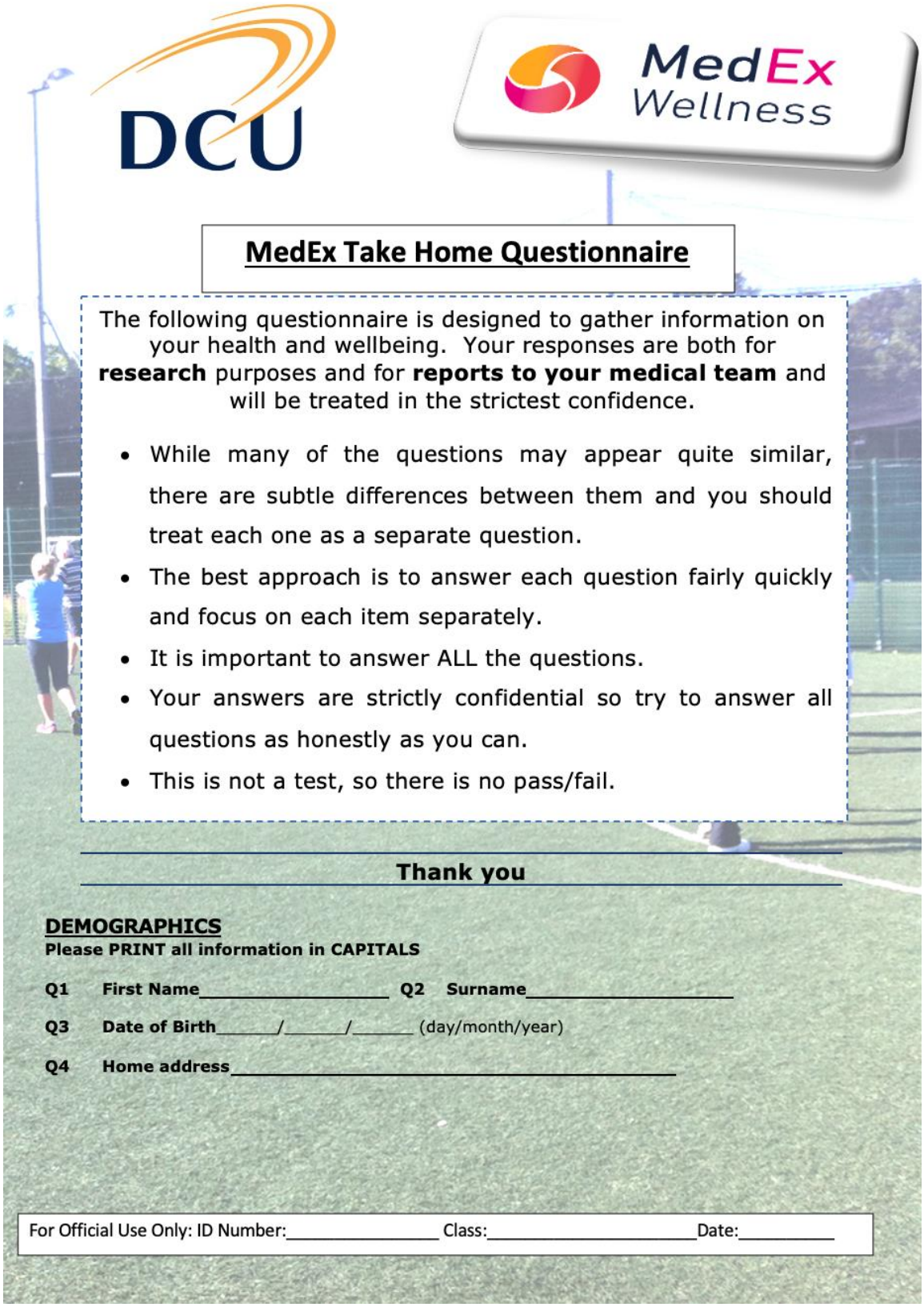
☐ Daily ☐ 4-6 times a week ☐ 1-3 times a week ☐ Less than once a week ☐ Never

Q.8 How often do you prepare food from fresh ingredients rather than pre-prepared food?

☐ Daily ☐ 4-6 times a week ☐ 1-3 times a week ☐ Less than once a week ☐ Never

The questionnaire is now complete. Thank you very much for your time.

