Co-production and evaluation of an evidence-based approach to promote physical activity for adults with health conditions

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Abstract

Physical activity (PA) as medicine is well-established, and targeting the most at-risk populations enhances the potential to impact public health (proportional universalism). Exercise Referral Schemes (ERSs) provide a promising framework to support PA behaviour change in inactive individuals with health conditions. Yet, due to a lack of scientific evidence and behaviour change theory underpinning the design of ERSs, there has been a lack of evidence of effectiveness. Translational research is required to improve the effectiveness of ERSs for promoting PA behaviour change and to ensure they reflect the needs of service users. Thus, the overarching aim of this PhD was to co-produce, pilot, and evaluate a PA referral scheme to support long-term behaviour change in individuals with health conditions. This process was underpinned by the Medical Research Council guidance for complex interventions and a pragmatic process and outcome evaluation framework.

Study one involved the co-production of a PA referral scheme with a multidisciplinary stakeholder group, providing an insight into a) factors that must be considered when translating evidence to practice in a PA referral setting, and b) challenges and facilitators of conducting participatory research involving multiple stakeholders. The co-production process highlighted cultural and pragmatic issues related to PA referral provision such as an 'exercise prescription' focus and fear of litigation. This process resulted in an intervention framework designed to be implemented within existing infrastructures. The framework involved 1-to-1 PA behaviour change consultations underpinned by Self-Determination Theory.

Study two explored the preliminary effectiveness and acceptability of the previously co-produced PA referral scheme (Co-PARS). Findings demonstrated that the Co-PARS elicited improvements in PA and cardiometabolic health at 12 weeks. Process data suggested, however, that further refinements were required to bring intervention delivery in-line with the intended PA behaviour change approach. These intervention adaptations were then implemented in preparation for study 3.

Study three consisted of a pragmatic, quasi-experimental trial that investigated the effectiveness of the refined Co-PARS, compared to usual care and a no-treatment control. Results extended that of the previous pilot study, in that clinically meaningful improvements were observed in cardiovascular health markers and mental wellbeing compared to usual care and no-treatment at 12 weeks. No changes were however, noted in PA or motivational variables. Embedded process evaluation revealed that intervention fidelity and participant attendance rates were improved from that of the previous pilot study.

Through this iterative process, a PA referral scheme was co-produced, piloted, and evaluated that was deemed effective at improving participant health and importantly, feasible to implement in practice. The intervention was underpinned by Self-Determination Theory, incorporating 1-to-1 behaviour change consultations, which focussed on facilitating long-term PA behaviour change. It is the iterative nature which the author wishes to emphasise as a vital process if we are to bridge the gap between scientific evidence and what works in practice. Of note, however, longer-term follow up is required to determine if such effects are sustained.

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This thesis is dedicated to Lorna Statham.

Declaration

I declare that the work contained in this thesis is my own.

Publications and communications resulting from this PhD work:

Peer-reviewed research papers

Buckley, B.J.R. Watson, P.M. Murphy, R.C. Graves, L.E.F. Whyte, G. & Thijssen, D.H.J. (2019). Carotid artery function is restored in subjects with elevated cardiovascular disease risk following a 12-week physical activity intervention. *Canadian Journal of Cardiology*, 35, 23-26. doi: 10.1016/j.cjca.2018.10.015.

Buckley, B.J.R. Thijssen, D.H.J. Murphy, R.C. Graves, L.E.F. Whyte, G. Gillison, F.B. Crone, D. Wilson, P.M. & Watson, P.M. (2018). Making a move in exercise referral: co-development of a physical activity referral scheme. *Journal of Public Health,* Advance online publication. doi: 10.1093/pubmed/fdy072.

Buckley, B.J.R. Thijssen, D.H.J. Murphy, R.C. Graves, L. E. F. Whyte, G. Gillison, F.B. Crone, D. Wilson, P.M. & Watson, P.M. (Under Revision). What happens after co-production? Preliminary effects and acceptability of a co-produced physical activity referral intervention.

Other publications completed by the candidate during PhD tenure:

Rigby, B.P. **Buckley, B.J.R**. Kelly, M.C. & Hanson, C.L. (2017). Exercise on Referral – Symposium hosted by the Physical Activity Special Interest Group of the Wolfson Research Institute for Health and Wellbeing, Durham University. *Sport and Exercise Psychology Reviews*, 13; 2.

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Conference communications

Buckley, B. J. R., Thijssen, D. H. J., Murphy, R.C., Graves, L. E. F., Whyte, G., Gillison, F.B., Wilson, P. M., Crone, D., & Watson, P. M. (2018). An evidence-based, co-produced physical activity referral scheme: A mixed-methods pilot trial. *International Society of Physical Activity and Health*, London. Oral.

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Buckley, B. J. R., Thijssen, D. H. J., Murphy, R.C., Graves, L. E. F., Whyte, G., Gillison, F.B., Wilson, P. M., Crone, D., & Watson, P. M. (2017). Making a move in exercise referral. *UK Society of Behavioural Medicine, Liverpool*. Oral.

Watson, P. M., Dohrn, I.M., Ståhle, A., Lundqvist, S., Hawkins, J. & **Buckley, B.J.R.** (2017). From potential to practice – how can we implement effective physical activity referral schemes? *European Public Health Conference, Stockholm*. Symposium (collaboration with Cardiff University, Karolinska Institutet, and Gothenburg University).

Buckley, B. J. R., Thijssen, D. H. J., Murphy, R.C., Graves, L. E. F., Whyte, G., Gillison, F.B., Wilson, P. M., Crone, D., & Watson, P. M. (2017). Making a Move in Exercise Referral: Feasibility of an evidence-based, co-developed physical activity referral scheme. *International Society of Behavioural Nutrition and PA, Vancouver.* Poster & Oral.

Buckley, B. J. R., Thijssen, D. H. J., Murphy, R.C., Graves, L. E. F., Whyte, G., Gillison, F.B., Wilson, P. M., Crone, D., & Watson, P. M. (2017). An evidence-based, co-produced physical activity referral scheme: A feasibility study. *Centre for Public Health: Public Health PhD Symposium*, Liverpool. Oral.

Buckley, B. J. R., Thijssen, D. H. J., Murphy, R.C., Graves, L. E. F., Whyte, G., Gillison, F.B., Wilson, P. M., Crone, D., & Watson, P. M. (2016). An Evidence-based, Co-Developed Physical Activity Referral Scheme. *British Heart Foundation Conference, Coventry.* Oral (1st Prize).

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List of Abbreviations

95% CI (95% Confidence Interval)

BCT (Behaviour Change Technique)

BP (Blood Pressure)

BMI (Body Mass Index)

BHF (British Heart Foundation)

CRF (Cardiorespiratory Fitness)

CAR (Carotid Artery Reactivity)

Co-PARS (Co-Produced Physical Activity Referral Scheme)

CCA (Common Carotid Artery)

ERS (Exercise Referral Scheme)

FMD (Flow-Mediated Dilation)

HR (Heart Rate)

MAP (Mean Arterial Pressure)

MCID (Minimum Clinically Important Difference)

MRC (Medical Research Council)

METs (Metabolic Equivalents)

MVPA (Moderate-to-Vigorous Intensity Physical Activity)

NHS (National Health Service)

NICE (National Institute for Health and Care Excellence)

PA (Physical Activity)

PCT (Primary Care Trust)

PHE (Public Health England)

RCT (Randomised Controlled Trial)

RPE (Rating of Perceived Exertion)

SDT (Self-Determination Theory)

SES (Socio-Economic Status)

SD (Standard Deviation)

SE (Standard Error)

WHO (World Health Organization)

1 INTRODUCTION

1.1 Thesis Structure

This thesis is organised into 8 chapters. Chapter 1 provides a brief introduction and background to the PhD, followed by defining the primary aims and objectives. Chapter 2 provides a critical review of related topics and contemporary research, as well as rationale for the proceeding research chapters. Chapter 3 describes the general methods used in the subsequent research. Chapters 4, 5, 6 and 7 detail three research studies that form the body of this PhD. Each chapter includes; a brief and specific introduction related to the aim of the particular study, description of methods, presentation of results, and a discussion of the findings in relation to related literature. Chapter 8 synthesises key findings from the overarching PhD and proposes implications for practice, policy, and future research.

1.2 Physical Activity Terminology

A confounding concept in physical activity (PA) and public health research is the varied terminology used to describe PA, exercise, inactivity, and sedentary behaviour. A recent participatory terminology consensus statement by the Sedentary Behaviour Research Network (Tremblay *et al*., 2017) sought to advance the standardisation of such definitions. For clarity the subsequent definitions from this consensus statement and Caspersen, Powell & Christensen (1985) are used throughout this thesis:

- Physical activity is defined as any bodily movement produced by skeletal muscle that results in energy expenditure.
- Exercise is a subset of PA that is planned, structured, repetitive, and has an objective to maintain or improve an aspect of physical fitness.

- Physical inactivity is defined as an insufficient PA level to meet the present PA recommendations or achieving <30 min/week moderate-intensity PA.
- Sedentary behaviour on the other hand, is any waking behaviour characterised by an energy expenditure ≤1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture.

1.3 Background

There is an ever-expanding wealth of evidence that demonstrates the efficacy of PA in the prevention and amelioration of lifestyle-related health conditions (Warburton *et al*., 2006; Knowler *et al*., 2009; Kahl 3rd *et al*., 2012; Lee *et al*., 2012; Drenowatz *et al*., 2016). The current UK PA guidelines are 150 minutes of moderate intensity PA or 75 minutes of vigorous PA or an equivalent combination of these two per week. Adults should also undertake PA to improve muscle strength on at least two days a week (WHO, 2010). These activity levels have been linked to a myriad of substantial health benefits, particularly for patients with lifestyle-related health conditions (Garber *et al*., 2011; Bakrania *et al*., 2015). Yet, physical inactivity has been identified as the fourth leading risk factor for global mortality (Department of Health, 2011). Despite efforts to alleviate physical inactivity, global statistics suggest that inactivity has increased in high-income countries by >5% from 2001 to 2016 (Guthold *et al*., 2018).

1.4 The Exercise Referral Process

In 2011 it was reported that >600 different exercise referral schemes (ERSs) were in operation across the UK, involving >100 000 participants (Pavey *et al*., 2011a; BHF, 2010). Such schemes typically follow a model outlined by the National Quality Assurance Framework for ERSs (Department of Health, 2001). As described in the model, the process begins with a referral from a qualified health professional (e.g. General Practitioner (GP), Nurse, Physiotherapist etc.) to an exercise referral practitioner. Patients are referred by a health professional based on

meeting eligibility criteria specific to the individual referral scheme. A subsidised exercise programme (typically varying between 8-26 weeks) is then 'prescribed' by the exercise referral practitioner. According to the National Institute for Health and Care Excellence (NICE, 2014), referral should be reserved for inactive individuals with a health condition and/or risk factor(s). Although much heterogeneity exists on a national scale, ERSs are *typically* commissioned by public health teams, based in local authorities (since 2012). Some initiatives are written into existing leisure contracts between local authorities and third party leisure providers. Further, Health and Wellbeing Boards set strategic priorities which inform what local authorities and the NHS commission.

Whilst several population-based approaches have been identified to support PA behaviour change, ERSs have been recognised as a more direct approach for clinical and population sub-groups (Williams *et al*., 2007). Systematic review evidence has demonstrated considerable uncertainty as to the clinical effectiveness and cost-effectiveness of ERSs (Pavey *et al*., 2011a; Pavey *et al*., 2011b). Of note, it has been proposed that such systematic review evidence has not represented the *true* potential of ERSs to elicit meaningful health outcomes (Beck *et al*., 2016). More specifically, ERSs demonstrate high heterogeneity, have not typically been underpinned by behaviour change theory, nor have they been developed to the point where they can reasonably be expected to have a worthwhile effect (Craig *et al*., 2008; discussed in detail in section 2.4.2). How to effectively translate scientific evidence to real-world practice is an ongoing challenge faced by researchers and healthcare providers. Particularly, how to facilitate PA behaviour change in inactive populations, especially those with (early onset) health conditions, is a paramount challenge for our healthcare system.

1.5 Rationale, Aims, and Objectives

The UK National Institute for Health and Care Excellence (NICE, 2014) have recommended that practitioners, policy makers, and commissioners only endorse ERSs that draw on behaviour change theory and collect robust evaluation data in line with the Standard Evaluation Framework for PA interventions (Cavill, Roberts, & Rutter, 2012). The NICE recommendations were formed due to a sparsity of evidence in relation to ERS effectiveness (Pavey *et al*., 2011a). Research is therefore needed to identify how to better incorporate scientific evidence and behaviour change theory into the design, implementation, and evaluation of ERSs.

This PhD aims to address the issue of translating scientific evidence to practice from an individual-based PA intervention perspective. Drawing on the Medical Research Council (MRC) guidance for complex interventions (Craig *et al.*, 2008), the overarching aim of this PhD was to follow an iterative approach to co-produce (chapter 4), pilot (chapter 5-6), and evaluate (chapter 7) a PA referral scheme. Note the intervention has been termed a 'PA referral scheme' rather than an 'exercise' referral scheme to more accurately represent its purpose; a holistic approach to facilitate sustainable PA behaviour change. Specifically, the objectives of the PhD were to:

1. Conduct a literature review summarising key lifestyle-related health conditions represented in primary care settings, how PA impacts such conditions, and a critical review of ERS literature as a potential solution (Chapter 2).
2. Co-produce a PA referral scheme with a multidisciplinary group of academics and local stakeholders (Study 1, Chapter 4).
3. Pilot a co-produced PA referral scheme with the aim of:

    a) Exploring preliminary effectiveness and intervention acceptability (Study 2a, Chapter 5).

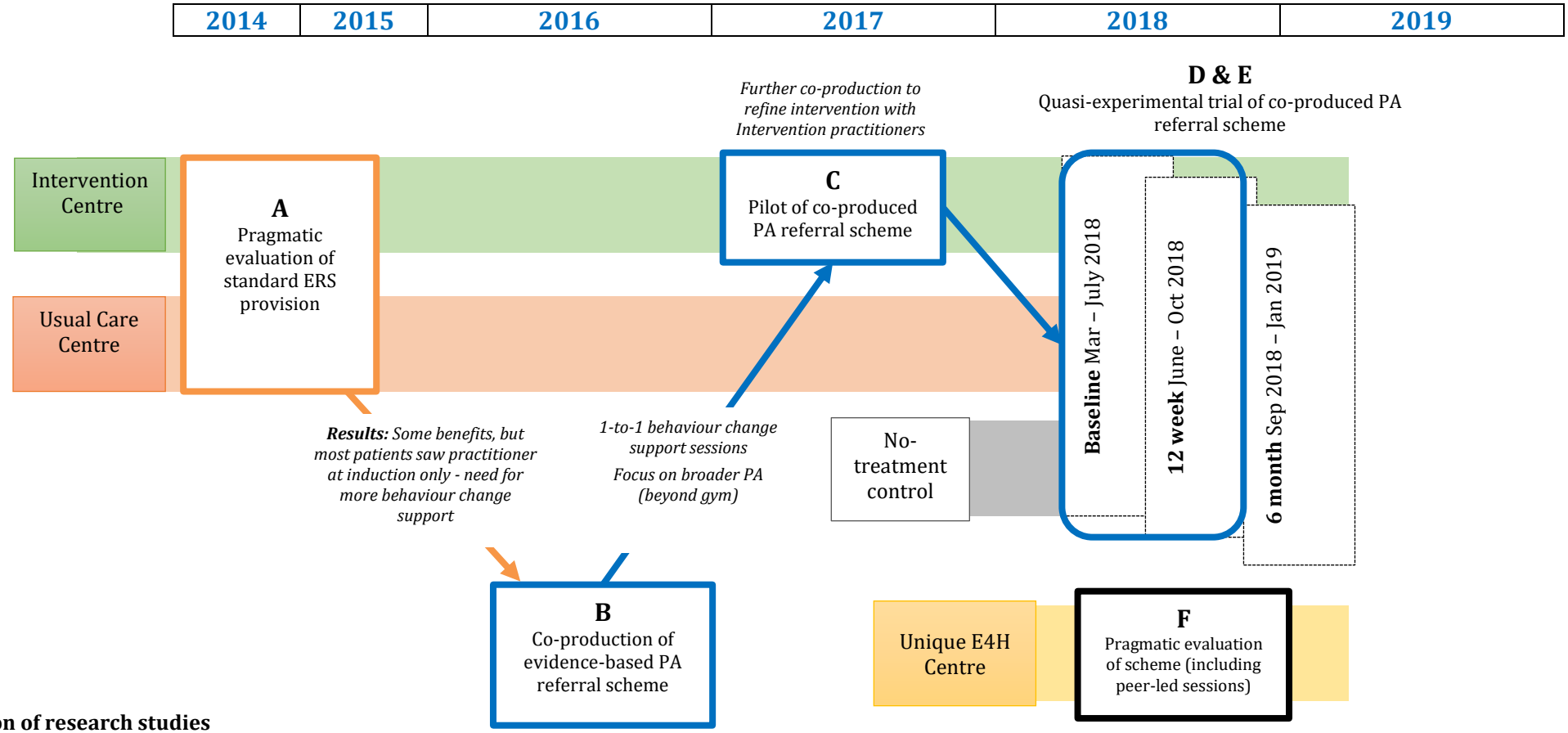
b) Investigating the cardio-protective effects of a real-world PA referral scheme in an at-risk cohort (Study 2b, Chapter 6).

