Physical well-being for women living with metastatic breast cancer

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This is to certify that the thesis entitled **"Physical well-being for women living with metastatic breast cancer"** submitted by **Jasmine Yee** in fulfilment of the requirements for the degree of Doctor of Philosophy is in a form ready for examination.

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Abstract

The benefits of increased physical activity on well-being for women with early stage breast cancer are well understood. However, its role for women living with metastatic disease is unknown due to their exclusion from physical activity and exercise research. The omission of this population from trials is primarily due to fear of skeletal-related events and high symptom burden. Having identified gaps in the knowledge about physical activity for women with metastatic breast cancer, the program of research herein was developed. Broadly, the aims of this thesis were to determine the physical capabilities and interests for physical activity of women living with metastatic breast cancer and to use this information to develop and pilot an appropriate physical activity intervention. In addition, it was identified that the accuracy of devices for measuring physical activity in this older age group was unknown, which led to the design of the final study to assess the accuracy of three physical activity monitors.

The first step towards designing an intervention was to understand the physical capabilities of women living with metastatic breast cancer. The first study aimed to describe physical function and fitness of this population in comparison to an age-matched healthy cohort. Patient-reported outcomes and physical measures of strength and fitness were obtained from 71 women with metastatic breast cancer and 71 healthy controls. Women with metastatic cancer possessed lower levels of fitness and less muscle strength than the healthy women. The metastatic group were also only around half as active as the healthy cohort, also experiencing higher symptom burden. There was a large variation in physical function observed in the cancer cohort, with many women exceeding the average fitness for their age.

In the development of an exercise program, consideration of the interests and preferences for physical activity is also important for enhancing efficacy and adherence. Through a structured interview, the second study aimed to determine physical activity preferences and to identify perceived barriers and benefits to activity in 62 women with metastatic breast cancer. The majority of women were interested in a program designed to increase physical activity and identified a strong preference for home-based activity. The most favoured type of activity was walking. Barriers included other commitments, pain and lack of motivation, with increased energy the most common perceived benefit of commencing a program.

With the exclusion of women with metastatic breast cancer from physical activity interventions, the safety and feasibility of such programs is relatively unknown. With an understanding of physical capacity and programming preferences obtained through the first

two studies, an intervention to address this gap was developed. The primary aim of the third study was to evaluate the safety and feasibility of a home-based program comprising of supervised resistance training and an unsupervised walking program. Fourteen women were randomised to either a control group or the physical activity intervention. Recruitment and retention rates were excellent, with no adverse events reported. There was high adherence and compliance to resistance training, but these were poor in the walking component. Trends in favour of the exercise group over the control group were observed for measures of physical function and symptom burden.

Throughout the first three studies, the measurement of physical activity was fundamental. One popular choice for researchers to capture activity levels is physical activity monitors. It was, however, identified that there is limited data to support their use in free-living in women of a similar age to those with metastatic breast cancer. The fourth study, therefore, aimed to establish the accuracy of the Actigraph™, SenseWear® and ActiHeart® physical activity monitors in older women in free-living. Thirty-three women wore the three devices for 14 days, and energy expenditure estimated by each device was compared to the reference method of doubly labelled water. At the group level, all three monitors demonstrated acceptable agreement for total energy expenditure but demonstrated larger error when capturing physical activity energy expenditure. When measuring energy expenditure in women over 50 years, the Actigraph™ was recommended as the preferred device, owing to its relatively superior performance and affordability.

In conclusion, the findings from this thesis inform clinicians and researchers that despite the heterogeneity of the metastatic breast cancer population, most women are interested and capable of being physically active. The finding that a partially supervised resistance and walking program is safe for this population adds further evidence to the limited knowledge in this area. In addition, physical activity may also be beneficial for improving well-being and helping women to manage their disease. With respect to the accurate assessment of physical activity, this thesis recommends the use of the Actigraph™ in older women.

Candidate's Statement

I, **Jasmine Yee**, hereby declare that the work contained within this thesis is my own and has not been submitted to any other university or institution in part or in whole as a requirement for any higher degree.

I, **Jasmine Yee**, hereby declare that I was the principal researcher of all work included in this thesis, including work published with multiple authors.

In addition, ethics approval from the University of Sydney Human Research Ethics Committee and the relevant area health services was granted for all the studies presented within the thesis. Participants were required to read a participant information document and informed consent was obtained prior to data collection.

Name _____

Signed _____

Date_____

Publications and Presentations

Work presented in this thesis has been published and/or presented in the following forums:

Refereed articles

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List of Terminology: Abbreviations and Units

1RM	1-Repetition Max
6MWT	Six-Minute Walk Test
AG	Actigraph™
AH	Actiheart®
ANOVA	Analysis Of Variance
BMI	Body Mass Index
BMD	Bone Mineral Density
DLW	Doubly Labelled Water
ECOG	European Collaborative Oncology Group
EORTC QLQ-30	European Organization For Research And Treatment Of Cancer Quality Of Life Questionnaire- 30
FACIT-F	Functional Assessment Of Chronic Illness Therapy: Fatigue
GLTEQ	Godin Leisure-Time Exercise Questionnaire
HER2	Human Epidermal Growth Factor Receptor 2
IPAQ	International Physical Activity Questionnaire
$kcal \bullet d^{-1}$	Kilocalories Per Day
kg	Kilogramme
$kg \bullet m^{-2}$	Kilogramme Per Metre Squared
LSA	Life-Space Assessment
MAPE	Mean Average Percentage Error
MET	Metabolic Equivalent
mCAFT	Modified Canadian Aerobic Fitness Test
$ml \bullet kg^{-1} \bullet min^{-1}$	Millilitres Per Kilogramme Per Minute
MVPA	Moderate-Vigorous Physical Activity

PAEE	Physical Activity Energy Expenditure
PAR-Q	Physical Activity Readiness Questionnaire
PARMED-X	Physical Activity Readiness Medical Examination
PROs	Patient-Reported Outcomes
PSFS	Patient-Specific Function Scale
QOL	Quality Of Life
RCT	Randomised Controlled Trial
RMR	Resting Metabolic Rate
SD	Standard Deviation
SW	Sensewear®
TEE	Total Energy Expenditure
UCT	Uncontrolled Trial
VO_{2MAX}	Maximal Oxygen Consumption
WK8	8-Week Post-Intervention
WK16	16-Week Post-Intervention

Preface

The work presented in this thesis consists of six chapters. Chapter 1 provides an introduction to metastatic breast cancer, its treatment and associated symptom burden. It also presents an overview of current scientific knowledge about the role of exercise and physical activity in both early and metastatic breast cancer. To inform an appropriate physical activity program for women with metastatic breast disease, an understanding of the physical capabilities of the population was required. Chapter 2 describes physical activity levels and fitness of this population in comparison to a healthy age-matched cohort. To further assist in the intervention design, interests and preferences for physical activity were explored in Chapter 3. With the information obtained in Chapters 2 and 3, a physical activity intervention was developed and piloted in Chapter 4. The final study, Chapter 5, investigates the validity of three physical activity monitors in older women, to inform future research in women living with metastatic breast cancer. Chapter 6 presents the concluding remarks for the thesis.

Chapter 2 contains an article published in the *Journal of Cancer Survivorship*. The language and formatting of this chapter are appropriate to the journal it was submitted. The remaining chapters will be submitted for publication in the near future.

All studies reported herein received ethical approval from the relevant Human Research Ethics Committees prior to commencing (Appendix). All women provided written informed consent prior to participation.

Chapter 1:

Introduction

Breast cancer

Cancer is a leading cause of illness, placing a substantial burden on individuals, families and the community. In Australia, the most commonly diagnosed cancer in females is breast cancer, and the risk of being diagnosed before the age of 85 is 1 in 8 [1]. In 2014, there were 15,270 cases of breast cancer in Australia [2], with this estimated to reach 17,210 in 2020 [1]. Whilst the incidence of breast cancer continues to rise, advances in detection and treatment for breast cancer mean that five-year relative survival has increased from 72% in 1982-86 to 89% in 2006-2010 [1]. In 2014 it is estimated that 3030 deaths in Australia resulted from breast cancer [2].

Although the causes of breast cancer are not well understood, various risk factors for its development have been identified. Female sex is a significant risk factor, along with increasing age and family history [3]. Lifestyle factors such as obesity and high alcohol consumption, particularly among post-menopausal women, contribute to increased breast cancer risk [1]. Menstrual and reproductive events are also established risk factors, with parity and breastfeeding providing a protective effect [3]. A review of over 50 epidemiological studies also reported an inverse association between physical activity and breast cancer risk, with the greatest reduction in risk seen at higher levels of activity [4].

Metastatic breast cancer

Metastatic cancer, also often referred to as secondary, advanced or stage IV cancer, occurs when cancer spreads from the original tumour to other parts of the body. In breast cancer, the most common site for metastasis is bone, followed by liver, lung and brain [5]. Of women who present with an initial diagnosis of early breast cancer, approximately 10% will go on to develop metastatic disease within 5 years [5]. In addition, 5-10% of women present with metastatic disease at the time of the initial diagnosis [6].

For women with metastatic breast cancer, the median survival is 2-3 years [7, 8]. However, individual survival is highly variable and can span from months to several years depending on tumour characteristics and location of metastases. For women with metastatic disease in Australia, data suggest that the five-year relative survival is around 40% [9]. Advancements in diagnosis and treatment for metastatic breast cancer has been impressive over the past few decades, leading to an increased number of therapies available for managing the disease [10]. These advances have resulted in a decline in breast cancer mortality, with many women now living for extended periods of time [2].

Treatment for metastatic breast cancer and related side-effects

Metastatic breast cancer is a heterogeneous disease with an unpredictable clinical course, making medical management extremely complex [10, 11]. The choice of treatment takes into consideration a number of factors such as the patient's age, menopausal status, comorbidities, performance status, psychosocial factors and treatment preferences. Other factors include the hormone receptor and human epidermal growth factor receptor 2 (HER2) status of the tumour, previous therapies and treatment response, disease-free interval, efficacy and toxicity of treatment [10]. Of particular importance is the location of metastatic lesions as women with bone-only metastases have a more favourable prognosis than those with spread to the viscera [11, 12]. Due to the heterogeneity of metastatic breast cancer and the many factors that influence treatment decisions, the treatment course varies substantially between individuals. The goals of treatment for metastatic breast cancer are not curative but aim for prolonged survival, disease control, relief of symptoms and improvement in quality of life [13, 14].

Endocrine Therapy

In Western countries, hormone receptor-positive tumours account for approximately 70% of all breast cancer cases [15]. The recommended first-line treatment for these women is endocrine therapy, unless there is proven endocrine resistance or severe organ dysfunction [11, 13]. As oestrogen can contribute to the growth of cancer, endocrine therapy works by interfering with oestrogen stimulation of breast cancer cells [16]. There are currently three commonly used classes of therapy; i) selective oestrogen receptor modulators that block oestrogen receptors but continue to mimic oestrogen effects (e.g. tamoxifen), ii) third-generation aromatase inhibitors, which reduce circulating oestrogen (e.g. anastrozole and exemestane), and iii) oestrogen receptor down-regulators that block oestrogen receptors and destroy them (e.g. fulvestrant) [17]. Many women benefit from the sequential use of endocrine therapies, with aromatase inhibitors the preferred first-line for those who are postmenopausal and fulvestrant as second-line therapy [15]. For premenopausal women, ovarian suppression or ablation may be offered in combination with endocrine therapy [18].

Whilst endocrine therapy is generally well-tolerated, there are several unfavourable symptoms that may present. Common but mild side effects of tamoxifen include hot flushes and irregular periods, with blood clots and uterine cancer reported in rare cases [17]. Women who take aromatase inhibitors are at an increased risk of osteoporosis, musculoskeletal symptoms and bone fracture [17].

Such side effects have the potential to exacerbate other chronic conditions, highlighting the importance of treatment selection in the presence of comorbidities.

Chemotherapy

Despite considerable side-effects, cytotoxic chemotherapy still plays a major role in managing metastatic breast cancer [11, 19]. Candidates for chemotherapy include those with hormone-negative tumours, bulky visceral disease, severe tumour-related symptoms or rapidly progressing disease [11, 20]. Cytotoxic chemotherapy is designed to destroy cancer cells, but in the process, normal cells are also damaged causing treatment toxicity. To manage this, multidrug regimens are often replaced with sequential single-agent therapies that reduce toxicity and allow for continued participation in daily life [11, 19, 21].

There are four preferred single cytotoxic agents for the treatment of metastatic breast cancer; anthracyclines (e.g. doxorubicin, epirubicin), taxanes (e.g. paclitaxel, docetaxel), anti–metabolites (e.g. capecitabine, gemcitabine) and non-taxane microtubule inhibitors (e.g. eribuline, vinorelbine) [18]. Traditionally, chemotherapy has been short-term with agents administered intravenously. However, this has shifted over the past decade to longer-term treatment with the emergence of cytotoxic oral agents such as capecitabine and vinorelbine [22]. These oral treatments have a number of advantages including increased convenience, ease of administration and fewer clinic appointments, resulting in a reduced impact on quality of life [23]. Other single agents and a range of chemotherapy combinations may also be administered depending on the clinical scenario. Whilst further discussion of cytotoxic regimens is outside the scope of this thesis, the National Comprehensive Cancer Network Guidelines provide synthesised evidence of all available therapies and indications for initiation [18]. There is no optimal chemotherapy regimen, with treatment choice dependant on factors such as treatment efficacy and toxicity, prior treatment, comorbid conditions and performance status [21].

Chemotherapy agents, whether used individually or in combination, can cause significant side effects. Nausea and vomiting are common across therapies despite improvements in anti-emetic therapy [24]. Other common side effects include fatigue, hair loss, neutropenia, cardiac toxicity and neuropathy [25]. Some cytotoxic agents also possess risks specific to that class of drug. For example, the use of taxanes may result in peripheral oedema, impacting on mobility [25].

Anti-HER2-targeted therapy

Prior to the introduction of new therapies, women with an HER2 positive tumour (HER2+) traditionally had a poor prognosis [26]. These women are now offered anti-HER2-targeted treatments, irrespective of hormone receptor status. The National Comprehensive Cancer Network Guidelines recommend two agents, pertuzumab plus trastuzumab, as the preferred first-line treatment [18]. These therapies bind to the HER2 protein, inhibiting proliferation of tumour cells. Anti-HER2-targeted therapy may be administered in combination with endocrine therapy or chemotherapy, or alone. The use of pertuzumab with trastuzumab can result in mild side effects such as diarrhoea, neutropenia, skin and nail infections, and infusion reactions. A more significant risk, albeit rare, is damage to the heart and subsequent cardiac dysfunction [27].

Bone-targeted therapy

Bone metastasis occurs in approximately 70% of women with metastatic breast cancer [28]. This can lead to skeletal-related events such as pathological fracture, causing significant morbidity and impacting on quality of life. The use of bisphosphonates and denosumab can reduce and delay the incidence of skeletal-related events [29]. Whilst neither agent has an impact on overall survival, denosumab has demonstrated superiority over the commonly used bisphosphonate zoledronic acid [30, 31]. These therapies can be administered orally or intravenously and may be used with or without other treatment [11]. As there is a continuing risk of skeletal-related events, treatment is ongoing unless tolerability or compliance issues arise [31].

Whilst generally well-tolerated, oral bisphosphonates can cause gastrointestinal issues. Intravenous administration is associated with side effects such as flu-like symptoms and bone pain after infusion [32]. Individuals taking denosumab may experience breathlessness, diarrhoea or bone, joint or muscle pain. More severe risks of both these therapies include osteonecrosis of the jaw and renal toxicity [32].

Surgery

There is no established benefit to removing the primary tumour in metastatic breast cancer so surgical resection is not routinely used [11]. However, surgery may be considered after initial systemic therapies for the palliation of symptoms of the breast tumour, such as skin ulceration, bleeding and pain [33]. Surgery also has a role in the localised control of the metastases site and may be indicated in

scenarios such as brain metastases or pleural effusion [18]. In the event of a fracture in a weight-bearing bone, or where one is inevitable, surgery may be used to stabilise the bone [25]. As with all treatments, surgery carries inherent risks. Individuals may experience pain, infection, seroma or lymphoedema, depending on the surgical site.

Radiation therapy

As an alternative to surgery, radiation therapy may be adopted to manage symptoms at the site of the primary tumour or distant metastases [18]. For metastatic bone pain, palliative radiotherapy is the most effective approach, with approximately two-thirds experiencing complete pain relief [34]. Common side effects of radiation include reddening and soreness of the skin, discomfort and swelling, fatigue and nausea.Practice guidelines provide evidence-based recommendations for medical management using the various treatment strategies. However, with chronic conditions such as hypertension, depression, arthritis and diabetes common in an older metastatic population [21], the applicability of guidelines to individuals with multiple comorbidities is often questionable. Clinicians creating treatments plans for this complex and heterogeneous population are required to identify and consider all other comorbid conditions. This makes treatment decisions challenging, often resulting in guidelines that are modified or disregarded for these women [21].

Treatment and outlook for women living with metastatic breast cancer are varied, making it difficult to generalise about those living with this disease. There are currently many available treatment options including endocrine therapy, chemotherapy, targeted therapies, surgery and radiation, and these are constantly evolving. Over the course of an individual's disease, treatment will typically involve several of these therapies alone or in combination.

Symptom burden

In addition to treatment-related side-effects, women with metastatic breast cancer also present with a variety of symptoms caused directly or indirectly by the metastatic lesion itself (Table 1) [5, 35, 36]. Due to the varying treatment approaches and heterogeneous nature of the disease, some women with metastatic breast cancer experience high levels of symptom burden whereas others are not significantly debilitated and are able to continue in their usual roles [37]. As a result of ongoing treatment and adjustments, recent research suggests that this population actually experience oscillating cycles of decline and reprieve [38].

Table 1. Common disease-related symptoms of metastatic breast cancer

Metastasis site	Prevalence of metastatic site	Common side effects
Bone	61%	Bone pain, fatigue, fracture, nerve entrapment, hypercalcaemia
Liver	49%	Discomfort at site of liver, nausea, loss of appetite, ascites, jaundice
Lung	41%	Cough, breathlessness, pleural effusion, pain, hemoptysis
Brain	28%	Headaches, confusion, nausea, memory problems, neurological issues, poor balance, weakness, seizure, pain

As metastatic breast cancer diagnosis is often viewed as a life-altering event, it can have a significant impact on psychological well-being [39]. A range of existential issues can arise such as feelings of hopelessness, uncertainty, fear of death, and loss of identity and independence [40]. Other evidence of poor psychological well-being may be signs of depression or anxiety [41]. Estimates of depression in this population range from 20-50%, although there is a much lower prevalence of major depressive disorders [35]. Psychological support, anxiolytics and antidepressants may be offered for treatment of depressive symptoms.

The most common symptoms that women with metastatic disease endure are pain and fatigue [42]. Pain may present as a symptom of bone or visceral metastasis or may be associated with treatments such as surgery or endocrine therapy. There are several intervention options for the treatment of pain. For neuropathic pain, analgesics such as antidepressants and anticonvulsants are often prescribed in combination with opioids, whilst some women gain relief from topical anaesthetics [41]. Glucocorticoids may also be indicated if the pain is of an inflammatory nature or a result of nerve compression. In addition to the role of bisphosphonates, denosumab and radiation therapy for bone pain, other treatment options include glucocorticoids, opioid or non-opioid analgesics or systemic radiopharmaceuticals [41].

Cancer-related fatigue is a persistent and debilitating symptom affecting 70% to 100% of those with cancer [43]. Fatigue is multidimensional, with factors contributing to its manifestation from the metastatic site itself, treatments, physical deconditioning and other comorbid conditions [42, 44]. Depressive symptoms, as well as inadequate sleep, pain and decreased cognitive function, are also associated with fatigue [42]. Fatigue has a profound effect physically, emotionally and mentally, often interfering with activities of daily living and causing a considerable decline in overall quality of life [45]. Some contributing factors to fatigue are more

amenable to intervention than others. Nonpharmacological management strategies include energy conservation, distraction, physical activity and psychosocial interventions such as cognitive behavioural therapy [46]. These have been examined primarily in early stage cancer but may also have a role in metastatic disease.

Whilst most symptoms and side effects of metastatic breast cancer are well-described in the literature, the level of physical deconditioning in this population remains unclear. One study investigating functional decline in this population reported that 92% of women possessed at least one physical impairment and 47% had deficits in muscle strength [47]. Another study found that women with metastatic breast cancer undergoing chemotherapy had marked impairment in cardiopulmonary function, with peak oxygen consumption 33% lower than healthy sedentary women [48]. Whilst deficits in function have been identified, the physical capabilities of this heterogeneous population are not well understood, particularly with respect to aerobic fitness and habitual physical activity level. These gaps led to the development of a cross-sectional study to identify physical function deficits of women living with metastatic breast cancer, described in Chapter 2.

Although many women with metastatic breast cancer experience debilitating side-effects, these are often overlooked as healthcare providers focus on treatment and improving survival [49]. While positive about medical care in general, women are dissatisfied with this approach and want more focus placed on ensuring good quality of life [49]. In the absence of supportive care, women engage in a number of strategies to help them live well with their disease [50]. Being physically active is a popular approach, with one cross-sectional study reporting that more than 50% of the population exercised at least twice a week [50]. Despite being a commonly adopted strategy, the role of physical activity and exercise for people with metastatic disease has not been well-established and will be explored in Chapter 4.

Physical activity and exercise interventions in women with early breast cancer

A wide variety of treatment strategies have been adopted to improve well-being in women with early breast cancer, including pharmacological, psychosocial and mind-body interventions [51, 52]. Physical activity and exercise are also popular supportive care choices. Whilst physical activity encompasses any movement carried out by the skeletal muscles above resting levels, exercise forms a subcategory of physical activity [53]. Exercise is activity that is planned and structured with the aim of improving or maintaining physical fitness [53]. There is a large body of evidence describing the role of exercise in women with early stage breast cancer. Systematic reviews summarising the evidence are presented in Table 3. Whilst some reviews focused on a particular symptom, treatment or exercise modality and others reported more broadly, all show a clear benefit from an exercise intervention [54-68].

The effects of exercise on patient-reported outcomes such as QOL and fatigue were favourable [54-57, 59-62]. As these systematic reviews examined mixed training modalities, it is unclear whether the benefit is attributable to resistance or aerobic training alone or in combination. Irrespective, exercise is accepted as a safe and effective therapy for managing fatigue and other disease-related symptoms in women with early breast cancer.

The systematic reviews consistently reported improvements in aerobic fitness and muscular strength with exercise training [54, 56-58, 60-62]. Upper body strength and function are important in breast cancer post-surgery for restoring the ability to perform activities of daily living and preventing disuse atrophy and associated impairments. One of the most recent reviews examining exercise and lymphoedema demonstrated that resistance and aerobic training are safe and effective and do not increase the risk or severity of lymphoedema [57].

Most of the systematic reviews on exercise and early breast cancer noted limitations such as a small number of studies, poor quality methodology and reporting of results, and short length of follow-up [54, 57, 58, 61, 69]. Despite these limitations, these reviews support the prescription of exercise for improving physiological, psychological and functional variables in early breast cancer patients. Given the benefits of exercise, the American College of Sports Medicine has recommended that cancer survivors follow the 2008 Physical Activity Guidelines for Americans [70]. This advice encourages survivors to engage, where possible, in 150 minutes per week of moderate-to-vigorous intensity exercise and include aerobic and resistance components [70]. It was noted in these Guidelines that prescription should be individualised and adapted to account for the limitations of each individual [70].

Table 3. Systematic reviews of exercise interventions in early breast cancer

Systematic review	**Review period**	**Included cancers**	**Exercise modality**	**Study design**	**Quality Assessment Procedure**	**# studies included**	**Outcomes**
Effects of supervised exercise on cancer-related fatigue in breast cancer survivors: a systematic review and meta-analysis [59]	2001-2013	Breast	Aerobic training ± resistance training	RCTs	Pedro scale [71]	9	*PROs* ↓ fatigue ↑ functional and physical well-being ↔ social and emotional well-being ↔ depression
Tai chi chuan exercise for patients with breast cancer: a systematic review and meta-analysis [63]	2004-2013	Breast	Tai Chi Chuan	RCTs	Cochrane Risk of Bias Assessment Tool [72]	9	*PROs* ↔ pain ↑ upper body strength ↑ flexibility ↔ in physical, emotional or social well-being ↔ QOL

Systematic review	Review period	Included cancers	Exercise modality	Study design	Quality Assessment Procedure	# studies included	Outcomes
Safety and efficacy of progressive resistance training in breast cancer: a systematic review and meta-analysis [57]	2006-2013	Breast	Resistance training	RCTs	Quality checklist designed based on established criteria [73]	15	*Physical Function* ↓ risk of lymphoedema incidence/exacerbation ↑ upper and lower body strength *PROs* ↑ QOL
Weight training is not harmful for women with breast cancer-related lymphoedema: a systematic review [60]	2001-2012	Breast	Resistance training	RCTs	Pedro scale [71]	8	*Physical Function* ↔ risk or severity of lymphoedema ↑ upper and lower body strength *PROs* ↑ QOL

Systematic review	Review period	Included cancers	Exercise modality	Study design	Quality Assessment Procedure	# studies included	Outcomes
Twenty-five years of research on the effects of exercise training in breast cancer survivors: A systematic review of the literature [54]	1988-2013	Breast	Aerobic ± resistance training	RCTs, UCTs	Not described	51 (37 RCTs)	*Physical Function* ↑ cardiorespiratory function ↑ upper and lower body strength *PROs* ↑ QOL ↓ depression
Progressive resistance training in breast cancer: a systematic review of clinical trials [56]	1995-2007	Breast	Resistance training ± other modalities	RCTs, CCTs, UCTs	Delphi List [74]	10 (5 RCTs)	*Physical Function* ↑ upper and lower body strength ↑ aerobic fitness *PROs* ↑ QOL, depression, anxiety and self-esteem

Systematic review	Review period	Included cancers	Exercise modality	Study design	Quality Assessment Procedure	# studies included	Outcomes
An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis [61]	2005-2009	Mix (breast 83%)	Aerobic and/or non-aerobic	RCTs, CCTs	10 internal validity characteristics [75]	82 (74 RCTs)	*Physical Function* ↑ aerobic fitness ↑ upper and lower body strength *PROs* ↑ QOL ↔ social or emotional well-being ↔ depression ↓ fatigue ↔ pain
Resistance exercise and secondary lymphoedema in breast cancer survivors –a systematic review [66]	1966-2015	Breast	Resistance	RCTs	Downs and Black risk of bias assessment [76]	9	*Physical Function* ↔ risk or severity of lymphoedema

Systematic review	Review period	Included cancers	Exercise modality	Study design	Quality Assessment Procedure	# studies included	Outcomes
Exercise and cancer rehabilitation: A systematic review [62]	1997-2009	Mix (breast 80%)	Aerobic and/or resistance training ± flexibility training	RCTs, CCTs, UCTs	Stevinson method [77]	10 (4 RCTs)	*Physical Function* ↑ physical function ↑ upper and lower body strength *PROs* ↑ QOL ↓ fatigue
Resistance Training in Cancer Survivors: A Systematic Review [58]	1993-2008	Mix (breast 83%)	Resistance training ± other modalities	RCTs, CCTs, UCTs	Pedro scale [71]	24 (10 RCTs)	*Physical Function* ↑ cardiopulmonary function ↑ muscle strength and endurance
Effects of exercise on quality of life in women living with breast cancer: a systematic review [55]	2001-2006	Breast	Aerobic, resistance, dance, tai chi	RCTs	van Tulder criteria [78]	9	*PROs* ↑ QOL

Systematic review	Review period	Included cancers	Exercise modality	Study design	Quality Assessment Procedure	# studies included	Outcomes
Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer [65]	2007-2015	Breast	Yoga	RCTs	Cochrane Risk of Bias Assessment Tool [72]	23	*PROs* ↑ QOL ↔ depression and anxiety ↓ fatigue
Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis [64]	1989-2006	Breast	Aerobic and/or resistance	RCTs	Author-developed predefined criteria	14	*Physical Function* ↑ aerobic fitness *PROs* ↑ QOL ↑physical function and well-being ↓ fatigue
The impact of exercise during adjuvant radiotherapy for breast cancer on fatigue and quality of life: a systematic review and meta-analysis [67]	1966-2015	Breast	Aerobic, resistance, yoga, qigong, tai chi, pilates	RCTs	Pedro scale [71]	9	*PROs* ↔ QOL ↓ fatigue

Systematic review	Review period	Included cancers	Exercise modality	Study design	Quality Assessment Procedure	# studies included	Outcomes
Breast-cancer related lymphoedema and resistance exercise: a systematic review [68]	2006-2015	Breast	Resistance	RCTs	Pedro scale [71]	6	*Physical Function* ↑ upper and lower body strength ↔ risk or severity of lymphoedema

RCT: Randomised controlled trial, CCT: Controlled clinical trial, UCT: Uncontrolled clinical trial, QOL: Quality of life

Exercise training in people with metastatic cancer

The role of exercise in breast cancer has traditionally focused on women with early stage disease. Women with metastatic disease are typically excluded because of fear of pathological bone fracture or other skeletal complications [79, 80]. In cases where they have been included, subgroup analysis is usually not possible due to such small numbers [42]. This exclusion is not limited to metastatic breast cancer and is also evident in metastatic disease from other primary tumours.

A summary of exercise interventions for metastatic cancer from all primary sites is shown in Table 4. These studies include either a population that was exclusively metastatic [79, 81-93] or if early stage patients were also included, an analysis of metastatic patients presented separately [94]. Only 12 studies described in 15 publications were identified, illustrating the preliminary nature of this work. These studies were predominantly a mix of randomised controlled trials [82, 89, 92-94] and uncontrolled trials [79, 81, 86-88]. Three case reports [83-85] were also presented, although their limited level of evidence was acknowledged, due to the limited literature in the area. The studies comprised a variety of populations, with four conducted solely in women with metastatic breast cancer [82, 85, 86, 92] and the remainder in other or mixed metastatic populations [79, 81, 83, 84, 87-91, 93, 94].