Appendix E. Questionnaire taken home on visit 1



DCU

MedEx Wellness

MedEx Take Home Questionnaire

The following questionnaire is designed to gather information on your health and wellbeing. Your responses are both for **research** purposes and for **reports to your medical team** and will be treated in the strictest confidence.

- While many of the questions may appear quite similar, there are subtle differences between them and you should treat each one as a separate question.
- The best approach is to answer each question fairly quickly and focus on each item separately.
- It is important to answer ALL the questions.
- Your answers are strictly confidential so try to answer all questions as honestly as you can.
- This is not a test, so there is no pass/fail.

Thank you

DEMOGRAPHICS

Please PRINT all information in CAPITALS

Q1 First Name_____ **Q2 Surname**_____

Q3 Date of Birth_____/_____/_____ (day/month/year)

Q4 Home address_____

For Official Use Only: ID Number:_____ Class:_____Date:_____

SECTION 1

Please use "✓" to indicate your answer in the following section.

Q1. In general would you say your health is;

Excellent	Very good	Good	Fair	Poor
1☐	2☐	3☐	4☐	5☐

Q2. The following questions are about activities you might do during a typical day

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Moderate activities, such as moving a table, pushing a vacuum, bowling or playing golf.	1☐	2☐	3☐
b Climbing several flights of stairs	1☐	2☐	3☐

Q3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a Accomplished less than you would like	1☐	2☐
b Were limited in the kind of work or other activities	1☐	2☐

Q4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a Accomplished less than you would like	1☐	2☐
b Didn't do work or other activities as carefully as usual	1☐	2☐

Q5. During the past 4 weeks how much of the time did pain interfere with your normal work (including work both outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
1☐	2☐	3☐	4☐	5☐

Q6. These questions are about how you feel and how things have been with you during the past month. For each question, please indicate the one answer that comes closest to the way you have been feeling.

	All of the time	Most of the time	A good bit of the time	Some of the time	None of the time
a Have you felt calm and peaceful?	1☐	2☐	3☐	4☐	5☐
b Did you have lots of energy?	1☐	2☐	3☐	4☐	5☐
c Have you felt downhearted and low?	1☐	2☐	3☐	4☐	5☐
d Has your health limited your social activities (like visiting friends or close relatives)?	1☐	2☐	3☐	4☐	5☐

Q7. Over the last two weeks how often have you been bothered by any of the following problems?

		Not at all	Several days	More than half the days	Nearly every day
A	Little interest or pleasure in doing things	1☐	2☐	3☐	4☐
B	Feeling down, depressed, or hopeless	1☐	2☐	3☐	4☐
C	Trouble falling or staying asleep, or sleeping too much	1☐	2☐	3☐	4☐
D	Feeling tired or having little energy	1☐	2☐	3☐	4☐
E	Poor appetite or overeating	1☐	2☐	3☐	4☐
F	Feeling bad about yourself- or that you are a failure or have let yourself or you family down	1☐	2☐	3☐	4☐
G	Trouble concentrating on things such as reading the newspaper or watching television	1☐	2☐	3☐	4☐
H	Moving or speaking so slowly that other people could have noticed? Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual	1☐	2☐	3☐	4☐

I **If you checked off ANY problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?**

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
1☐	2☐	3☐	4☐

Q8. In the last 7 days, about how many hours per 24 hour period did you spend sleeping?

	3 or less hours	4 hours	5 hours	6 hours	7 hours	8 hours	9 hours	10 hours	11 hours	12 or more hours
Weekdays	1☐	2☐	3☐	4☐	5☐	6☐	7☐	8☐	9☐	10☐
Weekends	1☐	2☐	3☐	4☐	5☐	6☐	7☐	8☐	9☐	10☐

Q9. During the past week, how would you rate your sleep quality overall (how well you sleep)?

Very bad	Fairly bad	Fairly good	Very good
1☐	2☐	3☐	4☐

If any of your answers give you concern please contact a member of MedEx staff or Dr. Noel McCaffrey who can deal with these concerns.

SECTION 2

Q1 Are you covered by: (Use "✓" to indicate your answer)

Full Medical Card or equivalent	GP visit card	Neither	Don't know
1 ☐	2 ☐	3 ☐	4 ☐

Q2. In the last 12 months, about how often did you visit your GP?