4. Pragmatically evaluate the effectiveness of a co-produced PA referral scheme via a quasi-experimental trial with embedded process evaluation (Study 3, Chapter 7).
5. Synthesise findings from studies 1 to 3, consider implications and make recommendations for policy, practice and future research (Chapter 8).

Figure 1-1. provides an overview of this PhD research and illustrates how it fits within a broader research agenda (directed by Dr Paula Watson) with the overarching aim of improving the PA referral provision in Liverpool.

Figure 1-1. Overview of Liverpool PA referral research (2014-present).

Orange outlines illustrate work completed prior to this PhD; **Blue outlines** illustrate the progression of these PhD studies (i.e. findings of one study informed subsequent work); **Black 'bold' outlines** illustrate work completed alongside this PhD work; **PA**, Physical activity; **ERS =** Exercise referral scheme; **E4H**, 'Exercise for Health' - the usual care exercise referral system in Liverpool.



Explanation of research studies

A. **Investigation of what's happening now** (prior research conducted by Dr Paula Watson's team). A pragmatic evaluation of usual care E4H provision at two different centres (2014-2015).

B. **Co-production of a PA referral scheme (Benjamin Buckley – PhD study 1).** Series of co-production workshops with E4H commissioners, service managers, exercise instructors, service users and academics, resulting in an evidence-based PA referral framework (2016).

C. **Pilot of the co-produced PA referral scheme (Benjamin Buckley – PhD study 2).** Testing the feasibility of the co-produced PA referral scheme at the Intervention centre, including 12-week health outcome data (2017).

D. **Evaluation of the co-produced PA referral scheme (Benjamin Buckley – PhD study 3).** Pragmatic 12-week evaluation of the co-produced PA referral scheme at the Intervention centre, compared with usual care and a no-treatment control group. Includes physiological, psychological and behavioural outcomes, plus process data to explore intervention fidelity and acceptability. Additional 6-month follow up will be completed post-PhD.

E. **Evaluation of the cost-effectiveness of the co-produced PA referral scheme** (simultaneous research conducted by another PhD student). Collection of data from patients taking part in [D] to establish the relative costs and potential cost-savings of the co-produced PA referral scheme in comparison with usual care and no treatment (results due mid-2019).

F. **Evaluation of a promising version of E4H provision in a single centre in Liverpool** (simultaneous research conducted by an MSc student). Collection of mixed method data from patients referred to the centre, including an investigation of the unique programme in operation – what works well and what we could learn from it for other centres.

2 LITERATURE REVIEW

Due to the complex nature and diverse patient cohorts of primary healthcare interventions, the aims of this literature review is three-fold: 1) Provide an overview of the key lifestyle-related health conditions commonly represented in primary healthcare settings, 2) discuss the concept of PA as medicine, and 3) critically review the literature surrounding ERSs as a tool to promote PA behaviour change.

2.1 Physical Inactivity: The 21st Century Epidemic

> *'We in the West are the first generation in human history in which the mass of the population has to deliberately exercise to be healthy' (Morris, 2009, p. Foreword)*

Approximately one-third of the population do not meet minimum PA levels to sustain health (Hallal *et al*., 2012), and despite well-funded efforts, global statistics have revealed >5% increase in physical *inactivity* in high-income countries from 2001 to 2016 (Guthold *et al*., 2018). Correspondingly, 35 million deaths per year have been attributed to physical inactivity (Lee *et al*., 2012), making physical inactivity one of the world's leading causes of death. Thus, understanding how to effectively increase habitual PA levels at the population level is of critical importance. Subsequently, PA as primary prevention is now a global policy agenda (GAPA, 2012; Guthold *et al*., 2018).

Since 2012, numerous countries have developed national PA strategies, though few have been successfully implemented (Sallis *et al.,* 2016). The metaphorical gap between PA policy and implementation success may be due to a lack of resources, cross-sectoral partnership, and clear strategies (Ding *et al*., 2017). Although it has been documented that 'there is no magic bullet to alleviate physical inactivity', several promising investments have been identified that work (GAPA, 2012). Two of which include 'PA and non-communicable disease (NCD) prevention

integrated into primary health care systems' and 'community wide programmes involving multiple settings and sectors' (GAPA, 2012). Furthermore, a recent report from the World Health Organization (WHO, 2018) has outlined a target of a 15% relative reduction in the global prevalence of physical inactivity by 2030. The framework calls for a 'systems-based' approach combining both upstream (e.g. policy actions) and downstream (e.g. individually focussed) methods. The report goes on to state that implementation of this action plan should be guided by the principle of proportionate universalism; with the greatest efforts directed towards the most at need (i.e. least active / most at-risk) populations (WHO, 2018).

In 2016 The Lancet released a series of PA publications with the aim of updating the 2012 series, which sought to identify the best available evidence to date for the relationship between human health and PA. An article in the 2012 series estimated that physical inactivity causes 9% of premature mortality, or more than 5.3 of the 57 million deaths that occurred worldwide in 2008 (Lee *et al*., 2012). This figure equates to as many deaths as tobacco causes globally, which is uniformly regarded as a leading NCD risk factor. The authors went on to project that if physical inactivity were decreased by 10 or 25%, more than 533 000 and more than 1.3 million deaths, respectively, could be averted each year (Lee *et al*., 2012). The 2016 series reported that global PA prevalence had not changed substantially and policy work was being developed, but not implemented at country level, with much work to be done (Sallis *et al*., 2016). For example, Ding *et al*., (2017) highlighted substantial economic costs attributable to physical inactivity, with a conservative estimate indicating an international cost of $53.8 billion worldwide. Furthermore, one paper focussed on the 'scaling up' of PA interventions to the population level, outlining that the global pandemic of physical inactivity requires a multisectoral, multidisciplinary public-health response (Reis *et al*., 2016). Finally, the last paper in the series investigated the protective effects of PA from sitting time (Ekelund *et al.,* 2016), discussed later in Section 2.1.1.1.2. This latter paper highlighted that health benefits may also be achievable by focusing on reducing sedentary behaviour, an effect that is independent from the benefits of exercise training / PA.

2.1.1 Physical Activity Guidelines

Meeting either the weekly moderate (150 minutes) or vigorous (75 minutes) PA guidelines, or an equivalent combination of the two has been shown to markedly reduce the risk of overall mortality (31%) compared to not meeting the guidelines (Arem *et al*., 2015).

The widely-adopted guidelines do not represent a threshold level or a 'magic' number for health benefits. In fact, Figure 2-1 displays a dose-response relationship between PA or fitness level and risk of disease. The curvilinear dose-response curve generally holds for coronary heart disease and Type 2 diabetes: the higher the level of PA or fitness, the lower the risk of disease, with the largest health benefits being achieved with a change from no PA to a small amount of PA. For additional increases in PA or fitness beyond this point, the return on investment is reduced (Department of Health, 2004). This message is supported by a more recent meta-analysis that found the "biggest bang for buck" for coronary heart disease risk reduction occurred at the lower end of the activity spectrum (Sattelmair *et al*., 2011). Such evidence warrants further consideration of the current PA guidelines. For example, 150 minutes per week may seem an unachievable amount of activity to some, whilst not enough to others. More intuitive guidelines could use a continuous approach, based on moving across an 'activity spectrum' from left (very little activity) to the right (highly active). Removing the 'active or inactive' status, which seems unhelpful from a behaviour change perspective. There is now compelling evidence for the health benefits of regular brisk walking, even if not meeting the recommended 150 minute dose (Brannan, Foster & Murphy, 2018). Below, some of the novel insights are discussed that may support a more detailed and personalised approach related to PA guidelines.

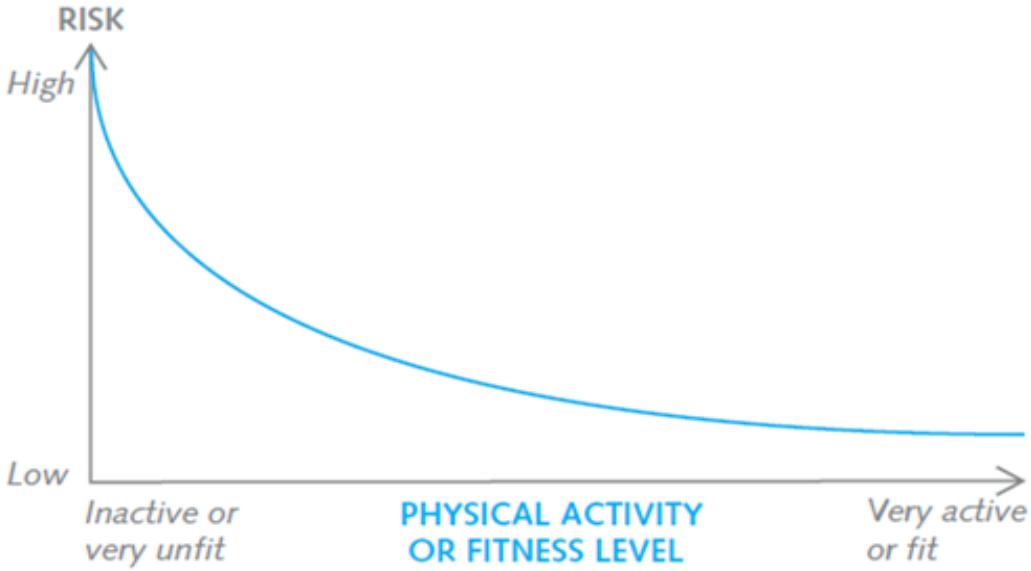


Figure 2-1. Thematic representation of the dose-response relationship between physical activity and risk of coronary heart disease and Type 2 diabetes mellitus (Department of Health, 2004).

2.1.1.1 Recent advances in physical activity evidence

2.1.1.1.1 Physical activity intensity

Light-intensity PA refers to an activity intensity <3 METs and can be accrued through incidental activities such as walking as a result of completing other tasks, household chores and other leisure-time activities (Carson *et al*., 2013). Jefferis *et al.* (2018) explored the effects of different patterns of PA on mortality risk in 1274 men (mean age 78.4 years) with a median follow up of 5 years. Measures included 7-day device-measured PA status and NHS records to determine all-cause mortality. Findings emphasised the importance of light-intensity PA for mortality reduction (14% reduction in mortality risk for each 30 minutes of light-intensity PA, following adjustment for all other PA intensities). Furthermore, the authors proposed that the volume of activity was more important than the duration of bouts. For example, previous guidelines have focussed on a minimum 10-minute bout duration to accrue any substantial health benefit (Department of Health, 2004). Contrary to this guidance, Jefferis *et al.* (2018) found no difference between bouts of 1-9 minutes and ≥10 minutes in duration. Although the study is

limited to older British men, it has potential implications as to the importance of light-intensity PA in older populations. Such findings highlight that substantial health benefits are not limited to solely moderate-to-vigorous intensity PA (MVPA). Correspondingly, the authors concluded meaningful health benefits can be realised through light-intensity PA with an emphasis on total PA volume, rather than bouts of at least 10 minutes. In support of these findings, a recent systematic review (Amagasa *et al*., 2018) concluded that light-intensity PA was inversely associated with all-cause mortality risk and associated favourably with several cardiometabolic risk factors including waist circumference, triglyceride levels, insulin, and metabolic syndrome. Importantly, these associations remained after adjustment for MVPA. In addition, data indicates that increasing light-intensity PA directly following a heart attack can reduce future mortality risk by ~60% (Ekblom *et al*., 2018). Thus, current guidelines that heavily focus on MVPA (Department of Health, 2011) may benefit public health by updating recommendations to emphasise the importance and benefits of light-intensity PA, independent of MVPA (Amagasa *et al.*, 2018).

The latest US PA guidance (Piercy, Troiano, & Ballard, 2018) subsequently abandoned the previous focus on MVPA bouts of at least 10 minutes as it was not supported by empirical evidence. This creates opportunity for more of a focus on sporadic, incidental activities including walking or cycling from place to place, stair climbing, and active daily chores (Piercy, Troiano, & Ballard, 2018). Further, given that high-intensity PA provides the 'biggest bang for your buck', sporadic bouts of incidental high (*relative)* intensity PA is a promising avenue of future investigation (Stamatakis *et al*., 2019).

2.1.1.1.2 Sedentary behaviour

In addition to the promotion of Light-intensity PA and MVPA, recent work has focussed on the importance of reducing sedentary behaviour. Sedentary behaviour is defined as any waking behaviour characterised by a low energy expenditure (≤1.5 METs), while in a sitting, reclining or lying posture (Tremblay *et al*., 2017). Importantly, sedentary behaviour is not simply a

result of physical inactivity but an independent behaviour. As such, an individual can meet the PA guidelines (i.e. classified as physically active) yet be highly sedentary at the same time. Sedentary behaviour occurs across all domains and is challenging to measure objectively.

An association between total sitting time and all-cause mortality was suggested in a meta-analysis, which demonstrated increased risk of premature death with increasing sitting time (Chau *et al*., 2013). These findings were reinforced by a study which judged the findings of eight systematic reviews based on the Bradford Hill's framework for assessing causation (Biddle *et al*., 2016). They concluded that there is reasonable epidemiological evidence for a causal relationship between sedentary behaviour and all-cause mortality, yet no evidence for dose-response relationship. Though, a more recent meta-analysis and systematic review found that for all-cause mortality and CVD, a threshold of 6-8 hours/day of total sitting was identified, above which the risk is increased (Patterson *et al*., 2018). A harmonised meta-analysis of data from more than 1 million men and women found high levels of moderate-intensity PA (i.e. 60-75 min/day) seemed to eliminate the increased risk of mortality associated with high sitting time (Ekelund *et al*., 2016). Whilst it may not be too surprising to find that the positive effects of being *highly* physically active can alleviate the detrimental effects of sedentary behaviour, it is important to note that large proportions of the adult population have low levels of PA and only a small subset (<5%) of our population meets a PA level that may offset the detrimental effect of sedentary behaviour (60-75 min of moderate-intensity PA per day; Biddle *et al*., 2016; Ekelund *et al.,* 2016). Thus, reducing both sedentary behaviour and physical inactivity are important public health agendas.