The studies varied in terms of sample size, methods and design (Table 4). Sample sizes were generally small, ranging from single case studies [83-85] to a larger cohort of 101 [92], with a median sample size of 32. The quality of these studies was assessed using the PEDro scale (Table 5), which consists of ten items to give a score out of ten [71]. Two items relating to blinding of participants and trainers were not rated as this is impractical in exercise interventions [58, 67]. Eight criteria were therefore assessed resulting in scores from 0 to 8, with studies scoring ≥4 out of 8 considered high quality [67]. As 6 out of the 12 studies were case reports or uncontrolled trials, the median quality score across studies was low (2 out of 8). Furthermore, as these case reports or uncontrolled trials did not have a control group, criteria such as randomisation, concealment of allocation and blinding of assessors could not be applied. Five RCTs were considered high

quality [81, 89, 92-94], with only one fulfilling all quality criteria [94]. One RCT scored 7 out of 8 [81], failing to adopt blinded assessment of outcome measures. The absence of blinded assessors was also evident in three additional RCTs [82, 89, 93]. Whilst blinding of this nature is technically possible with an exercise intervention, it may prove to be a logistical challenge due to the additional expertise and personnel required. There were also other common deficiencies across the six RCTs; three failed to report using a valid method of allocation concealment [82, 89, 92], three had >15% loss to follow-up [82, 92, 93] and four did not analyse using intention to treat [82, 89, 92, 93]. However, all of the RCTs demonstrated similarity between groups at baseline and appropriate between-groups statistical testing [81, 82, 89, 92-94]. The methods applied by the two highest quality studies [81, 94] should provide guidance for the design of future interventions.

The exercise interventions implemented across studies were heterogeneous (Table 4). Most studies included resistance training [81, 93, 94], aerobic training [84, 85] or a combination of both [83, 87]. Resistance training was prescribed two to three times per week in five studies [38, 50, 51, 40, 44], with program duration ranging from 6 [87] to 13 weeks [83]. The majority of these programs were conducted at a moderate intensity [81, 83, 87, 93, 94] in a gym or clinical facility [81, 83, 87, 94]. The three aerobic only interventions ranged from two sessions per week [84] to as many desired by the participant to obtain 150 minutes per week of moderate-intensity activity [92]. The duration of these aerobic programs was 6 weeks [84], 16 weeks [92] and 12 months [85]. The remaining trials used less traditional forms of activity such as yoga or repetitive motion exercises [82, 86], while others did not specify details of the intervention [88, 89].

As metastatic breast cancer and its treatments can have a negative impact on physical capacity [42, 49], maintenance and improvement of physical function play an important role in prolonging independence and regaining quality of life [95]. Of the five high-quality studies, three incorporated resistance training [81, 93, 94]. Two of these evaluated physical performance with reported improvements observed in muscular strength and other functional outcomes such as walking capacity [81, 94]. Both studies were carried out in a predominantly metastatic prostate population, with the inclusion of only three women (15%) who presented with metastatic breast [81]. Whilst these findings are promising, given the variations in treatment approach

and clinical course of the two metastatic diseases, the generalisability of these findings to women living with metastatic breast cancer is unclear. Most notably, of the studies that assessed safety, there were no adverse events related to the interventions [79, 81, 84, 85, 87, 92, 93].

All of the trials presented in Table 4 evaluated patient-reported outcomes (PROs), with four high-quality studies specifically examining the effect of the intervention on fatigue [81, 92-94]. Three of these reported either a significant improvement or a trend towards improvement in fatigue, with all three adopting resistance training alone or in combination with an aerobic component [81, 93, 94]. The only study with equivocal fatigue outcomes comprised an aerobic only training program [92]. However, higher than anticipated attrition in this study limited power for between-group comparisons [92]. Overall, findings from these preliminary studies suggest that exercise may have the potential for addressing cancer-related fatigue.

The majority of exercise interventions delivered to metastatic populations have prescribed training at a moderate intensity [81, 83-85, 92-94], with only a couple targeted to lower intensities [82, 87]. A moderate workload appears achievable for at least some women living with metastatic breast cancer but there is a paucity of evidence for exercise at higher intensities. Even though high-intensity training may be suitable for part of the population, safety and feasibility may be compromised in those with reduced physical function. Deficits in muscle strength [47] and aerobic fitness [48] have been identified in women undergoing chemotherapy, although physical capabilities more broadly are relatively unknown. To address this gap, a study was designed and conducted to describe the deconditioning and physical capacity of this heterogeneous population (Chapter 2). The findings from this cross-sectional study were then used to develop and conduct an appropriately pitched physical activity program (Chapter 4).

The design of an intervention with consideration for physical activity interests and preferences may encourage participation and enhance adherence. Eighty-four percent of 50 palliative cancer patients with an estimated life expectancy of between 3 and 12 months reported a preference to perform physical activity in the home [96]. It is currently unknown whether women living in the community with metastatic breast cancer share similar preferences to palliative care patients. The majority of exercise interventions for

metastatic populations have been conducted in a gymnasium or clinic environment [81, 83-87, 89, 94, 97], allowing access to specialised equipment and trainers. However, delivery of exercise in this setting may create barriers to participation and limit translation into the community. Physical activity preferences of women living with metastatic breast cancer are explored in Chapter 3 through structured interviews to assist in the development of the physical activity intervention.

The small number of studies investigating the role of exercise in metastatic cancer and limitations such as small diverse samples, uncontrolled trials and heterogeneous interventions, presents a challenge for generalising these findings and determining applicability to this population. Despite this, preliminary findings suggest that exercise may have a positive impact on physical and psychosocial well-being in individuals living with metastatic disease. Chapter 4 evaluates the safety, feasibility and efficacy of a physical activity intervention based on the preferences and physical capacity of women living with metastatic breast cancer, obtained for Chapters 2 and 3.

Table 4. Exercise interventions in metastatic cancer

Article	Participants	Study Design	Intervention	Outcomes Measures	Results	Quality Score^
The effect of a physical exercise program in palliative care: a phase II study Oldervoll, 2006 [87]	n= 47 Primary cancer: GI, breast, genitourinary, prostate, ovary, kidney, lung, other Met site: visceral and bone Current treatment: chemotherapy or hormone therapy	Uncontrolled trial	Duration: 6 weeks, 2x week Program: Circuit training (resistance and aerobic) of 50m duration Intensity: low Location: clinic	*Safety and tolerability* Adverse events Adherence *Physical function* 6m walk Timed sit-to-stand Functional reach *PROs* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) Fatigue Questionnaire (FQ)	*Safety and tolerability* No adverse events Adherence of 88% *Physical function* Significant improvement in walking distance and timed sit-to-stand *PROs* Significant improvement in emotional, role and social functioning Significant improvement in dyspnoea Improvements in fatigue approached statistical significance	1/8

Article	Participants	Study Design	Intervention	Outcomes Measures	Results	Quality Score^
Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases Cormie, 2013 [81] Functional benefits are sustained after a program of supervised resistance exercise in cancer patients with bone metastases: longitudinal results of a pilot study Cormie, 2014 [79]	n=30 Primary cancer: prostate Met site: bone Current treatment: not specified	Randomised controlled trial	Duration: 12 weeks, 2x week Program: resistance training of ~60m duration + walking Intensity: moderate Location: clinic	*Safety and tolerability* Adverse events Bone pain Attendance Compliance *Physical function* 1RM leg extension 400m and 6m walk Timed up and go Sensory organisation test *Body composition* Lean body mass BMD *PROs* Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Brief Symptom Inventory-18 (BSI) Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF)	*Safety and tolerability* No adverse events No significant changes in bone pain Attendance of 85% Compliance of 89% *Physical function* Significant improvements in muscle strength, aerobic capacity and ambulation Trend towards improvement in timed up and go and balance *Body composition* Significant increase in whole body lean mass and BMD at the hip *PROs* Significant increase in social functioning Trend towards improvement in physical functioning, role-physical and physical health Improvements in cancer-related fatigue approached statistical significance	7/8*

Article	Participants	Study Design	Intervention	Outcomes Measures	Results	Quality Score^
The effect of seated exercise on fatigue and quality of life in women with advanced breast cancer Headley, 2004 [82]	n=38 Primary cancer: breast Met site: not specified Current treatment: chemotherapy	Randomised controlled trial	Duration: 12 weeks, 3x week Program: seated exercise program of repetitive motion exercises of 30m duration Control: usual care Intensity: low-moderate Location: home	*PROs* Functional Assessment of Chronic Illness – Fatigue (FACIT-F)	*PROs* Physical and functional well-being decreased in both groups but the intervention group experienced significantly less decrease Fatigue increased in both groups but the intervention group experienced significantly less increase	3/8
Physical training during intrahepatic chemotherapy Kelm, 2003 [83]	n=1 Primary cancer: rectal Met site: visceral Current treatment: chemotherapy	Case study	Duration: 13 weeks, 2x week Program: resistance and aerobic training Intensity: moderate Location: clinic	*Physical function* Submaximal treadmill test FEV_1 and FVC *PROs* Gastrointestinal Quality of Life Index	*Physical function* Decrease in heart rate and lactate concentration Improved lung function *PROs* Improvement in quality of life	0/8

Article	Participants	Study Design	Intervention	Outcomes Measures	Results	Quality Score^
Aerobic exercise as additive palliative treatment for a patient with advanced hepatocellular cancer Crevanna, 2003 [84]	n=1 Primary cancer: liver Met site: visceral Current treatment: not specified	Case study	Duration: 6 weeks, 2x week Program: cycle ergometry of 35m duration Intensity: moderate Location: clinic	*Safety and tolerability* Adverse events *Physical function* VO2max Peak work capacity *PROs* Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)	*Safety and tolerability* No adverse events *Physical function* Increase in VO2max and peak work capacity *PROs* Improvement in physical functioning, mental health, pain, vitality and general health perception	0/8
Aerobic exercise for a patient suffering from metastatic bone disease Crevanna, 2003 [85]	n=1 Primary cancer: breast Met site: visceral and bone Current treatment: chemotherapy + radiotherapy	Case study	Duration: 52 weeks, 3x week Program: cycle ergometry of 50m duration Intensity: moderate Location: clinic	*Safety and tolerability* Adverse events *Physical function* VO2max 6m walk *PROs* Grimby's questionnaire Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)	*Safety and tolerability* No adverse events *Physical function* Increase in VO2max and 6m walk *PROs* Improvement in physical functioning, mental health, role function, social function, pain and vitality	0/8

Article	Participants	Study Design	Intervention	Outcomes Measures	Results	Quality Score^
Yoga for women with metastatic breast cancer: results from a pilot study Carson, 2007 [86]	n= 18 Primary cancer: breast Met site: not specified Current treatment: chemotherapy or not specified	Uncontrolled trial	Duration: 8 weeks, 1x formal session per week + 10min per day Program: 'Yoga of Awareness' program of 120m duration gentle stretches, meditation and discussion Intensity: not reported Location: clinic (10m/day at home)	*PROs* Daily symptom diary	*PROs* Significant improvement in daily invigoration and acceptance Trend for improvement in pain and relaxation	0/8

Article	Participants	Study Design	Intervention	Outcomes Measures	Results	Quality Score^
An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study Porock, 2000 [88]	n=9 Primary cancer: bowel, pancreas, melanoma, breast, oral Met site: not specified Current treatment: chemotherapy or radiotherapy or none	Uncontrolled trial	Duration: 28 days, several sessions per day Program: not specified – reported as 'a range of activities' Intensity: not reported Location: home	*PROs* Multidimensional Fatigue Inventory (MFI) Symptom Distress Scale (SDS) Hospital Anxiety and Depression Scale (HADS) Quality of Life Scale (QOL Scale)	*PROs* No change in fatigue Trend towards decreasing anxiety Improvement in QOL	1/8

Article	Participants	Study Design	Intervention	Outcomes Measures	Results	Quality Score^
Impacting QOL for patients with advanced cancer with a structured multidisciplinary intervention: a randomized controlled trial Rummans, 2006 [89] Will improvement in quality of life (QOL) impact fatigue in patients receiving radiation therapy for advanced cancer? Brown, 2006 [90] Improving the QOL of geriatric cancer patients with a structured multidisciplinary intervention: a randomized controlled Trial Lapid, 2007 [91]	n=49 Primary cancer: GI, lung, head/neck, brain, ovary, other Met site: not specified Current treatment: radiotherapy	Randomised controlled trial	Duration: 3 weeks, total of 8 sessions Program: conditioning, education and discussion of 90m duration Control: usual care Intensity: not reported Location: clinic	*PROs* The Spitzer QOL Uniscale Linear Analog Scales of Assessment (LASAs) Symptom Distress Scale (SDS) Profile of Mood States (POMS) Functional Assessment of Chronic Illness Therapy–Spiritual Well-Being (FACIT-SWB)	*PROs* QOL significantly decreased in control group but was maintained in intervention group	5/8*

Article	Participants	Study Design	Intervention	Outcomes Measures	Results	Quality Score^
Resistance exercise in men receiving androgen deprivation therapy for prostate cancer Segal, 2003 [94]	n=60 (being treated with palliative intent) Primary cancer: prostate Met site: not specified Current treatment: androgen deprivation therapy	Randomised controlled trial	Duration: 12 weeks, 3x week Program: resistance training Control: waitlist Intensity: moderate Location: gym	*Physical function* Chest press load test Leg press load test *Body composition* Skinfolds BMI Waist circumference *PROs* Functional Assessment of Cancer Therapy-Fatigue (FACIT-F) Functional Assessment of Cancer Therapy-Prostate (FACIT-P)	*Physical function* Significant increase in upper and lower body strength *Body composition* No difference *PROs* Improvements in fatigue approached statistical significance	8/8*

Article	Participants	Study Design	Intervention	Outcomes Measures	Results	Quality Score^
Randomized trial of a physical activity intervention in women with metastatic breast cancer Ligibel, 2016 [92]	n= 101 Primary cancer: breast Met site: visceral and bone Current treatment: chemotherapy or radiotherapy or targeted therapy or none	Randomised controlled trial	Duration: 16 weeks, total of 150min/wk Program: aerobic training Control: waitlist Intensity: moderate Location: gym and home	*Safety and tolerability* Adverse events Attrition *Physical function* Bruce Ramp Treadmill *PROs* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) Functional Assessment of Chronic Illness – Fatigue (FACIT-F)	*Safety and tolerability* No adverse events Attrition rate of 30% *Physical function* Non-significant improvement in test duration *PROs* Non-significant improvement in global QOL No change in fatigue	5/8*

Article	Participants	Study Design	Intervention	Outcomes Measures	Results	Quality Score^
A home-based exercise program to improve function, fatigue, and sleep quality in patients with stage IV lung and colorectal cancer: a randomized controlled trial Cheville, 2003 [93]	n= 65 Primary cancer: lung, colorectal Met site: not specified Current treatment: chemotherapy or radiotherapy	Randomised controlled trial	Duration: 8 weeks, 2 x week Program: resistance training + walking Control: waitlist Intensity: moderate Location: home	*Safety and tolerability* Adverse events Adherence *PROs* AM-PAC CAT AM-PAC Mobility Functional Assessment of Cancer Therapy– General (FACT-G) Functional Assessment of Chronic Illness – Fatigue (FACIT-F) Pain rating Sleep quality rating	*Safety and tolerability* No adverse events Adherence of 77% *PROs* Significant improvements in mobility, fatigue and sleep quality	5/8*

^Quality score determined by the PEDro scale [71] *Considered a high-quality study based on PEDro score ≥4

Table 5. Methodological quality of included exercise interventions in metastatic cancer using the PEDro scale

Article	**Study Design**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
Oldervoll, 2006 [87]	UCT	-	-	-	-	-	-	-	+	1/8
Cormie, 2013 [81] Cormie, 2014 [79]	RCT	+	+	+	-	+	+	+	+	7/8*
Headley, 2004 [82]	RCT	+	-	+	-	-	-	+	-	3/8
Kelm, 2003 [83]	CS	-	-	-	-	-	-	-	-	0/8
Crevanna, 2003 [84]	CS	-	-	-	-	-	-	-	-	0/8
Crevanna, 2003 [85]	CS	-	-	-	-	-	-	-	-	0/8
Carson, 2007 [86]	UCT	-	-	-	-	-	-	-	-	0/8
Porock, 2000 [88]	UCT	-	-	-	+	-	-	-	-	1/8
Rummans, 2006 [89] Brown, 2006[90] Lapid, 2007 [91]	RCT	+	-	+	-	+	-	+	+	5/8*
Segal, 2003 [94]	RCT	+	+	+	+	+	+	+	+	8/8*
Ligibel, 2016 [92]	RCT	+	-	+	+	-	-	+	+	5/8*
Cheville, 2013 [93]	RCT	+	+	+	-	-	-	+	+	5/8*

1: use of randomisation; 2: allocation was concealed; 3: similarity of groups at baseline regarding the most important prognostic factors; 4: blinding of assessors; 5: obtainment of key outcome measures from more than 85% of the subjects; 6: use of an intention to treat analysis; 7: reporting of results of between-group statistical comparisons of at least one key outcome measure; 8: reporting of point estimates and variability.

*Considered a high-quality study based on PEDro score ≥4 +: met criteria, -: did not meet criteria, RCT: Randomised controlled trial, CCT: Controlled clinical trial, UCT: Uncontrolled clinical trial, CS: Case Study

Monitoring physical activity

Physical activity helps those with early breast cancer manage their condition by improving physical and psychosocial well-being [54-62]. There is also preliminary evidence that physical activity may have a role in supportive care for the management of metastatic cancer [79, 81, 82, 87, 93, 94]. The findings of Chapters 2 and 3 will assist in the challenge to develop an intervention which encourages women living with metastatic disease to be physically active. Tools that adequately capture physical activity are important for monitoring and encouraging participation in the intervention.

There is a diverse range of direct and indirect methods available for measuring physical activity. They adopt approaches such as behavioural observation, questionnaires, motion sensors and calorimetry [98]. All techniques have inherent strengths and weaknesses. The method adopted by researchers and clinicians is often determined by affordability, participant burden, sample size, age and the outcome of interest.

Indirect physical activity measurement

There is a large array of indirect measures available to measure physical activity, including questionnaires and activity logs. In surveillance, these are often preferred over direct methods as they are practical, cheap, of low burden and easy to administer to large cohorts. There are many questionnaires available for capturing physical activity in healthy adults, including the Recent Physical Activity Questionnaire (RPAQ) [99], PA Assessment Tool (PAAT) [100] and Human Activity Profile (HAP) [101]. Questionnaires have also been developed for more defined populations, such as the Community Health Activities Model Program for Seniors (CHAMPS) [102] and the Physical Activity Scale for the Elderly (PASE) [103], designed for older adults. Two questionnaires commonly used to assess physical activity in oncology research are the Godin Leisure Time Leisure-Time Exercise Questionnaire (GLTEQ) [104] and the International Physical Activity Questionnaire (IPAQ)

The GLTEQ is a short four-item self-administered questionnaire. It captures the frequency of bouts of at least 15 minutes of light-intensity, moderate-intensity and vigorous-intensity physical activity during a typical

week [104]. The number of bouts at each level of intensity is multiplied by the corresponding metabolic equivalent (MET) to give a Leisure Score Index (LSI) [104]. The LSI can be used to rank individuals or to classify their level of activity. Individuals with an LSI ≥ 24 are classified as active and meeting physical activity guidelines, whilst individuals with an LSI <24 are classified as being insufficiently active [105]. Due to the brevity and simple administration of the GLTEQ, it was used in Chapters 2 and 3 to establish physical activity levels of the cohort.

One disadvantage of the GLTEQ is that it does not obtain information on the time spent at each level of intensity. Due to this weakness, the IPAQ [106] was adopted to assess behaviour change for the physical activity intervention described in Chapter 4. The IPAQ captures duration and frequency of physical activity of at least 10 minutes, across domains of leisure, work, transportation and household duties during the preceding week [106]. The number of minutes per week is obtained for walking, moderate-intensity and vigorous-intensity activity. The minutes for each category of activity are multiplied by the corresponding metabolic equivalent (MET) and summed to give MET-minutes per week (MET-min•wk^{-1}). To gain substantial health benefits through physical activity, the American College of Sports Medicine (ACSM) recommends at least 500-1000 MET-min•wk^{-1} [107]. Whilst the GLTEQ and IPAQ are both acceptable tools for measuring physical activity [105, 106], there are inherent limitations with self-report questionnaires, such as recall bias which may lead to over or underestimating physical activity [108]. The GLTEQ and IPAQ have been adopted throughout this thesis to supplement quantification by physical activity monitors.

Direct physical activity measurement

Direct measurements assess energy expenditure or movement and generally provide a more detailed and accurate measure of physical activity compared to indirect measures. The current reference method for the validation of physical activity in the field is doubly labelled water (DLW) [98]. It is used to measure total energy expenditure (TEE) in free-living, usually over a period of at least one week. Physical activity energy expenditure (PAEE) can also be calculated from DLW TEE by removing the resting metabolic rate (RMR) and the thermic effect of food [109].However, the use of DLW is limited by its high cost and complex

methodology. As a consequence, more practical and affordable approaches to measuring physical activity are necessary.

One of the earliest and most direct methods of measuring physical activity is through time-and-motion observation. A trained individual observes physical activity behaviours either live or on a video, and codes behaviours into categories whilst obtaining contextual information [110]. This provides qualitative and quantitative information and the ability to target specific physical activity behaviours. Direct observation is labour intensive and time-consuming, making it impractical over long periods.

Another of the early adopted methods for measuring physical activity is heart rate monitoring. Reviews have found that whilst energy expenditure at a group level is reasonably well predicted using heart rate, there are significant differences at an individual level [111]. The inaccuracy stems from factors such as caffeine, stress and body position, which disrupt the otherwise linear relationship between heart rate and energy expenditure [112].

Over the past decade, wearable physical activity monitors have evolved as a promising tool for measuring physical activity. These monitors can be worn for extended periods of time, allowing free-living physical activity to be captured. Monitors may be simple such as a pedometer to measure steps or include an accelerometer that quantifies the frequency, intensity and duration of physical activity. In addition to an accelerometer, more advanced monitors may also capture information such as heart rate, location and body position.

Two popular physical activity monitors amongst researchers are the SenseWear® and the Actigraph™. The SenseWear® integrates an accelerometer and multiple sensors that capture skin temperature, heat flux and galvanic skin response [113]. The data captured by the SenseWear® is processed by proprietary software to estimate energy expenditure. The Actigraph™ is a small tri-axial accelerometer worn at the waist, which records body movements as activity “counts” and uses these to predict energy expenditure. The validation of these two devices to measure energy expenditure has been primarily limited to healthy young adults and

confined to controlled laboratory environments [113, 114]. Few investigations have examined their validity under free-living conditions and their accuracy in similarly-aged women to those with metastatic breast cancer is unknown. To address this gap, both of these devices were compared to the reference method of DLW in older women during free-living in Chapter 5. Based on accuracy and reliability in the laboratory [115], the SenseWear® was also adopted to measure energy expenditure in the cross-sectional study of physical fitness in women living with metastatic disease (Chapter 2).

Consumer- and research-based wearable physical activity monitors are constantly appearing in the marketplace. In recent years, the ActiHeart® has emerged as a promising tool for predicting physical activity in research settings. It attaches to two chest electrodes, introducing a unique opportunity for researchers to present the device to participants as a heart monitor for determining safety without revealing its primary purpose. This allows for true habitual physical activity behaviour to be captured without providing motivation for increased activity as is often seen with monitoring [116]. The ActiHeart® combines heart rate with an accelerometer, allowing it to capture activities of the lower limb, such as cycling, that other physical activity monitors are unable to detect. As the ActiHeart® is waterproof, it can be worn at all times throughout the monitoring period, including during water activities. Validation studies of the ActiHeart® have produced conflicting results [117, 118], and its ability to accurately measure physical activity in older women is unknown. It was therefore included alongside the Actigraph™ and SenseWear® in the physical activity monitor validation study (Chapter 5). Due to the favourable features of the ActiHeart® that are not present in other monitors, it was also adopted to measure physical activity levels throughout the physical activity intervention in Chapter 4.

Assessment of physical fitness

In addition to physical activity, physical fitness is considered a significant indicator of mortality and morbidity [119]. Physical fitness also impacts on independence and quality of life, as a reasonable level of fitness is required to carry out activities of daily living. Measurements of fitness can be used to identify areas of physical function that require attention and to assess change that occurs with the implementation of a physical activity program.

There are a number of measurement approaches available to quantify physical fitness. The selection is based on many factors including the physiological variables of interest, access to equipment, the expertise of the assessor and characteristics of the participant. The most accurate tests are typically laboratory or gym-based, requiring expensive equipment, time and expertise. However, in several settings such as in the community, conducting such assessments is not feasible. Many field tests have therefore been designed that can be conducted to provide alternative measures of fitness using minimal equipment and resources.

As the studies in this thesis were designed to be carried out in the home, a number of field tests were adopted to assess aerobic fitness and muscle strength. A maximal aerobic fitness assessment, such as the beep test [120], can be carried out in the field and provides an accurate prediction of aerobic fitness. However, a maximal test was not appropriate for this metastatic population due to safety concerns and the inability to have medical personnel present for testing. As an alternative, sub-maximal tests such as the YMCA Step Test [121], the Rockport Walking Test [122] and the Modified Canadian Aerobic Fitness Test (mCAFT) were considered [123, 124]. The mCAFT involves stepping up and down double steps to a set cadence and allows maximal oxygen consumption ($VO2_{max}$) to be predicted from published equations [123]. Whilst not as accurate as a maximal test, the mCAFT was adopted as it has shown to be no different to a maximal treadmill test in a population similarly-aged to women living with metastatic breast cancer [125].

Isokinetic testing devices are considered the gold standard for assessing muscle strength [126]. These machines are typically located in research centres or gyms and are not appropriate for field testing due to

their size. An inexpensive and simple alternative for assessing muscle strength in the field is dynamometry. A systematic review which compared dynamometry to isokinetic testing concluded that dynamometry had moderate-to-good validity and reliability [126]. Given dynamometry's portability, cost and ease of use, it is considered an adequate tool for muscle strength assessment. Dynamometry was used to measure grip strength and lower limb strength throughout this thesis.

Patient reported outcomes

Many tools have been developed to assess patient-reported outcomes in breast cancer patients. Some, such as the Medical Outcomes Study 36-Item Health Survey (SF-36) and Medical Outcomes Study 8-Item Health Survey (SF-8), are generic measures designed to capture quality of life in a wide range of conditions and with a general population [127, 128]. Other generic surveys, including the European Quality of Life Questionnaire (EuroQol; EQ-5D) [129], are widely used for determining quality-adjusted life years associated with a health state. The EQ-5D is recommended for use in evaluative studies and policy research and can also be used for economic evaluation. Whilst generic measures allow comparison of quality of life across different conditions, disease-specific instruments may capture symptoms and distress that are of more relevance to women living with breast cancer [130].

The disease-specific European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was designed for use in cancer patients [131]. The EORTC QLQ-C30 is a reliable and valid measure that captures global quality of life and five domains of function; role, social, emotional, cognitive and physical. A high score on a functional scale represents a high level of functioning [132]. Symptoms including fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite, diarrhoea and constipation are also evaluated [132]. A high symptom score represents high symptom burden. EORTC QLQ-C30 normative values for women living with metastatic breast cancer are presented in Table 6 [132]. The EORTC QLQ-C30 was used to assess health-related quality of life and symptom burden in Chapters 2-4.

Table 6. EORTC QLQ-30 normative values for women living with metastatic breast cancer

		Mean	*(SD)*	Median	*[IQR]*
Global health status/QoL	QL	60.2	*(25.5)*	66.7	*[50-83.3]*
Physical functioning	PF	81.6	*(18.7)*	86.7	*[73.3-93.3]*
Role Functioning	RF	67.4	*(31.1)*	66.7	*[50-100]*
Emotional functioning	EF	65.9	*(24.6)*	66.7	*[50-83.3]*
Cognitive functioning	CF	80.5	*(23.2)*	83.3	*[66.7-100]*
Social functioning	SF	74.2	*(28.4)*	83.3	*[66.7-100]*
Fatigue	FA	36.3	*(27)*	33.3	*[11.1-55.6]*
Nausea and vomiting	NV	10.3	*(19.7)*	0	*[0-16.7]*
Pain	PA	30.9	*(29.6)*	33.3	*[0-50]*
Dyspnoea	DY	20.4	*(28.2)*	0	*[0-33.3]*
Insomnia	SL	33.1	*(32.6)*	33.3	*[0-66.7]*
Appetite loss	AP	21.7	*(31)*	0	*[0-33.3]*
Constipation	CO	19.2	*(28.8)*	0	*[0-33.3]*
Diarrhoea	DI	5.8	*(15.2)*	0	*[0-0]*
Financial difficulties	FI	18.6	*(28.6)*	0	*[0-33.3]*

Given the prevalence and debilitating nature of cancer-related fatigue [43], it was important to ensure fatigue was captured reliably. Whilst the EORTC QLQ-C30 contains a single fatigue item, more extensive fatigue-specific scales possess stronger psychometric properties [133]. There are a number of scales designed to measure fatigue specifically in cancer patients, including the Brief Fatigue Inventory (BFI) [134] and the Fatigue Severity Scale (FSS) [135]. Of the available fatigue scales, a systematic review of instruments recommends the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) due to its robust psychometric properties [133]. The FACIT-F consists of 13 items assessing tiredness, weakness and trouble with usual activities. A higher score indicates less fatigue, scored out of a maximum of 52 [136]. Reference values for women living with metastatic breast cancer have not been established. One examination in this population reported the mean FACIT-F score of 90 women was 32 [137]. Although the FACIT-Fatigue was initially developed to evaluate fatigue in cancer patients, it has also been validated in a general population [136]. Not surprisingly, a general population reported lower levels of fatigue with an average score of 44 [136]. The FACIT-Fatigue was adopted throughout this thesis to examine the intensity of fatigue and its impact on daily life.