0-200_____

Don't know 1 ☐

Q3 In the last 12 months, how many times did you visit a hospital emergency department as a patient?

0-200_____

Don't know 1 ☐

Q4. In the last 12 months, about how many visits did you make to a hospital as an outpatient? (Include all types of consultations, tests, operations, procedures or treatments**)**

0-200_____

Don't know 1 ☐

Q5. When you went to hospital as an outpatient, was this predominantly as a: (Use "✓" to select one answer only)

As a public patient ☐ 1

As a private patient ☐ 2

Don't know ☐ 3

Not applicable ☐ 4

Q6. In total, about how many nights did you spend in hospital in the last 12 months?

0-364_____

Don't know 1 ☐

Q7. When you stayed overnight in hospital, was this predominantly as a: (Use "✓" to select one answer only)

As a public patient 1 ☐

As a private patient 2 ☐

Don't know 3 ☐

Not applicable 4 ☐

Q8. In total during the last 12 months about how many days have you taken off work (If working) due to illness?

0-364_____

Don't know 1 ☐

Not applicable 2 ☐

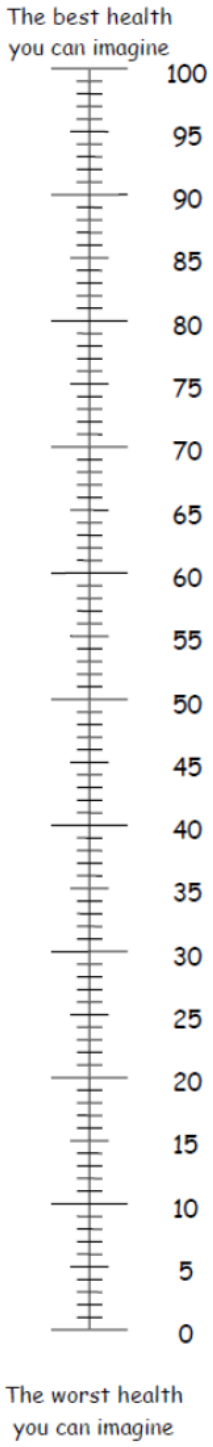
SECTION 3

Under each heading, please tick the ONE box that best describes your health TODAY.

Mobility (walking about)	
I have no problems walking about	☐
I have some problems walking about	☐
I have a lot of problems walking about	☐
Looking after myself	
I have no problems washing or dressing myself	☐
I have some problems washing or dressing myself	☐
I have a lot of problems washing or dressing myself	☐
Doing Usual Activities **(for example, hobbies, gardening, house work, doing things with family or friends)**	
I have no problems doing my usual activities	☐
I have some problems doing my usual activities	☐
I have a lot of problems doing my usual activities	☐
Having pain or discomfort	
I have no pain or discomfort	☐
I have some pain or discomfort	☐
I have a lot of pain or discomfort	☐
Feeling worried, sad or unhappy	
I am not worries, sad or unhappy	☐
I am a bit worried, sad or unhappy	☐
I am very worried, sad or unhappy	☐

SECTION 4

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the line that shows how good or bad your health is TODAY.



SECTION 5

Below are five statements that you may agree or disagree with. Using the 1 - 7 scale below, indicate your agreement with each item by placing the appropriate number on the line preceding that item. Please be open and honest in your responding.

- 7 - Strongly agree
- 6 - Agree
- 5 - Slightly agree
- 4 - Neither agree nor disagree
- 3 - Slightly disagree
- 2 - Disagree
- 1 - Strongly disagree

_____ In most ways my life is close to my ideal.

_____ The conditions of my life are excellent.

_____ I am satisfied with my life.

_____ So far I have gotten the important things I want in life.

_____ If I could live my life over, I would change almost nothing.

SECTION 6

Below are some statements about feelings and thoughts.

Please tick the box that best describes your experience of each over the last 2 weeks

Statements	None of the time	Rarely	Some of the Time	Often	All of the Time
I've been feeling optimistic about the future					
I've been feeling useful					
I've been feeling relaxed					
I've been dealing with problems well					
I've been thinking clearly					
I've been feeling close to other people					
I've been able to make up my own mind about things					

SECTION 7

Using the scales below please indicate how confident you are in the following items by ticking the appropriate %. Select the response that most closely matches your own, remembering that there are no right or wrong answers.