Sedentary behaviour epidemiological research has mostly comprised of self-reported proxy measures of sedentary behaviour, such as time spent sitting or screen time questionnaires. Note that correlations between self-reported sedentary behaviour questionnaires match poorly with objective measures of time spent sedentary (Chastin *et al*., 2018). A recent systematic review including studies that adopted these subjective measures, reported high variability in sedentary behaviours within and between countries in Europe (Loyen *et al*.,

2016). The United Kingdom demonstrated the highest within country variability with total sedentary time ranging from 295-620 min/day. Most identified studies used a single item self-report question to ascertain sedentary time, which did not assess the type or domain of sedentary behaviour. Further, due to the large variation in assessment methods, reported outcomes, and consequently, the findings within studies, sedentary time of European adults is currently unknown (Loyen *et al*., 2016). Such inconsistencies are represented more broadly in the sedentary behaviour epidemiological research. Key limitations in the evidence being a lack of standardised measures and use of single item self-reported measures that only measure one form of sedentary behaviour. Thus, different single-item questions are measuring different sub-types of sedentary behaviour. High quality measurement is essential in all elements of sedentary behaviour epidemiology, from determining associations with other health outcomes to the development and evaluation of behaviour change interventions (Atkin *et al*., 2012). Due to the limitations of both subjective and 'objective' (or more accurately, device-measured) measures of sedentary behaviour, Healy *et al.* (2011) has called for both to be utilised in future epidemiological work.

2.1.1.1.3 Resistance training – 'the forgotten tool'?

It is important to remember that resistance training twice per week is a key component of the PA guidelines (Department of Health, 2011). Despite advocating regular 'muscle strengthening activities', there has been very little emphasis upon this modality in either research or public health effort (Steele *et al*., 2017; Milton *et al*., 2018). Kim *et al*. (2018) analysed data from >70,000 men and women using the UK biobank comprising of a prospective cohort of > 0.5 million adults aged 40–69 years. A total of 832 all-cause, 177 cardiovascular and 503 cancer deaths over 5.7-year follow-up were recorded in participants who provided valid cardiorespiratory fitness (CRF) and grip strength data (with no history of heart attack/stroke/cancer at baseline). They concluded that improving both CRF and muscle strength, as opposed to either of the two variables alone, may be the most effective behavioural strategy to reduce all-cause and cardiovascular mortality risk (Kim *et al*., 2018). In other

words, aerobic and resistance training provide both independent and synergistic health effects. For example, whilst aerobic training is known to enhance CRF, resistance training is key to slowing the effects of aging such as loss of function and muscle mass (sarcopenia), reducing the risk of falls and maintaining quality of life, particularly for older adults (Chodzko-Zajko *et al*., 2009). These data reinforce the importance and recommendations for both weekly aerobic and resistance activities for good health and wellbeing, particularly as we age. Thus, an increased emphasis from the health and PA community is needed to stress the importance of strength and balance activities, and facilitate interventions that overcome the perceived barriers to this important component of the PA recommendations (Cavill & Foster, 2018).

2.2 PA in the Prevention and Treatment of Disease

Insufficient PA is one of the 10 leading risk factors for global mortality (WHO, 2018). People who are insufficiently physically active have a 20-30% increased risk of all-cause mortality compared to those who engage in at least 150 minutes of moderate intensity PA per week, or equivalent, as recommended by the World Health Organization (WHO, 2018). Recent research has extended earlier findings on the relationship between PA and disease to a wide variety of health outcomes. We now know that regular PA reduces the risk of numerous chronic diseases, preserves health and function (both physical and mental) as we age, and extends longevity (Church & Blair, 2009). Further, meta-epidemiological evidence from 205 randomized controlled trials (n = 339,274) has revealed equivalent effectiveness of exercise training compared to contemporary pharmacology intervention, in the context of mortality reduction (Naci & Ioannidis, 2013). This highlights the potency of 'PA as a medicine'.

The Department of Health (2016) have stated that they will create a healthier society by supporting people to make lifestyle changes to improve their physical and mental health and prevent avoidable diseases. On the forefront of this target, they aim to support people to give up smoking, improve dietary habits, and reduce drug use, obesity, alcohol intake and physical

inactivity. Diabetes treatment and prevention is a key agenda, with an aim to better reach the 5 million people at heightened risk of developing Type 2 diabetes via the NHS Diabetes Prevention Programme.

Cardiovascular diseases (CVD) are attributed to the majority of NCD-related mortality rates worldwide with 17.5 million deaths annually. It is of note that although diabetes is the fourth biggest NCD-related killer globally (1.5 million deaths annually), 90% of diabetics have Type 2 diabetes and the leading cause of mortality in this population is cardiovascular complications (Laakso, 2001; Li *et al*., 2014). Consequently, cardiovascular disease and diabetes (cardiometabolic conditions) are well established global health issues and a focus of this thesis.

It is important to acknowledge a change in the UK's leading cause of mortality compared to that of the global statistics presented above. The Northern Ireland Statistics and Research Agency (NISRA) have released new data for causes of death (NISRA, 2017). When combined with the 2016 national statistics for England, Wales and Scotland, these data demonstrated that dementia is now the leading cause of death in the UK (Office for National Statistics, 2016). Indeed, 70,366 deaths were caused by dementia, compared to 66,076 attributable to CVD, the previous leading cause of death in the UK prior to 2015.

In addition to physical health problems, mental illness has been recognised as an emergent public health concern. A recent index of 301 diseases found mental health problems to be one of the main causes of overall disease burden worldwide, accounting for 21% of years lived with a disability (Global Burden of Disease Study 2013 Collaborators, 2015). Depressive disorders have also been shown to contribute to the burden of heart disease on mortality and disability, with a direct and indirect impact on the length and quality of life (Ferrari *et al*., 2013). Although the overall number of people in the UK with mental health problems has not changed significantly in recent years, how people cope with such conditions appears to be getting worse. For example, the number of people who self-harm or have suicidal thoughts appears to be increasing (McManus *et al*., 2016). In addition, the number of people in the UK aged ≥16

years with symptoms of anxiety or depression has increased by 1.5% (to 19.7%) from 2013-2014 (Macrory, 2016). As it stands, ~1 in 4 people in the UK experience a mental health problem each year (McManus *et al* 2009). In England, 1 in 6 people report having experienced a common mental health problem (such as anxiety and depression) in any given week (McManus *et al*., 2016).

In light of the findings previously discussed, the following sections of this literature review cover the aetiology and impact of PA on major physical health problems of our time (i.e. CVD, Type 2 diabetes, dementia) before briefly considering systemic risk factors centrally involved in their development (Figure 2-4). The relevance of PA for mental health is then critically discussed.

2.2.1 Physical Activity and Physical Health

2.2.1.1 Cardiovascular Disease

2.2.1.1.1 Description and aetiology

Cardiovascular disease (CVD) is an umbrella term which includes all heart and circulatory diseases, including coronary heart disease, angina, heart attack, congenital heart disease, hypertension, stroke and vascular dementia (BHF, 2018). Such diseases, namely coronary heart disease, can present with serious acute events. A myocardial infarction, commonly termed heart attack, is an acute cardiac event due to a circulation disorder involving the coronary arteries. It is caused by ischaemia (lack of blood supply) typically from plaque build-up in the coronary arteries, and usually results in cardiac necrosis (tissue death). A stroke is a somewhat similar event but caused by an obstruction of a cerebral blood vessel and thus, principally affects the brain. A cardiac arrest on the other hand is an electrical disorder that can have a variety of causes, most commonly from an arrhythmia. An estimated 17.5 million people died from cardiovascular disease in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were

due to stroke. Most CVDs can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diet, obesity, physical inactivity, hypertension, diabetes, hyperlipidaemia, and harmful use of alcohol (WHO, 2016).

Atherosclerosis is a chronic, inflammatory disease of the arterial wall that underlies many of the common causes of cardiometabolic and cerebrovascular morbidity and mortality (Douglas & Channon, 2010). A normal, healthy artery comprises of three layers: An endothelial cell layer (tunica intima), which lines the lumen of all blood vessels; the tunica media, which is mainly comprised of smooth muscle cells that control vascular tone; and the tunica adventitia, which comprises of a surrounding layer of connective tissue containing micro-vessels (vasavasorum) that nourish the media (Douglas & Channon, 2010). Atherosclerosis or plaque is characterised by the formation of a lipid and cholesterol laden mass in the intima or media section of an artery. A proinflammatory state is often recognised by elevated inflammatory markers, e.g. C-reactive protein (CRP), and is commonly present in people with cardiometabolic disease.

Oxidative processes resulting in atherosclerosis include the transportation of low-density lipoprotein (LDL), among other macromolecules, into the vascular intima via endothelial cells. Trapped LDL is oxidised by reactive oxygen species (i.e. superoxide anions). Reactive oxygen species are inactivated by dietary anti-oxidants and enzymes. Oxidised LDL is ingested by macrophages and becomes a foam cell. Oxidised LDL has a greater affinity for foam cell formation, the intake of which, is not regulated by negative feedback (Nagy *et al*., 1998; Pirillo *et al*., 2013). Foam cells accumulate in the sub-intimal space, known as fatty streaks. A fibrous cap develops above the lipid dense core. Smooth muscle cells then proliferate and generate connective tissue and collagen. The plaque may calcify and may ultimately haemorrhage, rupture, or cause thrombosis. Figure 2-2 provides an illustration of the formation of foam cells and Figure 2-3 depicts an overview of atherosclerosis progression over time.

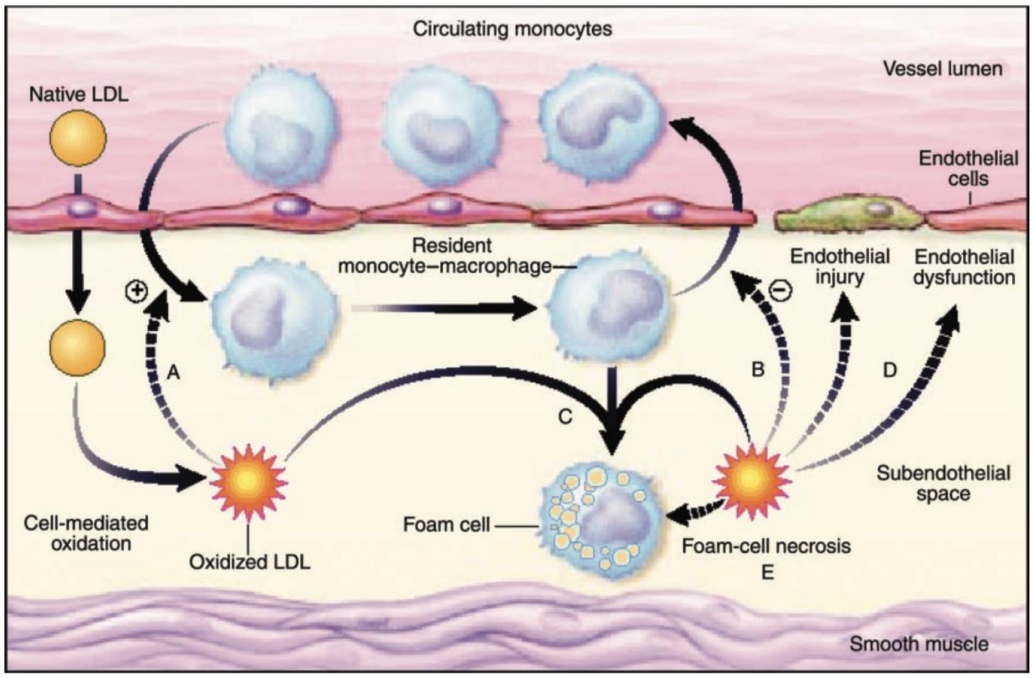


Figure 2-2. Oxidative modification hypothesis of atherosclerosis. LDL becomes entrapped in the sub-endothelial space where it is subject to oxidative modification by smooth muscle cells, endothelial cells, and macrophages. Oxidized LDL stimulates foam cell formation. Once formed, oxidized LDL also results in endothelial dysfunction and injury. (Stocker & Keaney, 2004).

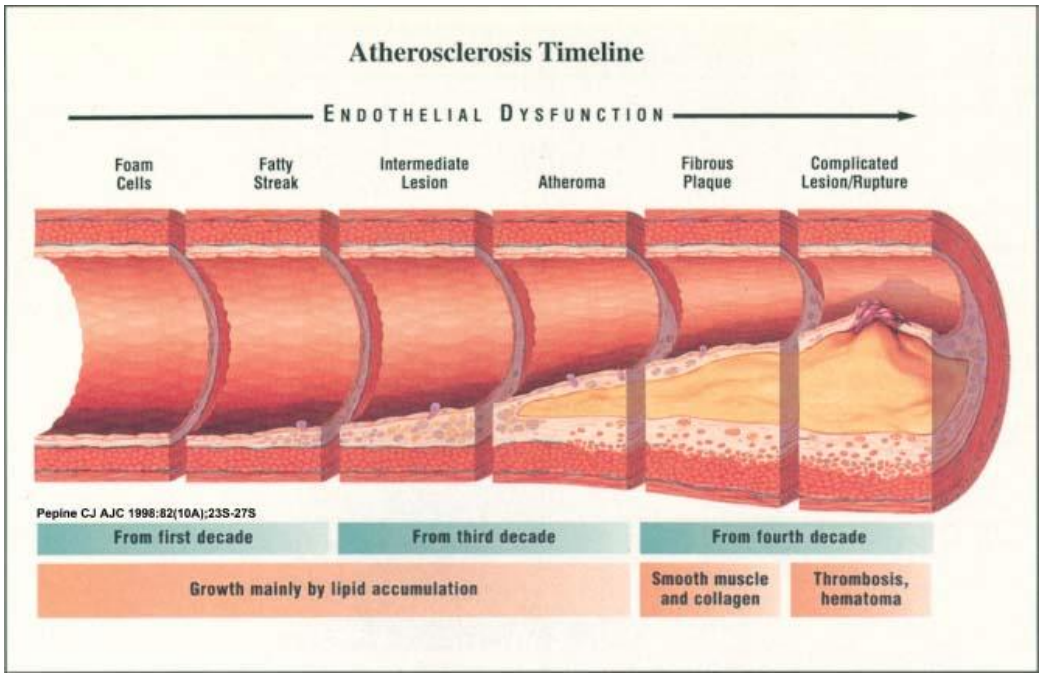


Figure 2-3. Atherosclerosis timeline, demonstrating the underlying role of endothelial dysfunction in the progression of atherosclerosis from foam cell formation to complicated lesion (Pepine, 1998).

2.2.1.1.2 Physical activity epidemiology and cardiovascular disease

Human cardiovascular physiology has evolved within an environment that necessitated substantial levels of PA (Bramble & Lieberman, 2004). It is therefore not surprising that we, *homo sapiens*, now face an epidemic of 'hypokinetically-induced' comorbidities. Accordingly, modern society is driving the evolution from the *homo sapiens* to the '*homo sedentarius*' (Levine, 2014).

The last five decades has seen an accumulating expanse of epidemiological and experimental data that has established a causal relationship between low PA levels and morbidity (Morris *et al*., 1953; Archer & Blair, 2011; Barry *et al*., 2014). The now ubiquitous notion that PA is medicine stemmed from the seminal work of Morris *et al.* (1953). The retrospective study found that in a cohort of 31,000, bus drivers had twice the incidence rate of myocardial infarctions compared to that of bus conductors. Morris repeated the study design in civil servants, comparing incidence of CVD and events between those delivering mail and those working in an office, demonstrating the same relationship. These publications laid the groundwork for PA epidemiology and stimulated the development of substantial research linking physical inactivity to increased risk of many NCDs (Das & Horton, 2012). In later work known widely as the Harvard College Alumni Study, Paffenbarger and colleagues (1983, 1986, and 1994) established an inverse relationship between PA and risk of myocardial infarction. By the 1990s a meta-analysis identified that inactivity was associated with a 1.9-fold increase in coronary heart disease risk (95 % CI 1.6-2.2; Berlin & Colditz, 1990).