With the potential for the physical and psychosocial sequelae of metastatic breast cancer to impact on independence, it may also impinge on an individual's ability to continue daily life in their environment of

choice. The Life-Space Assessment (LSA) is a relatively new tool that captures the spatial environment one occupies in daily living by determining how frequently they travel to various locations within and outside of the home, and the need for assistance when moving around [138]. The questionnaire is scored out of 120, with a higher score indicative of a higher pattern of mobility. The LSA was utilised to determine how mobile woman are within their home and community.

Aims of the thesis

Despite the benefits of exercise and physical activity in early stage breast cancer being extensively investigated, there are significant gaps in the knowledge around exercise and metastatic breast cancer. The lack of understanding of the physical capabilities of the population and the preliminary nature of exercise interventions in metastatic disease raised many uncertainties. In addition, the accuracy of devices used to measure physical activity in free-living is relatively unknown.

The aims of this thesis were therefore to:

1. Compare physical activity levels and physical capabilities of women with metastatic breast cancer to healthy counterparts to describe the impact of metastatic breast disease on physical activity level and physical function;

2. Identify physical activity preferences, barriers and benefits of women with metastatic breast cancer;

3. Based on preferences, develop and pilot a physical activity intervention for women with metastatic breast cancer and determine its safety and feasibility; and

4. Evaluate the accuracy of three physical activity monitors in free-living older women in order to inform future studies of women living with metastatic breast cancer.

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Chapter 2:

Physical activity levels and fitness in women with metastatic breast cancer

Author Contribution Statement

Candidate Name: Jasmine Yee

Paper Title: Physical activity and fitness in women with metastatic breast cancer

As the research supervisor of the above candidate, I confirm that the above candidate has made the following contributions to the above paper title:

- Conception and design of the research
- Data collection
- Analysis and interpretation of the findings
- Writing the paper and critical appraisal of content

Professor Sharon Kilbreath ..... Date.....

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Physical activity and fitness in women with metastatic breast cancer

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Abstract
Purpose This study aimed to explore differences in physical activity and fitness between women with metastatic breast cancer compared to healthy controls and factors associated with their physical activity levels.
Methods Seventy-one women with metastatic breast cancer, aged (mean (SD)) 57.7 (9.5) and 2.9 (3.1) years after the onset of metastatic disease, and 71 healthy controls aged 55.0 (9.4) years participated. Of those with metastatic disease, 27 % had bone-only metastases, 35 % visceral-only metastases and 38 % bone and visceral metastases. Patient-reported outcomes and physical measures of muscle strength and aerobic fitness assessments were obtained. Participants wore a SenseWear® physical activity monitor over 7 days, and the average steps/day and the time spent in moderate-to-vigorous intensity physical activity were determined.
Results Women with metastases were significantly (i) less aerobically fit than the control group (25.3 (5.4) vs. 31.9 (6.1) $mL \cdot kg^{-1} \cdot min^{-1}$; $P<0.001$); (ii) weaker (e.g. lower limb strength for the metastatic and control groups was 53.5 (23.7) vs. 76.0 (27.4)kg, respectively; $P<0.001$); (iii) less active, with the metastatic group attaining only 56 % of the mean daily step counts of the healthy women; and (iv) more symptomatic, reporting higher levels of fatigue and dyspnoea ($P<0.001$).
Conclusion Women living in the community with metastatic breast cancer possessed lower aerobic fitness, reduced muscular strength and less daily physical activity compared to healthy counterparts. They also experienced poorer functioning and higher symptom burden.
Implications for Cancer Survivors Women living with metastatic breast cancer may benefit from a physical activity programme to address their physical impairments.

Keywords Physical activity · Fitness · Strength · Metastatic breast cancer

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Introduction

In 2012, there were approximately 14,680 new breast cancers diagnosed and 2,940 breast cancer-related deaths in Australia. For women, the risk of developing breast cancer before the

age of 85 is one in eight [1]. Approximately 7 % of breast cancer cases will present as metastatic disease, and a further 10 % will develop metastases within 5 years of an early breast cancer diagnosis [2]. For these women, the 5-year relative survival is 41 % [3]. With advances in treatment significantly improving prognosis, identifying opportunities to optimise function and well-being has become increasingly important.

Although many women live long productive lives with metastatic breast cancer, there are numerous complex medical, social and emotional challenges that are present. Declines in quality of life and disease-related symptoms have been observed [4–6]. However, the physical status of this population remains unclear. For example, habitual physical activity levels in individuals with metastatic disease have not been previously described.

Women with metastatic cancer may be open to the idea of undertaking increased daily physical activity or structured exercise to improve their physical and psychosocial well-being. For instance, a cross-sectional study of community-dwelling palliative care patients reported that >90 % were interested in participating in a physical activity programme [7]. However, consideration is required to identify what barriers to greater activity participation may exist as well as the impact of their physical impairments. Barriers to participation in physical activity have not been explored in women living with metastatic breast cancer; however, it has been explored in a large cross-sectional study of persons treated for cancer, with stages ranging from I to IV. The five most common barriers that interfered with exercise participation were illness, joint stiffness, fatigue, pain and lack of motivation [8]. Physical impairments have been documented in women with metastatic breast cancer, with 92 % of the population reporting to have at least one physical impairment and almost 50 % a limitation in muscle strength [9]. Such existing impairments coupled with multidimensional barriers may impact on one's ability to carry out physical activity.

Physical activity promotion has become a focus of cancer rehabilitation therapy and research. Its effect on treatment-related side effects and quality of life in women with early stage breast cancer has been extensively documented [10–12]. Conversely, women with metastatic breast cancer have traditionally been excluded from physical activity interventions due to fear of pathological bone fracture and cancer-related fatigue, which is a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning [12–14]. However, a number of pilot and case series studies suggest that this group may experience appreciable physical and psychosocial benefits from increased levels of physical activity, including reduced fatigue, lower symptoms of dyspnoea and improved physical function [15, 16]. In order to deliver an appropriately designed exercise programme, it is necessary to understand the current physical capabilities of this population.

The aims of this study were therefore to determine the level of physical activity, fitness and patient-reported outcomes in women with metastatic breast cancer compared to similarly aged healthy controls as well as to explore the medical, demographic, patient-reported outcome and physical factors associated with physical activity.

Methods

Participants

Two groups of women were recruited: (i) women with metastatic breast cancer (n=71) and (ii) women with no history of cancer (n=71). Women with metastatic disease were recruited from the outpatient departments of six metropolitan cancer centres in Sydney. Eighty-one women were invited to participate in the study by their oncologist or breast nurse during a routine clinic visit. Women were eligible if they had been diagnosed with metastatic breast cancer and were able to communicate in English and in whom the oncologist expected survival of at least 6 months. Participants also had to be living in the community and ambulatory, as defined by an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3 [17].

Women with no history of cancer were recruited through internal advertising at The University of Sydney and via Register4, an online community for breast cancer research volunteers in Australia. Women were eligible if they had never had cancer, were living in the community and ambulatory and were able to communicate in English.

Participants in both groups were screened for cardiovascular, neurological and musculoskeletal risk factors using the Physical Activity Readiness Questionnaire (PAR-Q) [18]. Participants in whom medical evaluation was indicated discussed the study in detail with their oncologist or primary care physician to gain medical clearance (Physical Activity Readiness Medical Examination (PARmed-X) [18]) prior to enrolling in the study.

The study was approved by the Human Research Ethics Committee at each of the institutions where women were recruited, and all participants provided written informed consent.

Protocol

Assessments were undertaken in the participant's home or at another convenient location. Background information including medical history and medications was recorded. Measurements of stature, body mass, muscular strength, aerobic fitness and daily physical activity were obtained. As field tests of physical fitness have not been validated in women with metastatic breast cancer, tests validated in similarly aged

populations were selected. Patient-reported outcomes (PROs) were obtained from self-report questionnaires. A standardised protocol was implemented whereby participants were asked to rest for 10–15 min between the various physical assessments. Following these measurements, the participant wore a SenseWear® physical activity monitor for 1 week. Participants were instructed to maintain their usual activities throughout the monitoring period.

Measurements

Physical activity assessment Physical activity level was determined from the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [19] and from a physical activity monitor. The GLTEQ is a robust measure used to quantify physical activity [20, 19] and is commonly used to assess physical activity in cancer patients [21–23]. It is a simple measure that uses self-recall to quantify the frequency of vigorous, moderate and light-intensity physical activities performed for more than 15 min at a time, during a typical week. These frequencies were computed to give a total leisure time activity score.

Participants were asked to wear a SenseWear® armband (BodyMedia, Inc., Pittsburgh, PA, USA) [24–26] for all waking hours, except during water-based activities, for a period of seven consecutive days. The SenseWear® is a physical activity monitor worn over the triceps brachii muscle of the arm and is designed to capture typical activities of daily life including standing, sitting, walking, running and cycling. The device continuously samples physiological parameters including heat flux, galvanic skin response, skin temperature and near-body ambient temperature and includes a two-axis accelerometer. Data from these sensors are combined with gender, age, body mass and stature to estimate daily energy expenditure and amount of physical activity performed (SenseWear® Professional Software, version 7.0, BodyMedia, Inc., Pittsburgh, PA, USA). The SenseWear® has been shown to be highly reliable [27] and valid for use in healthy adults, with intraclass correlations of 0.80 to a gold standard for energy expenditure [26, 24]. Variables calculated from the SenseWear® include the time spent in moderate-to-vigorous intensity physical activity (MVPA) and steps taken per day (steps/day). The time spent in MVPA was determined using a criterion threshold ≥3 METs [28].

Fitness assessment Aerobic fitness was estimated using the Modified Canadian Aerobic Fitness Test (mCAFT) [29–31]. Participants were required to complete one or more 3-min stages of stepping up and down on a two-step bench. Following completion of each stepping session, heart rate was recorded using a heart rate monitor (FT4, Polar Electro Oy, Finland). If a participant did not reach the desired heart rate, the participant proceeded to the next, more demanding stepping stage. Sessions continued until the participant's heart rate exceeded 85 % of age-predicted maximal heart rate. The stepping cadence and duration of each exercise stage was regulated using music provided with the mCAFT protocol. Aerobic fitness was reported as maximal oxygen consumption (VO_{2max}), predicted from mCAFT equations which have been validated in a healthy adult population [29]. VO_{2max} for each participant was then compared to population normative values [32].

Handgrip strength was measured using hand dynamometry (Jamar Plus+; Sammons Preston Rolyon, Bolingbrook, IL, USA) [33]. Hand dynamometry has been shown to have excellent test-retest reliability in many studies, with intraclass correlation coefficient values ranging between 0.81 and 0.98 [34–36]. With the participant standing with feet hip distance apart, toes pointing forward and eyes looking straight ahead, participants grasped the dynamometer between the fingers and the palm at the base of the thumb. The dynamometer was held in line with the forearm at the level of the thigh with the arm slightly abducted so that it is not touching the body [31]. The participants were instructed to squeeze the handgrip as forcefully as possible to generate maximal force, performing at least three trials on each hand. The maximal absolute handgrip strength (handgrip $strength_{ABS}$) of the dominant limb was used for analysis.

Lower limb strength was measured using a back-leg dynamometer (Back-D; Takei Kiki Kogyo, Tokyo, Japan) [37]. Information on the reliability of such dynamometers is limited; however, one study observed significant correlation coefficients ($r=0.80$) when examining test and retest measures [37]. Participants stood on the footplate, with the scapulae and buttocks positioned flat against a wall. Participants flexed the legs until the knee extension angle was between 130° and 140° and then reached down with elbows fully extended. The pull bar of the dynamometer was placed in the hands, and the chain length was adjusted. Participants were instructed to extend the legs with maximal effort, pulling the bar simultaneously. At least three trials were performed, and the highest absolute score used to determine leg $strength_{ABS}$. Relative handgrip and leg strength was determined by dividing handgrip $strength_{ABS}$ and leg $strength_{ABS}$ by the participant's body mass to derive handgrip $strength_{REL}$ and leg $strength_{REL}$ to account for participants of different statures [38].

Patient-reported outcomes The 30-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30) [39, 40] was used, whereby items relating to five dimensions of functioning are rated: physical, role, social, emotional and cognitive. In addition, a range of items relating to symptoms are rated: fatigue,

nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea. This questionnaire has been used extensively in cancer patients with reliabilities ranging from 0.69 to 0.90 across the various dimensions and symptoms. A higher score for a functional scale represents better well-being, whereas a higher score for a symptom scale represents a higher burden of symptomatology. For analysis, function scales and symptoms were considered independently.

The Functional Assessment of Chronic Illness Therapy: Fatigue (FACIT-F) was used to assess the severity and impact of fatigue [41, 42]. The FACIT-F was originally designed to measure cancer fatigue and is commonly used in this population [43, 44]. The maximum score is 52, with a lower score indicative of more significant fatigue.

The Life-Space Assessment (LSA) was used to assess mobility based on the distance a person reports moving during the preceding 4-week period [45–47]. The LSA has demonstrated to have excellent test-retest reliability with an intraclass coefficient of 0.96 [45]. Questions establish movement to specific life spaces ranging from within one's home to beyond one's town. Specific levels are assessed by asking: "During the past 4 weeks, have you been to other rooms of your home besides the room where you sleep; to an area outside your home such as your porch, deck or patio, hallway of an apartment building, or garage; to places in your neighborhood, other than your own yard or apartment building; to places outside your neighborhood but within your town; and to places outside your town?" For each level, participants are asked how many days within a week they attained that level and whether they required help from equipment or another person. The scores for this questionnaire range from 0 to 120, with a higher score representative of a higher pattern of mobility.

Statistical analyses Independent *t* tests were used to assess differences between the metastatic and healthy groups on continuous variables. These comparisons were repeated using regression modelling that adjusted for age and body mass index (BMI) as part of a sensitivity analysis. Multiple regression was used to determine if any of the demographic, fitness or PRO variables (as reported in Table 2) were related to MVPA and steps/day. Candidates for inclusion in each initial multivariate model comprised those variables that attained $P<0.25$ on univariate analysis. A backward elimination approach from each initial model was used to progressively eliminate covariates that were not statistically significant at the 0.05 level. Variables were tested for collinearity, and only non-related variables were retained. Adequacy of the final model was assessed by examination of residuals. Means and standard deviations are presented unless otherwise stated. Statistical analyses were performed using IBM SPSS Version 20 for Windows (IBM Corp. Somers, NY, USA).

Results

Women with metastatic disease aged 57.7 (9.5)years, and healthy controls aged 55.0 (9.4)years. The BMI of the metastatic group was 27.3 (5.9) vs. 25.0 (4.4)$kg \cdot m^{-2}$ for the healthy group. Of those with breast cancer, the median and interquartile range for time since metastatic disease onset was 1.5 years (1.0 to 4.0 years; Table 1). Twenty-seven women had metastases to both bone and viscera (38 %), 25 to viscera only (35 %) and 19 to bone only (27 %). Forty-nine percent of women were receiving chemotherapy and 45 % receiving hormone therapy.

All women in the healthy group completed the physical assessments; however, not all of the metastatic group was able to do so. Of the 71 women with metastatic cancer, 53 (i.e. 75 %) completed all physical components of the study. Eight completed only PROs and physical activity monitoring, being unable to complete fitness testing for a variety of reasons, including living too far from the testing sites ($n=3$), undiagnosed hypertension ($n=2$), dyspnoea ($n=2$) and neuropathy ($n=1$). The remaining women ($n=10$) were able to complete either strength or aerobic testing, but not both. Reasons for being unable to complete both components included disease or treatment-

Table 1 Medical characteristics of the metastatic cancer group

	$n=71$
Time since primary BC diagnosis (years; mean (SD))	7.8 (5.5)
Time since MET diagnosis (years; mean (SD))	2.9 (3.1)
Time between primary BC and MET diagnosis (years; mean (SD))	5.0 (5.0)
ECOG (%)	
0	54
1	29
2	12
3	4
Location of metastasis (%)	
Bone only	27
Visceral only	35
Bone and visceral	38
Current treatment (%)	
Hormone therapy	45
Chemotherapy: oral	28
Chemotherapy: IV	21
Trastuzumab	17
No current treatment	6
Lapatinib	3
Radiotherapy	0
Lymphoedema (%)	
Present	20

BC breast cancer, *MET* metastatic breast cancer

related factors such as severe lymphoedema ($n=1$) and biomechanical limitations as a result of hip or knee replacements ($n=3$). Other reasons included restrictions expected in an older population such as arthritic pain ($n=2$), balance concerns ($n=1$) and cardiac issues ($n=3$). Notably, no adverse events occurred in those who were able to complete the assessments.

Levels of physical activity

The women with metastatic cancer were significantly less active, attaining only 56 % of steps/day (5,434 (3,174) vs. 9,635 (3,327) steps/day, $P<0.001$) of their healthy counterparts (Fig. 1). The metastatic group also spent a significantly lower duration engaged in MVPA (82 (78) vs. 142 (82)min, respectively, <0.001).

Levels of aerobic fitness and muscle strength

Women with metastatic disease had a significantly lower estimated VO_{2max} than the healthy women (Fig. 1; 25.3 (5.4) vs. 31.9 (6.1)mL•kg^{-1}•min^{-1}, $P<0.001$). More healthy women had a predicted VO_{2max} value above average for their age, based on population normative values, compared to the metastatic group (81 vs. 37 %, $P<0.001$). In addition, the metastatic group was also significantly weaker with respect to absolute and relative strength measures. Leg $strength_{ABS}$ for the metastatic and healthy groups was 53.5 (23.7) vs. 76.0 (27.4)kg ($P<0.001$), and leg $strength_{REL}$ was 0.76 (0.31) vs. 1.15 (0.45)kg•kg^{-1}, respectively ($P<0.001$). Handgrip $strength_{ABS}$ was 26.6 (6.0) vs. 30.2 (6.4)kg ($P=0.001$), and handgrip $strength_{REL}$ was 0.38 (0.09) vs. 0.46 (0.11)kg•kg^{-1}, respectively ($P<0.001$). Further analysis revealed that these results were insensitive to adjustment for age and BMI.

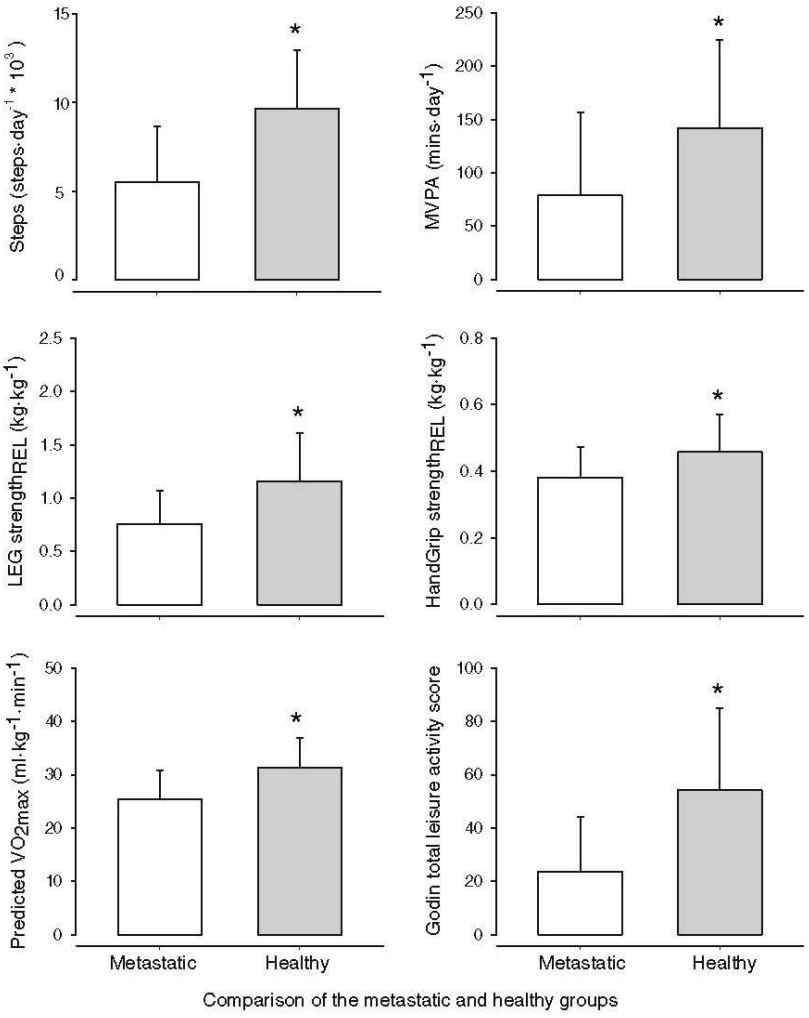

Fig. 1 Comparison of the metastatic group with the healthy group on physical activity and fitness measures. Mean and standard deviation are shown. *Asterisk* denotes significant between-group difference ($P<0.05$)

Patient-reported outcomes

FACIT-F demonstrated that fatigue was significantly higher in women with metastatic cancer compared to their healthy counterparts (38.0 (9.8) vs. 46.3 (4.6), $P<0.001$) (Table 2). Women with metastatic disease scored lower in all functional domains of the EORTC QLQ-30 ($P<0.001$) and were also more symptomatic, reporting higher levels of nausea, pain, dyspnoea, appetite loss, constipation and diarrhoea ($P<0.05$). The between-group comparisons of physical activity, fitness and PROs did not change significantly when adjusting for age and BMI.

Relationships with physical activity

Table 3 reveals the variables that were predictors of physical activity, with no strong evidence that having metastatic disease alters these associations. Handgrip and leg strength_{REL}, VO_{2max}, body mass and BMI were significantly related to MVPA ($P<0.001$). A number of fitness indicators and PROs were related to steps/day, including handgrip and leg strength_{REL}, VO_{2max}, FACIT-F, appetite loss and physical function ($P<0.05$).

Steps/day were significantly related to physical function, pain, age, BMI, VO_{2max} and leg strength_{REL}. This regression

Table 2 Comparison of demographics, physical measures and patient-reported outcomes between women living with metastatic breast cancer and healthy women

	Metastatic ($n=71$[a], mean (SD))	Healthy ($n=71$ mean (SD))	Between-group difference (95 % CI)	P
Age (years)	57.7 (9.5)	55.0 (9.4)	−2.7 (−5.8 to 0.4)	0.091
Height (m)	1.63 (0.07)	1.64 (0.06)	0.01 (−0.02 to 0.03)	0.605
Body mass (kg)	72.7 (16.9)	67.1 (12.5)	−5.6 (−10.5 to −0.7)	0.027
BMI ($kg \cdot m^{-2}$)	27.3 (5.9)	25.0 (4.4)	−2.3 (−4.0 to −0.5)	0.010
Physical fitness				
VO_{2max} ($mL \cdot kg^{-1} \cdot min^{-1}$)	25.3 (5.4)	31.9 (6.1)	6.6 (4.5 to 8.7)	<0.001
$\text{Handgrip strength}_{ABS}$ (kg)	26.6 (6.0)	30.2 (6.4)	3.6 (1.4 to 5.8)	0.001
$\text{Handgrip strength}_{REL}$ ($kg \cdot kg^{-1}$)	0.38 (0.09)	0.46 (0.11)	0.08 (0.04 to 1.11)	<0.001
$\text{Leg strength}_{ABS}$ (kg)	53.5 (23.7)	76.0 (27.4)	22.5 (13.6 to 31.4)	<0.001
$\text{Leg strength}_{REL}$ ($kg \cdot kg^{-1}$)	0.76 (0.31)	1.15 (0.45)	0.39 (0.26 to 0.53)	<0.001
Physical activity				
Steps/day	5434 (3174)	9635 (3327)	4200 (3088 to 5313)	<0.001
MVPA[b]	82 (78)	142 (82)	63 (36 to 91)	<0.001
GLTEQ	23.6 (20.6)	54.1 (30.7)	30.5 (21.9 to 39.2)	<0.001
Life-Space Assessment	77.2 (23.0)	90.1 (13.5)	12.9 (6.6 to 19.2)	<0.001
FACIT-F	38.0 (9.8)	46.3 (4.6)	8.3 (5.8 to 10.8)	<0.001
EORTC QLQ-30				
Function scales				
Global health	70.8 (20.4)	81.7 (15.0)	10.9 (5.0 to 16.9)	<0.001
Physical	78.4 (17.4)	95.0 (8.5)	16.6 (12.1 to 21.2)	<0.001
Role	79.8 (23.7)	95.5 (10.1)	15.7 (9.6 to 21.8)	<0.001
Emotional	78.5 (19.9)	85.9 (12.4)	7.4 (1.9 to 12.9)	0.009
Cognitive	84.3 (15.1)	91.1 (11.2)	6.8 (2.4 to 11.2)	0.003
Social	75.1 (24.9)	96.5 (8.9)	21.4 (15.1 to 27.6)	<0.001
Symptoms				
Fatigue	31.3 (21.0)	14.4 (11.9)	−16.9 (−22.6 to −11.2)	<0.001
Nausea/vomiting	6.8 (14.2)	1.2 (5.9)	−5.6 (−9.3 to −2.0)	0.002
Pain	18.5 (23.0)	11.0 (18.9)	−7.5 (−14.5 to −0.5)	0.035
Dyspnoea	21.6 (25.3)	4.7 (13.0)	−16.9 (−23.6 to −10.2)	<0.001
Insomnia	26.8 (30.7)	21.1 (24.7)	−5.6 (−14.9 to 3.6)	0.230
Appetite loss	12.7 (22.1)	2.3 (10.3)	−10.3 (−16.1 to −4.6)	0.001
Constipation	18.3 (25.7)	1.9 (12.5)	−16.4 (−23.2 to −9.7)	<0.001
Diarrhoea	8.0 (16.4)	2.8 (10.9)	−5.2 (−9.8 to −0.5)	0.029
Financial difficulties	26.8 (30.7)	21.1 (24.7)	−5.6 (−14.9 to 3.6)	0.230

ABS absolute, *REL* relative

[a] Missing data for the following variables (number of cases missing): VO_{2max} (17), handgrip strength (10), leg strength (11) and steps and MVPA (6)

[b] MVPA refers to minutes spent in moderate-to-vigorous intensity physical activity (≥3 METS) per day

Table 3 Association of the combined group's demographics, physical measures and patient-reported outcomes with steps/day and MVPA

	MVPA			Steps/day		
	β	95 % CI	P	β	95 % CI	P
Age (years)	−0.4	−1.9 to 1	0.553	−41.8	−101.8 to 18.2	0.171
BMI ($kg \cdot m^{-2}$)	−7.8	−10.1 to −5.5	<0.001	−74.0	−181 to 32.9	0.173
Body mass (kg)	−2.6	−3.4 to −1.8	<0.001	−25.8	−63.2 to 11.5	0.174
Fitness measures						
VO_{2max} ($mL \cdot kg^{-1} \cdot min^{-1}$)	6.0	3.5 to 8.5	<0.001	210.1	110.3 to 309.8	<0.001
Fitness percentile	1.3	0.8 to 1.8	<0.001	40.6	19 to 62.1	<0.001
Handgrip $strength_{ABS}$ (kg)	1.9	−0.4 to 4.3	0.108	63.2	−29.5 to 155.9	0.180
Handgrip $strength_{REL}$ ($kg \cdot kg^{-1}$)	465.0	347.1 to 582.8	<0.001	6945.4	1369.8 to 12520.9	0.015
Leg $strength_{ABS}$ (kg)	0.3	−0.3 to 0.9	0.320	27.1	4.9 to 49.2	0.017
Leg $strength_{REL}$ ($kg \cdot kg^{-1}$)	75.6	39.7 to 111.5	<0.001	2207.8	761.7 to 3653.9	0.003
GLTEQ	0.7	0.2 to 1.2	0.010	51.6	32.4 to 70.8	<0.001
Life-Space Assessment	0.5	−0.2 to 1.2	0.174	35.2	5.8 to 64.6	0.019
FACIT-F	1.1	−0.8 to 2.9	0.258	138.3	67.1 to 209.5	<0.001
EORTC QLQ-30						
Function scales						
Global	0.6	−0.2 to 1.3	0.152	32.3	0.9 to 63.7	0.044
Physical	0.4	−0.6 to 1.5	0.411	73.9	34.3 to 113.5	<0.001
Role	0.4	−0.4 to 1.2	0.315	47.9	17.8 to 77.9	0.002
Emotional	0.4	−0.4 to 1.2	0.329	21.8	−11.9 to 55.5	0.202
Cognitive	−0.7	−1.7 to 0.4	0.199	6.1	−36.2 to 48.3	0.777
Social	0.3	−0.6 to 1.1	0.504	43.9	10.9 to 76.9	0.010
Symptoms						
Fatigue	−0.5	−1.4 to 0.3	0.206	−60.5	−92.4 to −28.5	<0.001
Nausea/vomiting	−0.8	−2.1 to 0.5	0.228	−51.8	−104.8 to 1.2	0.055
Pain	0.0	−0.6 to 0.7	0.953	−13.7	−40.7 to 13.3	0.319
Dyspnoea	−0.2	−0.9 to 0.5	0.518	−21.0	−48.7 to 6.6	0.134
Insomnia	0.1	−0.4 to 0.6	0.737	−13.9	−33.9 to 6.1	0.171
Appetite loss	0.0	−0.8 to 0.9	0.952	−47.6	−82 to −13.1	0.007
Constipation	0.3	−0.4 to 1	0.414	−2.9	−32.8 to 27	0.848
Diarrhoea	−0.4	−1.3 to 0.6	0.470	−38.4	−77.8 to 1	0.056
Financial difficulties	0.1	−0.4 to 0.6	0.737	−13.9	−33.9 to 6.1	0.171

MVPA refers to moderate-to-vigorous intensity physical activity (≥3 METS)

ABS absolute, *REL* relative

model explained 42 % of the variance ($P<0.001$). MVPA was significantly related to body mass and handgrip $strength_{REL}$, explaining 45 % ($P<0.001$) of the variance. Notably, having metastatic disease did not explain either of these models. For both of these models, some data were missing for a variety of reasons, as outlined above, so these findings should be interpreted with some caution.