How confident are you that you can…
(Please use "✓" to indicate your answer)

1. Motivate yourself to get at least 30 minutes of activity a day, 3 times per week?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
0% 10 20 30 40 50 60 70 80 90 100%
Somewhat Confident

2. Motivate yourself to attend at least 1 MedEx class a week?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
Confident 0% 10 20 30 40 50 60 70 80 90 100%
Somewhat Confident

3. Use safe, effective exercise technique (e.g. warm-up, stretching)?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
0% 10 20 30 40 50 60 70 80 90 100%
Somewhat Confident

4. Plan exercise sessions that will be at least moderately difficult (e.g. have you breathing a little hard, your heart rate increases)?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
Confident 0% 10 20 30 40 50 60 70 80 90 100%
Somewhat Confident

5. Monitor your exercise progress by recording what exercises you do, how often you do them and for how long?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
0% 10 20 30 40 50 60 70 80 90 100%
Somewhat Confident

6. Set realistic, weekly exercise goals for yourself (e.g. exercising 3 days/week)?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
Confident 0% 10 20 30 40 50 60 70 80 90 100%
Somewhat Confident

7. Monitor and regulate the intensity of your exercise so that it is moderately difficult?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
0% 10 20 30 40 50 60 70 80 90 100%
Somewhat Confident

8. Develop solutions to cope with potential barriers that can interfere with your exercise?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
Confident 0% 10 20 30 40 50 60 70 80 90 100%
Somewhat
Confident

9. Schedule exercise sessions into your weekly routine so that you get at least 30 minutes of exercise a day, 3 times per week?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
0% 10 20 30 40 50 60 70 80 90 100%
Somewhat
Confident

10. You can return to exercise even if you have relapsed (returned to a sedentary/physically inactive state) for several weeks?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
Confident 0% 10 20 30 40 50 60 70 80 90 100%
Somewhat
Confident

11. You can return to exercise even if you have relapsed (returned to a sedentary/physically inactive state) several times?

Not at all ___:____:____:_____:____:____:_____:_____:_____:_____:_____: Completely Confident
0% 10 20 30 40 50 60 70 80 90 100%
Somewhat
Confident

Please continue to the next page

SECTION 8

This section is about exercise support from FRIENDS. Please use a "✓" to indicate how much of the time the following statements relate. If these statements do not relate to friends please tick "none" instead of leaving it blank.

How much of the time during the past three months, friends (this can include fellow MedEx participants)...		None	Rarely	A Few Times	Often	Very Often	Does Not Apply
Q.1 Exercised with me	**Friends**	1☐	2☐	3☐	4☐	5☐	6☐
Q.2 Offered to exercise with me	**Friends**	1☐	2☐	3☐	4☐	5☐	6☐
Q.3 Gave me helpful reminders to exercise ("are you going to exercise tonight?")	**Friends**	1☐	2☐	3☐	4☐	5☐	6☐
Q.4 Gave me encouragement to stick with my exercise program	**Friends**	1☐	2☐	3☐	4☐	5☐	6☐
Q.5 Changed their schedule so we could exercise together	**Friends**	1☐	2☐	3☐	4☐	5☐	6☐
Q.6 Discussed exercise with me	**Friends**	1☐	2☐	3☐	4☐	5☐	6☐
Q.7 Planned for exercise on recreational outings	**Friends**	1☐	2☐	3☐	4☐	5☐	6☐
Q.8 Helped me plan activities around my exercise	**Friends**	1☐	2☐	3☐	4☐	5☐	6☐

The questionnaire is now complete. Thank you very much for your time.

MedEx Wellness

DCU Sport

Name : **Date:**

Height	**cm**	**Weight**	**kg**	**BMI**	
Waist	cm		Hip	Cm. Ratio:	

RIf the answer is yes to any of the follow 4 questions do not perform the sit and reach.