Subsequent research, summarised in Blair (2009) has established in 40,000 subjects from the widely-respected Aerobics Centre Longitudinal Study, that low CRF is the strongest predictor of mortality. Such findings are supported by a recent 15-year follow-up, prospective cohort study that suggested the beneficial impact of PA on CVD may outweigh the negative impact of BMI among middle-aged and elderly individuals (Koolhaas *et al*., 2017). Nonetheless, further health benefits can be gained via maintaining a healthy weight. These findings emphasize the

importance of PA for everyone across all BMI strata, whilst also highlighting the elevated CVD risk associated with physical inactivity, including among normal weight individuals (Koolhass *et al.,* 2017). Physical inactivity and low CRF are now well-established major risk factors for all-cause mortality and in particular, lifestyle-related health conditions (Sui *et al*., 2007; Gray *et al*., 2015).

2.2.1.1.3 Mechanisms of physical activity benefit

The benefits of PA and exercise have been traditionally judged by their capacity to modify cardiometabolic risk factors such as blood pressure, lipids (e.g. cholesterol and triglycerides), insulin resistance, and obesity (Thompson *et al*., 2003). As summarised by Thijssen *et al*. (2010) "*exercise-induced improvements in vessel wall function and structure represent a 'vascular conditioning' effect, which provides a plausible mechanistic explanation for the cardioprotective benefits of exercise, independent of the impact of exercise on traditional cardiovascular risk factors*" (p. 866).

Endothelial dysfunction has been regarded as a critical factor in the pathogenesis of cardiometabolic disease (Pepine *et al*., 1998; Van den Oever *et al*., 2010). Endothelial cells act as an interface and functional link between circulating blood flow and vessel walls; alterations in endothelial cell phenotype can have marked effects on vessel wall structure and function (Douglas & Channon, 2010). Endothelial dysfunction occurs when the endothelial cells have been injured or exposed to metabolic stress. Endothelium-derived nitric oxide is one of the most important signalling molecules produced by the endothelium. This multifunctioning signalling molecule is critically involved in the maintenance of metabolic and cardiovascular homeostasis. For example, loss of endothelial nitric oxide bioavailability is the hallmark of dysfunction in vascular disease (Douglas & Channon, 2010). Endothelial cell damage could be due to changes in hemodynamic forces (i.e. shear (Cunningham & Gotlieb, 2004)), drug induced cytotoxicity, mechanical device implant-induced injury (i.e. stent), and/or immune-mediated mechanisms (Tesfamariam & DeFelice, 2007). Nitric oxide has been deemed an

antiatherogenic molecule, due to its ability to: elicit vasodilation, thus decreasing shear and pressure; decrease platelet aggregation and adhesion; decrease monocyte adhesion and macrophage transformation; decrease smooth muscle cell proliferation; decrease reactive oxygen species; and decrease oxidised LDL and foam cell formation (Pohl *et al*., 1986; Sukhovershin *et al*., 2015).

A recent *Sports Medicine* review summarised that chronic PA can attenuate oxidative stress and inflammation, leading to a potential reduction in health complications (Mury *et al*., 2018). Mechanisms underlying these benefits may include improved endothelial integrity, upregulation of the nitric oxide pathway and improved sensitivity of α and β adrenoceptors (Mueller *et al*., 1982; Deanfield *et al*., 2007; Thijssen *et al*., 2010; Green *et al*., 2017). Adaptation via hemodynamic stimuli is proposed to lead to an improvement in endothelial integrity and/or function (Thijssen *et al*., 2010; Green *et al*., 2017). Specifically, exercise training may elicit a shear stress-mediated upregulation of endothelium-derived nitric oxide synthase (eNOS), subsequently leading to a larger nitric oxide availability (Deanfield *et al*., 2007). Therefore, repeated shear stress stimulation of eNOS bioactivity during regular PA may improve endothelial integrity and function. Central and peripheral artery vascular health, however, may be mediated by different, independent mechanisms. This latter topic is explored further in Chapter 6.

2.2.1.2 Type 2 Diabetes Mellitus

2.2.1.2.1 Description and aetiology

Diabetes is a metabolic condition in which the body does not produce sufficient amounts of insulin (Type 1) to regulate blood glucose or where the insulin produced is unable to work effectively (Type 2). Type 1 diabetes is caused by auto-immune destruction of the insulin secreting cells in the pancreas, which often starts at a relatively young age. Thus, lifelong treatment via insulin medication is necessary. Development of Type 2 diabetes, however, is linked to a poor lifestyle and takes several decades to develop. Alarmingly, a recent report has

revealed a 41% increase in the diagnosis of Type 2 diabetes in individuals under the age of 25 years in England and Wales in the last 4 years (National Diabetes Paediatric Audit, 2018). Type 2 diabetes accounts for approximately 90% of total diabetes prevalence and despite extensive research of the condition, its aetiology is not fully understood (National Collaborating Centre for Chronic Conditions, 2008).

The condition has been deemed a 'micro- and macro-vascular time bomb' with the current UK prevalence (~3 million) estimated to more than double by 2030 (Knowler *et al*., 2009). Based on the 2007/2008 NHS budget (~£90.7 billion), it was estimated that 10% was spent on diabetes care (Diabetes in the UK 2010: Key statistics on diabetes). The Framingham heart study (Kannel & McGee, 1979) was the first to identify an increase in CVD in men and women with Type 2 diabetes and identify CVD as the leading cause of mortality in this population. Ninety percent of Type 2 diabetics are overweight/obese and the effect of hyperglycaemia and other risk factors contributing to atherosclerotic vascular disease is now well-established (Li *et al*., 2014).

Type 2 diabetes is progressive in nature requiring lifestyle management at all stages. Despite contentious beliefs of the causes of Type 2 diabetes, it is generally accepted that the disease has strong genetic and environmental components, and impairment of insulin sensitivity and insulin secretion are key elements in its pathogenesis (DeFronzo, 2004). The condition is characterised by hyperglycaemia, hyperinsulinaemia secondary to a reduction in insulin action at the liver and skeletal muscle (i.e. insulin resistance), and relative insulin deficiency (Olokoba *et al*., 2012).

During diabetes progression, pancreatic β-cells compensate for insulin resistance via adequate insulin secretion. Hyperinsulinaemia will occur if insulin resistance persists. Hyperinsulinaemia will persist until the pancreas β-cells cannot suppress glucose production in the liver and compensate for the dysfunction of glucose uptake in skeletal muscle, resulting in hyperglycaemia (DeFronzo, 2004). One issue for disease management is that individuals

with Type 2 diabetes mellitus can remain asymptomatic for many years before clinical diagnosis (American Diabetes Association, 2003). Generally, the later the diagnosis, the worse the prognosis. Insulin resistance, impaired glucose tolerance, and overt diabetes, are associated with an increased risk of CVD. The three conditions share a common presence of heightened oxidative stress. The common soil hypothesis postulates that, oxidative stress may be the pathogenic mechanism linking insulin resistance with both β-cell and endothelium dysfunction; eventually progressing into overt cardiometabolic disease (Ceriello & Motz, 2004).

2.2.1.2.2 Physical activity epidemiology and Type 2 diabetes

For decades, PA has been considered a cornerstone for diabetes management, along with diet and medication (Sigal *et al*., 2006). In one of the most clinically relevant diabetes RCTs; the Diabetes Prevention Programme Group (DPP; Knowler *et al*., 2002) measured diabetic incidence rates in pre-diabetics following either a metformin or a lifestyle protocol (e.g. 150-min PA per week, aim of 7% weight loss, and health education classes). Interestingly, the lifestyle protocol reduced diabetes incidence by 58% compared to placebo, which was significantly more effective than pharmacology (31%; $P<0.05$). A 10-year follow-up revealed a 34% and 18% reduction in the incidence of Type 2 diabetes in the lifestyle and metformin group, respectively (Knowler *et al*., 2009).

Specific guidance encourages individuals with Type 2 diabetes to complete aerobic exercise 3 days/week and resistance training 2 days/week as well as increasing total daily PA levels (Colberg *et al.,* 2010). A combination of regular aerobic and resistance training has been shown to be the most effective method for optimal improvements in glycaemic control (Sigal *et al*., 2007). Such findings provide promising support for both the prevention and management of Type 2 diabetes via increased PA levels. Unfortunately, only 39% of adults with Type 2 diabetes are reported to be physically active (Morrato *et al*., 2007). Thus, methods to facilitate PA behaviour change in this population are warranted.

Plotnikoff *et al*. 2011 compared standard Type 2 diabetes care (education only) to standard care supplemented with an 8-week individualised community-based PA programme. Whilst the supplemental group demonstrated significant increases in PA and CRF, both groups realised significant reductions in HbA1c (glycated haemoglobin; ~3-month average of glucose control). The authors concluded that PA counselling in addition to standard care was effective for promoting PA behaviour change, resulting in health-related outcomes among individuals with Type 2 diabetes (Plotnikoff *et al*., 2011).

As 90% of Type 2 diabetics are overweight or obese (Li *et al*., 2014), the independent effects of PA, CRF and obesity are particularly important for this population. Obesity has been shown to independently increase mortality risk by 20% and 28% in women and men, respectively (McGee, 2005). Moreover, an overweight individual can reduce their risk of developing Type 2 diabetes by up to 58% via reducing their body weight by 7% (Chan *et al*., 1994). It is intriguing, however, that up to 40% of individuals with a body mass index (BMI) within a normal range (18-25 kg/m^2) harbour metabolic abnormalities typically associated with obesity, such as hypertension, dyslipidaemia, non-alcoholic fatty liver disease, and CVD (Weiss, Bremer, & Lustig, 2013). In contrast, decreasing CRF by 1 metabolic equivalent (MET; 3.5 $ml.kg.^{-1}min^{-1}$) has been shown to increase mortality risk by 13% (Kodama *et al*., 2009). A meta-analysis (Barry *et al*., 2014) sought to quantify the joint association of CRF and weight-status on all-cause mortality. Findings illustrated that when compared to normal weight-fit individuals, unfit individuals had twice the risk of mortality regardless of BMI, and interestingly, 'obese-fit' individuals had a similar mortality risk as 'normal weight-fit' individuals.

When looking at diabetes risk specifically, a prospective population-based study with >38, 000 participants looked at the independent impact of PA and adiposity (Hjerkind *et al*., 2017). The authors concluded that although being physically active reduced the risk of developing diabetes, independent of being overweight or obese, there was no evidence to suggest that PA could entirely compensate for the adverse effect of adiposity on diabetes risk. Thus, both PA and adiposity are crucial risk factors to target in the prevention and management of diabetes.

2.2.1.2.3 Mechanisms of physical activity benefit

Position stands by the American College of Sports Medicine and American Diabetes association (Albright *et al*., 2000; Colberg *et al*., 2010) summarised the available evidence on PA and diabetes prevention/management. The papers present evidence on numerous beneficial physiological changes in Type 2 diabetics as a result of a physically active lifestyle, including, improved cardiac structure and function, enhanced oxygen extraction, and lower blood pressure at rest and during exercise. In addition, regular PA has important effects on diabetes-specific risk factors such as metabolic impairment (glucose control and insulin resistance; Albright *et al*., 2000; Colberg *et al*., 2010). In fact, PA has several positive acute impacts on the human body that are particularly beneficial to Type 2 diabetics, chiefly enhanced glycaemic control (Schneider *et al*., 1984). Enhanced glycaemic control is, however, diminished 72 hours after an episode of PA, reinforcing the importance of *regular* activity in diabetic populations. The benefits of PA on Type 2 diabetes management and prevention are typically realised through acute and chronic improvements in insulin action (resulting in improved glycaemic control).

Increases in skeletal muscle glucose transporter-4 (GLUT4) expression, 5'-AMP-activated protein kinase (AMPK) expression, and insulin activation of glycogen synthase have all been shown to contribute to increased insulin sensitivity following increased PA (Hughes *et al*., 1993; Prior *et al*., 2015). Whilst PA enhances these mechanisms contributing to glucose homeostasis, the effects are not universally long-lasting. For example, though the beneficial effects of PA occur at a systemic and cellular level, many effects (e.g. upregulation of AMPK and GLUT 4) appear to diminish within 3 to 10 days of detraining (Ivy, 1996). Conversely, some benefits of PA are longer lasting (in aerobically trained individuals) such as skeletal muscle capillarisation and fat distribution (Prior *et al*., 2015; Hjerkind *et al*., 2017).

As previously discussed, central adiposity is a key factor in Type 2 diabetes progression (Hjerkind *et al*., 2017); waist circumference alone has been shown to account for 40% of the

variance in insulin action, whereas age explained only 2% when waist circumference was controlled for (Ivy, 1996). Larsen *et al*. (2014), in a cross-sectional study of >500 participants, demonstrated that sitting time and leisure PA differentially associated fat distribution. More specifically, high levels of PA were associated with less visceral fat, even after controlling for several confounders including socioeconomic status and traditional CVD risk factors. Mechanisms responsible for fat distribution are not well understood, though it has been suggested that visceral fat is especially sensitive to the adrenal-driven adipocyte lipolysis (breakdown of fats) that occurs with increased activity (Murphy *et al*., 2012).

2.2.1.3 Dementia

2.2.1.3.1 Description and aetiology

Dementia is one of the major causes of disability in older people worldwide. It is a topical public health problem estimated to have an annual societal cost of >£23 billion in the UK alone (Luengo-Fernandez *et al*., 2010). Dementia is caused by permanent damage or death of brain cells and is manifested by loss of memory, language, thinking, orientation, learning capacity and judgement. Alzheimer's disease is the leading cause of dementia, estimated to account for ~60% of cases, followed by vascular dementia (WHO, 2012). Currently, no cure exists, therefore drug therapies typically target dementia symptoms, yet there is a lack of robust evidence supporting their impact (Petersen *et al*., 2018).

Paciaroni & Bogousslavsky (2013) highlighted in an editorial piece that there is an important relationship between cardiometabolic health and dementia. Supported by several animal studies, but also recent observational studies in humans, it is observed that generalised atherosclerosis and its risk factors play a pivotal role in the aetiology of dementia. Despite a paucity of research directly linking cardiometabolic health with Alzheimer's disease, the prevention of chronic vascular disease by identifying and treating known modifiable risk factors may reduce the incidence of mild cognitive impairment, vascular dementia and thus, dementia more generally (Paciaroni & Bogousslavsky, 2013; Grover & Somani, 2016). The

treatment and more importantly, interlinked preventative efforts towards cardiometabolic and cerebrovascular conditions are thus a timely public health agenda.

2.2.1.3.2 Physical activity epidemiology and dementia

Research is beginning to develop momentum with regards to investigating the effects of PA on dementia. A recent modelling study (Van Baal *et al*., 2016) found that lifetime spending on health and social care related to dementia was highest for the physically inactive. The authors demonstrated that inactive persons live shorter lives and spend a larger proportion of their life with dementia compared to their more active counterparts. Aligned with the PA dose-response message previously discussed (Department of Health, 2011; WHO, 2015), there is a large reduction in dementia prevalence from inactive to low-active individuals, yet, the magnitude of reduction is markedly reduced from low-active to those meeting the PA guidance (Van Baal *et al*., 2016). In other words, our return on investment for PA reduces as we get more active.