Discussion

The aim of this study was to develop an understanding of the physical activity and fitness of women with metastatic breast cancer. Women with metastatic disease, whilst overall of lower fitness than a similarly aged healthy cohort, were able to participate in this study. Interestingly, some women with metastatic disease exceeded the fitness and walking capacity of women without cancer, indicating a wide range of physical abilities.

As expected, the metastatic group displayed significantly decreased aerobic fitness and strength compared to the healthy group. Aerobic fitness in the metastatic group was, on average, 21 % lower than healthy controls. Notably, when aerobic fitness was presented as age-adjusted normative scores [32], many in the metastatic group outperformed their healthy peers, including 21 women who exceeded the average fitness band for their age. Furthermore, all women with metastatic disease who were able to undergo aerobic fitness assessment demonstrated VO_{2max} values greater than that required for

functional independence, i.e. 15 $mL \cdot kg^{-1} \cdot min^{-1}$ [48, 49]. These findings suggest that limitations to participation in aerobic type activities are not a consequence of reduced aerobic fitness. For those unable to perform activities of daily living, other factors such as pain, fatigue, comorbidities and strength need to be considered.

Previous research reported that women with metastatic breast cancer possess aerobic fitness, on average, 33 % less than that of healthy sedentary women [23], larger than the 21 % difference in this study. Possible explanations for this discrepancy may include the use of a sub-maximal, home-based, aerobic step test in this study. Although the mCAFT has been validated [29], the risk of under- or overestimating VO_{2max} increases as compared to completing a maximal aerobic assessment in a laboratory [23]. Another possible explanation is a response bias in participant selection. All women recruited to the aforementioned study [23] were receiving some form of cytotoxic chemotherapy. However, in the current study, only 49 % of women were undergoing chemotherapy.

Not surprisingly, our findings revealed that the metastatic group also experienced significantly lower functioning across all domains and higher symptomatology when compared to their healthy peers. It has been suggested that interventions designed to address clusters of symptoms, such as the combination of fatigue, nausea, decreased appetite and dyspnoea [6], may be more efficacious than those targeting individual symptoms. To date, the role of physical activity to address this symptom cluster has not been explored. However, as fatigue, in particular, is reduced with increased physical activity [50], the role of regular exercise is worth exploring.

Despite presenting with poor quality of life, the metastatic group in this study reported higher functioning and less symptomatology compared to other studies of women living with metastatic cancer [51, 23]. This may be explained by the potential difference in participant characteristics and treatment regimens in such a heterogeneous population. For example, a large percentage of our cohort has metastases confined to bone, for which median survival is longer compared to those with visceral disease. This more indolent disease course is often treated with less aggressive treatment, and patients generally have fewer symptoms [52]. The level of function demonstrated by this cohort of women with metastatic disease was surprising, particularly that many were above average fitness of women without cancer of the same age. In addition, many women presented with mild or no symptoms related to their cancer. For this cohort of women, symptoms and physical capacity may be less of a barrier to being physically active compared to the general metastatic breast cancer population.

The metastatic group was significantly more sedentary, achieving only 56 % of steps/day and 58 % of MVPA compared to the healthy group (Fig. 1). Several fitness indicators and symptoms were associated with physical activity, although there was no strong evidence that having metastatic disease contributed significantly. When the healthy and metastatic groups were combined, a range of outcomes including higher levels of physical function, aerobic fitness and leg $strength_{REL}$, low levels of pain, low BMI and being younger explained higher daily step counts. MVPA was associated with low body mass and increased handgrip $strength_{REL}$. In neither model of physical activity did having metastatic disease contribute significantly. This reiterates that these women with metastatic cancer, whilst deconditioned, did not appear to be significantly debilitated by their disease.

The physical limitations experienced by women with metastatic disease could potentially be improved through physical activity programmes. Those who were least active demonstrated low levels of aerobic fitness and strength. A programme incorporating both of these aspects could address these underlying impairments. As persons with metastatic cancer have historically been encouraged to rest, there have been few investigations into the impact of structured exercise or lifestyle physical activity interventions in this population. Whilst minimal evidence is currently available, pilot interventions suggest that physical activity has the capacity to decelerate the decline in physical performance in metastatic cancer patients, with the potential to improve or maintain mobility and independence in daily life [15, 16]. Research examining physical activity preferences in patients with metastatic disease found that 84 % of patients would be interested in a programme that could be conducted at home and that 72 % reported walking as their preference [7]. As such, a starting point for this population might be the implementation of a walking programme. In our cohort, the median steps/day were 4,655, with only 15 % achieving >8,000 steps/day, the level at which most health benefits are achieved in older populations [53]. However, as physical activity levels vary extensively in this population, a patient-specific approach with individualised guidance is recommended. Whether structured exercise programmes or lifestyle physical activity interventions are more clinically efficacious for health and quality of life in this population is currently unclear.

Although this study has many strengths, there were also a few limitations. It is likely that women in this study were functioning higher as compared to the average metastatic population. With its focus on physical activity, it is possible that there was a response bias in both groups whereby those with a particular interest in their personal fitness, higher physical abilities or a keenness to participate volunteered for the study. For practical purposes, robust field measures were used to assess physical fitness in both groups in place of gold standard laboratory measures. Another limitation relates to the potential underestimation of physical activity due to activities not captured via the SenseWear® armband, such as cycling or swimming.

In summary, individuals with metastatic breast cancer possessed reduced aerobic fitness, lower strength and more sedentary physical activity levels compared with age-matched healthy controls. They also experienced poorer functioning and higher symptom burden. Although those with metastatic cancer experienced such deficits, the population examined in this study was still capable of functioning independently and should be encouraged to be physically active. Whilst structured exercise and lifestyle physical activity interventions have previously focused on women with early stage breast cancer, this research identifies a need to investigate the potential benefits for women living with metastatic disease.

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Conflict of interest The authors declare that they have no conflict of interest.

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Chapter 3:

Physical activity preferences, barriers and benefits in women with metastatic breast cancer

Abstract

Physical activity may help community-dwelling women with metastatic breast cancer to live well and to manage their disease. Understanding their specific physical activity interests may be beneficial in the development of interventions to enhance adherence and efficacy. The aims of this project were to determine physical activity preferences and to identify perceived barriers and benefits of activity, in women with metastatic breast cancer. Characteristics associated with interest in physical activity were also explored. Participants (n=62) comprised community-dwelling and ambulatory women diagnosed with metastatic breast cancer, with a mean age of 58.2 (9.5) y. Following the physical and patient-reported outcome assessment described in Chapter 2, women completed a structured interview to determine physical activity preferences, barriers and benefits. Seventy-four percent were interested in a physical activity program. There was a strong preference for home-based activity (72%), with the majority preferring to walk (89%). The most common barrier to participation was other commitments (20%). Perceived benefits of physical activity included increased energy (33%). In conclusion, the majority of women expressed interest in a physical activity program and identified strong preferences regarding mode and environment of activity. Understanding physical activity preferences, perceived benefits and barriers facilitates the design of an intervention that enhances the likelihood of being effective and acceptable in this unique population.

Introduction

Breast cancer is the most common cancer among women in Australia [1]. The risk of being diagnosed with breast cancer before the age of 85 is one in eight [1]. For those who present with metastatic disease, the five-year relative survival is 41% [1]. As survival rates improve with advancements in the detection and treatment of metastatic breast cancer, promoting a healthy lifestyle to optimise well-being in women living with this condition becomes increasingly important.

Despite the importance, research overall has predominantly focused on the adverse health outcomes and negative experiences of women living with metastatic breast cancer [2]. This lack of focus on living well is reflected in a recent study that reported whilst women were positive about the medical management of their disease, many were dissatisfied with the support given to manage their side-effects to ensure good overall quality of life [3]. As women with metastatic breast cancer focus on living well with their disease, one coping strategy that has been identified is increasing physical activity [4].

In women with early breast cancer, physical activity has been widely examined and proven to alleviate side effects and improve quality of life [5, 6]. The same focus has not been directed to women living with metastatic breast cancer. Only a few trials have been conducted in this population [7-9], of which the most recent investigated the efficacy of an aerobic exercise intervention with equivocal outcomes [10]. There are also a small number of studies in individuals with metastatic disease originating from a range of other tumours [11-14]. A systematic review suggests that increased levels of physical activity may have physical and psychosocial benefits, including assisting women with metastatic disease to live well [15].

Commencement and adherence to a physical activity program are difficult for the general population, and even more challenging for those living with cancer [16]. As described in Chapter 2, women with metastatic breast disease are approximately 50% less active than a healthy cohort. Given their decreased activity and the potential role of physical activity, the design of interventions based on physical activity preferences may be beneficial for ensuring engagement in this unique population.

One cross-sectional study surveyed activity preferences amongst community-dwelling palliative care patients and observed that more than 75% were interested in participating in a physical activity program [17]. These findings suggest that women living with metastatic breast cancer may also be interested in increasing physical activity or commencing structured exercise in their daily lives.

Physical activity may help community-dwelling women with metastatic breast cancer to live well and to manage their disease. However, little is known about their specific physical activity interests. Such knowledge may assist in the design of interventions to enhance adherence and maximise efficacy. The purpose of this study was to i) determine physical activity preferences, and to identify perceived barriers and benefits to activity in women with metastatic breast cancer and ii) explore characteristics associated with interest in commencing a physical activity program.

Methods

Design

Structured interviews were completed with women with metastatic breast cancer following participation in the cross-sectional study described in Chapter 2. This study explored the differences in physical activity level and fitness between this metastatic population and healthy controls.

Participants

Sixty-two women with metastatic breast cancer were recruited from outpatient clinics of six Sydney cancer centres between May 2011 and January 2013. During a routine clinic visit, women were invited to participate in the study by their oncologist or breast nurse. Women were eligible if they had a confirmed metastatic breast cancer (Stage IV) diagnosis, were living in the community and ambulatory (Eastern Cooperative Oncology Group Performance Status (ECOG) ≤3 [18]), able to communicate in English and had a clinician-estimated life expectancy greater than 6 months.

The study was approved by the Human Research Ethics Committee of the Sydney South West Area Health Service (X10-0308) and all women provided written informed consent.

Protocol

An interview was conducted one week following the assessment of physical fitness, physical activity level and patient-reported outcomes reported in Chapter 2.

Identification of physical activity preferences, barriers and benefits

Perceptions of physical activity were obtained from a structured interview completed face-to-face or via telephone. The first question addressed interest in participating in a program designed to increase physical activity. For women who answered “no” to this

question, the interview was discontinued. For women who expressed interest in a program, the interview continued and women were asked to rate confidence in their ability to increase physical activity on a 10-point Likert scale. Women were then asked to indicate their interest in receiving professional support for physical activity as either 'definitely,' 'probably,' 'unsure', 'probably not' and 'definitely not'. With open-ended questions, women were asked to indicate the following: favoured environment for exercise, preferred mode of exercise, greatest perceived barriers to increasing or maintaining physical activity levels, and largest perceived benefits of increasing their physical activity.

Factors associated with interest in physical activity

Factors were drawn from measures related to physical function and patient-reported outcomes, further described in Chapter 2.

Demographic and clinical information. Demographic information was collected. Medical history included medications, location of metastases and year of primary and metastatic cancer diagnoses.

Physical Measures. Anthropometric information including height and weight was collected. Physical activity was assessed using the Godin-Shephard Leisure-Time Physical Activity Questionnaire (GLTPAQ) [19]. Women who scored ≥24 on the moderate-to-strenuous leisure score index (LSI) were classified as active, and women who scored <24 were classified as inactive [20]. Women categorised as active according to the GLTPAQ were also classified as achieving the current American College of Sports Medicine (ACSM) physical activity guidelines for cardiorespiratory exercise [20, 21]. The Modified Canadian Aerobic Fitness Test (mCAFT) was used to estimate aerobic fitness [22]. This fitness estimate was then compared to population normative values [23] and women were classified as being above or below average based on age. Dynamometry was used to measure handgrip (Jamar Plus+; Sammons Preston Rolyon, Bolingbrook, USA) [24] and lower limb strength (Back-D; Takei Kiki Kogyo, Tokyo, Japan) [25].

Patient-Reported Outcomes. The 30-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30) was used to assess physical, social, role, cognitive and emotional functioning, and a range of symptoms including fatigue, nausea and vomiting, diarrhoea, dyspnoea, pain, appetite loss, insomnia and constipation [26]. For each functional scale, a higher score represented better well-being. Women with a symptom score above 50 indicated a moderate to high level of need [27], and these women were classified as being symptomatic.

Statistical analyses

Descriptive statistics were used to describe participant characteristics and physical activity preferences, barriers and benefits. Women were dichotomised as to whether or not they expressed interest in a physical activity program. The association between interest and each potential predictor was explored using Chi Square analysis. To prepare continuous data for Chi Square analysis, a receiver operating curve (ROC) was used to identify the optimal predictor cut-off point. Associations with cell frequencies less than five were not considered further. Means and standard deviations are presented unless otherwise stated. Statistical analyses were performed using IBM SPSS Version 20 for Windows (IBM Corp. Somers, NY).

Results

Demographic and clinical characteristics are reported in Table 1. The mean age of participants was 58.2 (9.5) y and their mean body mass index (BMI) was 27.0 (5.7) $kg \bullet m^{-2}$. The median and interquartile range of duration since metastatic disease onset was 2.0 y (1.0 to 4.0 y). Twenty-four percent of women (n=15) met current physical activity recommendations.

Table 1. Demographic and clinical characteristics of participants

Characteristics	All (n=62)	Interest in PA (n=46)	No Interest in PA (n=16)
Demographic			
Age (y; mean (SD))	58.2 (9.5)	57.1 (9.2)	61.3 (9.9)
Living with others (n (%))	49 (79)	35 (76)	14 (88)
Not working (n (%))	46 (74)	33 (72)	13 (81)
Clinical			
Time since primary BC diagnosis (y; median (IQR))	6.5 (3.0 to 11.0)	7.0 (3.9 to 10.0)	5.0 (2.3 to 11.8)
Time since MET diagnosis (y; median (IQR))	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	1.0 (1.0 to 3.0)
ECOG (n (%))			
0	33 (56)	25 (54)	8 (50)
1	17 (29)	12 (26)	5 (31)
2	7 (12)	5 (11)	2 (13)
3	2 (3)	1 (2)	1 (6)
Location of Metastasis (n (%))			
Bone Only	17 (27)	12 (26)	5 (31)
Visceral Only	23 (37)	18 (39)	5 (31)
Bone and Visceral	22 (36)	16 (35)	6 (38)
Current Treatment (n (%))			
Hormone Therapy	24 (39)	19 (41)	5 (31)
Chemotherapy: Oral	18 (29)	15 (33)	3 (19)
Chemotherapy: IV	13 (21)	9 (20)	4 (25)
Trastuzumab	4 (6)	0 (0)	4 (25)
No current treatment	3 (5)	3 (7)	0 (0)
Lymphoedema present (n (%))	13 (21)	10 (22)	3 (19)
Number of comorbidities (n (%))	2.6 (1.8)	2.7 (1.7)	2.4 (2.2)
Physical			
BMI ($kg \bullet m^{-2}$; mean (SD))	27.0 (5.7)	27.1 (5.9)	26.4 (5.0)
Active (n (%))	15 (24)	10 (22)	5 (32)
Fitness above average* (n (%))	18 (38)	14 (38)	4 (40)
Handgrip strength (kg; mean (SD))	26.7 (6.1)	26.7 (5.1)	26.9 (8.7)
Lower limb strength (kg; mean (SD))	54.1 (22.3)	55.9 (21.3)	48.2 (25.4)
Patient-Reported Outcomes			
Function (mean (SD))			
Physical	78.6 (16.5)	78.1 (15.9)	80.0 (18.5)
Role	78.2 (22.9)	77.2 (23.7)	81.3 (21.0)
Emotional	77.7 (19.7)	74.8 (20.1)	85.9 (16.3)
Cognitive	83.6 (14.9)	83.0 (14.7)	85.4 (16.0)
Social	74.7 (24.7)	74.6 (24.0)	75.0 (27.2)
Symptomatic (n (%))			
Fatigue	14 (23)	11 (24)	3 (19)
Nausea/Vomiting	3 (5)	2 (4)	1 (6)
Pain	11 (18)	9 (20)	2 (13)
Dyspnoea	10 (16)	9 (20)	1 (6)

*ACSM age-based population norms [23], BC=breast cancer; MET=metastatic breast cancer; PA= physical activity

Seventy-four percent of participants (n=46) reported that they would be interested in participating in a program aimed at increasing their level of physical activity. The majority of participants preferred a program that could be carried out in or near their own home (72%), with walking (89%) and swimming (28%) being the most popular modalities of activity (Table 2). Forty percent of women were extremely confident in increasing their level of physical activity, with an average of 7.9 on a Likert scale of 1-10.

Table 2. Physical activity preferences of participants who were interested in participating in a physical activity program

	n=46	%
How would you rate your confidence in your ability to increase your physical activity level if you decided that you really wanted to?		
1-2 (Not at all confident)	0	0
3-5	6	14
6-8	20	46
9-10 (Extremely confident)	17	40
How interested would you be in receiving professional support and encouragement as you try to increase your physical activity?		
Definitely not/Probably not	1	2
Unsure	2	5
Definitely/Probably	41	93
If you were to participate in a physical activity program, in what environment/s would you prefer to perform exercise?*		
At home	33	72
Group environment (e.g. community group)	13	28
In a gym	18	39
If you were to participate in a physical activity program, what type of exercise would you like to perform?*		
Walking	41	89
Swimming	13	28
Cycling	2	4
Aerobics	3	7
Resistance training	9	20
Aquaerobics	5	11
Wii/Xbox	1	2
Tai Chi	3	7
Yoga	3	7
Dragonboating	2	4
Dancing	1	2

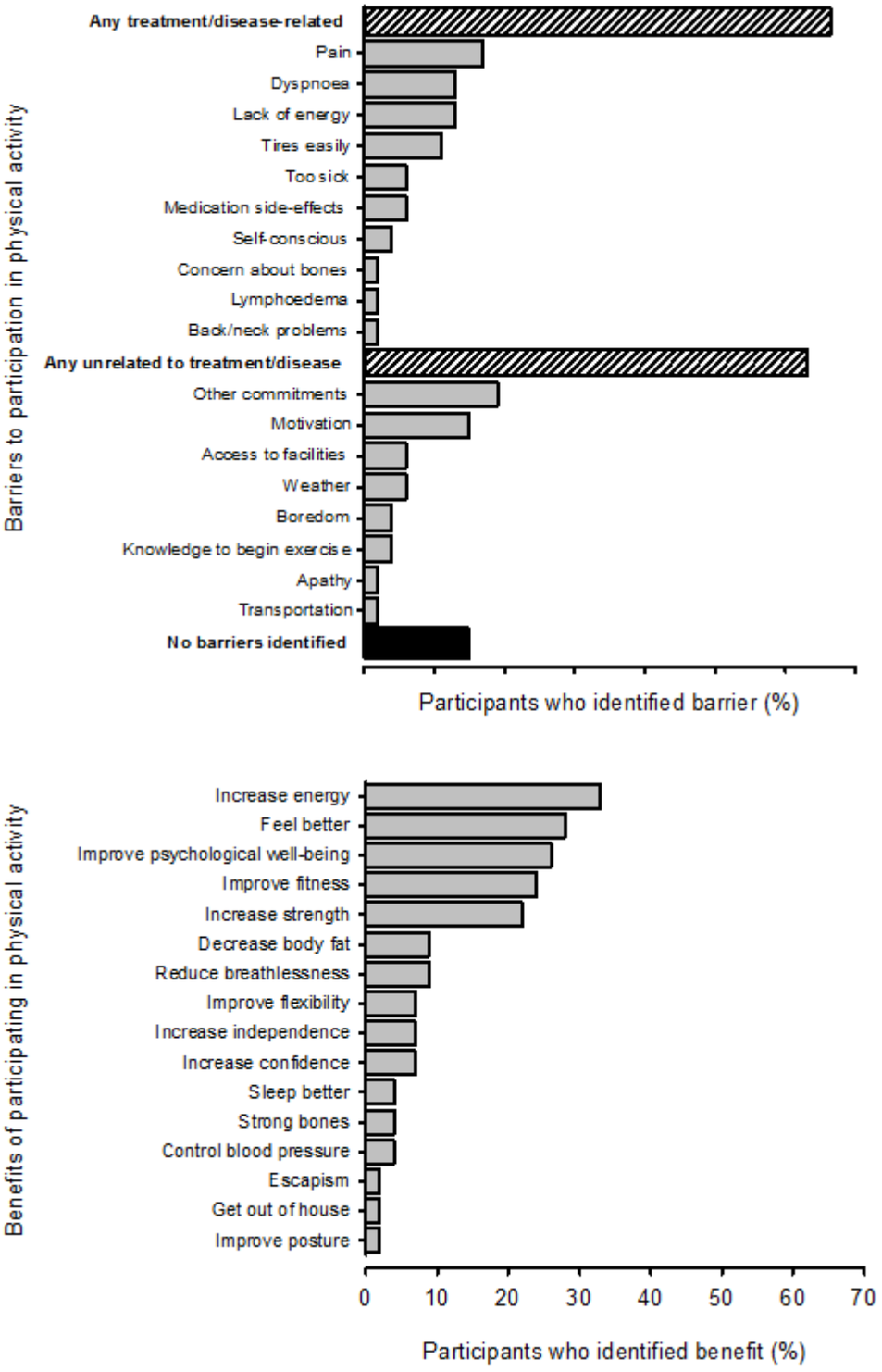
*Participants may have selected multiple responses

Sixteen women (26%) were not interested in commencing a physical activity program. Reasons for not wanting to participate included being too ill (n=5), already doing enough exercise (n=4), too old (n=3), not enough time (n=3) and musculoskeletal concerns (n=1). Chi square analysis revealed there was no pattern with respect to age, time since diagnosis, location of metastasis or any other physical function or patient-reported outcome between those who did and did not express interest in a physical activity program.

Eighty-nine percent of those participants interested in physical activity identified barriers to commencing a program (Figure 1). More than half of the identified barriers may be related to their disease or treatment (63%), with the most common being pain (17%). The proportion of inactive women who reported a disease or treatment-related barrier (67%) was higher than in those who were already active (40%). Barriers which did not appear to be related to disease course were also identified, including other commitments (20%), motivation (13%) and access to facilities (7%).

Of those interested in physical activity, perceived benefits of commencing a program included increased energy (33%), feeling better (28%), improved psychological well-being (26%) and improved fitness (24%) (Figure 1). Increased energy was identified as a potential benefit in 60% of women who were already active compared to 25% in women who were inactive.

Figure 1. Barriers and benefits to increasing physical activity identified by participants interested in a physical activity program (n=46). The individual barriers and benefits are solid grey bars. Hatched bars represent the percentage of participants who identified any barrier related or unrelated to treatment. Women could identify multiple barriers and benefits.



Discussion

Side effects of treatment for metastatic breast cancer can have a significant impact on health and quality of life. Despite this, women perceive that their healthcare providers often overlook the management of side effects, and want greater focus placed on living well with their disease [3]. Preliminary research has shown that for some women with metastatic breast cancer, increased physical activity may be beneficial for improving physical and psychosocial well-being [15]. Determination of preferences for physical activity and an understanding of current exercise behaviours may assist in the development of interventions designed to enhance adherence and effectiveness.

Similar to findings from participants living in community-dwelling palliative care [17], the majority of women in this cohort reported interest in commencing a program to increase their physical activity, with a preference for a home-based intervention. Whilst the palliative care cohort had an expected survival of less than one year, the participants in the current study had a life expectancy of at least six months, with some likely to survive for several years. Despite metastatic patients expressing a preference for home-based activity, preliminary exercise intervention trials have typically been conducted in a gymnasium, hospital or community centre [9, 13, 28]. In recently reported physical activity research of women living with metastatic breast cancer, despite all participants being provided with a gym membership and exercise coaching, the majority opted for a home-based program [10]. Although home-based activity present challenges such as maintaining adherence and compliance by the participant to a program, the integration of an intervention into the home has advantages over these resource-intensive interventions and has the ability to be delivered to the community on a large scale.

Women identified walking as the most favoured activity, similar to trends observed in both palliative care patients [17] and cancer survivors [29, 30], as well as in a general older population [31]. Walking programs are advantageous as they require minimal supervision, cost and equipment, and can be undertaken at a time suitable to the individual. Advances in the development of e-technology for health means that there is now a range of devices on offer to support exercise prescription with minimal supervision, including smartphone applications which can be used to monitor physical activity. A slightly more sophisticated approach that has recently attracted consumer interest is fitness trackers. Wearable devices like the FitBit (Fitbit Inc., San Francisco, CA) and Shine (Misfit Wearables, San Francisco, CA) use accelerometer-based technology to capture data, including information such as the number

of steps walked, quality of sleep and estimated energy expenditure. Many of these devices provide engaging visual feedback on progress towards individualised goals. Incorporating the use of this technology into a physical activity program may be beneficial for increasing motivation and improving adherence [32].

The most commonly reported perceived benefits of increasing physical activity identified by women living with metastatic cancer were increased energy, feeling better and improved psychological well-being. A higher proportion of women who were already active reported benefits relating to energy and psychological well-being compared to inactive women. Previous research has suggested that cancer survivors may only engage in regular physical activity if they perceive that participation will decrease treatment-related side effects [33]. In addition, participation in physical activity may strengthen perceptions that physical activity may attenuate treatment-related side effects such as fatigue [33]. Many women in this cohort appear unaware of the benefits of physical activity for symptom management [15], highlighting a potential role for patient education. Further research is warranted to explore the impact of physical activity participation and education on the perception of barriers and benefits in those with metastatic disease.

Perceived barriers play a major role in physical activity participation. Categorisation of barriers as being either health-related or unrelated to disease course resulted in an almost equal number of participants reporting barriers under each category. The identification of time constraints, lack of motivation and apathy as barriers to physical activity is not a novel finding, with similar barriers reported by cancer survivors [34, 35]. Although not explored, some health-related barriers such as pain may also be due to other comorbidities or age-related ailments. While some barriers may not require oversight by a skilled fitness professional, women who experience barriers such as dyspnoea and pain may benefit from starting a program under the guidance of an exercise specialist.

Despite identifying barriers, most women were confident in their ability to increase physical activity. Comparison with prior studies is limited due to the paucity of studies on physical activity self-efficacy in individuals with metastatic disease. One study evaluating self-efficacy found a mean value of 41% among 86 women receiving adjuvant breast cancer treatment [38], lower than in the present study (7.9 on a 10-point Likert scale). This variance may be explained by the cohort of women in the present study having been previously exposed to an acute bout of physical testing (see Chapter 2), which has been shown to increase physical activity self-efficacy through successful past performance accomplishments [39]. Whilst self-efficacy is considered the primary determinant of behaviour change [40], it should be noted that outcome expectations also have an influential role [41]. To ensure compliance with a

physical activity program, women with metastatic breast cancer would likely require clinician support to establish informed expectations and overcome barriers to participation.

The absence of an association between physical function and patient-reported outcomes between those who did and did not express interest in a physical activity program is of importance. In contrast to previous research in cancer survivors [29, 30], the current study did not find age to be a significant contributor to interest in physical activity. This may be the result of medical management and secondary deconditioning significantly decreasing physical capacity in this metastatic population, irrespective of age. Notably, there was no difference in interest in physical activity based on quality of life, symptom severity or clinical characteristics, including the location of the metastases. This indicates that women who are unwell are not necessarily less likely to be interested in physical activity than women who are well.

There may be an expectation that women living with metastatic breast cancer are deconditioned and sedentary. However, 24% of our cohort met current recommended physical activity guidelines for cardiorespiratory exercise [20], demonstrating that at least a small group within this population were capable of being physically active. Findings from Chapter 2 demonstrated that over 30% of the cohort possessed above average aerobic fitness for their age. Nevertheless, there was also a substantial proportion of the cohort who were inactive. Similar to the therapeutic role of physical activity in many chronic conditions such as heart disease, hypertension, type 2 diabetes and osteoporosis [21], physical activity also has a potential role in the management of metastatic disease [15].

There were some limitations inherent in this study. There was a possibility of clinician bias in referring patients to the study, and a response-bias whereby participants with a particular interest in fitness or with higher physical capacity volunteered. Conversations between the research team and the participants while completing the assessments in Chapter 2 may have influenced attitudes towards physical activity. We did not collect information about pre-cancer diagnosis activity levels, which may have impacted on preferences and attitudes towards a physical activity program. To participate in this study, participants had to be community-dwelling and ambulatory, limiting the generalisability of these findings to people with more debilitating disease.

In conclusion, the high level of interest in a physical activity program, coupled with a portion of women already meeting physical activity guidelines, suggests feasibility for a program in those living with metastatic breast cancer. There was a strong preference for a home-based program, with walking the favoured type of activity. Insight into physical activity preferences, perceived benefits and

barriers facilitates the design of an intervention that enhances the likelihood of being both effective and acceptable in this unique population.