1. Back pain which is worsened by stooping or bending forward. YES/NO	**2. Sciatica. (Leg pain caused by a bulging lumber disc. YES/NO**	**3. A known lumber disc bulge. YES/NO**	**4. Cancer affecting your spin. YES/NO**

Sit-and-reach	**Trial 1:**	**Best Result:**
	Trial 2:	
	Trial 3:	
Sit-to-stand	**Trial 1:**	**Best Result:**
	Trial 2:	
Handgrip Dominant hand (Circle) R L	**Trial 1:**	**Mean of 3 trials:**
	Trial 2:	
	Trial 3:	

6 Minute Walk Test					
20 m		320 m	*	620 m	
40 m	*	340 m		640 m	*
60 m		360 m	*	660 m	
80 m	*	380 m		680 m	*
100 m		400 m	*	700 m	
120 m	*	420 m		720 m	*
140 m		440 m	*	740 m	
160 m	*	460 m		760 m	*
180 m		480 m	*	780 m	
200 m	*	500 m		800 m	*
220 m		520 m	*	820 m	
240 m	*	540 m		840 m	*
260 m		560 m	*	860 m	
280 m	*	580 m		880 m	*
300 m		600 m	*	900 m	

DATE:

Please Circle: ***Baseline / 3 Month / 6 Month / 12 Months***

1. Name: _____ Last Lap:_____ Total: _____

2. Name: _____ Last Lap:_____ Total: _____

3. Name: _____ Last Lap:_____ Total: _____

Appendix G. Summary of main effects for participant demographics on health-related measures

Health-related outcomes	Age			Sex			Income			Educational Status			Marital Status			Working status			Smoking Status		
	df	*F*	sig	df	*F*	sig	df	*F*	sig	df	*F*	sig	df	*F*	sig	df	*F*	sig	df	*F*	sig
Physical functioning																					
6MTT	(1, 163)	9.6	**.002**	(1, 163)	0.7	.395	(3, 163)	0.5	.663	(4, 163)	1.1	.367	(2, 163)	0.4	.663	(2, 163)	1.5	.221	(1, 163)	1.3	.256
Sit to stand	(1, 163)	2.8	.096	(1, 163)	0.6	.449	(3, 163)	1.9	.140	(4, 163)	1.7	.147	(2, 163)	0.2	.791	(2, 163)	3.7	**.027**	(1, 163)	1.2	.270
Handgrip	(1, 165)	3.8	.054	(1, 165)	76.4	**.000**	(3, 165)	0.2	.927	(4, 165)	0.1	.990	(2, 165)	1.9	.147	(2, 165)	2.3	.106	(1, 165)	0.1	.720
Sit and reach	(1, 162)	10.8	**.001**	(1, 162)	6.1	**.015**	(3, 162)	1.4	.250	(4, 162)	0.9	.480	(2, 162)	3.5	**.033**	(2, 162)	1.1	.340	(1, 162)	0.0	.919
Body composition																					
BMI	(1, 165)	0.0	.978	(1, 165)	2.3	.133	(3, 165)	0.6	.618	(4, 165)	1.9	.120	(2, 165)	0.8	.430	(2, 165)	3.6	**.029**	(1, 165)	2.3	.133
Waist to hip ratio	(1, 165)	3.4	.068	(1, 165)	47.9	**.000**	(3, 165)	0.4	.777	(4, 165)	0.6	.697	(2, 165)	0.5	.635	(2, 165)	1.6	.209	(1, 165)	4.8	**.030**
Blood biomarkers																					
Fasting glucose	(1, 116)	0.0	.976	(1, 116)	3.0	.086	(3, 116)	0.5	.711	(4, 116)	1.5	.212	(2, 116)	0.4	.679	(2, 116)	0.3	.754	(1, 116)	0.0	.915
Triglycerides	(1, 132)	1.4	.247	(1, 132)	3.6	.061	(3, 132)	0.1	.941	(4, 132)	1.2	.300	(2, 132)	0.3	.731	(2, 132)	1.7	.183	(1, 132)	0.9	.347
LDL cholesterol	(1, 131)	0.0	.899	(1, 131)	1.8	.188	(3, 131)	2.1	.102	(4, 131)	1.0	.396	(2, 131)	1.1	.347	(2, 131)	1.0	.375	(1, 131)	3.4	.068
HDL cholesterol	(1, 131)	1.7	.195	(1, 131)	7.4	**.007**	(3, 131)	0.6	.590	(4, 131)	2.2	.072	(2, 131)	0.9	.400	(2, 131)	1.4	.249	(1, 131)	0.0	.926
hsCRP	(1, 101)	0.0	.967	(1, 101)	2.9	.090	(3, 101)	0.5	.673	(4, 101)	1.3	.266	(2, 101)	2.0	.145	(2, 101)	2.7	.073	(1, 101)	1.4	.232
Psychological health																					
PHQ8	(1, 109)	2.2	.144	(1, 109)	0.8	.376	(3, 109)	4.0	**.009**	(4, 109)	0.6	.644	(2, 109)	1.2	.303	(2, 109)	0.6	.527	(1, 109)	3.3	.070
EQ-VAS	(1, 109)	1.0	.320	(1, 109)	0.2	.676	(3, 109)	0.7	.567	(4, 109)	3.4	.059	(2, 109)	0.4	.697	(2, 109)	0.9	.418	(1, 109)	5.3	**.023**
SWLS	(1, 109)	7.8	**.006**	(1, 109)	0.1	.914	(3, 109)	3.9	**.010**	(4, 109)	1.6	.182	(2, 109)	0.9	.407	(2, 109)	0.3	.706	(1, 109)	0.5	.482
Psychosocial det																					
Self-efficacy	(1, 109)	1.4	.223	(1, 109)	0.2	.626	(3, 109)	0.7	.583	(4, 109)	0.2	.919	(2, 109)	0.2	.842	(2. 109)	0.1	.930	(1, 109)	1.9	.176