Fenesi *et al*. (2016) found physical exercise moderated the relationship between genotype and dementia in a population-based study. Specifically, the odds of developing dementia were deemed higher in 'non-exercisers' than 'exercisers' (OR=1.98, 95% CI=1.44, 2.71) for those not at a genetic predisposition for developing the condition. Given that most individuals are not at a genetically-elevated risk, physical exercise may be an effective strategy for preventing dementia (Fenesi *et al*., 2016). In support of this finding, a recent systematic review and meta-analysis of prospective studies included >117,000 participants with a maximum follow up of 28 years. The authors concluded that PA was protective against all-cause dementia, however they suggested that PA was more protective against Alzheimer's disease than it is for all-cause dementia, vascular dementia, and cognitive decline. Another systematic review reported that PA conveys a mild reduction on cognitive decline, but did not observe a dose-response relationship (Olanrewaju *et al*., 2016). In contrast, a recent large scale, multicentre RCT (Lamb *et al*., 2018) found that a 4-month aerobic and strength exercise programme of moderate-to-

high intensity (in addition to usual care) did not slow cognitive decline at 12-months follow-up in participants with mild-to-moderate Alzheimer's disease. In fact, it is possible that the intervention may have worsened cognition at 12-months. The exercise intervention improved physical fitness in the short-term, although this did not translate into activities of daily living, behavioural outcomes, or health related quality of life in the long-term. It is important to note, however, that the intervention consisted of 4-months structured exercise with no focus on lifestyle-based PA and no underpinning of behaviour change theory. The authors noted 'good' exercise compliance, with 65% of participants attending more than three quarters of the scheduled sessions. Without long-term behaviour change, however, it is perhaps not surprising that participant health/behavioural changes were not found at 12 months following a 4-month intervention. Therefore, large scale *PA* behaviour change trials are warranted in those at-risk of developing Alzheimer's disease. In agreement with the findings of Lamb *et al*. (2018), a population-based cohort study with participants who were over 75 years, demonstrated no significant effect of PA and risk of severe cognitive impairment or dementia (Deckers *et al*., 2017).

In summary, there is increasing evidence that higher levels of PA may be associated with reduced risk of cognitive decline. Yet, such conclusions are limited by a large variability in study design, assessment of cognition, definitions of dementia, a focus on exercise prescription rather than PA behaviour change, and use of self-reported PA measures. More broadly, residual confounding (not adequately accounting for potential confounders i.e. inaccurately measured or even unknown variables) and generalisability of findings are pertinent concerns in epidemiological research. Despite such limitations, the American Academy of Neurology have published a guidance update, which now recommends regular 'exercise' advice from a clinician to those with mild cognitive impairment (Petersen *et al*., 2018). Hopefully, future research will be more focussed on lifestyle-based PA behaviour change.

2.2.1.3.3 Mechanisms of physical activity benefit

Evidence is now beginning to emerge that lifestyle factors may have a profound impact on neurodegenerative conditions, previously deemed unmodifiable conditions resulting from advancing age and genetic predisposition (Yau *et al*., 2014). Experimental evidence has demonstrated that 700 new neurons are created (neurogenesis) in the hippocampus each day despite an overall reduction in neuron turnover as we age (Spalding *et al*., 2013). This is important, as a reduction in hippocampal neurons has negative impacts on cognitive function and is a key process in the pathogenesis of neurodegenerative disorders (Kee *et al*., 2007). Exciting research has proposed that 'physical exercise' may upregulate neurotrophins such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF), which have been recognized as primary mediators of neurogenesis (Yau *et al*., 2014). Although this research is in its infancy, it provides promising foundations for a more preventative view of neurodegenerative conditions.

The mechanisms involved in the pathogenesis of dementia (or Alzheimer's disease) can be categorised into systemic (impaired glucose metabolism, inflammation, and oxidative stress) and specific (trophic factors, amyloid burden, and calcium toxicity; Schelke *et al*., 2018). It is interesting to note that the systemic mechanisms are identical to those underlying CVDs and Type 2 diabetes, previously discussed. Thus, the systemic interventions identified in Figure 2-4 are important targets for the prevention of many cardiometabolic, cerebrovascular, and potentially even neurodegenerative conditions (Schelke *et al*., 2018).

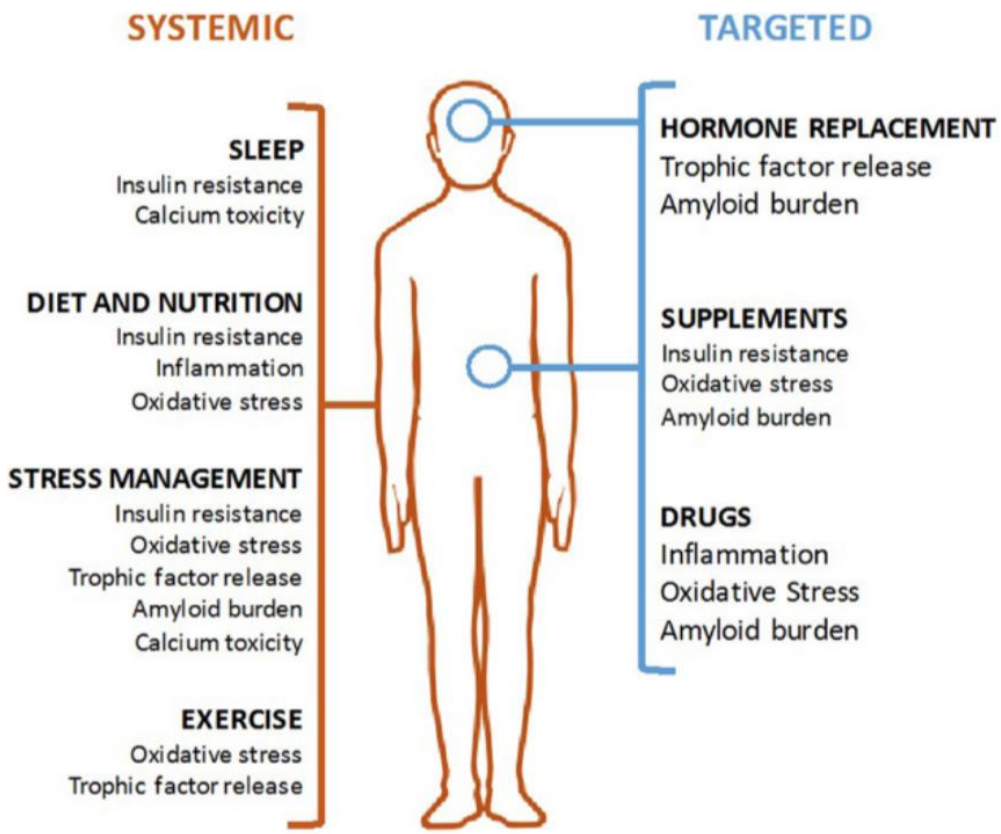


Figure 2-4. Modalities of dementia (Alzheimer's disease) prevention. Systemic interventions (in orange) should be the foundation of any prevention programme, whilst targeted interventions (in blue) can be used for Alzheimer's specific indications. Adapted from Schelke *et al*. (2018).

2.2.2 Physical activity and mental health

Promotion of positive mental wellbeing. Wellbeing has been defined as a balance between an individual's psychological, social, and physical resources and their psychological, social, and physical challenges (Dodge *et al*., 2012). Self-reported wellbeing has been considered an indicator of health status, with studies demonstrating a relationship with healthier physiological responses to stress, reduced probability of developing disease and improved immunity (Chida & Steptoe, 2008). Physical activity has been shown to positively enhance mental wellbeing at any age (Physical Activity Guidelines Advisory Committee, 2018). Until recently, little was known regarding the link between PA and wellbeing changes across the lifespan, with even less understood about causality and underlying mechanisms (Hyde, Maher & Elavsky, 2013).

In a representative sample of European adults from 27 countries, Marques *et al*. (2016) explored the relationship between achieving the recommended PA levels and several dimensions of self-reported wellbeing. The authors concluded that achieving the recommended PA levels was related to better wellbeing in several domains. Furthermore, more frequent PA was linearly associated with better wellbeing in several domains and as a summary score (Marques *et al*., 2016). Further studies are, however, needed to investigate the causality between PA and wellbeing, as well as to examine the effect of PA interventions to promote people's subjective wellbeing.

Treatment of mental illness. Mental illness is a rapidly expanding public health issue. Estimates by WHO (2016) demonstrated >154 million people globally suffer from depression, and that mental illness affects and is affected by chronic conditions such as cancer, CVDs, and diabetes. Individuals with long-term physical health conditions, for example, are up to 3 times more likely to experience mental health problems than the general population (Naylor, 2013). Mental health conditions tend to have a larger impact on health state utility than physical health conditions. The mental health conditions associated with the highest decrements in

utility are depressive and anxiety disorders (Roberts *et al.,* 2014). Alarmingly, only 24% of people in England with a common mental health problem receive treatment (McManus *et al*., 2009).

Evidence of the mental health benefits of PA is less well documented than for the physical effects. Although, it has been proposed that PA may have effects on treating depression comparable to Prozac or behavioural therapy (Dunn *et al*., 2005). A Cochrane meta-analyses and systematic review pooled findings from 39 intervention studies investigating the effect of exercise on depression (*n*=2326; Cooney *et al*., 2014). The authors found that exercise was moderately effective for reducing symptoms of depression, which was comparable to pharmacological treatment.

A subsequent meta-analysis sought to investigate the effect of exercise on individuals with depression whilst controlling for publication bias (Schuch *et al*., 2016). The study included the interventions used in the Cochrane review (Cooney *et al*., 2014) with additional research added from searches of major electronic databases. This resulted in 25 RCTs comparing exercise to a non-active arm for individuals with depression. The authors concluded that exercise had a large and significant effect on depression, with powerful anti-depressant effects, including for major depressive disorder. They proposed that previous meta-analyses may have underestimated the beneficial effects of exercise due to publication bias.

Prevention of mental illness. By the year 2020, WHO (2010) predicted that depression would make one of the greatest contributions to the overall disease burden. Given the high prevalence of depression globally, and its burden on wellbeing and the healthcare system, it would be intuitive to shift focus towards the prevention of mental illness. In a review of 30 prospective, longitudinal research studies, Mammen & Faulkner (2013) concluded that from a population health perspective, promoting PA may reduce the risk of developing depression. In 25 of the included studies, baseline PA was negatively associated with risk of subsequent depression. In

addition, there was promising evidence that any level of PA, including low levels (e.g. walking <150 minutes per week) may prevent future depression onset (Mammen & Faulkner, 2013).

Interestingly, the associations between PA and symptoms of depression and anxiety appear to be bi-directional (Silva *et al*., 2012). In a sample of >9000 participants, Silva *et al*. found regular PA was associated with reduced likelihood of depressive and anxiety symptoms. In a converse analysis, participants with anxiety and depressive symptoms at baseline had higher odds of not meeting the recommended levels of PA at follow-up.

A recent cross-sectional paper published in *The Lancet*, *Psychiatry* investigated the association between physical exercise and mental health in 1.2 million participants (Chekroud *et al*., 2018). The main finding was that those that exercised had ~40% better self-reported mental health than those that did not exercise, after controlling for several potential confounders including BMI, physical health, and socio-demographics. The authors also investigated the amount and type of exercise people did. It was highlighted that those who exercised for bouts of 45 minutes seemed to have better mental health than those who exercised for less than 30 minutes or more than 60 minutes. In addition, those that exercised 3-5 times per week reported better mental health than those outside of that range, demonstrating a potential inverted U-shaped curve for physical exercise dose and mental health. As this was a cross-sectional study with self-reported data, however, causal mechanisms cannot be determined. Although, an expanding body of evidence does suggest substantial positive effects of exercise and PA on mental health (Cooney *et al*., 2014; Schuch *et al*., 2016).

2.3 UK Exercise Referral: A Public Health Panacea for Physical Activity Promotion?

Whilst several population-based approaches have been identified to facilitate increased PA levels (Trost *et al*., 2014), exercise referral schemes (ERSs) have been recognised as a more direct approach for clinical and population sub-groups (Williams *et al*., 2007). These

programmes are of particular interest as the referral originates from a respected healthcare professional such as a general practitioner (GP) who sees the most at-risk populations. Aligned with this perspective, the principle of proportionate universalism states that the greatest efforts should be directed towards the most at-risk populations (Marmot *et al*., 2010). As such, ERSs were thought of as a 'public health panacea for PA promotion' and proliferated throughout the UK since the early 1990s (Dugdill *et al*., 2005).

2.3.1 UK exercise referral: The current picture

There are >600 different ERSs in operation across the UK, which typically involve referral for inactive/sedentary individuals with or at-risk of developing health conditions to a subsidised exercise programme (typically 8-26 weeks) at a local fitness centre (Pavey *et al*., 2011a; 2011b; Rowley *et al*., 2018). Although grouped under the term 'ERSs', they are highly heterogeneous in terms of duration, delivery environment, eligibility criteria, funding, and local demographic (Department of Health, 2001). Several guidance documents exist for UK ERSs that aim to provide support for those developing, delivering, evaluating, and commissioning these programmes. The National Quality Assurance Framework for ERSs (Craig *et al*., 2001) provides guidance and recommendations for quality standards. The British Heart Foundation exercise referral toolkit (BHF, 2010) comprises of 6 guidance documents each specific to a particular perspective in the exercise referral system, including guidance for; healthcare professionals, exercise professionals, coordinators, commissioners, evaluators, and information on qualifications and training. Finally, the NICE (2014) guidance updated previous evidence-based recommendations for UK ERSs (NICE, 2006). In response to a lack of robust evidence of clinical and cost effectiveness (Pavey *et al*., 2011a; 2012), NICE (2014) recommended that practitioners, policy makers, and commissioners should only endorse ERSs that a) include behaviour change components and b) include evaluation to determine effectiveness.

Evidence of the impact of participation in ERSs on health/behaviour when compared to usual care has been deemed equivocal (Williams *et al*., 2007; Pavey *et al*., 2011b; Pavey *et al*., 2012).

It has been proposed that there are fundamental issues with the UK exercise referral infrastructure that limit the ability of ERSs to promote PA behaviour change (Markland & Tobin, 2010). Some exercise referral programmes lack any systematic approach to facilitating long-term PA behaviour change and have typically focused on short-term exercise prescription and adherence rather than long-term behaviour/health outcomes (Craig *et al*., 2001). Such system-based issues may have stemmed from the 1990s when ERSs were rapidly implemented at scale, without underpinning theory or appropriate evidence-base (Sowden *et al*., 2008). For perspective, one GP hour of patient contact time costs the NHS £242 (Unit costs of health and social care, 2017). In contrast, it costs ~£225 to put an individual through a 12-week ERS (NICE, 2014). If ERSs can be developed and successfully implemented to promote PA as an effective management tool for health conditions, the potential cost savings are substantial.

A primary issue for exercise referral initiatives is participant adherence. Systematic review data has reported wide-ranging uptake and adherence rates for ERSs (28-100% and 12-93%, respectively; Pavey *et al.*, 2012). It has been suggested that adherence is greater in areas of high socioeconomic deprivation and people living in areas of high deprivation place a higher value on ERSs than those living in areas of lower deprivation (Edwards *et al*., 2013). This is important, as it is those that live in low socioeconomic areas that suffer the most from health inequalities (Mackenbach *et al*., 2008). Thus, it is these populations that provide promise for ERSs to have a substantial public health impact (Edwards *et al*., 2013). If adherence can be improved overall, or if eligibility criteria for ERS narrowed to specific populations most likely to benefit, ERSs could be cost-saving (Edwards *et al*., 2013).