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Chapter 4:

Safety and efficacy of a physical activity program for women with metastatic breast cancer

Abstract

Background: Physical activity for women with early breast cancer is well recognised for improving quality of life. Whilst typically excluded from interventions, women with metastatic breast cancer may also benefit from physical activity.

Objective: To i) investigate the safety and feasibility of a partially supervised physical activity program for women with metastatic breast cancer and ii) explore the efficacy of the program.

Methods: Fourteen women with metastatic breast cancer were randomised to either a control group or an 8-week home-based physical activity intervention comprising of supervised resistance training and an unsupervised walking program.

Results: The recruitment rate was 93%. Adherence to the resistance and walking components of the program was 100% and 25%, respectively. No adverse events were reported. When the mean change scores from baseline to post-intervention were compared, trends in favour of the exercise group over the control group were observed for 6MWT distance (+40 ± 23m vs. -46m ± 56m, respectively) and FACIT-Fatigue score (+5.6 ± 3.2 vs. -1.8 ± 3.9, respectively).

Limitations: The recruitment strategy used targeted women who were high functioning and excluded those confined to a chair or bed. The sample size was small, limiting the power of between-group comparisons.

Conclusions: A partially supervised home-based physical activity program for women with metastatic breast cancer is feasible and safe. The dose of the resistance training component was well tolerated and achievable in this population. In contrast, adherence and compliance to the walking program were poor. Preliminary data suggest a physical activity program may lead to improvements in physical capacity and may help women to live well with their disease. There is a need for future research to identify safe and optimal exercise parameters.

Introduction

Advances in the management of metastatic breast cancer mean that for many women their disease can be viewed as chronic, albeit incurable [1]. With survival increasing, these women may live for several years with a high level of symptom burden, commonly experiencing fatigue, depression, insomnia and pain [2-4]. However, as seen in Chapter 2, some women living with metastatic disease are not significantly debilitated and are able to continue the roles and activities similar to pre-diagnosis [5]. Whilst healthcare providers often focus on survival, women living with metastatic breast cancer want more emphasis placed on alleviating symptoms and living well with their disease [6]. One of many strategies identified by women for living well is increasing daily physical activity [7].

For women with early breast cancer, the physical and psychosocial benefits of physical activity and exercise have been well documented [8, 9]. These programs generally focus on improving quality of life, with prescription similar to that for a cancer-free population. Women with metastatic disease have traditionally been excluded from physical activity or exercise interventions, with conventional advice to avoid exercise due to fear of pathological fracture and a conservative view that fatigue is best treated with rest [10, 11]. However, in a systematic review of metastatic cancer, evaluation of eight studies suggested that exercise interventions had the potential to improve physical performance outcomes [12].

Preliminary research of exercise programs for individuals with metastatic cancer has been typically conducted in a gymnasium, hospital or community centre [10, 11, 13]. Programs in these environments are generally resource intensive, requiring specialised equipment and supervision by exercise professionals, creating potential barriers to their translation into clinical practice. A program that can be delivered in the participant's home may not only increase the potential for implementation but was also identified as a preference for women living with metastatic breast cancer in Chapter 3. Incorporating patient preferences in the design of a physical activity intervention may enhance adherence and retention to the program.

This study evaluated a home-based physical activity intervention in community-dwelling women living with metastatic breast cancer. The primary purpose of this phase I/II study was to evaluate the feasibility and safety of delivering a partially supervised program for this population. In addition, the efficacy of the physical activity program was explored with respect to physical performance, physical activity level and patient-reported outcomes.

Methods

Trial Design

This study was a pilot randomised controlled trial, adhering to the CONSORT Statement for non-pharmacological treatments [14]. Permuted block randomization was performed using a computer-generated random numbers list by an individual external to the study. Participants were stratified according to whether they presented with bone-only or visceral ± bone metastases. Randomization was performed in blocks of 4, 6 and 8 with an allocation ratio of 1:1 to either exercise or a control group. Sequentially numbered opaque envelopes containing group allocation were opened by the researcher in the presence of participants following the baseline assessment.

Participants

Women with metastatic breast cancer who participated in the studies described in Chapters 2 and 3 and resided in close proximity to the University of Sydney were invited to participate. Fourteen women were enrolled between October 2012 and July 2013. Inclusion criteria included: stage IV breast cancer, living in the community, mentally competent to follow instructions, Eastern Cooperative Oncology Group (ECOG) performance status of 0-3 [15], over 18 years of age and an oncologist-expected survival of at least 4 months. Individuals participating in regular physical activity, determined as “high” activity by the International Physical Activity Questionnaire (IPAQ), were excluded. Other exclusion criteria included the inability to communicate in English or experiencing pain or other neuromuscular or musculoskeletal symptoms that limit physical activity.

Women in both groups completed the Physical Activity Readiness Questionnaire [16] to screen for cardiovascular, neurological and musculoskeletal risk factors. Participants who required medical evaluation discussed the study with their oncologist or primary care physician to gain medical clearance prior to enrolling in the study.

The study was conducted in accordance with the protocol, approved by the Human Research Ethics Committee of the Sydney Local Health District (X11-0344). All participants provided written informed consent.

Intervention

Control group (n=6)

The control group was asked to maintain their habitual level of physical activity, and no advice on exercise or physical activity was provided.

Exercise group (n=8)

The intervention comprised an 8-week program of 16 exercise sessions conducted in the participant's home or a local park, supervised by an Exercise Physiologist. An unsupervised walking program was also prescribed for the duration of the 8-week intervention.

Each supervised session consisted of a 10-15 minute brisk walk followed by 30-40 minutes of resistance training. The short walk at the beginning of each session was monitored via a pedometer and Borg's rating of perceived exertion (RPE), with a target zone of 11-13 to reflect a moderate intensity [17]. By accompanying the participant on this walk, the Exercise Physiologist was able to monitor and provide feedback on appropriate exercise intensity. The resistance exercises included chest press, horizontal row, upright row, bicep curl, calf raises, lunges and either sit-to-stands or squats. Each exercise was individualised based on training experience and baseline strength. Upper body exercises were delivered using a Smart Stick™ and Smart Toner® (Twist Sport Conditioning Inc., North Vancouver, Canada) and the lower body exercises used body weight resistance, with the addition of hand weights as required. Each resistance exercise involved 2 sets of 10-12 repetitions, with one-minute recovery between each set. Resistance training was performed at a moderate intensity, targeting 6-7 out of 10 on the Adult OMNI Perceived Exertion Scale (OMNI-RES) [18]. Resistance training was progressive for each exercise, with resistance increased when the participant's perceived exertion fell below the target range. Exercise diaries were maintained by the Exercise Physiologist at each session.

The unsupervised walking program was conducted in the same manner as the supervised walk, with steps counted using a pedometer and a target RPE of 11-13 [17]. Women were asked to walk on days they were not seeing their trainer and encouraged to increase the number of steps taken each week by 10%.

Women in both groups were contacted weekly to document their physical activity outside of the study, appointments with medical or allied health professionals and changes to medication.

Primary Outcomes: Feasibility and Safety

Feasibility of the physical activity program was determined through recruitment and retention rates, adherence and compliance to the intervention, and safety. Recruitment rate was determined by the percentage of eligible patients who enrolled, with retention calculated as the percentage of participants who completed the study. Adherence and compliance rates were retrieved from exercise diaries and determined as outlined in Table 1. Adherence was defined as attendance at sessions, with compliance examined in terms of average exercise intensity and volume. Participants were considered to be adherent or compliant if they achieved at least 90% of the respective prescribed component. Safety was measured by the number of adverse events related to the intervention.

Table 1.Measures of adherence and compliance to the supervised and unsupervised training components of the program.

	Supervised	Unsupervised
	Resistance training	*Walking program*
Adherence	$\frac{\text{Attended sessions}}{\text{Prescribed sessions}} \text{ x } 100\%$	
Compliance		
Exercise intensity	$\frac{\text{Reported OMNI} - \text{RES}}{\text{Prescribed OMNI} - \text{RES}} \text{ x } 100\%$	$\frac{\text{Reported RPE}}{\text{Prescribed RPE}} \text{ x } 100\%$
Exercise volume	$\frac{\text{Performed repetitions}}{\text{Prescribed repetitions}} \text{ x } 100\%$	$\frac{\text{Performed steps}}{\text{Prescribed steps}} \text{ x } 100\%$

RPE=Borg's Rating of Perceived Exertion, OMNI-RES= Adult OMNI Perceived Exertion Scale

Secondary Outcomes: Preliminary Efficacy

The preliminary efficacy outcomes were physical performance, physical activity level and patient-reported outcomes, assessed using the standardised tests described in Chapter 2. Assessments were conducted in the participant's home or at The University of Sydney. All variables were measured prior to the intervention (Baseline), following the intervention (Wk8) and 8 weeks post-intervention (Wk16). All outcomes measures were performed by the same assessor who was not blinded to group allocation.

Physical Performance

The Modified Canadian Aerobic Fitness Test (mCAFT) was used to assess aerobic fitness [19, 20]. Aerobic fitness was reported as VO2max (ml•kg-1•min-1) predicted from mCAFT equations [19]. The six-minute walk test (6MWT) was used as a measure of functional capacity [21]. Participants were instructed to walk between two markers 20 metres apart as many times as possible in six minutes. The participants were asked to walk as fast as they could at a pace they could maintain for the test duration, and given standardised encouragement every minute. The total distance covered in six minutes was used for analysis.

A back-leg dynamometer (Back-D; Takei Kiki Kogyo, Tokyo, Japan) [22] was used to evaluate lower limb strength (kg). Handgrip strength (kg) of the dominant limb was measured using hand dynamometry (Jamar Plus+; Sammons Preston Rolyon, Bolingbrook, USA) [23]. Women were verbally encouraged by the assessor to produce a maximal effort. Three trials were performed with each dynamometer, and if the relative difference was within 10%, no additional trial was required. The highest score from three reproducible trials was retained for analysis.

Physical Activity

Physical activity was determined from the International Physical Activity Questionnaire (IPAQ) [24] and from a physical activity monitor. The IPAQ is a simple seven-day recall measure used to quantify physical activity and is commonly used in cancer populations [25-27]. The total score requires the summation of minutes and frequency of physical activity, which is used to score each type of activity by its energy requirements to calculate a score in MET-minutes of activity per week (MET-min•wk-1) [24].

Participants were asked to wear an ActiHeart™ physical activity monitor [28] continuously for a period of seven days. The ActiHeart™ device connects to two ECG electrodes under the left breast, one placed lateral of the xiphoid process and the other on the same horizontal plane as lateral as possible. The ActiHeart™ combines a uniaxial accelerometer with a heart rate monitor to calculate a range of physical activity variables. The variable used for analysis in this study was daily physical activity energy expenditure (PAEE) (ActiHeart Software, Version 4, CamNtech Ltd, Cambridge, United Kingdom).

Patient-Reported Outcomes

The Functional Assessment of Chronic Illness Therapy: Fatigue (FACIT-F) is designed to measure cancer fatigue [29, 30]. It was used to assess the severity and impact of fatigue in this study, with a maximum score of 52. A lower score is indicative of more significant fatigue.

The 30-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30) was also used [31, 32]. Items relating to physical, role, social, emotional and cognitive functioning were rated, with a higher score representative of better well-being. Symptoms including fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea were also rated. In contrast to the functional scales, a higher score for a symptom scale represents a higher burden of symptomology.

Statistical Analyses

Given the exploratory nature of the study, sample size was established based on available funding and resources. Group allocation was coded to enable blinded analysis. Measures of feasibility and safety were determined using descriptive statistics. The unadjusted mean change from baseline in physical activity, physical performance and patient-reported outcomes were compared between the two groups using descriptive statistics. Glass's delta was used to calculate the effect size of the intervention. An effect size of less than 0.2 was considered small, 0.5 considered medium and more than 0.8 considered large [33]. Probability testing was not used to compare groups due to the small sample size. Mean and standard deviation (SD) have been reported unless otherwise stated. IBM SPSS version 20 for Windows (IBM Corp. Somers, NY) was used for statistical analyses.

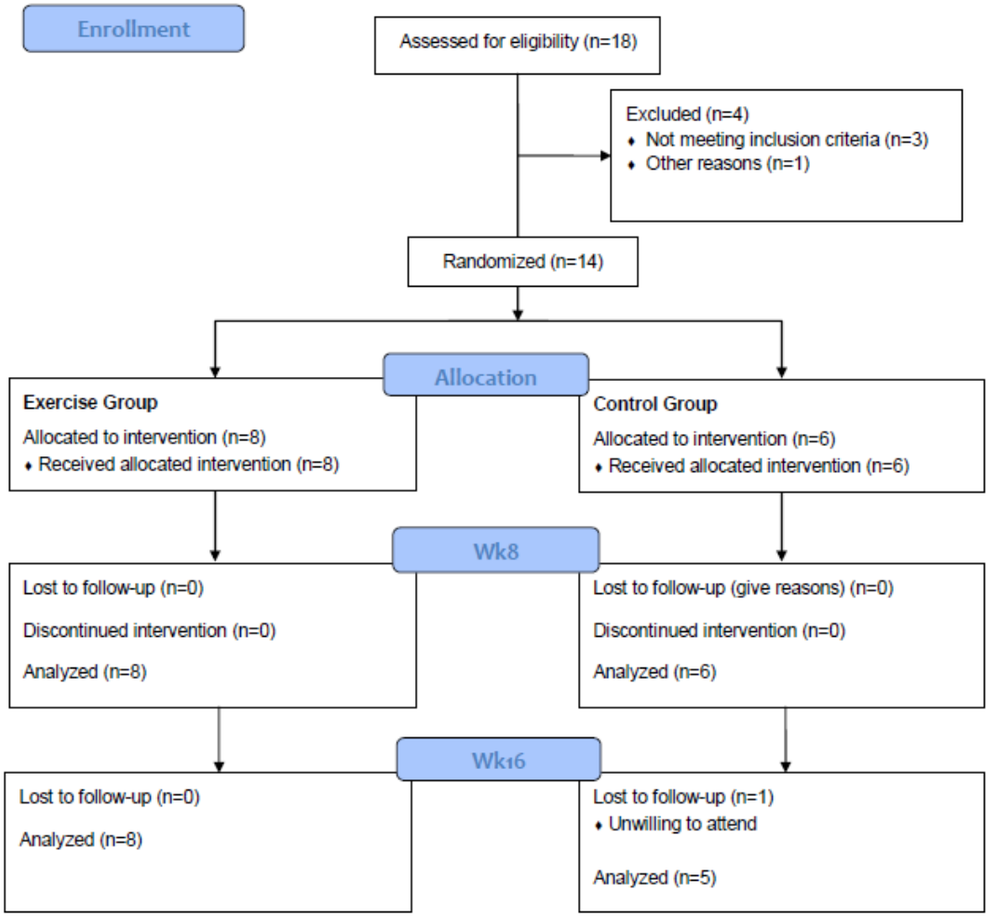
Results

Recruitment and retention

Participant disposition through recruitment, assessment and intervention phases are shown in Figure 1. Of the 18 women approached to participate, all expressed interest. Three women were ineligible due to already participating in regular exercise (n=2) or moving out of the area (n=1). Fifteen were eligible to participate, however, one woman was not able to commit to the study at the time of initial contact. Fourteen women were therefore enrolled into the study, generating a recruitment rate of 93%. Eight women were allocated

to the exercise group and six women to the control group. Retention was good in both the exercise and control groups (100% and 83%, respectively), with one control lost to follow-up at Week 16.

Figure 1. Flow of participants through study



Participant Characteristics

Participant characteristics are shown in Table 2. Notably, 67% in the control group were receiving chemotherapy compared to 13% in the exercise group.

Table 2. Demographic and baseline physical characteristics of the control and exercise groups. Values are mean ± SD or n (%).

	All n=14	Control group n=6	Exercise group n=8
Age (y)	62.2 ± 10.6	65.0 ± 6.9	60.1 ± 12.7
Height (m)	1.63 ± 0.07	1.62 ± 0.05	1.64 ± 0.08
Body mass (kg)	75.2 ± 16.3	74.1 ± 16.9	76.1 ± 17.0
BMI ($kg \bullet m^{-2}$)	28.3 ± 5.7	28.1 ± 5.6	28.4 ± 6.2
Time since primary breast cancer diagnosis (y)	9.8 ± 6.5	11.0 ± 5.5	8.9 ± 7.4
Time since metastatic breast cancer diagnosis (y)	3.5 ± 4.2	4.8 ± 4.6	2.6 ± 3.9
Number of co-morbid conditions	3.0 ± 2.5	3.3 ± 2.6	2.8 ± 2.6
ECOG			
0	4 (29)	2 (33)	2 (25)
1	8 (57)	3 (50)	5 (63)
2	2 (14)	1 (17)	1 (13)
Location of Metastasis			
Bone Only	4 (29)	1 (17)	3 (38)
Visceral Involvement	10 (71)	5 (83)	5 (63)
Current Treatment			
Hormone Therapy	7 (50)	1 (17)	6 (75)
Chemotherapy	5 (36)	4 (67)	1 (13)
No current treatment	2 (14)	1 (17)	1 (13)
Education			
School certificate	5 (36)	3 (50)	2 (25)
University degree	9 (64)	3 (50)	6 (75)
Marital Status			
Married	6 (43)	2 (33)	4 (50)
Other	8 (57)	4 (67)	4 (50)
Employment			
Not working	10 (71)	3 (50)	7 (88)
Income			
≤$52,000	8 (57)	4 (67)	4 (50)
Menopausal status			
Peri-	2 (14)	0 (0)	2 (25)
Post-	12 (86)	6 (100)	6 (75)
Physical performance			
VO_{2max} ($ml \bullet kg^{-1} \bullet min^{-1}$)	23.4 ± 6.3	21.9 ± 4.6	24.3 ± 7.4
6MWT (m)	520.6 ± 116.4	506.3 ± 93.9	531.4 ± 136.2
Leg strength (kg)	59.6 ± 17.0	62.3 ± 15.8	56.6 ± 18.6
Hand strength (kg)	26.7 ± 5.7	26.5 ± 2.8	26.8 ± 7.4
Physical activity			
PAEE (kJ)	2829 ± 1887	2714 ± 814	3143 ± 2362
IPAQ ($MET\text{-}min \bullet wk^{-1}$)	1790 ± 2018	1898 ± 2471	1709 ± 1785

Adherence and safety

Adherence and compliance to the supervised resistance training component of the physical activity program were excellent (Table 3). All eight women attended 100% of the 16 supervised sessions with all sessions completed at the prescribed intensity and volume. In contrast, only 2 women adhered to the walking program. Compliance with walking intensity was found in 71% of participants, however, no participants achieved the desired volume of walking. No adverse events or safety concerns related to the intervention occurred.

Table 3.Rates of adherence and compliance to the supervised and unsupervised training components of the program. Values are n (%).

	Supervised	Unsupervised
	Resistance training	*Walking program*
Adherence to prescribed sessions		
90-100%	8 (100)	2 (25)
75-89%	0 (0)	1 (13)
50-74%	0 (0)	3 (38)
25-49%	0 (0)	1 (13)
0-24%	0 (0)	1 (13)
Compliance with exercise intensity*		
90-100%	8 (100)	5 (71)
75-89%	0 (0)	2 (29)
50-74%	0 (0)	0 (0)
25-49%	0 (0)	0 (0)
0-24%	0 (0)	0 (0)
Compliance with exercise volume*		
90-100%	8 (100)	0 (0)
75-89%	0 (0)	0 (0)
50-74%	0 (0)	2 (29)
25-49%	0 (0)	5 (29)
0-24%	0 (0)	0 (0)

**data missing for unsupervised component (n=1)*

Preliminary efficacy outcomes

Figure 2 and Table 4 present the changes in physical measures from Baseline to Week 8 and Baseline to Week 16 in both groups. A large effect size was observed in the exercise group for 6MWT and leg strength at both time points. Measures of physical activity and strength show a consistent trend in favour of the exercise group.

Figure 2. Results of (A) 6MWT, (B) FACIT-F, (C) leg strength and (D) IPAQ in each group at each assessment. Values are mean and 95% confidence interval.

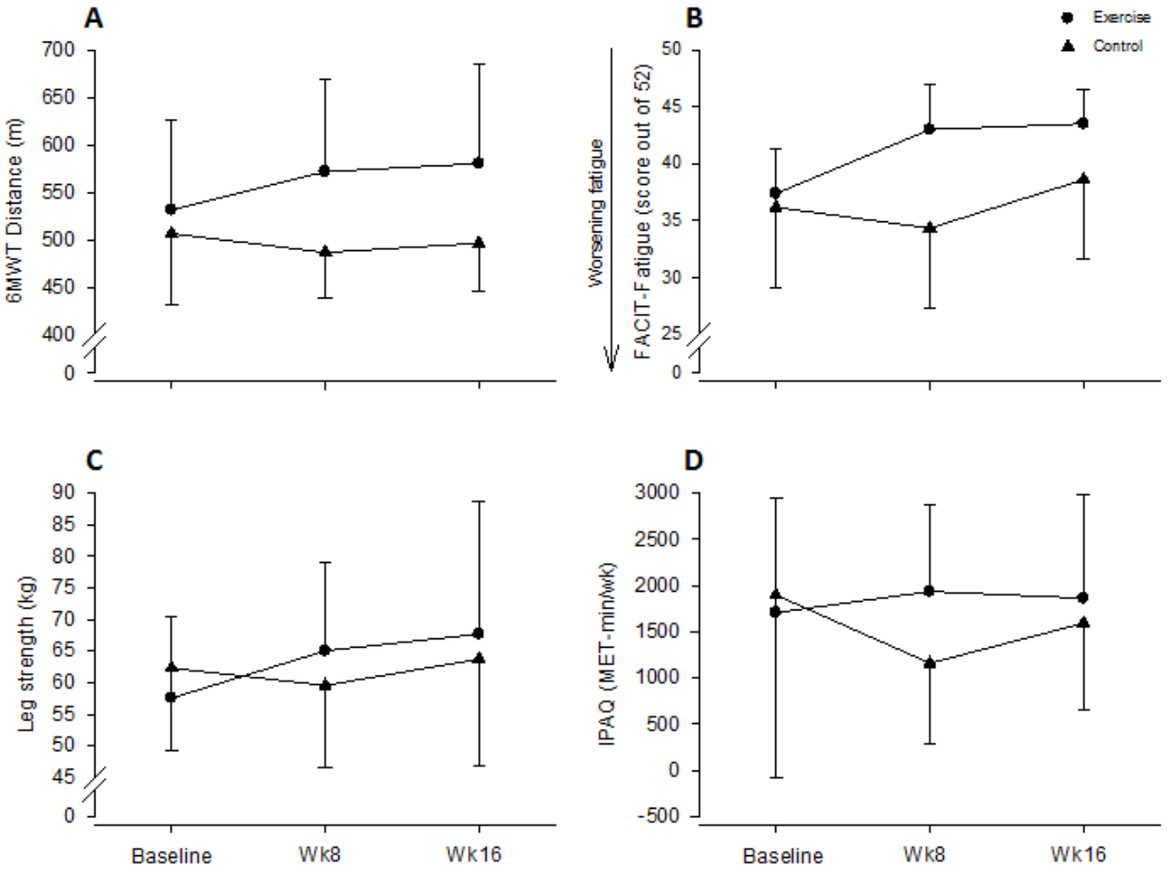


Table 4. Change in physical and activity measures from Baseline at Week 8 and Week 16

	Wk8 – Baseline				Wk16 - Baseline			
	Control Mean (SD)	Exercise Mean (SD)	Between-group difference (95% CI)	Effect Size	Control Mean (SD)	Exercise Mean (SD)	Between-group difference (95% CI)	Effect size
Body mass (kg)	0.9 (0.8)	2.1 (2.8)	1.1 (-1.3 to 3.5)	1.45*	-0.4 (1.7)	3.1 (2.3)	3.4 (0.8 to 6.1)	2.07*
Physical performance								
VO_{2max} ($ml \bullet kg^{-1} \bullet min^{-1}$)	-0.2 (0.1)	1.6 (1.8)	1.8 (0.3 to 3.3)	14.85*	-0.2 (0.2)	0.1 (1.0)	0.2 (-1.0 to 1.3)	0.71
6MWT (m)	-46 (56)	40 (23)	86 (38 to 134)	1.54*	-11 (26)	49 (35)	59 (15 to 104)	2.26*
Leg strength (kg)	-2.8 (5.5)	7.5 (11.3)	10.3 (-0.7 to 21.2)	1.87*	1.7 (6.1)	13.5 (15.6)	11.8 (-3.1 to 26.6)	1.92*
Hand strength (kg)	0.1 (2.2)	1.8 (1.3)	1.7 (-0.7 to 4.1)	0.76	-0.4 (1.5)	1.6 (2.2)	2.0 (-0.5 to 4.4)	1.29*
Physical activity								
PAEE (kJ)	-746 (1177)	-129 (657)	494 (-561 to 1549)	0.56	-569 (1171)	293 (700)	862 (-336 to 2060)	0.74
IPAQ ($MET\text{-}min \bullet wk^{-1}$)	-738 (1622)	228 (915)	966 (-514 to 2447)	0.60	-611 (2046)	155 (1051)	767 (-1106 to 2638)	0.37

*denotes large effect size based on Glass's delta >0.8, VO_{2max} =maximal oxygen consumption, 6WMT= six-minute walk test, PAEE=physical activity energy expenditure, IPAQ=International Physical Activity Questionnaire

Patient-reported outcome data are presented in Table 5. There was an increase in physical function and decrease in fatigue in the exercise group as measured by the EORTC QLQ-C30 and FACIT-fatigue. A consistent trend in favour of the exercise group was also observed across the physical, role, emotional and social function scales of the EORTC QLQ-C30.

Table 5. Change in patient-reported measures from Baseline at Week 8 and Week 16

	Wk8 – Baseline				Wk16 - Baseline			
	Control Mean (SD)	Exercise Mean (SD)	Between-group difference (95% CI)	Effect size	Control Mean (SD)	Exercise Mean (SD)	Between-group difference (95% CI)	Effect size
FACIT-F	-1.8 (3.9)	5.6 (3.2)	7.5 (3.3 to 11.6)	1.92*	0.8 (5.7)	6.1 (3.6)	5.3 (-0.3 to 10.9)	0.93*
EORTC QLQ-C30								
Function Scales								
Global Health	-2.8 (14.6)	5.2 (15.4)	8.0 (-9.7 to 25.7)	0.55	-6.7 (10.9)	7.3 (21.6)	14.0 (-9.1 to 37.1)	1.28*
Physical	-6.7 (7.3)	5.8 (6.6)	12.5 (4.4 to 20.6)	1.71*	1.3 (9.9)	4.2 (8.7)	2.8 (-8.6 to 14.3)	0.29
Role	-11.1 (20.2)	8.3 (8.9)	19.4 (2.1 to 36.7)	0.96*	-16.7 (20.4)	8.3 (12.4)	25.0 (3.2 to 46.8)	1.22*
Emotional	-6.9 (9.7)	7.3 (13.7)	14.2 (-0.1 to -28.6)	1.46*	5.0 (4.6)	7.3 (10.4)	2.3 (-8.7 to 13.2)	0.50
Cognitive	2.8 (16.4)	2.1 (5.9)	-0.7 (-14.2 to 12.8)	0.04	6.7 (15.0)	0 (12.6)	-6.7 (-23.6 to 10.3)	0.45
Social	-8.3 (14.0)	12.5 (17.3)	20.8 (2.1 to 39.6)	1.49*	-3.3 (7.5)	4.2 (21.4)	7.5 (-14.6 to 29.6)	1.01*
Symptoms								
Fatigue	0.0 (7.0)	-6.9 (13.2)	-6.9 (-20 to 6.1)	0.99*	2.2 (9.3)	-5.6 (17.8)	-7.8 (-26.9 to 11.4)	0.85*
Nausea/Vomiting	0.0 (10.5)	-4.2 (11.8)	-4.2 (-17.4 to 9.1)	0.40	-10.0 (14.9)	2.1 (18.8)	12.1 (-9.8 to 34.0)	0.81*
Pain	5.6 (8.6)	-8.3 (19.9)	-13.9 (-31.4 to 3.6)	1.61*	-6.7 (36.5)	-14.6 (13.9)	-7.9 (-38.9 to 23.0)	0.22
Dyspnoea	5.6 (13.6)	0 (17.8)	-5.6 (-24.6 to 13.5)	0.41	6.7 (14.9)	0 (17.8)	-6.7 (-27.8 to 14.4)	0.45
Insomnia	5.6 (25.1)	0 (17.8)	-5.6 (-30.4 to 19.3)	0.22	6.7 (14.9)	-4.2 (11.8)	-10.8 (-27.2 to 5.5)	0.73
Appetite Loss	11.1 (17.2)	0 (0)	-11.1 (-29.2 to 7.0)	0.65	0 (0)	0 (0)	0 (0)	0
Constipation	-5.6 (13.6)	0 (17.8)	5.6 (-13.5 to 24.6)	0.41	-13.3 (18.3)	0 (17.8)	13.3 (-9.2 to 35.9)	0.73
Diarrhoea	11.1 (27.2)	0 (0)	-11.1 (-39.7 to 17.5)	0.41	6.7 (14.9)	8.3 (23.6)	1.7 (-24.5 to 27.8)	0.11
Financial Difficulties	5.6 (25.1)	0 (17.8)	-5.6 (-32.9 to 21.8)	0.22	6.7 (14.9)	-4.2 (11.8)	-10.8 (-27.2 to 5.5)	0.73

*denotes large effect size based on Glass's delta >0.8

Discussion

This study investigated the safety and feasibility of a partially supervised home-based physical activity program for community-dwelling women living with metastatic breast cancer. The program was well-accepted and feasible with preliminary findings warranting further investigation as a potentially effective intervention for improving physical function and quality of life in this population.