Note: 6MTT = 6 minute time trial; BMI = body mass index; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQol Visual Analogue Scale; SWLS = Satisfaction with Life Scale; LDL = low density lipoprotein; HDL = high density lipoprotein; hsCRP = high sensitivity C-reactive protein; Psychosocial det = psychosocial determinants of physical activity.

Number in **BOLD** indicate $p \leq 0.05$

Appendix H. Summary of post hoc analysis on primary outcome variables with a significant main effect for time

Outcome	Timepoint	p	Standard error	df	C.I	Cohen's D
LIPA	BL – 3 m	.249	0.04	139.34	(-0.19, 0.03)	0.03
	BL – 6 m	**.014**	0.05	135.92	(-0.30, -0.02)	0.06
	BL – 12 m	1.00	0.06	144.83	(-0.22, 0.09)	0.02
	3 m – 6 m	.794	0.05	118.18	(-0.21, 0.06)	0.03
	3 m – 12 m	.1.00	0.06	127.53	(-0.14, 0.18)	0.01
	6 m – 12 m	.537	0.06	107.86	(-0.06, 0.25)	0.04
Number of sedentary bouts 11-30 min	BL – 3 m	.069	0.29	160.15	(-1.52, 0.03)	0.11
	BL – 6 m	.173	0.33	137.46	(-1.62, 0.16)	0.11
	BL – 12 m	.396	0.42	131.72	(-1.91, 0.35)	0.10
	3 m – 6 m	1.00	0.31	107.17	(-0.83, 0.85)	0.00
	3 m – 12 m	1.00	0.43	117.91	(-1.18, 1.10)	0.00
	6 m – 12 m	1.00	0.47	107.40	(-1.30, 1.20)	0.01
Time in sedentary bouts 11-30 min	BL – 3 m	.066	5.18	164.45	(-27.17, 0.51)	0.46
	BL – 6 m	.109	5.85	135.14	(-29.65, 1.68)	0.50
	BL – 12 m	.531	7.76	131.64	(-34.09, 7.47)	0.42
	3 m – 6 m	1.00	5.44	105.32	(-15.28, 13.97)	0.03
	3 m – 12 m	1.00	7.73	115.57	(-20.74, 20.77)	0.00
	6 m – 12 m	1.00	8.41	104.73	(-21.94, 23.29)	0.02
Total number of sedentary bouts	BL – 3 m	.296	1.29	142.22	(-6.01, 0.89)	0.19
	BL – 6 m	.087	1.41	133.81	(-7.26, 0.28)	0.25
	BL – 12 m	.211	1.54	137.24	(-7.40, 0.85)	0.22
	3 m – 6 m	1.00	1.48	121.94	(-4.90, 3.04)	0.07
	3 m – 12 m	1.00	1.78	147.93	(-5.48, 4.04)	0.04
	6 m – 12 m	1.00	1.59	109.91	(-4.06, 4.48)	0.02

Numbers in **BOLD** indicate $p < 0.05$.