A systematic, mixed methods review found that adherence rates for community-based, group exercise interventions was ~69% on average (Farrance *et al*., 2016). They proposed that incorporating the views of service users into programme design may provide guidance for innovative interventions leading to improved adherence. Furthermore, it has been suggested that certain populations may be more suited to the exercise referral process. It has been proposed that research is needed to ascertain what types of PA are most appropriate for

certain population sub-groups (Rowley *et al*., 2018). An alternative perspective, is that if researchers, policy-makers and practitioners are to improve adherence and outcomes from these schemes, it may be necessary to develop a more holistic referral infrastructure that incorporates both behaviour change components and a focus on PA as opposed to the more traditional focus on exercise prescription (Duda *et al*., 2014; Oliver *et al*., 2016; Reis *et al*., 2016).

Campbell *et al*. (2015) provided an updated systematic review of the effectiveness of UK ERSs following the well-cited Pavey *et al*. (2011a). Campbell and colleagues pooled findings from eight RCTs, (one additional RCT and one qualitative studies to Pavey *et al*.) culminating 5190 participants. They found a pooled mean increase of 55 minutes of MVPA for ERSs compared to controls. Yet, cost effectiveness analyses revealed considerable uncertainty with large variance (£8,000 to £79,000 per quality adjusted life year; QALY) dependent on the sub-population (Anokye *et al*., 2011; Campbell *et al*., 2015).

Such systematic review findings (Pavey *et al*., 2011a; Campbell *et al*. 2015), however, have been deemed an unfair representation of the *potential* of ERSs to impact public health (Beck *et al*., 2016). This isn't an issue with the systematic reviews themselves, per se, but the limitations of RCT data that have made minimal reference to behaviour change theory, limited focus on long-term PA behaviour change, and have lacked multi-stakeholder involvement (NICE, 2014). Thus, such controlled evaluations do not represent diverse perspectives or the complexity of context (Pawson, 2013). In addition, there has been no known focus on the development of ERSs to the point where they were deemed to have a worthwhile effect in practice, as recommended by the MRC guidance for the evaluation of complex interventions (Craig *et al*., 2008). Furthermore, exercise referral effectiveness has been estimated based on selected morbidities, and there may be other conditions not included in the systematic-analyses that are alleviated following an ERS. Finally, all data used to determine clinical/cost effectiveness has been derived from self-reported PA measures. The only objective measures included in the systematic reviews were body weight and blood pressure, arguably removed from appropriate

primary outcomes of a holistic PA intervention (Catenacci & Wyatt, 2007; Johns *et al*., 2014). Thus, research is warranted that has high ecological validity and utilises appropriate and objective health outcomes, to better answer how ERSs can impact public health.

2.3.2 UK exercise referral: Recent progress and future directions

Despite an equivocal picture of UK exercise referral effectiveness (NICE, 2014), there is a growing body of evidence demonstrating improvements in intervention design and potential public health impact. A recent systematic review of 13 studies highlighted promising evidence of ERSs impact on cardiovascular and mental health outcomes (Rowley *et al*., 2018), though limited research for musculoskeletal disorders (Steele *et al*., 2017). Overall, ERSs resulted in significantly increased self-reported PA levels and adherence to prescribed PA over time as well as reduced blood pressure and BMI. For those referred for mental health reasons, significant reductions in anxiety and depression were reported. In terms of the interventions, longer-term ERSs (e.g. ~20 weeks) were more likely to be effective at increasing PA levels and improving cardiometabolic health markers than shorter interventions. Further, the use of one-to-one gym-based exercise sessions incorporating both resistance and aerobic training (as well as group exercise sessions) was deemed effective (Rowley *et al*., 2018). Despite this support for short-term benefits, the focus of ERSs has remained with gym-based initiatives with little attention directed to long-term PA behaviour change.

A retrospective pragmatic evaluation of an ERS for adults with physical and/or mental health conditions investigated the change in self-reported PA levels and anthropometric measures at 6-months follow-up (McGeechan *et al*., 2017). The intervention incorporated a 12-week exercise programme including a choice of supervised gym access, group classes and swimming. The authors concluded that the increase in PA levels at 6 months emphasised promising potential for ERSs to improve the health of adults with existing health conditions. Whilst changes in PA levels are often reported to be of short-term (Pavey *et al*., 2011b), these findings demonstrated a significant impact on PA (moderate effect size) at 6 months, with no change

between week 12 and 6-month follow-up. These results are promising, as research suggests individuals who have engaged in a new behaviour for ≥6 months are more likely to engage in that behaviour in the long-term (Fortier *et al*., 2012). Despite this, the authors documented substantial patient drop out with 211/494 participants completing the 12-week scheme and 135/494 completing 6-month follow-up. A 'number needed to treat' approach is the number of patients you would need to treat to prevent one additional negative outcome (death, stroke, MI etc.). If one were to take such an approach with the above study (McGeechan *et al*., 2017), inferences are likely to be substantially less promising (due to the high dropout rates). Accounting for adherence is an important perspective for commissioners and public health researchers interested in cost-effectiveness.

Exercise referral schemes have also shown promise for increasing PA in specific sub-populations. In a multi-centre, cluster RCT, Gaskin *et al*. (2017) demonstrated that a 12-week ERS improved self-reported PA at 6 and 12-month follow-up in prostate cancer patients. The intervention group reported increased volume of PA at 12 weeks and increased intensity of PA at 6 months (33 minutes more vigorous-intensity PA compared to control). No changes in secondary outcomes were reported including measures of quality of life, anxiety and depressive symptoms. It was noted, however, that measures of quality of life, anxiety and depressive symptoms were relatively high at baseline, which may explain the lack of effect. Further, a slight decline in PA volume at 12 months (though not significant) indicated a need for ongoing support, practitioner follow-up sessions, and community-based programmes that promote long-term behaviour change (Gaskin *et al*., 2017).

In contrast, Stewart *et al*. (2017) investigated the short-term effects of an ERS reportedly aligned to NICE (2014) UK best practice guidelines (though it is unclear exactly how this was achieved) using a longitudinal design. The study mapped outcome measures to those associated with key health concerns of the local area (Scotland). Following a 12-week ERS, they observed significant improvements in objectively measured lung function and VO_2peak as well as several psychosocial outcomes including quality of life and mood state (for those that

adhered to the intervention). The study did however, report substantial participant drop-out, did not include a control, and presented data per protocol. Thus, further research is needed to substantiate these findings. Of interest, data inferred that for all health-related physical fitness measures, individuals who presented with the least favourable baseline profile benefited the most. This response may provide promise for the potential for ERSs to impact health inequalities, based on our knowledge of proportional universalism. Conversely, this finding may simply represent a 'regression to the mean' effect, whereby the more extreme a measurement at baseline, the more likely it is to be closer to the mean on a subsequent follow up.

Another study utilised a variety of objective health markers to assess the impact of three exercise interventions, though device-measured PA was not included (Webb *et al*., 2016). The authors compared: 1. a continuously monitored exercise programme based within a university; a community-based outdoor exercise programme; and a Welsh ERS. Whilst the lab-based university programme achieved more intense exercise and correspondingly more pronounced health effects, significant cardiovascular risk-lowering health benefits (biomolecular markers, blood pressure, arterial stiffness and blood lipids) were achieved via both the community- and exercise referral-based delivery modes (Webb *et al*., 2016).

Whilst these findings highlight the potential benefits of using appropriate and objective health measures when evaluating complex real-world PA initiatives, the utilisation of device-measured PA remains sparse. Future work is in progress that aims to measure PA via accelerometry to evaluate the effectiveness of a large-scale ERS augmented with web-based behavioural support for at-risk populations (Ingram *et al*., 2018). Nevertheless, an interesting point of discussion is what is defined as success with regard to exercise referral. Traditional markers of success have typically included attendance, weight loss, and blood pressure (McNair *et al*., 2005). In practice, however, exercise referral impact perceived by end-users and practitioners has been appreciated in a more holistic manner incorporating a diverse set of psychosocial outcomes (Mills *et al*., 2012). Correspondingly, it has been recommended that

evaluations of ERSs incorporate qualitative and quantitative measures to contribute to the development of a comprehensive evidence-base (Dugdill, Stratton, & Watson 2009). Such an approach may facilitate the capture of additional health benefits that arise from non-medical forms of healthcare beyond the traditional measures of success.

Attempts to incorporate behaviour change theory into ERS provision, both within and outside the UK exist but are limited (Lawton *et al*., 2009; Jolly *et al*., 2009; Murphy *et al.,* 2012; Duda *et al*., 2014; Littlecott *et al*., 2014). The successful implementation of behaviour change theory is important; a meta-analysis by Gourlan *et al*. (2015) has suggested that theory-based interventions are more likely to be efficacious in promoting PA. Similarly, Mckay *et al*. (2003) and Dugdill *et al*. (2005) have advocated that more holistic evaluation research is needed, incorporating behavioural, psychosocial, and physiological health outcome measurements that better address the complexity of physical inactivity and public health. There are numerous psychological theories that can be drawn upon in behaviour change interventions, one of the most prominent theories utilised within a PA context is Self-Determination Theory (SDT; Deci & Ryan, 1985; Teixeira *et al*., 2012). Self-Determination Theory is a psychological theory based on the premise that motivation for behaviour change can be autonomous (e.g. related to enjoyment and choice) or controlled (e.g. related to guilt, pressure and/or coercion) and it is how the individual perceives their environment/reason for change that is important (Ryan & Deci, 2000). According to SDT, an individual has three innate psychological needs that can facilitate autonomous motivation and adherence to a particular behaviour: autonomy (e.g. perception of choice and personal input), competence (e.g. individuals feel efficacious and perceive that they can meet the demands placed upon them), and relatedness (e.g. individuals feel supported and/or connected with others). Strong evidence exists in support of SDT in diverse situations including: positive health behaviour change (Ng & Ntoumanis, 2012); weight loss (Silva *et al*., 2011); medication adherence and quality of life (Williams *et al*., 2009); and PA participation (Edmunds, Ntoumanis, & Duda, 2006; Fortier *et al*., 2012; Teixera *et al*., 2012).

In an attempt to incorporate and analyse behaviour change theory principles in an ERS setting, Duda *et al*. (2014) completed an exploratory, cluster RCT comparing a standard provision ERS with a scheme grounded in SDT (Deci & Ryan, 1985). Duda and colleagues identified significantly increased PA and improved quality of life and wellbeing outcomes, in both the standard and theory-based ERSs. The results indicated that both interventions increased PA levels at 6-months to a degree that would improve health, though no between group differences were found. The authors suggested this may have been due to the intervention not being delivered as intended i.e. a lack of fidelity, as there was no difference in the level of needs support provided by instructors in the two conditions (standard vs SDT-grounded). This highlights a key challenge of implementing behaviour change theories in practice. Needs-supportive communication strategies may come more naturally to some practitioners than others, hence some of the instructors in Duda *et al*.'s (2014) study were found to be delivering in a needs-supportive manner without training, whereas others underwent the training but were less needs-supportive in their communication. Moreover, the lack of difference between groups could be explained by the fact practitioners' use of behaviour change techniques often deviate from intended protocols (Beck *et al*., 2016). It is noteworthy, however, that the authors conducted a process evaluation that supported the SDT model; i.e. patients for whom needs satisfaction increased, became more autonomously motivated and more physically active (Duda *et al.,* 2014).

Similarly, another example of a holistic research approach, the Wales National Exercise Referral Scheme (NERS), consisted of a 16-week programme that included behaviour change techniques and on-going one-to-one support, designed to promote long-term PA levels. A pragmatic randomised controlled trial evaluated the effect of the Welsh NERS vs usual care in a sample of 2160 inactive individuals (Murphy *et al*., 2010; 2012). The study identified significantly increased PA in participants randomised to the NERS compared to those receiving usual care (albeit, for CVD referrals only). For patients referred for mental health problems, depression and anxiety improved, despite a lack of effect on PA. The Welsh NERS provides a

promising example of the potential of PA referral schemes to elicit a variety of meaningful health outcomes, when incorporating evidence-based practice (Moore *et al*., 2012; Murphy *et al*., 2012). Mediation analyses demonstrated that effects of the Welsh NERS on PA were largely explained via improvements in autonomous motivation. Interestingly, the least active patients who entered the scheme typically experienced the greatest improvements in autonomous motivation (Littlecott *et al*., 2014). A process evaluation of the Welsh NERS, however, identified that despite having a promising impact on PA and mental health, motivational interviewing, goal-setting, and patient follow-up protocols were delivered poorly (Moore *et al*., 2013). This therefore raises questions as to the importance of these components, if positive outcomes were achieved anyway or that the mechanistic details are less important than we currently think. Finally, the primary outcome, PA, was measured via a 7-day recall questionnaire, which may raise questions regarding the validity of the study's implications.

Despite promising research emerging, there is still a sparsity of robust evaluations that have incorporated *objective* behavioural, psycho-social, and/or physical health outcomes. Alarmingly, no known studies to date have included long-term follow-up of such measures. Further, participant adherence continues to be problematic in the more recent ERS literature, potentially a result of a lack of attention given to process evaluation and behaviour change theory. Hanson and colleagues (2013) undertook a naturalistic observation to evaluate the efficacy of an ERS in Northumberland for increasing PA levels and to identify predictors of engagement. The study noted significantly increased (self-reported) PA at 6 months for those who completed the scheme compared to baseline in a cohort of >2000 participants covering nine different leisure centres. Both personal and referral characteristics were found to be predictors of uptake and length of engagement with the ERS. For example, greater BMI and deprivation were negative predictors whilst, increasing age and referral from a cardiac rehabilitation nurse were positively associated with 12-week adherence. Leisure site was a significant predictor of uptake as well as 12 and 24-week adherence (Hanson *et al*., 2013). Patterns of ERS uptake and engagement are complex and different population sub-groups may

require different support to increase PA levels, or may not be suitable for traditional ERSs, at least in isolation (Morgan *et al*., 2016; Kelly & Barker, 2016). Further work is needed to elucidate the predictors and barriers of ERS uptake and engagement to better inform future intervention development.

In summary, research on exercise referral has made some promising advances for increasing participant health. Yet, there has been limited reference to the delivery, theories, or techniques of health behaviour change that typically underpin interventions to promote an increase in long term PA (Michie *et al*., 2009). Indeed a recent systematic review, meta-analysis, and meta regression concluded that the effectiveness of behavioural interventions was improved when delivery included more extensive and face-to-face contact (Haghighi, Mavros, & Singh, 2018). Thus, if exercise referral initiatives are to reach a point where they may have a worthwhile effect, investment in intervention development and mixed methods pilot work is needed prior to conducting definitive trials (Craig *et al*, 2008). This includes the need for appropriate, objective outcome measures, incorporation of local stakeholders, and embedded process evaluation to elucidate the active ingredients that are crucial for replication.

2.4 Efficacy versus Effectiveness in Sport and Exercise Medicine

"*Science, I had come to learn, is as political, competitive, and fierce a career as you can find, full of the temptation to find easy paths*."

(Paula Kalanithi, When Breath Becomes Air, 2016; p. 27)

The lack of successful implementation of research knowledge into community settings where it can have the most impact is a primary problem for the public health sector (Nutbeam, 1996; Brownson *et al*, 2006). Typically, academics are focussed on scientific-rigour and reliability, whilst service commissioners need immediate, clear answers (Lamont *et al*., 2016). As previously touched on, research that has demonstrated the numerous health benefits of PA, has *typically* used interventions that were too intensive and expensive to scale up at a

population level (Lawton *et al.,* 2008; Reis *et al*., 2016). One emerging area of scrutiny is the use of efficacy trials to inform real-world practice. Efficacy, demonstrated in phase I-III clinical trials, denotes "the extent to which a drug has the ability to bring about its intended effect under ideal circumstances" (Hill, 2012, page 2). In contrast effectiveness, demonstrated in phase IV clinical trials, denotes "the extent to which a drug achieves its intended effect in the usual clinical setting" (Hill, 2012, page 3). Replace drug with your variable of choice e.g. PA intervention, and it becomes clear that effectiveness is what matters to commissioners and patients.