Feasibility

This study demonstrated the feasibility to recruit and retain patients with metastatic breast cancer into a longitudinal exercise intervention. Recruitment rates for resistance exercise trials in early breast cancer are typically lower than observed in this study [34-36]. One explanation for this finding may be that the women in the present study had previously expressed interest in increasing their level of physical activity, following participation in the studies of physical activity and fitness presented in Chapters 2 and 3. While 88% of women referred to the original cross-sectional study participated (Chapter 2), there may have been clinician bias whereby those referred were higher functioning and more motivated to participate in regular physical activity than the average metastatic disease population. Excellent retention to the study may be the result of the implementation of a home-based program, identified as a preference for physical activity in Chapter 3. This is further supported by a recent study of an aerobic intervention in the same metastatic population, which found that although participants were provided with a gym membership and exercise coaching, they primarily completed the intervention at home [37].

The adherence to the supervised component of the physical activity intervention was excellent, with 100% of prescribed resistance training sessions attended by participants. Within these sessions, compliance with prescribed intensity and volume was also high. The high adherence and compliance rates of resistance training may be attributed to the supervision of these sessions by an Exercise Physiologist, promoting participation and motivation.

Despite both the resistance and walking components of the program being home-based, adherence to the unsupervised walking program was poor. The low adherence highlights the importance of the role of the Exercise Physiologist as an external motivator and indicates the need for strategies to promote exercise adherence in the absence of a trainer. Given that walking does not require

supervision by an exercise specialist, one approach may be to facilitate social support by encouraging women to walk with family or friends. Whilst none of the women successfully increased their walking volume as prescribed, it was encouraging that the majority were compliant with walking at a moderate intensity. This finding is important as is indicates that women were able to achieve the desired level of intensity without the supervision of a trainer or sophisticated equipment. These findings support the implementation of a home-based training program on a larger scale but highlight the need to identify and include strategies to foster adherence to unsupervised exercise in this environment.

Although the physical activity program was home-based, the resistance training sessions were supervised by an Exercise Physiologist. This level of supervision may have contributed to the lack of any adverse events related to the intervention, a finding similar to previous studies of individuals with metastatic disease [11, 38, 39]. However, given the large number of resources required to run this component of the program, it has a number of barriers for integration into care. With the high level of adherence and compliance to the resistance training sessions, it appears reasonable for supervision to taper off with appropriate mechanisms in place for maintaining adherence. Findings from this study suggest that an appropriately designed and partially supervised moderate-intensity resistance and lifestyle physical activity program is well tolerated and safe for some women with metastatic breast cancer.

Efficacy Outcomes

The between-group differences observed in measures of physical performance, physical activity and patient-reported outcomes can be used to inform the design of a larger randomised controlled trial. The intervention used in the current study was not only well-tolerated, but there was a medium to large effect for all physical performance measures in the exercise group. Physical activity measures also favour the exercise group. However, the magnitude and direction of change differs between the IPAQ and the ActiHeart™. Given the limited evidence supporting IPAQ's ability to assess change in intervention studies [40], physical activity measured by the ActiHeart™ may provide a more accurate insight. In addition to the positive physical outcomes, there was a trend for improvement in patient-reported outcomes in favour of the exercise group. These findings align with a systematic review of exercise in people with metastatic disease [12], suggesting that it may help women living with metastatic breast cancer to live well and to manage their condition.

Whilst this study was not powered to detect statistical significance, the consideration of clinical relevance provides further insight into the findings. For the physical performance measures adopted, the magnitude of clinically meaningful change has not been established for individuals with metastatic disease. However, one study of the 6MWT in older adults with mild to moderate mobility limitations, described a small meaningful change with an increase of 19m, and a substantial change with 47m [41]. With respect to fatigue measured by FACIT-F, the established minimal clinically important difference in a mixed cancer population was 3 points [42]. The exercise group demonstrated clinically meaningful improvements in both these measures of physical function and fatigue. The preliminary evidence is promising and supports the need for further research to explore the most efficacious frequency, intensity, duration and mode of intervention in this population.

A recent aerobic exercise trial in women with metastatic breast cancer demonstrated equivocal effects on physical function [37]. The authors noted the heterogeneous nature of the population and the impact this has on variations in response to exercise, limiting the ability to detect changes in functional outcomes. Given this heterogeneity, traditional measures used to assess such outcomes may not be suitable and tools that focus on the patient's opinion of their function may be more appropriate. For example, the Patient-Specific Function Scale [43] allows patients to identify activities that are impacted by their condition, capturing limitations that are often missed in other outcomes measures.

Study Limitations

As a phase I/II study examining the effects of exercise in women with metastatic breast cancer, certain limitations should be considered when interpreting these findings. Our recruitment strategy targeted women who were high functioning and excluded those with ECOG 3-4. However, some women were low functioning, with three women covering ≤400m in the 6MWT. In addition, two of these women were classified as ECOG 2, i.e. ambulatory and capable of self-care but unable to carry out any work activities. Although the intervention in this current study was found to be feasible and safe, it may not be feasible for women who spend the majority of their time confined to a bed or chair (i.e. ECOG 3 and 4). Similarly, it may not be sufficiently challenging for women who are high functioning and active. As seen in Chapter 2, physical capabilities are highly variable in women living with metastatic breast cancer. Given the disparate physical and psychosocial function observed, future interventions could be designed to target or carefully stratify subgroups of the metastatic population, such as on the basis of ECOG. While the benefits of exercise are well understood for women with early breast cancer [44-46], there is a need to address gaps in knowledge with respect to exercise and metastatic breast

cancer. Appropriately powered randomised controlled trials are required to confirm the safety and efficacy of physical activity programs in this population.

Conclusion

Preliminary evidence from this randomised controlled trial suggests that a partially supervised moderate-intensity resistance and lifestyle physical activity program for women with metastatic breast cancer is feasible and safe. The dose of the supervised resistance training component was well tolerated and achievable in this population. However, issues with adherence and compliance to the walking program were evident. Initial efficacy data suggest that a physical activity program may lead to improvements in physical activity level, physical fitness and functional capacity, and may help women to live well with their disease. These preliminary findings justify the need for future research to identify safe and optimal exercise parameters.

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Chapter 5:

Validation of three activity monitors for assessment of energy expenditure in older women

Abstract

BACKGROUND: Accurate measurement of physical activity is important in the context of managing lifestyle diseases. The reference method for assessing total energy expenditure (TEE) and physical activity energy expenditure (PAEE) in free-living conditions is doubly labelled water (DLW), but it is expensive and requires technical expertise for processing and analysis. Physical activity monitors are therefore an attractive alternative approach for capturing energy expenditure, but their accuracy for estimating energy expenditure in older women remains uncertain.

PURPOSE: This study aimed to i) validate three physical activity monitors for TEE assessment in older women under free-living conditions using DLW as the reference method and ii) determine the accuracy of the PAEE estimates obtained by these monitors.

METHODS: Thirty-three older women aged 60.7 ± 7.1 y with a BMI of 26.9 ± 5.0 $kg \bullet m^{-2}$ participated in this study. Women wore Actigraph™, SenseWear® and ActiHeart® physical activity monitors for 14 consecutive days. Reference values for TEE and PAEE were determined using a standardised protocol for DLW.

RESULTS: A repeated measures analysis of variance determined that mean TEE did not differ significantly amongst DLW and the physical activity monitors (p=0.07). Actigraph™ had the highest level of agreement for TEE with DLW (r_c=0.74). All monitors underestimated TEE by 6% compared to DLW. A repeated measures analysis of variance determined that mean PAEE differed amongst monitors (p<0.01). There was a significant difference between DLW and SenseWear® (p<0.01) but not between DLW and Actigraph™ (p=0.07) or DLW and ActiHeart® (p=0.13). PAEE obtained from DLW was underestimated by all test methods, ranging from 17% in ActiHeart® and Actigraph™ to 40% in SenseWear®.

CONCLUSION: At the group level, the Actigraph™, SenseWear® and ActiHeart® demonstrated acceptable levels of agreement with a reference measure of TEE in older women under free-living conditions. The agreement was greater for estimating TEE than PAEE. Further research is required to improve the accuracy of energy expenditure estimates in these PA monitors.

Introduction

Three physical activity monitors, the Actigraph™, SenseWear® and ActiHeart®, were used to describe physical activity in women living with metastatic breast cancer in Chapters 2 and 4. Despite their adoption for these studies, the ability of these devices to accurately quantify energy expenditure in this population or a similarly-aged cohort is unknown.

With low levels of physical activity identified as a key risk factor for mortality, individuals who participate in regular physical activity experience better health than those who are sedentary [1, 2]. They also possess reduced risk for common chronic conditions such as heart disease, hypertension, depression, diabetes and breast cancer [1, 2]. Given the relationship between physical activity and health outcomes, the accurate measurement of physical activity is important for surveillance and evaluation of interventions.

The most direct measure of quantifying physical activity is through time-and-motion observation, classification and analysis. However, this approach does not always lead to precise quantification of energy expenditure [3]. The 'gold standard' technique for measuring energy expenditure is direct calorimetry, though this approach has limited practical application for assessment under free-living conditions [4]. A widely acknowledged reference method for quantifying total energy expenditure (TEE) in free-living is doubly labelled water (DLW) [5]. DLW can also be combined with resting metabolic rate (RMR) and the thermic effect of food to provide the most accurate measure of free-living physical activity energy expenditure (PAEE). However, high cost and technical complexity limit the use of DLW in clinical and community settings [6]. In such environments, more affordable and practical methods of measuring energy expenditure are required.

Researchers have expressed considerable interest in physical activity monitors in recent years as an alternative objective approach for measuring energy expenditure. Two of the most frequently used monitors are the Actigraph™ and SenseWear®. The Actigraph™ GT3x (AG) is a small tri-axial accelerometer typically worn at the waist. The SenseWear® (SW) is worn on the upper arm and includes multiple sensors in addition to an accelerometer. The information captured by these physical activity monitors can be used to estimate energy expenditure. Most validation studies of these two devices have been carried out under controlled laboratory conditions, with only a few investigations examining their validity in true free-living conditions. Energy expenditure estimation by the Actigraph™ and SenseWear® has been investigated in many populations, including children [7], healthy adults [8] and women with

COPD [9], with varying degrees of accuracy. The ability of these monitors to accurately capture free-living energy expenditure in older women has not been adequately explored.

The ActiHeart® is one of many new physical activity monitors that has entered the marketplace and demonstrates a potential for increased accuracy and usability. The ActiHeart® clips onto two standard ECG chest electrodes and estimates energy expenditure by combining heart rate and body movement. Theoretically, the addition of heart rate should provide a better estimate of energy expenditure than accelerometry alone [10]. As such, the ActiHeart® is capable of capturing activities that other physical activity monitors are generally unable to detect, such as cycling or resistance training. The ActiHeart® is also waterproof so can be worn continuously throughout monitoring, including for water activities such as bathing or swimming. A small number of studies have produced conflicting results between the agreement of the ActiHeart® with DLW in children, young men and adults [11, 12]. The ability of the ActiHeart® to validly measure energy expenditure in healthy older women under free-living conditions has not been evaluated.

The aim of this study was to validate the Actigraph™, SenseWear® and ActiHeart® physical activity monitors for total energy expenditure (TEE) assessment in older women under free-living conditions, using doubly labelled water as the reference method. The accuracy of physical activity energy expenditure (PAEE) estimates obtained by these monitors was also investigated.

Methods

Participants

Thirty-three women aged 50 years and over participated. Women enrolled in a breast cancer research database maintained at the University of Sydney, including those with and without breast cancer, were contacted and invited to participate. Additional recruitment occurred through advertisements placed in the University of Queensland's staff and alumni newsletters. Women were eligible if they were able to communicate in English and agreed to comply with study procedures. Participants were screened for age, body mass index (BMI) and physical activity levels to ensure a range of these characteristics. The study was approved by the Human Research Ethics Committees at The University of Sydney (08-2011/14053) and The University of Queensland (2011000931). All women provided written informed consent.

Study design

At the baseline assessment, anthropometric measurements were taken and the participant ingested the initial dose of doubly labelled water. The participant was also fitted with three physical activity monitors; an Actigraph™, SenseWear® and ActiHeart®, and trained in the appropriate collection of urine samples for DLW analysis. Owing to battery and memory limitations of the monitors, a second visit occurred on Day 7 at a location convenient for the participant. The purpose of this visit was to ensure the DLW urine samples were being collected as instructed and to fit the participant with a new set of activity monitors. A final visit occurred on Day 14, at which point the monitors and urine samples were collected.

Anthropometry

Whilst the participant was wearing light clothing, body mass (kg) was recorded using a digital scale to the nearest 0.1 kg. A wall-mounted stadiometer was used to measure height to the nearest 0.1 cm. Body mass index (BMI; $kg \bullet m^{-2}$) was calculated from these measurements.

Reference method: doubly labelled water

DLW was adopted as the reference method for measuring total energy expenditure (TEE). DLW procedures were conducted according to the International Atomic Energy Agency protocol [13]. A baseline urine sample was collected from each participant for the determination of the background isotope enrichment level of both oxygen ^{18}O and deuterium ^{2}H [14]. Participants were then given an oral dose of DLW ($^{2}H_2O$ and $H_2{}^{18}O$) based on their body mass. For each kg of body water, women ingested 0.083g $^{2}H_2$ (99.8 atom % excess; Sigma Aldrich, Milwaukee, WI) and 2.083g ^{18}O (10 atom % excess; Taiyo Nippon Sanso, Yokogawa, Japan). To calculate the actual dose administered, the drinking container was weighed before and after dosing. Each participant provided a urine sample at five hours following initial ingestion, with further samples on first voiding for the following fourteen days. Urine samples were stored at 4°C in the refrigerator at the participant's home until collection by the researcher. The samples were then transferred to a -80°C freezer at The University of Queensland until analysed.

All samples were analysed in duplicate at the Queensland University of Technology in the Energy Metabolism Laboratory. TEE ($kcal \bullet d^{-1}$) was calculated using the multipoint method [13]. This involved calculating the $^{2}H_2$ and ^{18}O dilution spaces and elimination rates. Sample ^{18}O and ^{2}H enrichment data were linearised using a logarithmic transformation; each data point had the background isotopic

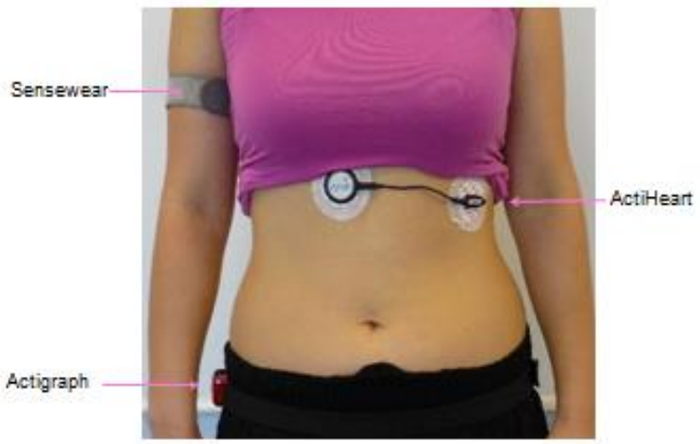
enrichment subtracted and the $\log_e$ value obtained. Data were plotted as $\log_e$ sample enrichment versus time, linearity confirmed and elimination rates calculated [13].

Reference values for physical activity energy expenditure (PAEE) were calculated as 0.9 TEE – RMR [12]. This removed energy expenditure due to resting metabolic rate (RMR) and the thermic effect of food (assumed at 10% TEE) [12]. PAEE was defined as the calories a participant expended above resting energy expenditure. TEE was measured by DLW and RMR was assumed using the Schofield equations [15].

Test methods: activity monitors

Participants received an Actigraph™ (AG), SenseWear® (SW) and ActiHeart® (AH) at their first visit (Figure 1). They were instructed to wear the SW and AG for all waking hours, only removing them while sleeping and during water activities such as bathing and swimming. The AH was worn continuously for the whole data collection period. Participants received detailed written and oral instructions outlining the correct use of each activity monitor. Participants also kept a diary of when they removed each monitor and noted activities performed during the time of removal.

Figure 1. Positioning of the ActiGraph™, Sensewear® and ActiHeart®



Actigraph™

The Actigraph™ GT3x model is a triaxial accelerometer worn on the right hip. Data were sampled in 60s epochs and the Freedson VM3 equation was applied to raw Actigraph™ counts to calculate TEE [16]. As the Actigraph™ was removed when the participant

retired to bed, RMR for the equivalent period of time was added to TEE reported by the Actigraph™. This gave 24-hour data to enable comparison with DLW. PAEE was calculated as 0.9 TEE – RMR. RMR was assumed using the Schofield equations [15].

SenseWear®

The SenseWear® is a multi-sensor monitor worn over the triceps brachii of the upper arm. A range of movement and physiological variables are captured by these sensors which continually collect information. Energy expenditure is estimated by combining these variables with sex, age, body mass and stature. The data were sampled at 60s epochs and used to estimate energy expenditure. The primary analysis was conducted with SenseWear® Professional Software Version 7.0 (BodyMedia Inc., PA, USA), with secondary analysis using Versions 8.0 and 8.1. No information is available on how raw data is processed using the SW proprietary algorithms.

ActiHeart®

The ActiHeart® consists of a two-lead electrode sensor system attached to the skin underneath the left breast. It contains a uniaxial accelerometer that measures bodily movements, combined with a pulse monitor to capture heart rate. These data are combined with sex, age, stature, body mass and sleeping heart rate to estimate energy expenditure. The data were sampled in 15s epochs and analysed using the group HR calibration model to estimate TEE and PAEE (ActiHeart® Software, Version 4, CamNtech Ltd, Cambridge, UK). The AH software uses the Schofield equation to estimate RMR [15].

Missing activity monitor data

Participants maintained a physical activity diary for the duration of the study. Women recorded the type and length of physical activity they participated in each day. If monitors were removed during a period of expected wear, the reason was noted. Where the AG or SW was removed for water activities, corresponding metabolic equivalent (MET) values were calculated using the compendium of physical activities [17]. All other gaps in data were filled with 1.5 METs.

Data from each activity monitor were excluded from analysis if there were more than 2 full days missing over the 14 day period. Participants with 1 or 2 days missing were assigned the same TEE as another day of similar physical activity, as documented in the physical activity diary.

Statistical analyses

Descriptive statistics were used to describe the population and to assess mean and differences of mean TEE and PAEE estimates from the test and reference methods. Repeated measures analysis of variance (ANOVA) and *post hoc* tests were used to determine

whether there was a significant difference in energy expenditure between the test and reference methods. The agreement between measurements obtained with test and reference methods were analysed using Lin's concordance correlation [18] and Bland-Altman plots with their associated limits of agreement [19]. Mean absolute percentage error (MAPE) of each of the test methods compared with the reference method was calculated to determine the degree of disparity with the following formula: ((mean difference test method-reference method)*100)/reference method [20]. Percentage similarity data pairs for each test method compared with the reference method were calculated using the formula: (((reference method+ test method)/2)/reference method)*100. Percentage similarity histograms allow visual comparison between methods with the highest peak showing the greatest accuracy and the narrowest spread showing the best precision between method pairs [21]. At the time of data collection, SenseWear® Professional Software Version 7.0 was available. Since then Versions 8.0 and 8.1 have been released; a secondary analysis was therefore undertaken in which TEE and PAEE were derived from these later versions. For all tests, significance was set at $p<0.05$. Means are presented as mean ± standard deviation (SD) unless otherwise stated.

Results

Participant characteristics are presented in Table 1. Participants ranged in age from 51 to 76 y, with a mean age of 60.7 (7.1) y. On average, women were overweight with a body mass of 72.0 (14.4) kg and body mass index of 26.9 (5.0) $kg \bullet m^{-2}$ (range 19.2 – 41 $kg \bullet m^{-2}$). The most common comorbid conditions were osteoarthritis (27%), cancer (21%) and high cholesterol (21%).

Table 1. Characteristics of participants

Characteristic		Age Group (y; n)		
		50-<60	60-<70	70+
Age (y; mean (SD))	60.7 (7.1)	19	9	5
BMI ($kg \bullet m^{-2}$; n)				
18-<25 (Healthy weight)	10	7	2	1
25-<30 (Overweight)	20	2	7	0
30+ (Obese)	3	1	3	1
Activity level* (n)				
Low	9	4	2	3
Moderate	18	10	6	2
High	6	5	1	0
Comorbidities (n)				
Cancer	7			
Heart disease	0			
Hypertension	5			
High cholesterol	7			
Diabetes	1			
Asthma	0			
Depression/anxiety	4			
Osteoarthritis	9			
Osteoporosis/osteopenia	4			
Thyroid problems	6			

*Determined by the International Physical Activity Questionnaire (IPAQ); BMI = body mass index.

Missing physical activity data

Total energy expenditure, as measured by DLW, was obtained for all 33 participants. Owing to subject compliance and technical issues, some data from the SenseWear® (n=1), ActiHeart® (n=5) and Actigraph™ (n=3) were determined as invalid. There was no pattern with respect to age, BMI or physical activity level between those who did or did not have valid data.

Total energy expenditure (TEE)

Estimates of TEE from DLW, AG, SW and AH are shown in Table 2. A repeated measures ANOVA determined that mean TEE did not differ significantly amongst DLW and the physical activity monitors (p=0.07). The test method with the highest level of agreement with DLW was the AG (r_c=0.74). The SW agreed least with DLW on TEE (r_c=0.49).

Table 2. Energy estimates for reference and test methods

	n	Mean ± SD	Range	Agreement		MAPE*
				r_c	95% CI	
TEE						
Reference (TEE_{DLW})	33	2437 ± 359	1827-3455			
TEE_{SW}^	32	2285 ± 311	1770-2896	0.49	0.26 to 0.67	6.2
TEE_{AH}^	28	2269 ± 341	1805-3004	0.57	0.33 to 0.73	6.9
TEE_{AG}^$^{\Delta}$	30	2280 ± 402	1736-3108	0.74	0.59 to 0.85	6.4
PAEE						
Reference ($PAEE_{DLW}$)	33	814 ± 218	296-1298			
$PAEE_{SW}$^	32	486 ± 250	153-1072	0.00	-0.15 to 0.15	40.3
$PAEE_{AH}$^	28	680 ± 244	274-1408	0.30	0.04 to 0.52	16.5
$PAEE_{AG}$^^{t}	30	678 ± 266	298-1208	0.52	0.31 to 0.69	16.7

TEE= total energy expenditure, subscript indicates monitor, SW = SenseWear®, AH = ActiHeart®, AG = Actigraph™; PAEE = physical activity energy expenditure, subscript indicates monitor, SW = SenseWear®, AH = ActiHeart®, AG = Actigraph™, *mean absolute percentage error ^TEE/PAEE provided by device $^{\Delta}$RMR added to account for sleeping ^{t}Derived from TEE_{AG} using 0.9 TEE-RMR

For TEE, the MAPEs were similar for all monitors (SW=6.2, AH=6.9 and AG=6.4; Table 2). Secondary analysis of SW software versions demonstrated MAPEs ranged from 6.2 with Version 7 to 9.5 with Version 8.1, indicating Version 7 possessed the least error (Table 3).

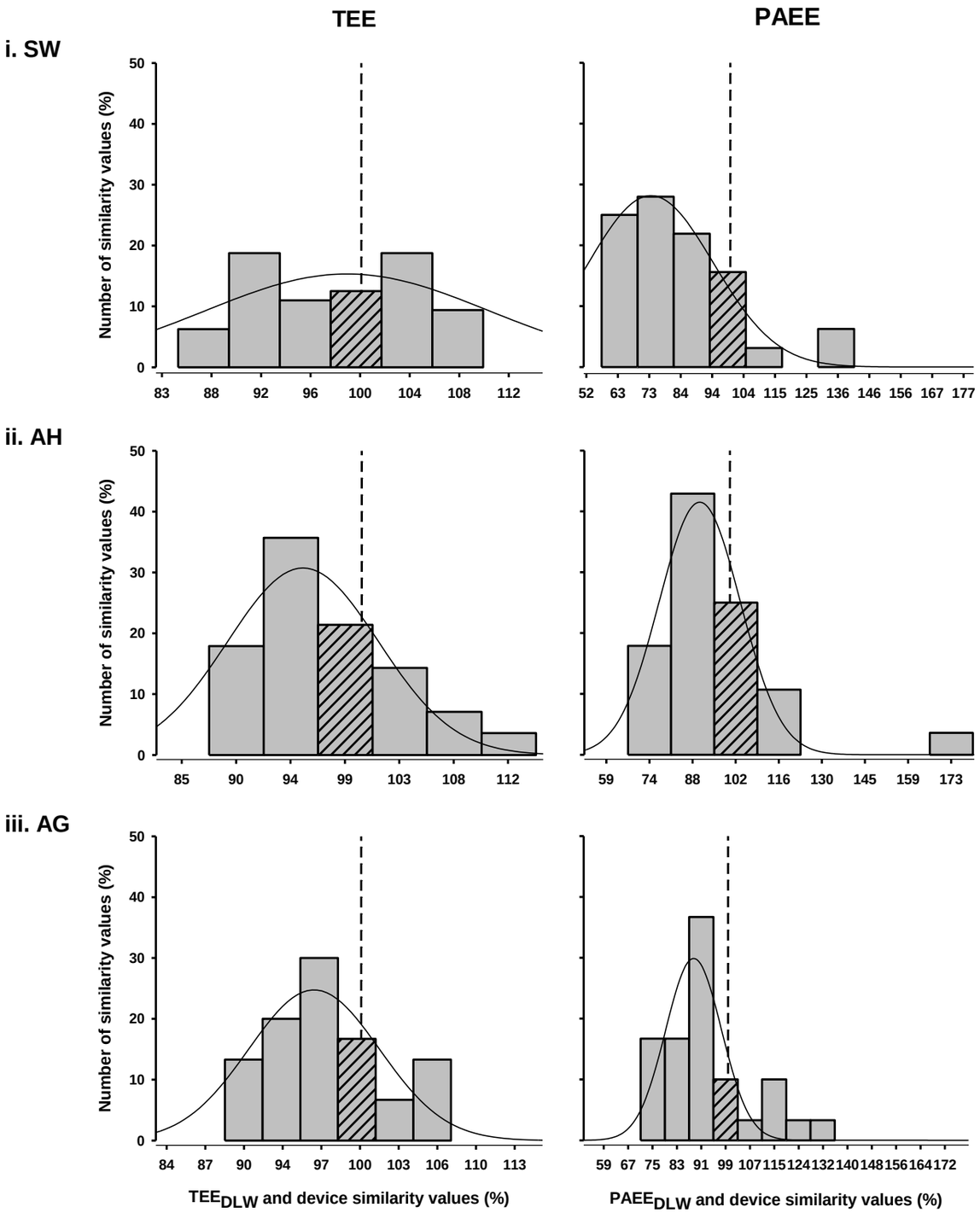
Table 3. Energy estimates for reference and SenseWear® software Versions 7, 8 and 8.1

	Mean ± SD	Range	MAPE*
TEE			
Reference (TEE_{DLW})	2437 ± 359	1827-3455	
TEE_{SW7}	2285 ± 311	1770-2896	6.2
TEE_{SW8}	2233 ± 326	1728-2894	8.4
$TEE_{SW8.1}$	2205 ± 290	1717-2880	9.5
PAEE			
Reference ($PAEE_{DLW}$)	814 ± 218	296-1298	
$PAEE_{SW7}$	486 ± 250	153-1072	40.3
$PAEE_{SW8}$	358 ± 227	19-805	56.0
$PAEE_{SW8.1}$	317 ± 193	22 -701	61.1

TEE= total energy expenditure, subscript indicates monitor, SW = SenseWear®, AH = ActiHeart®, AG = Actigraph™; PAEE = physical activity energy expenditure, subscript indicates monitor, SW = SenseWear®, AH = ActiHeart®, AG = Actigraph™; *mean absolute percentage error

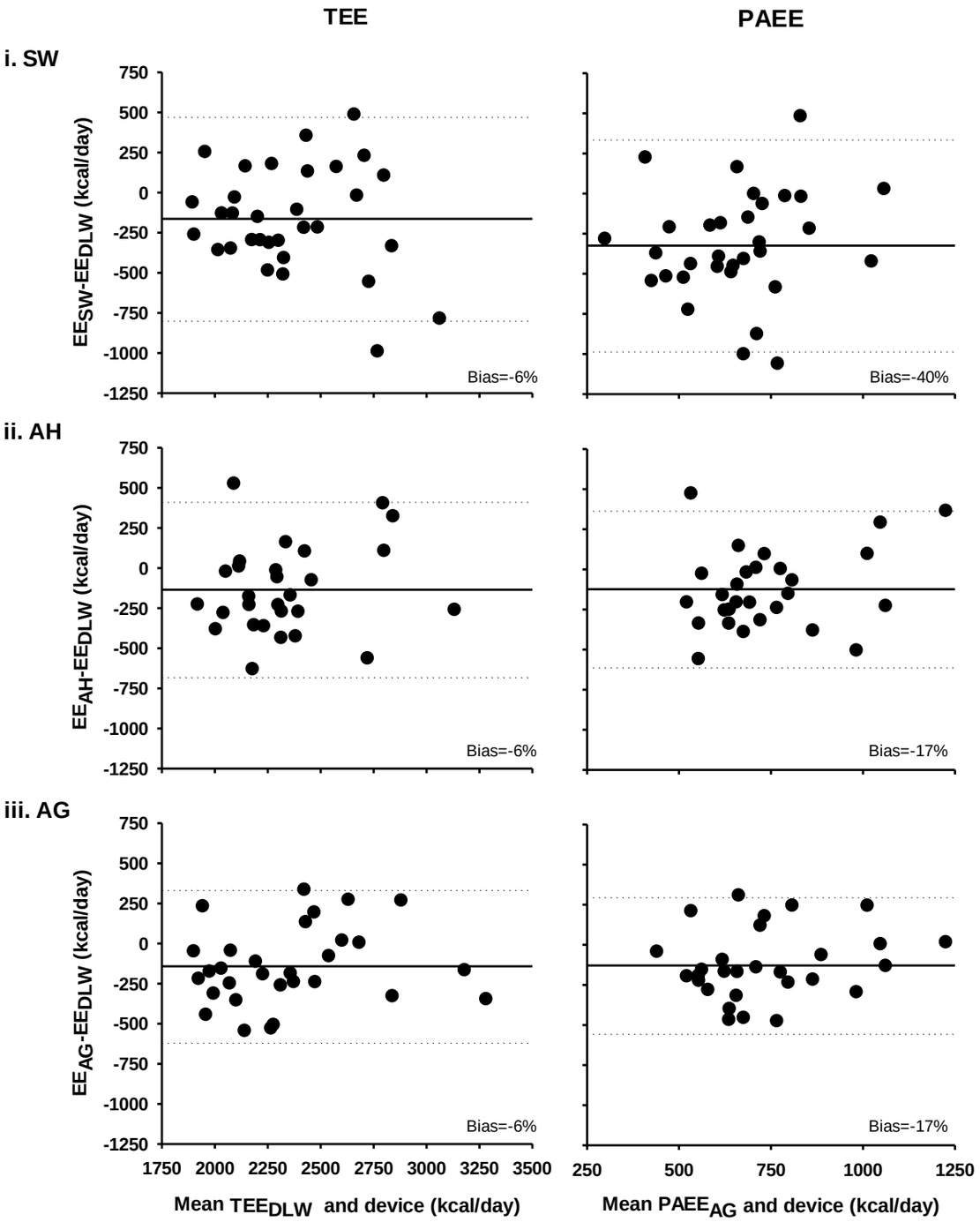
Figure 2 shows a higher degree of accuracy and precision for the AH and AG compared to SW for estimates of TEE. Bland-Altman plots reveal the difference between DLW and the test methods (y-axis) against the average of each method and DLW (x-axis) (Figure 3). The narrowest limits of agreement were for AG (range: 1043 kcal•d^{-1}, 44% of mean) and slightly higher for AH (range: 1094 kcal•d^{-1}, 46% of mean). Values were higher still for SW (range: 1301 kcal•d^{-1}, 55% of mean). All test methods underestimated TEE by 6% compared to DLW at the group level with no evidence of proportional systematic bias.