Note: LIPA = light intensity physical activity

Appendix I. Summary of simple effects analysis on time*primary CD interaction effect for the 6MTT

Primary CD		Baseline				3 months				6 months				12 months			
		MD	SE	sig	95% CI	MD	SE	sig	95% CI	MD	SE	sig	95% CI	MD	SE	sig	95% CI
Cancer	*CVD*	87.5	18.0	.000	(34.3, 140.7)	142.6	21.1	.000	(80.4, 204.9)	116.9	23.1	.000	(28.8, 185.0)	97.6	24.6	.001	(24.7, 170.5)
	Respiratory	152.9	20.7	.000	(91.7, 214.0)	236.2	25.0	.000	(162.2, 310.1)	210.6	27.6	.000	(129.0, 292.3)	183.8	29.4	.000	(96.9, 270.8)
	Metabolic	91.4	24.0	.002	(20.4, 162.3)	141.0	29.1	.000	(55.0, 226.9)	101.3	32.0	.025	(6.7, 195.8)				
	Neuro/MSK	116.9	29.7	.001	(29.1, 204.7)	173.5	35.6	.000	(68.3, 278.7)	171.3	38.6	.001	(39.2, 303.3)				
	Unspecified	138.1	33.1	.001	(40.1, 236.0)	177.1	40.8	.000	(56.5, 297.7)	159.4	44.7	.002	(45.2, 273.6)				
Respiratory	*CVD*	-65.4	19.0	.001	(-121.6, -9.2)	-93.5	22.8	.001	(-161.0, -26.0)	-93.7	25.0	.003	(-167.7, -19.8)	-86.2	26.2	.017	(-163.8, -8.7)
	Metabolic					-95.2	30.0	.024	(-183.8, -6.6)	-210.6	27.6	.015	(-292.3, -129.0)	-111.8	29.4	.000	(-213.5, -10.0)

Note: CD = chronic disease; MD = mean difference; SE = standard error; 95% CI = 95 % confidence interval; CVD = cardiovascular disease; Neuro/MSK = neurological/musculoskeletal

Appendix J. Summary of simple effects analysis on time*primary CD interaction effect for the PHQ8

Primary CD		Baseline				3 months				6 months				12 months			
		MD	SE	sig	95% CI	MD	SE	sig	95% CI	MD	SE	sig	95% CI	MD	SE	sig	95% CI
Respiratory	*CVD*									2.7	0.8	.022	(0.2, 5.2)	4.0	0.9	.000	(1.4 to 6.6)
	Metabolic									3.6	1.1	.025	(0.2, 6.9)	3.9	1.2	.015	(0.4 to 7.4)
	Cancer					2.8	0.9	.043	(-0.4, 4.6)					4.6	1.0	.000	(1.6 to 7.5)

Note: CD = chronic disease; MD = mean difference; SE = standard error; 95% CI = 95 % confidence interval; CVD = cardiovascular disease; Neuro/MSK = neurological/musculoskeletal

Appendix K. Summary of simple effects analysis on time*primary CD interaction effect for the SWLS

Primary CD		Baseline				3 months				6 months				12 months			
		MD	SE	sig	95% CI	MD	SE	sig	95% CI	MD	SE	sig	95% CI	MD	SE	sig	95% CI
Respiratory	*CVD*													-3.9	1.3	.049	(-7.7, -0.01)
	Cancer	-3.6	1.2	.046	(-7.2, -0.03)					-3.7	1.2	.040	(-7.3, -0.1)	-6.8	1.5	.000	(-11.2, -2.4)

Note: CD = chronic disease; MD = mean difference; SE = standard error; 95% CI = 95 % confidence interval; CVD = cardiovascular disease; Neuro/MSK = neurological/musculoskeletal

Appendix L. Summary of simple effects analysis on time*primary CD interaction effect for the WEMWBS

Primary CD		Baseline				3 months				6 months				12 months			
		MD	SE	sig	95% CI	MD	SE	sig	95% CI	MD	SE	sig	95% CI	MD	SE	sig	95% CI
Respiratory	*CVD*													-3.9	1.3	.049	(-7.7, -0.01)
	Cancer	-3.6	1.2	.046	(-7.2, -0.03)					-3.7	1.2	.040	(-7.3, -0.1)	-6.8	1.5	.000	(-11.2, -2.4)