2.4.1 The need for a complex systems approach

Evidence-based medicine is a concept developed to facilitate the selection of the best available evidence to inform clinical decision-making, whilst acknowledging the potential impact of bias (Sackett *et al*., 1996). Figure 2-5 highlights the traditional evidence-based medicine hierarchy, depicting systematic reviews and meta-analyses of high-quality RCTs at the top, i.e. the gold standard of scientific evidence representing results with the least bias. It is of note, however, this hierarchical model does not consider real-world application or implementation success (ecological validity).

Figure 2-5. Traditional evidence-based medicine hierarchy – adapted from Murad *et al*. (2016).

Whilst RCTs represent the gold standard in the academic domain, these highly-controlled environments lack ecological validity and provide little information about the challenges faced by policy-holders and practitioners when implementing interventions in the real world (Sanson-Fisher *et al*., 2007; Watson *et al*., 2012). Rather than completely disregarding RCTs due to these pragmatic and ecological limitations, however, more of an appreciation and acceptance of real-world methodologies is warranted. Indeed, better 'research preparation' is required prior to definitive evaluations, particularly for complex interventions. For example, PA and public health researchers could make better use of feasibility and pilot phases to enhance the rigour and usefulness of future more definitive trials (El-Kotob & Giangregorio, 2018).

Despite major investment in research and policy, many public health challenges remain. To date, evidence underpinning responses to these challenges has largely been grounded in linear

models of cause and effect (Rutter *et al*., 2017). A number of definitions for a complex intervention exist in the literature, although consistent elements include multiple interacting components and non-linear, causal pathways (Petticrew, 2011). From a health perspective, translational research refers to the transfer of research knowledge to those populations for which it is intended, ensuring that it is *implemented* correctly (Woolf, 2008). It goes beyond the 'bench-to-bedside' research focus and aims to directly inform practice. This type of research struggles with complex problems involving human behaviour, organisational inertia, infrastructure and resource constraints, as well as the messiness of proving the effectiveness of moving targets under conditions that are not controlled by investigators (Woolf, 2008).

Finally, whilst outcome evaluation is crucial to answer the question "does it work?" it is only through understanding the implementation of interventions in real-world contexts is it possible to "*build a cumulative understanding of causal mechanisms, design more effective interventions, and apply them appropriately across groups and settings*" (Craig *et al*., 2008, P. 7; Moore *et al*., 2012). In other words, a shift in thinking is needed, away from linear, causal models, to consideration of the ways in which processes and outcomes within a system drive change. Instead of asking whether an intervention works to fix a problem, researchers should aim to identify if and how it contributes to reshaping a system in a favourable way (Rutter *et al*., 2017).

2.5 Methodology, Aims and Objectives

The previous chapters have demonstrated the importance of PA as medicine (Section 2.2) and the challenges of translating scientific evidence to real-world practice (Section 2.4). Despite promise as a tool to facilitate at-risk population PA behaviour change, evidence of UK exercise referral effectiveness is limited (NICE, 2014). Such schemes originally proliferated throughout the UK unsupported by scientific-evidence or underpinned by behaviour change theory. In light of this, NICE (2011) called for these schemes to be evaluated. Yet, adherence to evaluation

frameworks is often poor and there has been limited priority given to process evaluation components – i.e. what intervention components work /or not in practice.

One potential solution may be the utilisation of research-practice partnerships (Hanson & Jones, 2017). The importance of trans-disciplinary partnerships has long been recognised in public health (Roussos & Fawcett 2000). More recently, there has been renewed interest in and advocacy for the adoption of co-production as a means of co-creating value across the public sector (Clarke *et al*., 2017). The concept was first coined in 1970 when social policy recognised the benefits of including end-users in the delivery of their own public services (Realpe & Wallace, 2016). Co-production therefore emphasises the importance of collaboration between service providers and service users. Since conceptualisation, various terminology has evolved, yet a recent definition appears to be popular within the medical and public health literature: 'the involvement of public service users in any of the design, management, delivery and/or evaluation of public services' (Osborne, Radnor & Strokosch, 2016). In a healthcare context, such participatory, co-production methods should draw on stakeholder knowledge in addition to the available scientific evidence in both the design, and crucially, the delivery of services (Batalden *et al*., 2016; Hunter & Visram, 2016). A participatory, co-production research approach may facilitate knowledge translation and production. Such action orientated, collaborative research may provide researchers with a tool to help bridge the gap between scientific-evidence and real-world practice. Multi-stakeholder involvement provides important insights into the feasible implementation of interventions in the real world. In turn, this may lead to interventions that are more context-sensitive and sustainable within local infrastructures (Harden *et al*., 2016).

This PhD was underpinned by a phased approach outlined by the Medical Research Council (MRC) guidance for the development and evaluation of complex interventions (Craig *et al*., 2008). The MRC recommend that "before undertaking a substantial evaluation you should first develop the intervention to the point where it can reasonably be expected to have a worthwhile

effect" (Craig *et al*., 2008, p.9). Figure 2-6 outlines the MRC phased approach used to underpin the subsequent chapters.

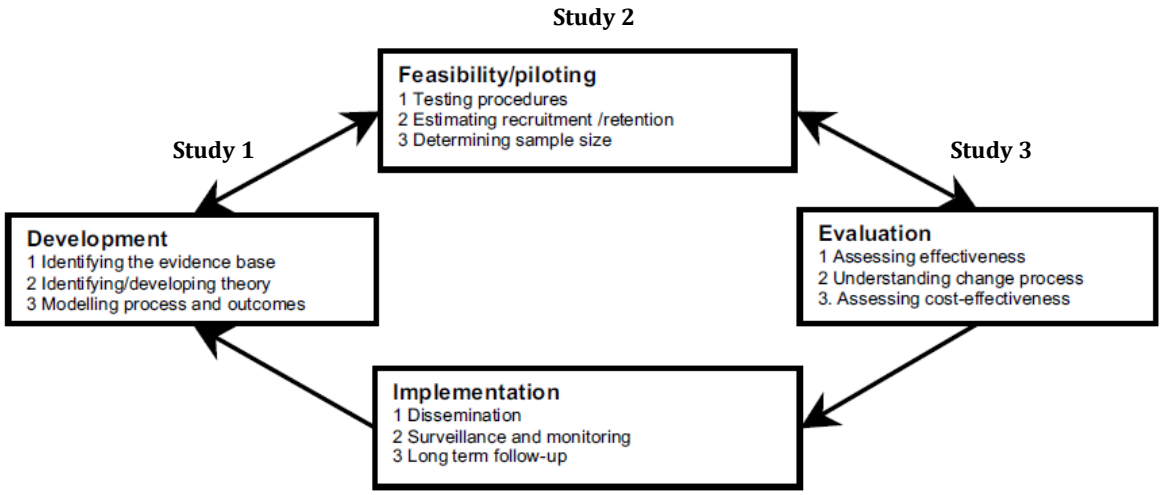


Figure 2-6. MRC-phased approach for complex intervention development and evaluation adapted from Craig *et al*. (2008).

Focussing on both outcome and process components, the following pragmatic PhD aimed to iteratively co-produce, pilot, and evaluate an evidence-based approach to promote PA for adults with health conditions. Specific objectives were to:

Study 1: Co-produce a PA referral scheme with a multidisciplinary group of academics and local stakeholders (*Chapter 4*).

Study 2: Pilot a co-produced PA referral scheme with the aim of:

a) Exploring preliminary effectiveness and intervention acceptability (*Chapter 5*).

b) Investigating the cardio-protective effects of a real-world PA referral scheme in an at-risk cohort (*Chapter 6*).

Study 3: Pragmatically evaluate the effectiveness of a co-produced PA referral scheme via a quasi-experimental trial with embedded process evaluation (*Chapter 7*).

2.5.1 Rationale

The methodology outlined above was chosen in order to address the current gaps in the literature, and were underpinned by a pragmatic evaluation framework (Bauman & Nutbeam, 2013). Specifically, the evidence-base for UK exercise referral has typically lacked reference to behaviour change theory and interventions have been evaluated without any prior development work (NIICE, 2014). Thus, through utilising participatory research methodology, we aimed to co-produce a PA referral scheme that was deemed appropriate for the local resources and demographic by a multidisciplinary stakeholder group (Study 1).

Whether this co-produced scheme was feasible in practice, however, required investigating. Both outcome and process evaluation components would therefore be needed to investigate the preliminary health impact and identify intervention teething problems. As such, the intervention components needing further refinement could be adapted prior to a more definitive trial.

Following any necessary intervention refinement, study 3 aimed to evaluate the co-produced PA referral scheme via a quasi-experimental trial. This design would allow for the evaluation of health outcomes (CRF), but also process information regarding intervention acceptability through embedded process evaluation. It was decided that an RCT was not feasible for two reasons: 1. It was not ethical to randomise at the individual level as it was important participants could choose the most suitable fitness centre, and 2. It was important to carry on working with the same fitness centre (following the co-production (study 1) and pilot work (study 2)) in order to develop the intervention to the point where it was deemed to have a worthwhile effect (Craig *et al.,* 2008). In summary, this phased research approach was deemed the most appropriate (over more traditional RCT designs) in order to iteratively develop and evaluate a PA referral scheme with high ecological validity.

3 GENERAL METHODS

3.1 Introduction

This chapter describes general information regarding data collection and analyses from the experimental conditions for the physiological, behavioural and psychosocial outcome measures used in studies 2 and 3. Methods for study 1 (co-production phase) and specific study protocols are detailed within the methods sections of the respective chapters (chapters 4-7).

3.2 Experimental Conditions

Experimental protocols were conducted in a temperature controlled (20-22 °C) laboratory at the Research Institute for Sport and Exercise Sciences at Liverpool John Moores University. For multiple laboratory visits, participants attended at the same time of day as their baseline testing. Prior to laboratory visits, participants were instructed to avoid strenuous exercise for 24 hours, fast for ≥6 hours and abstain from caffeine and alcohol for ≥12-hours. All study procedures were approved by NHS Ethics Committees (Study 1: 16/EM/0157; Study 2: 16/WA/0231; Study 3: 18/NW/0039; see appendix 3) and adhered to the Declaration of Helsinki.

3.3 Anthropometrics

For each participant, anthropometric measures of height and body mass were collected according to the anthropometric standardisation manual (Lohman, Roche & Martorell, 1991). Height was measured using a portable stadiometer (SECA, Hamburg, Germany) with the participant's head in the Frankfort Plane. Body mass was measured in minimal clothing and without shoes, using an electronic scale (SECA 799, Hamburg, Germany). Waist circumference was measured with a flexible tape measure between the lowest rib and iliac crest. Body mass index (BMI; mass/height^2) and waist to height ratio (height/waist circumference) were subsequently calculated.

3.4 Vascular Function

3.4.1 Brachial artery flow-mediated dilation

Flow-mediated dilation (FMD) provides a non-invasive assessment of endothelial function by measuring a peripheral artery's vasodilator capacity (Harris *et al*., 2010; Thijssen *et al*., 2011). The method involves placement of a cuff around the forearm, distal to the site being scanned, which is then inflated for a period of 5 minutes to elicit localised ischaemia. Following cuff deflation, a rapid re-introduction in blood flow (reactive hyperaemia) occurs, increasing shear stress (pressure exerted on vessel wall) which in turn, causes vasodilation (Pyke & Tschakovsky, 2007). See Figure 3-1 for a visual representation of the technique.

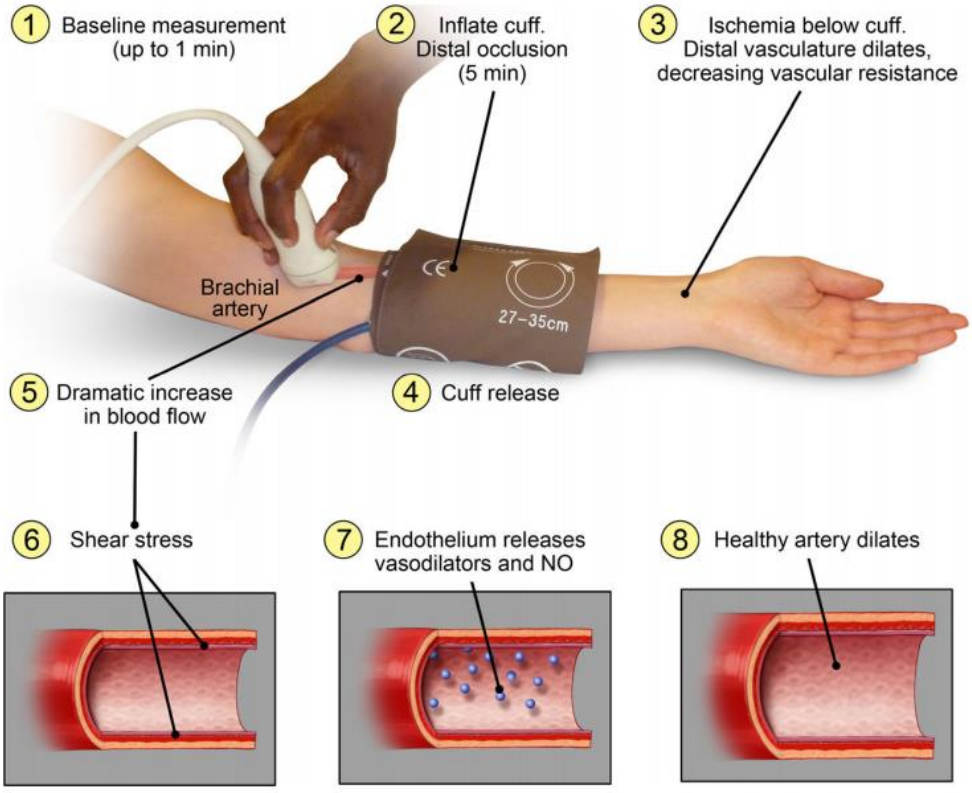


Figure 3-1. Brachial artery flow-mediated dilation (FMD) protocol. 1. one minute baseline measurement, 2. Five minutes of cuff occlusion (distal to site being scanned) and 4. Three minutes of reactive hyperaemia (adapted from Weissgerber, 2014).

Assessment of brachial artery FMD (Figure 3-2) was performed in-line with published guidance (Thijssen *et al*., 2011). A rapid (inflation and deflation) pneumatic cuff (D.E. Hokanson, Bellevue, WA, USA) was positioned around the left forearm with the proximal border adjacent to the medial epicondyle. Duplex mode ultrasound was used to image the vessels, via a high-resolution ultrasound machine (Terason, 3300, Teratech) attached to a 10-12-MHz probe. This enabled two-dimensional imaging of the vessel diameter (B-mode), and determination of blood flow velocity (Doppler; Figure 3-3; Harris *et al*., 2010). Ultrasound parameters were optimised to achieve a satisfactory image of the artery diameter (B-mode) from which, the ultrasound probe's position was maintained for the remainder of the protocol. Simultaneously, brachial artery blood flow velocity was assessed via Doppler ultrasound with an insonation angle of 60°. Baseline arterial diameter and blood flow velocity were recorded for one minute. Following this, the cuff was inflated to suprasystolic (~220 mmHg) for five minutes to induce local ischaemia. Following cuff deflation, arterial diameter and blood flow velocity recordings were continued for a further three minutes.