Figure 2. Percentage similarity histograms of total energy expenditure and physical activity energy expenditure measured by each device versus doubly labelled water. The 100% similarity reference line is indicated in each plot.



TEE= total energy expenditure, PAEE = physical activity energy expenditure, SW = SenseWear®, AH = ActiHeart®, AG = Actigraph™, DLW=doubly labelled water

Figure 3. Bland-Altman plots showing the differences in the mean total energy expenditure and physical activity energy expenditure between each device and doubly labelled water.



TEE= total energy expenditure, PAEE = physical activity energy expenditure, SW = SenseWear®, AH = ActiHeart®, AG = Actigraph™, DLW=doubly labelled water

Physical activity energy expenditure (PAEE)

Mean values and ranges of PAEE from DLW and the test methods are shown in Table 2. A repeated measures ANOVA determined that mean PAEE differed significantly amongst monitors ($p<0.01$). Post hoc tests revealed a significant difference between DLW and SW ($p<0.01$) but not between DLW and AG ($p=0.07$) or DLW and AH ($p=0.13$).

A poor level of concordance between PAEE measured by the test and reference methods was observed (Table 2). AG had the highest level of agreement (r_c=0.52) and SW the least agreement (r_c=0.00).

For PAEE, the MAPEs for the AH and AG relative to DLW were similar (16.5 and 16.7 respectively; Table 2). The SW demonstrated a much larger degree of error (40.3). Whilst all versions of SW software revealed a high MAPE (Table 3), Version 7.0 provided the smallest degree of error (SW_7=40.3 v SW_8=56 v $SW_{8.1}$=61.1).

The percentage similarity histograms present the underestimation of all three monitors compared to DLW (Figure 2). Figure 3 shows limits of agreement were similar for AG (range: 911 kcal•d^{-1}, 127% of mean) and AH (range: 962 kcal•d^{-1}, 130% of mean) and much higher for SW (range: 1320 kcal•d^{-1}, 200% of mean). PAEE obtained from DLW was underestimated by all test methods, ranging from 17% in AH and AG to 40% in SW. There was no evidence of proportional bias across the range of measured PAEE.

Discussion

This study was unique in its assessment of the validity of three physical activity monitors to estimate energy expenditure exclusively in women over 50 years under free-living conditions. Understanding the accuracy of monitors such as the Actigraph™, SenseWear® and ActiHeart® is important for physical activity and population health researchers and clinicians. All three monitors provided estimates of TEE similar to DLW, however, demonstrated large error and variability for estimates of PAEE. The findings of this study support the use of physical activity monitors for group-level estimates of energy expenditure but emphasise the need for caution in use of monitors dependent on the energy outcome of interest.

Previous investigations of TEE or PAEE captured by the Actigraph™, SenseWear® and ActiHeart® compared to DLW under free-living conditions are summarised in Table 4. There are large variations in accuracy depending on the outcome of interest, population, device model and version of software used.

Table 4. Findings from previous validation research comparing doubly labelled water with the Actigraph™, SenseWear® and ActiHeart®

Model (software/equation)*	Citation	EE reported	n	Population	Findings
Actigraph					
AM7164 (F, N, H1, H2, SW, L, Y1, Y2)	Leenders [22]	TEE	13	Females, 21-37y	***B*** TEE_F:-21%, TEE_{H1}:-21%, TEE_{H2}:-2%, TEE_S:-4%, TEE_N:-20%, TEE_L:-10%, TEE_{Y1}:-32%, TEE_{Y2}:-25%
MTI/CSA (E, P)	Reilly [23]	TEE	85	Children, 3-6y	***B*** TEE_E:5%, TEE_P:-5%
GT1M (C, C+LPF)	Rotheny [24]	TEE	22	Adults, 20-67	***B*** TEE_C:6%, TEE_{C+LPF}:-2%
GT1M (H, S, F)	Assah [25]	PAEE	33	African adults, 25-50y	***B*** $PAEE_H$:23%, $PAEE_S$:23%, $PAEE_F$:-6%
GT1M (C,F)	Colbert [26]	PAEE	56	Adults, 65+ y	***M*** $PAEE_C$: 23%, $PAEE_F$:24%
Actiheart					
(HRG)	Rousset [27]	TEE	41	Adults, middle-aged	***M*** TEE:13%
(HRS)	Farooqi [9]	TEE, PAEE	19	COPD females, 59-80y	***B*** TEE:-9%, PAEE:-35%
(HRS, HRG)	Silva [11]	TEE, PAEE	17	Males, 20-38y	***B*** TEE_{HRS}:3%, TEE_{HRG}:8%, $PAEE_{HRS}$:-20%, $PAEE_{HRG}$:-10%
(HRG)	Villars [28]	PAEE	35	Males, 18-55y	***B*** PAEE:-9%
(HRS, HRG)	Assah [29]	PAEE	33	African adults, 25-50y	***B*** $PAEE_{HRS}$:-5%, $PAEE_{HRG}$:-9%
(HRS)	Lof [30]	PAEE	20	Females, 22-45y	***B*** PAEE:15%
Sensewear					
Pro 2 (v5.1, v6.1)	Arvidsson [31]	TEE	20	Children, 14-15y	***B*** $TEE_{5.1}$:9%, $TEE_{6.1}$:-6%
Pro 2 (v5.1, v6.1)	Backlund [32]	TEE	22	Obese children, 8-11y	***B*** $TEE_{5.1}$:-<1%, $TEE_{6.1}$:-18%
Pro 3 (v6.1)	Brazeau [33]	TEE	20	Adults, 18-45y	***B*** TEE: 3%
Pro 3 (v6.1)	Koehler [34]	TEE	14	Male endurance athletes	***B*** TEE:-2%
Pro 3 (v6.0)	Rousset [27]	TEE	41	Adults, middle-aged	***M*** TEE:9%
Mini (v7)	Calabro [35]	TEE, PAEE	29	Adults, 60-78y	***M*** TEE:8 %, PAEE:28%
Pro 3, Mini (v5.0)	Calabro [36]	TEE, PAEE	28	Children, 10-16y	***M*** TEE_{P3}:11%, TEE_M:12%, $PAEE_{P3}$; 30%, $PAEE_M$:29%
Pro 2 (v5.1, v6.1)	Farooqi [9]	TEE, PAEE	19	COPD females, 59-80y	***B*** $TEE_{5.1}$:<1%, $TEE_{6.1}$:-9%, $PAEE_{5.1}$:-12%, $PAEE_{6.1}$:-35%
Pro 3, Mini (v6.1)	Johannsen [8]	TEE, PAEE	30	Adults, 24-60y	***B*** TEE_{P3}:-4%, TEE_M:-1%, $PAEE_{P3}$:-22%, $PAEE_M$:-21%
(v5.1, v6.1)	Mackey [37]	TEE, PAEE	19	Adults, 70-79	***B*** $TEE_{5.1}$:1%, $TEE_{6.1}$:-1%, $PAEE_{5.1}$:-19%, $PAEE_{6.1}$:-27%
Pro 2 (v5.1, v6.1)	Slinde [38]	TEE, PAEE	62	Lactating females, 24-41y	***B*** $TEE_{5.1}$:3%, $TEE_{6.1}$:-8%, $PAEE_{5.1}$:-1%, $PAEE_{6.1}$:-59%
(v7)	Tanhoffer [39]	TEE, PAEE	14	Spinal cord injury, 23-65y	***B*** TEE:16%, PAEE:- 3%
Pro 3 (v5.12)	Colbert [26]	PAEE	56	Adults, 65+ y	***M*** PAEE:27%

*not complete for all devices as information not specified in original article, ***B***=bias, ***M***=mean absolute percent error (MAPE), E=Ekelund, P=Puyau, C=Crouter, F=Freedson, C+LPF=Crouter plus low-pass filter, N=Nichols, H1=Hendelman 1, H2=Hendelman 1, SW=Swartz, L=Leenders, Y1=Yngve 1, Y2=Yngve 1, HRS= individual step test calibration of heart rate, HRG= group heart rate calibration, TEE=total energy expenditure, PAEE=physical activity energy expenditure, P3=Sensewear Pro 3, M=Sensewear Mini

Actigraph™

The Actigraph™ is one of the most widely used and investigated physical activity monitors. However, this is the first study to our knowledge to examine the accuracy of the triaxial Actigraph™ GT3x in true free-living. The Actigraph™ possessed a reasonably small bias when estimating TEE. This is consistent with a study of 22 adults demonstrating comparability between the preceding GT1M model and DLW, which found the Actigraph™ had a bias between -2% and 6% [24]. In contrast to the reasonable estimates of TEE, a considerably larger error was observed in estimates of PAEE. Previous studies comparing PAEE from the GT1M to DLW reported a MAPE of 24 in adults aged over 65 [26] and bias ranging from 23% to -6% in African adults [25]. The smaller magnitude of error associated with the measurement of TEE compared to PAEE by the GT3x is consistent with the trend seen in the earlier GT1M model [24-26].

Equations used by the Actigraph™ GT3x differ to those adopted for earlier uniaxial models such as the GT1M. The GT3x VM3 cut-points used in this study were developed in a group of 50 healthy young adults in a laboratory setting [16]. They were obtained using a protocol of treadmill running and walking, demonstrating good relative validity with indirect calorimetry [40]. The developers of these cut-points acknowledge that they may not be generalisable to other age groups, especially older adults [16]. The also noted that these equations may not detect light intensity or sedentary behaviour [16]. Our findings of underestimation of energy expenditure confirm that the VM3 cut-points based on treadmill activity may not directly apply to energy expenditure estimation in free-living. Many activities of daily living involve only minimal acceleration at the waist, limiting the activities detected by the device. Despite these limitations, our findings showed the Actigraph™ GT3x provided a reasonable estimate of energy expenditure in older women. Further improvement of the algorithms, particularly with respect to PAEE, is necessary for improving the accuracy of the Actigraph™.

SenseWear®

Consistent with previous research, the SenseWear® underestimated TEE and PAEE. A study of older adults aged 60-78 years, using the same version of software as the present study, observed a similar-sized MAPE (8) for TEE compared to DLW [35]. Studies examining TEE captured by the SenseWear® in younger adults [8, 33] and athletes [34] report biases between -4% and 3%, smaller than those seen in older populations. The accuracy of TEE captured by the SenseWear® varies considerably across clinical populations, with bias ranging from -18% in obese children [32] to 16% in spinal cord injury [39]. Given the original SenseWear® algorithms were developed

in predominantly healthy younger adults, the extrapolations adopted to provide estimates for other populations may explain the varying levels of accuracy across cohorts [41]. Additional work on the SenseWear® is required to develop specific algorithms to accurately estimate total energy expenditure in older adults.

Similar to the Actigraph™, the SenseWear® was less accurate estimating PAEE than TEE. This is consistent with a recent study of older adults which reported a much larger MAPE for PAEE compared to TEE (28 vs. 8, respectively) [35]. Similarly, large underestimations of PAEE are also evident in comparisons of older models of SenseWear® with DLW. Investigations in older adults have reported bias of -27% [37] and a MAPE of 27% [26]. Comparable patterns of findings are also evident in other populations including children [36] and older women with COPD [9]. The consistent underestimation of PAEE by the SenseWear® suggests that the default threshold used for the classification of PAEE may be too high, and possibly fails to capture physical activity carried out at low intensity.

The SenseWear® estimates of energy expenditure were most accurate using software Version 7.0 (MAPEs: TEE_{SW7}=6.2 vs. TEE_{SW8}=8.4 and $TEE_{SW8.1}$=9.5). Owing to the proprietary nature of the algorithms used to transform sensor data into energy expenditure, the changes implemented between versions of software are not transparent and it is not possible to identify specific features of the equations. Whilst previous research has not compared the versions used in this study, similar observations have been made with earlier versions. In one study of obese children [32] using software Versions 5.1 and 6.1, TEE was more accurately captured in the earlier version of the software (v5.1: -<1% vs. v6.1:-18%). Similarly, a study of older women with COPD also found large differences in estimates of PAEE (v5.1: -12% vs. v6.1:-35%) [9]. Findings suggest that updates to software may not necessarily improve the validity of assessing energy expenditure and could actually reduce accuracy. Researchers should consider this when selecting which software to use and not assume that the most recent version is the most appropriate for the outcome or population of interest. Furthermore, the variation between versions also makes comparison across studies using different monitors and software difficult.

ActiHeart®

The ActiHeart® has not been examined as extensively as other available physical activity monitors. There have been no studies to date that compare energy expenditure from the ActiHeart® to DLW in healthy older adults. However, our finding that the ActiHeart® underestimates TEE is supported by a study of 19 older women with COPD which reported a similar bias (-9%) [9]. These findings are in contrast to a study of physically active young men which reported the ActiHeart® overestimated TEE by 8% [11]. Comparisons of PAEE obtained by the ActiHeart® to DLW have presented similarly variable findings, ranging from an underestimation of 35% in

women with COPD [9] to an overestimation of 15% in young females [30]. Studies of males under 55 y [11, 28] and African adults [29] have compared more favourably with underestimations of PAEE of 8-10%. These healthy adult populations [11, 28, 29] possess higher levels of daily energy expenditure than women with COPD [9] and those in this study, whose movement occurs primarily at the lower end of the activity spectrum. These data suggest that lower levels of activity observed in older and clinical populations may impact the ability of the ActiHeart® to accurately estimate PAEE. This is further supported by an investigation comparing the ActiHeart® to indirect calorimetry where it was seen that the ActiHeart® was better able to predict energy expenditure during physical activity than sedentary behaviour [10]. A study in children similarly found no correlation between the ActiHeart® and sedentary behaviour, observing it only becomes accurate with activities above 2.5 METs [42]. As with the Actigraph™, this may be the result of the equations being developed with treadmill walking and running in controlled laboratory conditions [10], limiting the applicability to other activities of free-living.

The manufacturer currently recommends conducting a step test during setup of the ActiHeart® for individual calibration and subsequently increased accuracy. However, we were unaware of this feature at the time of data collection so this approach was not utilised. Previous studies that have adopted individual calibration have reported varying degrees of validity. One study of 17 young males which compared individual calibration to standard group calibration, reported that individual calibration was more accurate for TEE but not PAEE [11]. Findings from a study of African adults provided conflicting results, demonstrating that individual calibration resulted in a lower error for PAEE and was, therefore, beneficial [29]. Whether individual calibration of the ActiHeart® in this study would have provided a more accurate estimation of energy expenditure than group modelling is not clear.

Comparison of SenseWear®, Actigraph™ and ActiHeart®

Whilst the monitors likely overestimated or underestimated energy expenditure during various activities, all three monitors provided good overall approximations of TEE. This is particularly impressive given the difficulties in capturing physical activity in free-living and that these monitors are primarily validated in laboratory conditions. Although DLW is a highly acceptable reference method for measuring energy expenditure in free-living, there are potential sources of error which must be considered when interpreting validation results. Given the measurement error of DLW is 5-10% [5], the underestimation of TEE by 6% means it is plausible that all three monitors are able to reasonably predict TEE at the group level. However, the wide limits of agreement and absence of proportional systematic bias indicate a considerable random error and large variability for individual estimations. The use of any of

these physical activity monitors may be suitable for group level estimations of TEE, however, may lead to misclassification of physical activity levels in individuals.

The performance of the monitors for estimating PAEE was poor in comparison to TEE. All three monitors underestimated PAEE, likely contributing to the underestimation of TEE. The equations used to estimate energy expenditure in these monitors were developed predominantly using young active adults who were required to run or walk on a treadmill [10, 16, 43]. As such, the underestimation of PAEE may suggest a limited ability to discriminate light from sedentary activity, which is more difficult to detect than activities of higher intensity. Given a large amount of time is spent sedentary and in light activity over a day, the inability to distinguish would add considerable error over time [44]. As RMR is calculated predominantly from participant characteristics and alone can account for 60-80% of TEE [45], it is not surprising that there is a comparatively low error for measuring TEE compared to PAEE.

Each of the three monitors holds a different position in the marketplace, particularly with respect to cost. The Actigraph™ is the cheapest, with the SenseWear® and ActiHeart® more than three times its price. Whilst the presence of multiple physiological sensors in the SenseWear® and ActiHeart® should theoretically improve the precision of energy expenditure estimates, they did not show any improvement in accuracy compared to the single-sensor Actigraph™. Although the ActiHeart® performed similarly to the Actigraph™, the number of technical and compliance issues that arose with the ActiHeart® should be considered. In addition to energy expenditure, these monitors are also able to capture other measures of physical activity. As such, these devices may be beneficial for assessment of other outcomes such as steps taken, sedentary behaviour and intensity of physical activity, although these were not evaluated in this study. Given the varying price points and findings of this study, the Actigraph™ may be the preferred tool of choice for researchers when examining free-living energy expenditure in older women.

The use of doubly-labelled water as the reference method allowed for the validity of the Actigraph™, SenseWear® and ActiHeart® to be assessed concurrently. It is important however that the PAEE data be interpreted with caution as RMR was not measured but instead estimated using Schofield equations [15]. As the Actigraph™ and SenseWear® were removed in the evening, assumptions that the participant was resting during this time may have led to underestimations of energy expenditure. As is the case in the constantly evolving field of objective physical activity monitoring, the conclusions presented are applicable only to the device models and software versions used in this study.

At the group level, the Actigraph™, SenseWear® and ActiHeart® demonstrated acceptable levels of agreement with a reference measure of TEE in older women in free-living conditions. All monitors had a better agreement for estimates of TEE compared with PAEE. Further research is required to advance the ability of these monitors to accurately capture PAEE. Based on the accuracy and cost of the three monitors, the Actigraph™ may be the preferred tool for estimating energy expenditure in this population. When considering the use of a physical activity monitor, researchers and clinicians should not only consider the desired outcome when choosing a device to collect data but also the data processing method adopted.

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Chapter 6:

Concluding remarks

Overview of main findings

This thesis investigated important issues of physical activity and exercise in women with metastatic breast cancer with a view to addressing important gaps in the literature. Chapter 1 provided a background to breast cancer and explored available treatments for metastatic disease and associated side effects. Previous research into the role of physical activity across the breast cancer continuum was presented, which demonstrated that the benefits for women with early stage cancer are well understood [1-17]. In contrast, there is little information on its role for women living with metastatic disease. Six randomised controlled trials [18-23] were identified across all metastatic populations, of which five were deemed high quality [18-22]. Seven additional studies were located, describing uncontrolled trials or case reports. Resistance training interventions were conducted in three of the high-quality studies, with promising results observed for improving physical function and decreasing fatigue [18, 19, 22]. Gaps in the understanding of physical activity for this population were identified, leading to the program of research reported herein. The broad aims of this thesis were to determine the physical capabilities and interests for physical activity of women living with metastatic breast cancer and to use this knowledge to develop and pilot an appropriate physical activity intervention. In addition, it was identified that the accuracy of body-worn monitors for measuring physical activity in this older age group was largely unknown, which led to the design of the final study in which the accuracy of three physical activity monitors was determined.

To design a physical activity intervention for women with metastatic breast cancer, an understanding of the physical capabilities of the population is first required. The presence of symptoms and subsequent decline in quality of life has been described in women with metastatic disease [24-26], however, the physical status of the population is unclear. The findings from Chapter 2 described physical activity levels and fitness of women with metastatic breast cancer, along with their physical and psychosocial well-being. To further understand the impact of metastatic disease, women were compared to an age-matched cohort of women without metastatic cancer. Not surprisingly, women with metastatic disease possessed significantly lower levels of aerobic fitness and strength when compared to an age-matched healthy cohort. The women with metastatic disease were also more sedentary, completing around half as much physical activity as their healthy counterparts. Whilst overall the cancer group was deconditioned, some women with metastatic disease demonstrated a higher level of fitness and activity than their healthy peers. Unexpectedly we found that approximately 30% of women with metastatic breast cancer possessed aerobic fitness levels above average for their age. This highlighted the heterogeneity and wide range of physical abilities of the metastatic breast cancer cohort.

Another finding drawn from Chapter 2 was that women with metastatic breast cancer reported lower functional status than healthy women across all domains: global, physical, role, emotional and social. In addition, they demonstrated higher symptom burden, experiencing greater levels of pain, nausea, dyspnoea, constipation, diarrhoea and appetite loss than the age-matched healthy cohort. Although as a group the women with metastatic disease reported poor quality of life, many presented with minimal symptoms related to their cancer. Overall this cohort reported higher levels of functioning and lower symptom burden than other studies of women living with metastatic disease, indicating this cohort may be functioning higher than the average woman living metastatic breast cancer.

With some insights gained into the physical status of the metastatic population, an intervention could be developed in which women were capable of participating. However, given that adherence to physical activity may be particularly challenging for cancer patients [27], consideration of activity interests and preferences is also important for maximising acceptance and efficacy in this unique population. Interviews revealed that the majority of women living with metastatic breast cancer were interested in a physical activity program (Chapter 3). Women demonstrated a strong preference for home-based activity, with walking being their preferred exercise modality. Women also favoured a range of other activities including swimming and resistance training. The strong interest, coupled with demonstrated physical capacity, demonstrated feasibility for a physical activity program for women living with metastatic breast disease.

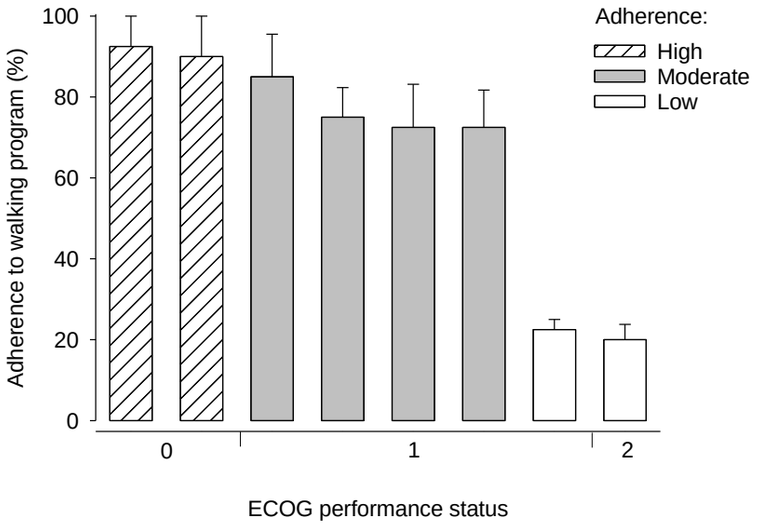
With most studies excluding women with metastatic breast cancer, little data exist on the safety and feasibility of physical activity interventions in this population. As the first step in addressing this gap, an intervention was developed with knowledge gained from Chapters 2 and 3. An 8-week home-based multi-mode program was delivered within a randomised controlled intervention (Chapter 4). An Exercise Physiologist attended the participant's home twice a week to supervise resistance training sessions. Women were also asked to walk on days of the week they were not seeing their exercise trainer, with the aim of increasing the number of steps taken each week by at least 10%. An important finding of this study was that no adverse events related to the intervention were noted.

The feasibility of supervised resistance training was demonstrated through high recruitment rates and 100% adherence and compliance to training sessions. The adherence and compliance rates for this component were higher than previous research, which may have been influenced by the external motivator of an Exercise Physiologist turning up at the front door for each session, along

with the consideration of physical activity preferences in designing the intervention for this unique population. Overall, supervised resistance training was shown to be safe and acceptable for women with metastatic breast cancer.

Adherence to the walking component was poor, with only two women completing the prescribed number of training sessions. To allow for further analysis of adherence data, women were divided into three groups based on adherence rate to the walking program; low (0-49%), moderate (40-89) and high (≥90%). When grouped by ECOG performance status, this revealed that the most adherent women were high functioning and active with no limitations due to their disease (ECOG 0; Figure 1) [28]. All of the women who achieved a moderate level of adherence were classified as ECOG 1, ambulatory and able to carry out light activity. The poorest level of adherence was seen in the lowest functioning participant with an ECOG of 2,i.e. ambulatory but unable to carry out any work activities. As some women exhibited physical impairments limiting activity, it is possible that these women were not physically capable of achieving the prescribed dose of the walking program.

Figure 1. Adherence to the walking program grouped by ECOG performance status. Values are mean and standard error.



The majority of women were compliant with walking at a moderate intensity, however, no participants successfully increased their steps by 10% each week. Despite the poor compliance to walking volume, some women did increase steps above baseline levels (Figure 2). If women had increased steps by 10% per week as prescribed, the number of steps taken in Week 1 should have doubled by Week 8. Four women increased weekly steps throughout the intervention, with three women more than doubling their Week 1 step counts in Week 8. Adherence to the walking program was higher in those who were more active but did not predict which

women increased weekly step counts. Despite overall poor adherence to the walking program, the majority of women improved their walking capacity throughout the intervention (Figure 3). The increase in six-minute walk test distance ranged from 6-9% in the women with low adherence, which did not differ from the mean change in those with higher adherence. Although adherence to the walking component of the physical activity intervention was poor, most women still obtained some benefit to their physical function.

*Figure 2.Steps taken per week by each participant during Weeks 1 and 8. * represents steps more than doubled during the intervention*

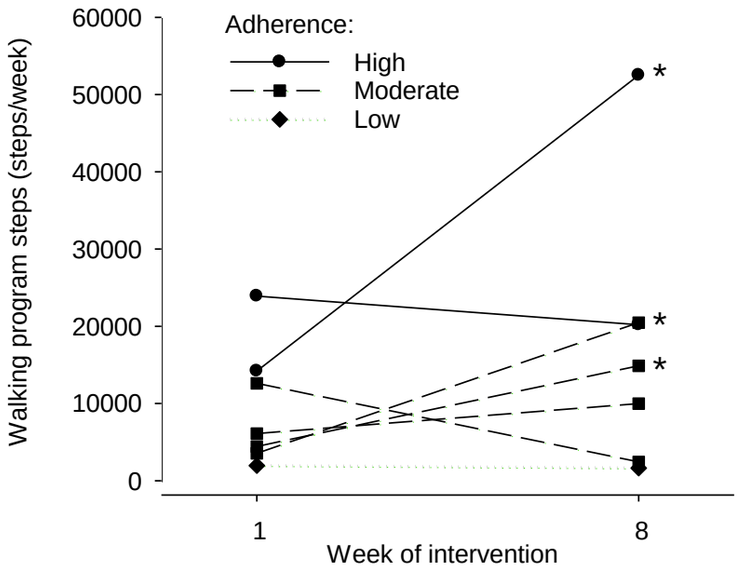
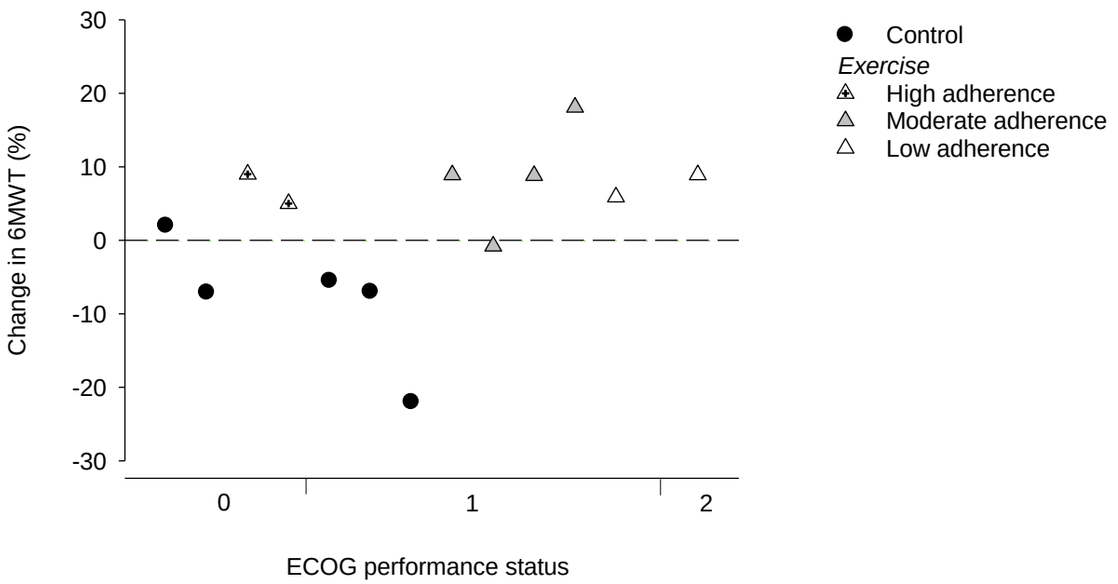


Figure 3.Change in six-minute walk test from Baseline to Week 8 for each participant. There is missing data for one control.