Note: CD = chronic disease; MD = mean difference; SE = standard error; 95% CI = 95 % confidence interval; CVD = cardiovascular disease; Neuro/MSK = neurological/musculoskeletal

Appendix M. Outcome measure were there was a significant main effect for time in study 2 (chapter 5)

Outcome measures	3 months	6 months	12 months
Physical activity and sedentary behaviour			
Sedentary time			
Standing time			
LIPA		↑ BL	
MVPA			
Step count			
Number of sedentary bouts <10 min			
Time sedentary bouts <10 min (min)			
Number of sedentary bouts 11-30 min[a]			
Time sedentary bouts 11-30 min (min)[a]			
Number of sedentary bouts 31-60 min			
Time sedentary bouts 31-60 min (min)			
Number of sedentary bouts > 60 min			
Time sedentary bouts > 60 min (min)			
Total number of sedentary bouts[a]			
Physical function			
6MTT	↑ BL	↑ BL	↑ BL, ↑ 3 m
Sit to stand	↑ BL	↑ BL	↑ BL
Handgrip			↑ BL
Sit and reach			
Body composition			
Weight			
BMI			
Waist circumference	↑ BL	↑ BL	↑ BL
Hip circumference	↑ BL	↑ BL	↑ BL, ↑ 3 m, ↑ 6 m
Waist to hip ratio			
Blood biomarkers			
Fasting glucose			
Triglycerides			
HDL-C			
LDL-C[b]			
hsCRP			
Psychological health			
PHQ8	↑ BL	↑ BL	↑ BL
EQ-VAS	↑ BL	↑ BL	↑ BL
SWLS		↑ BL	
SWEMWBS			
Psychosocial determinants of physical activity			
Barriers self-efficacy[b]			
Self-regulatory self-efficacy[b]			
Intentions for Exercise[b]			
Family support			
Friend support			

↑ BL = Significant improvement between baseline and indicated timepoint
↑ 3 m = Significant improvement between 3 months and indicated timepoint
↑ 6 m =Significant improvement between 6 months and 12 months
[a] Significant main effect for time with insignificant post hoc and no identified timepoint of change
[b] Significant main effect for time with a negative outcome
Note: LIPA = light intensity physical activity; MVPA = moderate intensity physical activity; 6MTT = 6 minute timed trial; BMI = body mass index; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQoL Visual Analogue Scale; SWLS = Satisfaction with Life Scale; SWEMWBS = The Short Warwick Edinburgh Mental Wellbeing Scale

Appendix N. Outcome measures were there was a significant main effect for attendance in study 2 (chapter 5)

Outcome measures	Main effect for attendance
Physical activity and sedentary behaviour	
Sedentary time	
Standing time	
LIPA	X
MVPA	X
Step count	X
Number of sedentary bouts <10 min	
Time sedentary bouts <10 min (min)	
Number of sedentary bouts 11-30 min	
Time sedentary bouts 11-30 min (min)	
Number of sedentary bouts 31-60 min	
Time sedentary bouts 31-60 min (min)	
Number of sedentary bouts > 60 min	
Time sedentary bouts > 60 min (min)	X
Total number of sedentary bouts	
Physical function	
6MTT	
Sit to stand	
Handgrip	
Sit and reach	
Body composition	
Weight	X
BMI	X
Waist circumference	
Hip Circumference	X
Waist to hip ratio	
Blood biomarkers	
Fasting glucose	
Triglycerides	
HDL-C	
LDL-C	
hsCRP	
Psychological health	
PHQ8	X
EQ-VAS	X
SWLS	X
SWEMWBS	X
Psychosocial determinants of PA	
Barriers self-efficacy	X
Self-regulatory self-efficacy	X
Intentions for Exercise	X
Family support	
Friend support	

X indicates variables where a significant association with attendance was identified in study 2 (chapter 5)
Note: LIPA = light intensity physical activity; MVPA = moderate intensity physical activity; 6MTT = 6 minute timed trial; BMI = body mass index; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; PHQ8 = 8-item Patient Health Questionnaire; EQ-VAS = EuroQoL Visual Analogue Scale; SWLS = Satisfaction with Life Scale; SWEMWBS = The Short - Warwick Edinburgh Mental Wellbeing Scale