All women who completed exercise training had previously indicated interest in physical activity, (Chapter 3) prior to enrolling in the randomised controlled trial. Data were examined in the context of this information to identify any indicators of poor adherence. As part of the interview, a snapshot of self-efficacy was obtained by asking women to rate to what extent they were confident in their alibility to increase physical activity on a scale from 0 to 10, with 10 being extremely confident. Responses to this question appear related to adherence to the unsupervised walking program (Figure 4). Women with high or moderate adherence were generally confident about their ability to increase physical activity. The two women with low adherence reported low confidence, with scores of 3/10 and 5/10. Adherence was further examined with respect to individual preferences for physical activity (Table 1). Both low adherent participants expressed a preference for a home-based program with walking which comprised part of the intervention that was delivered. Although only half of the women indicated resistance training as a preference, high adherence and compliance to this component was observed. In summary, women with low levels of self-efficacy for undertaking physical activity were less likely to adhere to the unsupervised walking program, despite identifying this mode as a preference for activity.

Figure 4. Confidence in ability to increase physical activity vs. adherence to the unsupervised walking program. There is missing data for one participant.

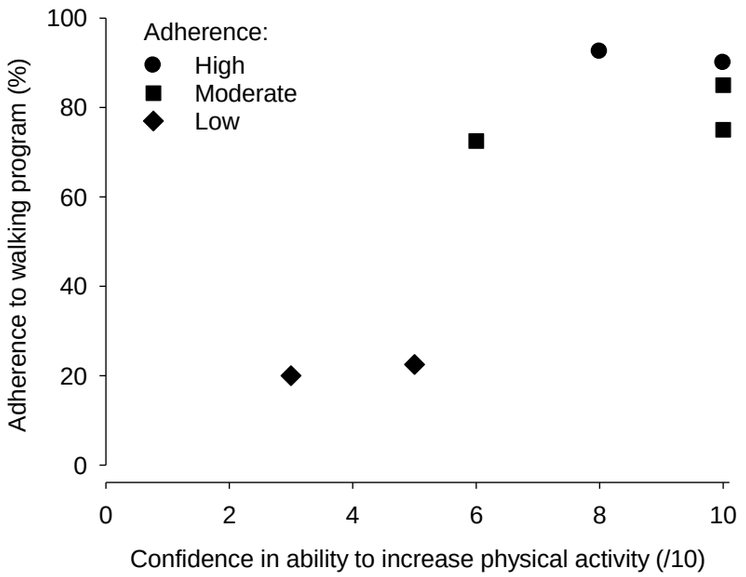


Table 1. Physical activity preferences in low, moderate and high adherers to the walking program. Values are n.

	Adherence^		
	Low (n=2)	Moderate (n=4)	High (n=2)
If you were to participate in a physical activity program, in what environment/s would you prefer to perform exercise?			
At home	2	2	1
If you were to participate in a physical activity program, what type of exercise would you like to perform?*			
Walking	2	1	2
Resistance training	1	1	2

^ Low=0-49%, Moderate=50-89%, High=≥90% *Participants may have selected multiple responses

In addition to being generally well-tolerated, the intervention also provided promise for improving physical function and reducing symptoms. Although the sample size was not powered for probability testing, positive changes were observed for aerobic fitness and muscle strength. Improvements were also observed in patient-reported outcomes, including social and role function, and symptoms of fatigue and pain. These preliminary findings provide a platform from which larger trials can be developed to explore the optimal mode, frequency, intensity and duration of exercise for women living with metastatic breast cancer.

The quantification of physical activity levels was central in describing habitual physical activity (Chapter 2) and changes to physical activity as a result of a lifestyle intervention (Chapter 4). Physical activity monitors are often favoured for this kind of research due to their affordability and practicality. However, many of these devices were have been validated in a laboratory under controlled conditions, with limited data to support their use in a free-living environment for women of a similar age as those with metastatic breast cancer. The accuracy of Actigraph™, SenseWear® and ActiHeart® physical activity devices in older women in free-living was explored in Chapter 5. This was achieved by comparing energy expenditure estimated by each device to the reference method of doubly labelled water. All three devices presented acceptable estimates of total energy expenditure but demonstrated a larger error when capturing physical activity energy expenditure. Of the three monitors, the Actigraph™ was recognised as the preferred tool for measuring energy expenditure in women over 50 years, owing to its comparatively superior performance and reduced cost.

Clinical implications

As research on the role of physical activity for women with breast cancer has historically focused on early stage disease, it has created gaps in the scientific knowledge about its role for those living with metastatic spread. Exclusion of these women from interventions is due to fear of skeletal-related events and the presence of symptoms such as fatigue and cachexia [29, 30]. Clinicians are reluctant to encourage physical activity for the same reasons [30], despite recommendations from the American College of Sports Medicine that individuals with metastatic disease should reduce sedentary behaviours and avoid an inactive lifestyle [31]. The challenge for researchers is therefore not only to address gaps in the evidence but also to change clinical thinking as supporting evidence continues to emerge.

The most valuable finding of this program of research was that a partially supervised home-based physical activity intervention is safe and feasible for women living with metastatic breast cancer (Chapter 4). Preliminary evidence also suggested physical activity may provide benefit by improving function and quality of life, although further research is still required. Notwithstanding the uncertain role of physical activity in metastatic breast cancer, its role in managing and preventing other comorbidities alone warrants encouragement by clinicians for their patients. Advice on physical activity is likely to be well received given that most women with metastatic breast cancer are interested in being physically active (Chapter 3). Disinterest in physical activity was not related to being unwell, so clinicians should not make assumptions about a patients' willingness to participate based on health status. Oncologists, GPs, nurses and other multi-disciplinary team members can encourage participation in lifestyle physical activities like walking, with confidence that the safety risk is low. Participation in structured activity, such as resistance training, should also be advocated by clinicians and women referred to an exercise professional for the development of an appropriate program.

Women with metastatic breast cancer represent a heterogeneous population, with many receiving well-tolerated treatments whilst others endure more toxic regimens due to aggressive disease. Recognition of the variability with respect to physical capacity and symptoms is important for all clinicians and exercise specialists in particular. Whilst some of the population were active and able to maintain their work and households roles, those at the lower end of the spectrum were sedentary and experienced high symptom burden (Chapter 2). Not only does physical ability vary across this continuum but the needs of the individual will also likely differ. A one-size fits all approach is therefore not appropriate for research and the implementation of patient-centred care is necessary for this unique population.

Whilst an exercise prescription developed outside of a clinical trial would ideally reflect more individual consideration, the delivery of a patient-centred approach in Chapter 4 was relatively successful. The strong preference women demonstrated for a home-based physical activity program guided the design of the intervention. During informal discussions, many women indicated this was a preference as they were already overwhelmed with medical appointments that consumed significant amounts of not only their time but also of caregivers. The majority of women nominated walking as the preferred type of activity. Although adherence to the walking program was lower than anticipated, several women did achieve substantial progress of walking their volumes throughout the intervention. In comparison, the interest in resistance training was somewhat lower but excellent adherence and compliance to the supervised component was observed. Thus, identification of physical activity preferences alone does not necessarily translate to high levels of adherence or compliance, and other programming considerations such as supervision may have an impact. Whilst the program was shown to be safe for this population, it should be noted that high-impact activities were intentionally avoided to minimise the risk of skeletal-related events [32] and are not recommended for inclusion. In conclusion, these findings support the implementation of a patient-centred approach by exercise specialists and provide an example of a safe exercise prescription.

Adherence levels to the unsupervised walking program appeared to be influenced by physical performance status and an individual's confidence in their ability to engage in physical activity. These factors did not appear to play a role in supervised resistance training as all women achieved excellent adherence and compliance to this component. With respect to the walking component, women with unrestricted function and a high level of self-efficacy demonstrated high adherence, suggesting that this subgroup of women does not require additional strategies to support participation in the unsupervised walking program. However, some women with lower levels of function and low self-efficacy had poor adherence to walking. To be adherent to the walking program, women needed to walk five days a week in addition to undertaking two resistance training sessions. For women with impaired function, the prescribed dose was likely too high and they were not physically capable of achieving it. A reduced frequency of walking may be more appropriate for this subset of women, commencing with two sessions per week with gradual progression over the duration of the intervention.

Physical activity self-efficacy describes an individual's expectation that they will be able to achieve the desired outcome. In Social Cognitive Theory, self-efficacy has been identified as a predictor of physical activity adherence, with high self-efficacy motivating behaviour [33]. Thus, it is not surprising that woman with low confidence in their ability to increase physical activity had difficulty adhering to the unsupervised walking program. However, adherence to resistance training in these women was excellent, suggesting

that supervision may assist in overcoming poor self-belief. To enhance self-efficacy, there are four sources of efficacy information to consider [34]. The most potent of these forms is 'mastery experiences' that reflect prior accomplishment and reinforce confidence in the ability to succeed again [34]. Ensuring success with small obtainable goals and avoiding the risk of failure by doing too much too soon is critical. In the context of the walking program, commencing with a reduced and achievable number of sessions would likely boost self-efficacy, and subsequently adherence. Additional strategies to build self-efficacy, such as education and goal setting, may further improve the ability of women to successfully participate in a physical activity program.

Although inclusion of exercise preferences likely had a large influence on adherence rates, the contribution of an Exercise Physiologist attending the participant's home should not be underestimated. On days when women were feeling unwell or lacked motivation, they openly confessed they would not have completed the exercise of their own accord if the trainer had not arrived to motivate them. This is an important consideration for exercise specialists as it is not financially viable for most women to have supervision at every training session. Whilst further research is needed to investigate the success of tapering off supervision over time, strategies must be implemented for maintaining adherence. As social support plays a significant role in enhancing exercise adherence [35], one approach could be to partner each woman with an "exercise buddy". The identification of a friend or family member to exercise alongside may be seen as a motivating factor and will also assist in building self-efficacy. This peer support could be further supported with commercial wearable technologies, with devices like the Fitbit® (Fitbit Inc., San Francisco, CA) providing a fun and interactive way of monitoring physical activity. Such devices enable support through social media platforms in addition to tracking progress towards daily step goals, motivating individuals to keep moving. Innovative approaches that boost engagement are likely the key to maximising adherence during unsupervised training sessions.

In addition to providing motivation for individuals to be active as previously discussed, wearable physical activity monitors also allow researchers to capture physical activity levels for the purposes of surveillance and describing the efficacy of interventions. The ability of monitors to accurately estimate physical activity and assess energy expenditure is essential. Even though monitors like the Fitbit® are attractive to the mass market, limited evidence exists about their validity [36]. For this reason, researchers still generally use physical activity monitors developed primarily for clinical research. If working with a population of older women, one of the most widely used devices, the Actigraph™, is recommended for use if the outcome of interest is energy expenditure. The high cost of the SenseWear® and ActiHeart® is not justified as neither was more accurate than the relatively inexpensive Actigraph™. If researchers

already have access to SenseWear® or ActiHeart® monitors, their use is acceptable for determining estimates of total energy expenditure. However, if physical activity energy expenditure is the desired outcome, adoption of the ActiHeart® is satisfactory whilst the SenseWear® is not recommended. It should be noted that all of these devices also provide information on other physical activity indicators not evaluated in this study. These monitors may have a role in capturing data such as steps taken, time in moderate-vigorous intensity activity, and sedentary behaviour.

The choice of physical activity monitor should be determined by the outcome of interest as well as the population being investigated. The accuracy of the Actigraph™, SenseWear® and ActiHeart® is highest in healthy young adults, the population typically used for development of devices and their associated algorithms for estimating physical activity [37]. A relatively small number of validation studies have been performed in other age groups and across clinical populations. Movement patterns of these groups can vary considerably, so without validation in the population of interest, the accuracy of monitors should not be assumed. Findings from specific validation studies can potentially be extrapolated to other groups if metabolic profiles and movement patterns are known to be similar.

Future directions

The findings of this thesis extend the knowledge base relating to physical activity for individuals with metastatic cancer. Several questions have been addressed, however many aspects on the role of physical activity warrant further investigation. The safety and feasibility of a partially supervised home-based physical activity intervention has been demonstrated, but its effectiveness must now be established. Large randomised controlled trials with sufficient power would allow efficacy to be examined.

As physiological adaptations generally start to occur within the first two months of exercise, an 8-week intervention should be sufficient to induce improvement in physical capacity. However, as adaptations continue beyond this point, a longer program may result in more substantial benefits. Although adherence to the resistance training component of the intervention in this thesis was excellent, supervision at every training session was likely a contributing factor. This design was important to ensure that the intervention was safe but required a significant amount of resources to conduct, reducing the feasibility of delivering a longer intervention and limiting the potential for translation into routine care. Given the absence of adverse events, it would appear feasible to safely scale back supervision over the duration of the program. A six-month program consisting of varying levels of supervision

would allow for longer term efficacy to be assessed with fewer resources than the current intervention. Such a model could entail supervision initially at each session, dropping to once a week after the first month, fortnightly during the third month and unsupervised sessions during the final three months. With reduced supervision, approaches such as the use of telehealth could be implemented to motivate participation and assist with progression. Development of a website or mobile phone application containing demonstrations of each exercise and short educational videos building skills related to exercise self-efficacy would further support and encourage women. Well-designed strategies encouraging self-management of physical activity may allow programs of extended duration to run without placing an increased strain on resources.

Follow-up periods subsequent to physical activity interventions in metastatic populations are generally short. In this thesis, many of the benefits obtained from the intervention were maintained two months following the end of the program. However, it is unknown whether benefits would be sustained longer term. Assessments scheduled at 3, 6, 12 and 24 months post-intervention may provide insight into sustained benefits whilst considering participant burden. It should be acknowledged that recruitment into longer studies may prove difficult given the age and high disease load of the population. Eligibility criteria for enrollment may need to reflect survival for the duration of the intervention rather than completion of the study, with the recognition that some participants may be lost to follow-up as a result of death. Extended follow-up periods will provide a better understanding of the long-term benefits of physical activity.

Further research is also needed to determine the optimal exercise mode for women living with metastatic disease. The physical activity intervention in Chapter 4 demonstrated that a combined resistance and walking program may be beneficial, although it is currently unclear which mode of physical activity is most efficacious. A pragmatic research design comparing resistance training, aerobic training, and resistance and aerobic training in combination, should be considered. This would determine which type of physical activity is best overall, as well as for addressing particular symptoms or side-effects. It is also unclear what exercise intensity, frequency and duration yield the largest benefits. However, it is likely that the optimal prescription will vary across the population, largely determined by an individual's level of physical function.

The linking of physical activity interests to findings from the intervention further highlighted the heterogeneity of the cohort and identified sub-groups of women. The ability of women to adhere to the prescribed physical activity program appeared largely related to their physical performance status. For future studies, it would appear beneficial to stratify women with metastatic breast cancer

into more homogenous groups. The use of a performance scale such as ECOG [28] to achieve this would result in the ability to deliver a more targeted intervention to each sub-group. Whilst women with ECOG 0-2 were included in the intervention described in Chapter 4, this stratification may accommodate participation by women with even lower levels of function. Using this approach, women would be streamed into one of several interventions following baseline assessment. Women with an ECOG of 0 could commence with a program similar to that delivered in this thesis, with reduced resistance training supervision as the program progresses. However, women with an ECOG of 2 for example, would require adjustment to the prescribed dose of the walking program and would benefit from additional strategies to build self-efficacy. These low functioning women would also require closer monitoring of program adherence and compliance in comparison to those with a higher performance status.

Although grouping of women into smaller homogenous subsets may lead to improved efficacy, appropriate tools for measuring the effect of the intervention are required. With the large variability in function across the population, traditional outcome measures may not be appropriate due to the potential of fixed-items being irrelevant to an individual's needs. There are a number of patient-specific instruments measuring physical function, including the popular Patient-Specific Function Scale (PSFS) [38]. The PSFS allows patients to identify impairments that are most relevant to them, with outcomes focusing on the evaluation of these impairments over time.

Another avenue warranting exploration is the health economics of physical activity as a therapy for improving well-being in metastatic breast cancer. The disease creates a significant economic and societal burden through direct costs of medical treatment and indirect costs such as loss of income and caregiver burden [39]. The debilitating effects of metastatic disease can also exacerbate existing health problems or promote further comorbidities, placing an additional burden on individuals and the health care system. Observations of quality of life and survival, along with information such as productivity, hospital admissions and drug prescription may provide a snapshot of the magnitude of costs of living with metastatic breast cancer. If exercise is shown to be a cost-effective strategy for managing metastatic disease, this may have a major role in shifting clinical practice.

The accurate measurement of energy expenditure pre- and post-intervention is important for evaluating a physical activity program. Whilst the Actigraph™ is recommended for use in healthy women aged over 50 years, its accuracy in similarly aged women living with metastatic breast cancer is unclear. It is possible that the presence of a tumour or subsequent treatment may alter an individual's metabolic profile or movement pattern, creating a relationship between activity and energy expenditure unknown to the device. Of the physical activity monitors designed for clinical research, future studies are required to determine which is most appropriate for

use in this population. In addition, consumer-wearable monitors like the Fitbit® should be included in further validation studies to determine their suitability as a research tool. Determination of the accuracy of physical activity monitors in women with metastatic breast cancer will allow for selection of the most suitable device for evaluating the efficacy of a physical activity intervention.

Conclusion

The limited understanding of the role of physical activity in metastatic disease is attributable to the exclusion of this population from clinical research. This omission is traditionally due to a perceived increase in safety risk and concern over symptoms. Findings in this thesis confirm that women living with metastatic breast cancer are interested and capable of being physically active. In addition, the intervention study offers further evidence to the small body of knowledge that partially supervised physical activity is safe for this population and may be beneficial for improving well-being. It is, therefore, time for more focus to be placed on the role of physical activity for metastatic populations. With respect to the accurate assessment of physical activity, this thesis recommends the use of the Actigraph™ in older women.

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Appendix:

Ethics approval for all studies

Ethics approval for Chapters 2 and 3

SYDNEY SOUTH WEST
AREA HEALTH SERVICE
NSW HEALTH

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH DEVELOPMENT OFFICE
LEVEL 3, BUILDING 92
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050

TELEPHONE: (02) 9515 6766
FACSIMILE: (02) 9515 7176
EMAIL: lesley.townsend@email.cs.nsw.gov.au
REFERENCE: X10-0308 & HREC/10/RPAH/541

13 December 2010

A/Professor S Kilbreath
Faculty of Health Sciences
University of Sydney
PO Box 170
LIDCOMBE NSW 1825

Dear Professor Kilbreath,

Re: Protocol No X10-0308 & HREC/10/RPAH/541 - "Physical fitness and physical activity in women with metastatic breast cancer living in the community"

The Executive of the Ethics Review Committee, at its meeting of 25 November 2010, considered your correspondence of 16 November 2010. In accordance with the decision made by the Ethics Review Committee, at its meeting of 10 November 2010, ethical approval is granted.

The proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

This approval includes the following:

- Recruitment Advertisement (Master Version 1, 16 November 2010)
- Participant Information Statement (Master Version 2, 16 October 2010)
- Participant Consent Form (Master Version 1, 13 October 2010)
- Screening Questionnaires (incl. PAR-Q & YOU and PARmed-X) (Master Version 1, 16 November 2010)

- Assessment Booklet (incl. Patient Details and Contact, Godin Leisure-Time Exercise Questionnaire, FACT – Fatigue Questionnaire, EORTC QLD-C30 (Version 3), UAB Study of Aging Life-Space Assessment, Baseline Physical Measures, 1 week repeat questionnaires, and Exit Interview) (Master Version 1, 16 November 2010)

- Physical Activity Monitors Instructions (Master Version 1, 16 November 2010)

- Safety Protocol for Home Visits (undated)

You are asked to note the following:

- **This letter constitutes ethical approval only. You must NOT commence this research project at ANY site until you have submitted a Site Specific Assessment Form to the Research Governance Officer and received separate authorisation from the Chief Executive or delegate of that site.**

- This approval is valid for four years, and the Committee requires that you furnish it with annual reports on the study's progress beginning in December 2011.

- This human research ethics committee (HREC) has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review and is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

- You must immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.

- You must notify the HREC of proposed changes to the research protocol or conduct of the research in the specified format.

- You must notify the HREC and other participating sites, giving reasons, if the project is discontinued at a site before the expected date of completion.

- Where appropriate, the Committee recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purposes of conducting this study.

Should you have any queries about the Committee's consideration of your project, please contact me. The Committee's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Sydney South West Area Health Service website.

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The Ethics Review Committee wishes you every success in your research.

Yours sincerely,

Lesley Townsend
Executive Officer
Ethics Review Committee (RPAH Zone)

HERC\EXCOR\10-12

Ethics approval for Chapter 4

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH DEVELOPMENT OFFICE
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050

TELEPHONE: (02) 9515 6766
FACSIMILE: (02) 9515 7176
EMAIL: lesley.townsend@email.cs.nsw.gov.au
REFERENCE: X11-0344 & HREC/11/RPAH/543

NSW GOVERNMENT Health
Sydney Local Health District

8 December 2011

Professor S Kilbreath
Faculty of Health Sciences
Physiotherapy, O Block
University of Sydney
PO Box 170
LIDCOMBE NSW 1825

Dear Professor Kilbreath,

Re: Protocol No X11-0344 & HREC/11/RPAH/543 - "A physical activity intervention for women living in the community with metastatic breast cancer"

The Executive of the Ethics Review Committee, at its meeting of 1 December 2011, considered your correspondence of 24 November 2011. In accordance with the decision made by the Ethics Review Committee, at its meeting of 9 November 2011, ethical approval is granted.

The proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research.*

This approval includes the following:

- Recruitment Advertisement (Master Version 1, 25 October 2011)
- Participant Information Letter (Master Version 2, 24 November 2011)
- Participant Information Statement (Master Version 3, 24 November 2011)
- Participant Consent Form (Master Version 1, 19 October 2011)

General Correspondence
PO Box M30
Missenden Road, NSW, 2050
Email: slhn.esu@sswahs.nsw.gov.au
Website: www.health.nsw.gov.au/sydlhn/

Sydney Local Health District
ABN 17 520 269 052
Level 11 North, King George V Building
83 Missenden Rd
CAMPERDOWN, NSW, 2050
Tel 612 9515 9600 Fax 612 9515 9610

- Safety Protocol for Home Visits (Master Version 1, 19 October 2011)
- Screening Booklet (Master Version 1, 19 October 2011)
- Assessment Booklet (Master Version 1, 25 October
- Instructions: Physical Activity Monitors (Master Version 1, 25 October 2011)
- Instructions: Heart Monitor (Master Version 1, 25 October 2011)
- Exercise Diary (Master Version 1, 25 October 2011)
- Physician Letter (Master Version 19 October 2011)
- Training Manual (Master Version 1, 25 October 2011)

You are asked to note the following:

- **This letter constitutes ethical approval only. You must NOT commence this research project at ANY site until you have submitted a Site Specific Assessment Form to the Research Governance Officer and received separate authorisation from the Chief Executive or delegate of that site.**

  On the basis of this ethics approval, authorisation may be sought to conduct this study within any NSW public health organisation and/or within any private organisation which has entered into an appropriate memorandum of understanding with the Sydney Local Health District, Sydney Local Health Network or the Sydney South West Area Health Service.

  The Committee noted that authorisation will be sought to conduct the study at the following sites:

  - Royal Prince Alfred Hospital
  - Concord Repatriation General Hospital

- This approval is valid for four years, and the Committee requires that you furnish it with annual reports on the study's progress beginning in December 2012.
- This human research ethics committee (HREC) has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review and is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.
- You must immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.

- You must notify the HREC of proposed changes to the research protocol or conduct of the research in the specified format.

- You must notify the HREC and other participating sites, giving reasons, if the project is discontinued at a site before the expected date of completion.

- Where appropriate, the Committee recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purposes of conducting this study.

Should you have any queries about the Committee's consideration of your project, please contact me. The Committee's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Sydney Local Health District website.

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The Ethics Review Committee wishes you every success in your research.

Yours sincerely,

Lesley Townsend
Executive Officer
Ethics Review Committee (RPAH Zone)

HERC\EXCOR\11-07

Ethics approval for Chapter 5

THE UNIVERSITY OF SYDNEY

RESEARCH INTEGRITY
Human Research Ethics Committee
Web: http://sydney.edu.au/ethics/
Email: ro.humanethics@sydney.edu.au

Address for all correspondence:
Level 6, Jane Foss Russell Building - G02
The University of Sydney
NSW 2006 AUSTRALIA

Ref: [SA/KFG]

23 August 2011

Professor Sharon Kilbreath
Head, Discipline of Physiotherapy
Faculty of Health Sciences
Cumberland Campus - C42
The University of Sydney
Email: sharon.kilbreath@sydney.edu.au

Dear Prof Kilbreath

I am pleased to inform you that the Human Research Ethics Committee (HREC) approved your protocol entitled "**Validation of three physical monitors in older community-dwelling women**" at its meeting held on 16 August 2011.

Details of the approval are as follows:

Protocol No.:	**08-2011 / 14063**
Approval Period:	**August 2011 – August 2012**
Annual Report Due:	**31 August 2012**
Authorised Personnel:	**Prof Sharon Kilbreath** **Prof Glen M Davis** **Prof Leigh Ward**
Documents Approved:	**Recruitment Flyer (version 2, submitted 16/08/2011)** **Participant Information Statement (version 2, 16/08/2011)** **Participant Consent Form (version 1, 11/07/2011)** **Instructions: Physical Activity Monitors (version 1, 14/07/2011)** **Validation of Activity Monitors (version 1, 19/07/2011)** **Instructions for Urine Sample Collection (version 1, 18/07/2011)** **Physical Activity Monitors – Diary (version 1)** **International Physical Activity Questionnaire - IPAQ (short last 7 days self-administered format)**

The HREC is a fully constituted Ethics Committee in accordance with the National Statement on Ethical Conduct in Research Involving Humans-March 2007 under Section 5.1.29.

The approval of this project is conditional upon your continuing compliance with the National Statement on Ethical Conduct in Research Involving Humans.

A report on this research must be submitted every 12 months to the Human Research Ethics Committee from the final approval period or on completion of the project, whichever occurs first. Failure to submit reports will result in withdrawal of ethics approval for the project. Please download

Manager Human Ethics
Dr Margaret Faedo
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Human Ethics Secretariat:
Ms Karen Greer **T:** +61 2 8627 8171 **E:** karen.greer@sydney.edu.au
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ABN 15 211 513 464
CRICOS 00026A

the Annual Report/Completion Report Form from the Human Ethics website at: http://sydney.edu.au/research_support/ethics/human/forms.

The HREC approval is valid for four (4) years from the Approval Period stated in this letter and is conditional upon submission of Annual Reports. If your project is not completed by four (4) years from the approval period, you will have to submit a Modification Form requesting an extension. Please refer to the guideline on extension of ethics approval which is available on the website at: http://sydney.edu.au/research_support/ethics/human/extension.

Chief Investigator / Supervisor's responsibilities to ensure that:

1. All serious and unexpected adverse events should be reported to the HREC within 72 hours.
2. All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.
3. You must retain copies of all signed Consent Forms and provide these to the HREC on request.
4. It is your responsibility to provide a copy of this letter to any internal/external granting agencies if requested.
5. All research participants are to be provided with a Participant Information Statement and Consent Form, unless otherwise agreed by the Committee. The following statement must appear on the bottom of the Participant Information Statement: Any person with concerns or complaints about the conduct of a research study can contact the Manager, Human Ethics, University of Sydney on +61 2 8627 8176 (Telephone); + 61 2 8627 8177 (Facsimile) or ro.humanethics@sydney.edu.au (Email).
6. Any changes to the protocol including changes to research personnel must be approved by the HREC by submitting a Modification Form before the research project can proceed. Please refer to the website at http://sydney.edu.au/research_support/ethics/human/forms to download a copy of the Modification Form.
7. A Completion Report should be provided to the Human Research Ethics Committee at the completion of the Project.

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Dr Stephen Assinder
Chair
Human Research Ethics Committee

THE UNIVERSITY OF QUEENSLAND

Institutional Approval Form For Experiments On Humans Including Behavioural Research

Chief Investigator:	A/Prof Sharon Kilbreath
Project Title:	The Validation Of Three Physical Activity Monitors In Older Community-Dwelling Women
Supervisor:	None
Co-Investigator(s):	Prof Glen Davis, A/Prof Leigh Ward
Department(s):	Faculty of Health Sciences (University of Sydney); School of Chemistry and Molecular Biosciences (UQ)
Project Number:	2011000931
Granting Agency/Degree:	
Duration:	31st December 2012

Comments:

Expedited review on the basis of approval from the University of Sydney HREC, dated 23/08/2011.

Name of responsible Committee:-
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:-
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Date: 24·8·2011 Signature: _____