This method of vascular health was selected as it is widely used in clinical research (Greyling *et al*., 2016), likely due to its prognostic value. For example, FMD is predictive of cardiovascular events in both asymptomatic individuals and those with cardiovascular diseases (Thijssen *et al*., 2011). Meta-analyses have shown that brachial FMD is inversely associated with CVD incidence (Inaba *et al*., 2010) and a 1% decrease in FMD is associated with a 13% higher risk of a future cardiovascular event (Inaba *et al*., 2010; Green *et al*., 2011).

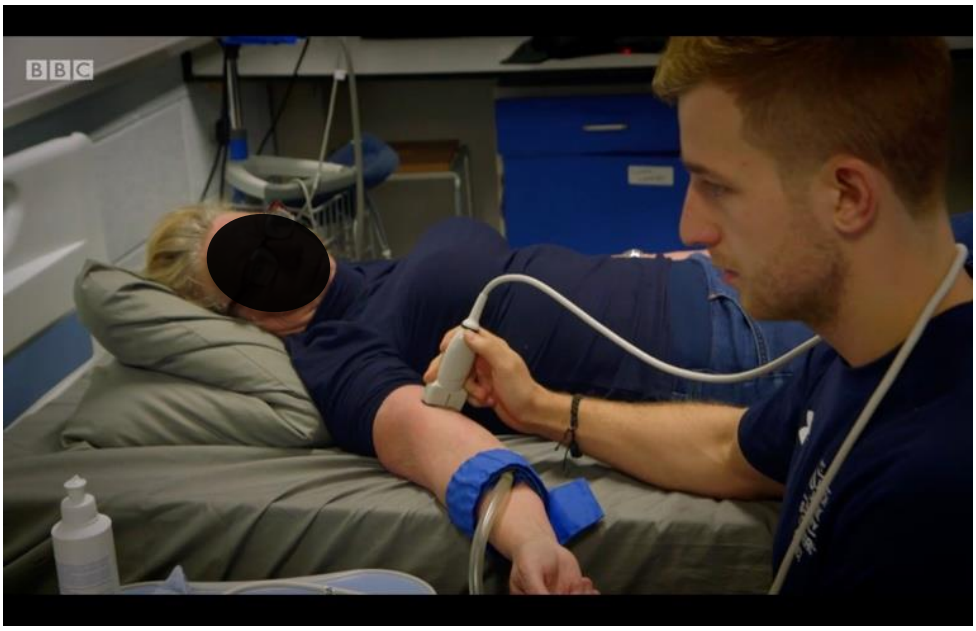


Figure 3-2. Assessment of brachial artery endothelial function using the flow-mediated dilation (FMD) technique (BBC – Trust Me I'm a Doctor).

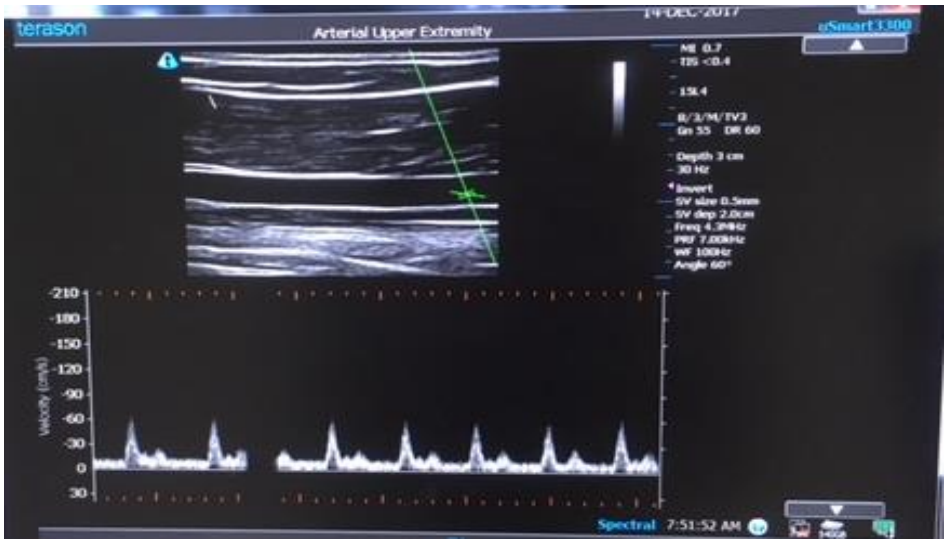


Figure 3-3. Simultaneous acquisition of brachial artery diameter using B-mode imaging and arterial blood flow velocity via Doppler ultrasound.

3.4.2 Carotid Artery Reactivity

Activation of the sympathetic nervous system (SNS) is an important and clinically-relevant prognostic stimulus to examine coronary artery function (Schachinger *et al*., 2000). For example, the cold pressor test (CPT; i.e. placing one hand in ice slush), is a potent sympathetic stimulus resulting in coronary artery vasodilation or, depending on health status, constriction (Nitenberg *et al.,* 2004; Monahan *et al*., 2013). The invasive and technical nature of angiography, however, means that the large scale clinical use of this test is impractical.

Both coronary and carotid arteries demonstrate some similarities in anatomy, in that both arteries have a relatively high content of elastic fibres and are prone to atherosclerosis development. Further, similarities have been observed in their vasomotor function, in particular, the reactivity to sympathetic stimulation. This reactivity leads to either vasodilation in healthy participants, or paradoxical vasoconstriction in those with disease (Rubenfire *et al*., 2000; Van Mil *et al*., 2017). The subsequent use of the CPT to determine carotid artery reactivity (CAR) as a surrogate marker of coronary/cardiovascular health is growing.

To measure CAR, the left common carotid artery was measured 2 cm proximal to the bulbous. A two-dimensional image of the artery was obtained via a high-resolution ultrasound machine (Terason, 3300, Teratech) and a 10-12-MHz probe. Settings were adjusted to optimise the longitudinal, B-mode image of the lumen-arterial wall interface (as done with the FMD technique explained previously). Simultaneously, carotid artery blood flow velocity was assessed via Doppler ultrasound with an insonation angle of 60°. After a 1-minute baseline, the participant immersed their hand (up to the wrist) in ice slush (~4.0°C) for 3 minutes. During this period, the participant was instructed to remain still, not hyperventilate, and the ultrasound probe's position was maintained until the end of the test.

3.4.3 Vascular Function - Analyses

Both FMD and CAR data were analysed using custom designed automatic edge-detection and wall-tracking software, a reproducible and valid method (Green *et al*., 2002), largely independent of investigator bias (Woodman *et al*., 2001). To analyse arterial diameter, a region of interest is manually selected based on image clarity and contrast between artery walls and lumen. Within this region of interest, a pixel-density algorithm automatically identifies the angle-corrected near-and far-wall e-lines for every pixel column (Black *et al*., 2008). A second region of interest is then selected to include the Doppler waveform, which automatically detects peak wave for blood flow velocity (Figure 3-4; Black *et al*., 2008). Each frame is subsequently analysed at a rate of 30 Hz, which enables synchronised arterial diameter, blood flow velocity, blood flow (the product of arterial cross sectional area and blood velocity) and shear rate (4 x blood velocity / arterial diameter) data to be acquired (Figure 3-5; Black *et al*., 2008).

The CAR test involves one additional step compared to the FMD technique as it is calculated via 10 second bins (Figure 3-6). Peak diameter change (CAR%, CAR_{mm}) and area-under-the-curve for diameter change (CAR_{AUC}) were calculated from the 10 second intervals exported from the automatic edge-detection software previously discussed. The peak diameter and CAR_{AUC} infers either vasoconstriction (negative value) or vasodilation (positive value).

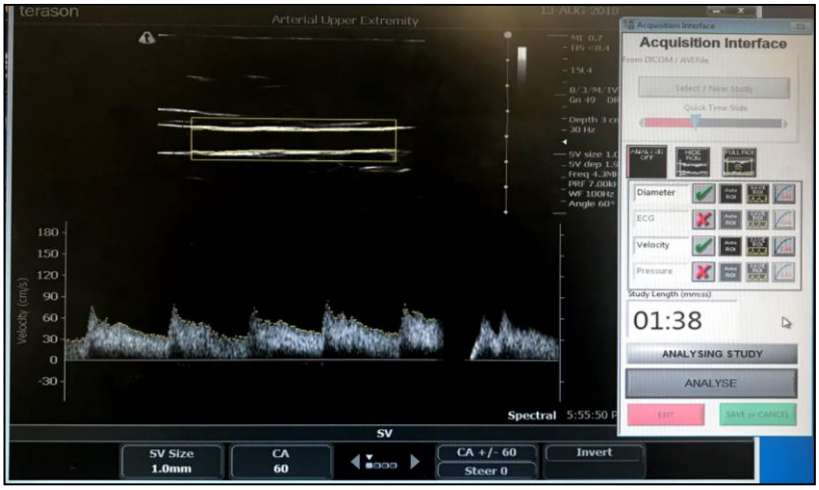


Figure 3-4. Analysis of flow-mediated dilation (FMD) data using custom designed automatic edge-detection and wall-tracking software. The yellow boxes represent regions of interest (ROI) that have been select to identify the arterial wall-lumen interface and the Doppler waveform.

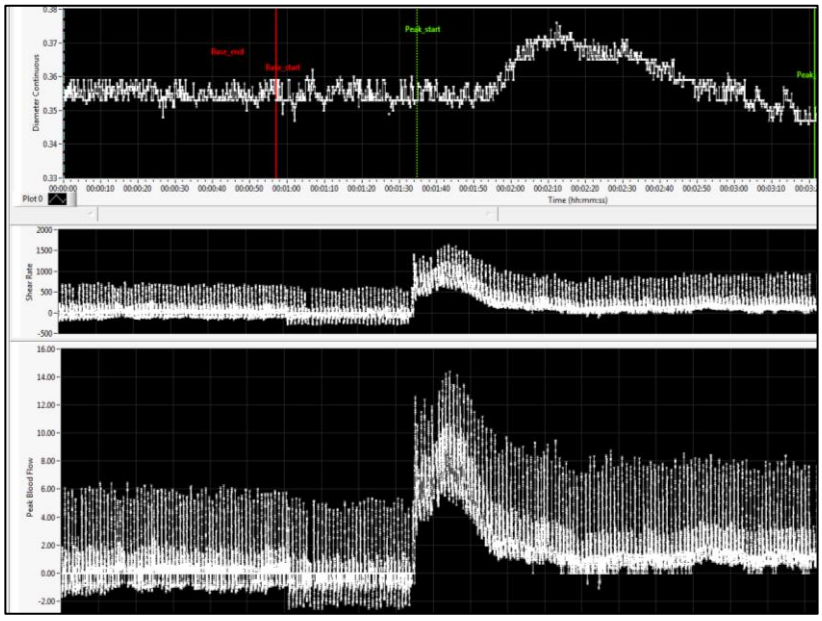


Figure 3-5. An example output from the analysis of flow-mediated dilation (FMD) data using custom designed automatic edge-detection and wall-tracking software. The top box provides continuous arterial diameter data, the middle box provides shear rate data, and the lower box provides blood flow data (estimated from diameter and velocity).

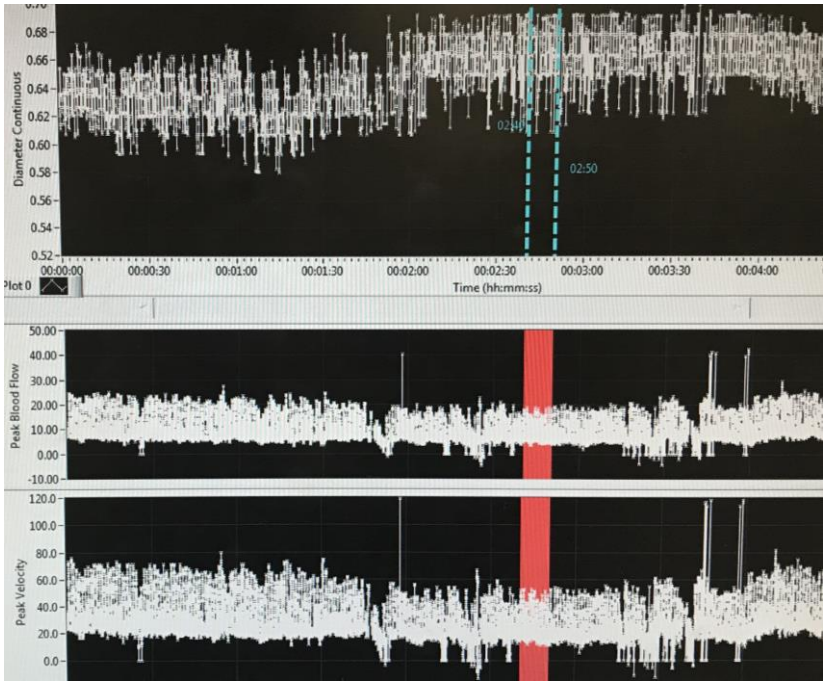


Figure 3-6. An example output from the analysis of carotid artery reactivity (CAR) data using custom designed automatic edge-detection and wall-tracking software. The blue dashed lines and highlighted red zone below them illustrate a selected 10-second bin used for analyses.

3.5 Physical Activity Levels

Physical activity as medicine is well established and as this body of research has grown, so too has the search for methods of measurement that are valid, reliable and responsive to change. A review of reviews (*n*=63 reviews) looked at the current evidence-base for the techniques available to measure PA (Dowd *et al*., 2018). Findings revealed that self-reported measures of PA have been the most frequently examined for methodological effectiveness, with high variability in their findings. In comparison, the evidence examining device-measured PA demonstrated lower variability for validity and reliability. Responsiveness to change, however, remains under-researched. Dowd *et al*. concluded that although no perfect PA measurement tool exists, researchers should aim to incorporate device-based measures, specific to the behaviours of interest, when examining PA in free-living environments (Dowd *et al*., 2018).

It has been noted however, that validity and reliability terminology in PA and SB research is used '*synonymously, possibly incorrectly, and we all get confused*' (Kelly *et al.*, 2016, P.6). Kelly *et al*. have argued that we have created a false hierarchy in PA and SB science, with doubly labelled water at the top. For instance, doubly labelled water is the 'gold standard' when measuring total PA energy expenditure. When investigating bouts of PA intensity, duration or the context or domain of activity, however, doubly labelled water is no longer acceptable. Thus, the validity and reliability of PA measures should *not* be tested against a 'gold standard' for a single component/outcome of PA, unless that is the specific area of interest (i.e. total PA energy expenditure). For example, accelerometers have commonly (and largely inappropriately) been compared to doubly labelled water as a criterion validity variable (see review paper by Plasqui & Westerterp, 2007: *Physical activity assessment with accelerometers: an evaluation against doubly labelled water*). As such, PA measurement should be validated in the appropriate setting in which the measure is to be used (i.e. laboratory vs free-living environments), and compared to the appropriate 'gold standard' based on the best available measure for that *specific* component of interest of PA or SB (i.e. bouts of MVPA, time spent walking etc.). The Edinburgh Framework is a recent and promising attempt to facilitate a more nuanced use of validity and reliability testing in PA and SB research (Kelly *et al*., 2016). Until such frameworks are more widely accepted, more of a critical awareness of appropriate validity and reliability testing is warranted.

3.5.1 Device-based measurement: Actigraph GT3x Activity Monitor

Moderate-to-vigorous PA (MVPA) was assessed via the commercially available tri-axial ActiGraph GT3x accelerometer (ActiGraph, Pensacola, FL, USA; Figure 3-7), which has been validated in a comparable population, although in a laboratory environment (Kelly *et al*., 2013) and deemed a reliable measure of free-living PA (Aadland & Ylvisåker, 2015). Hip-based PA monitors were chosen as they have been demonstrated to enhance sensitivity (compared to wrist-based monitors) for identifying PA intensity thresholds (i.e. MVPA; Rosenberger *et al*.,

2013). Participants were instructed to wear the monitor on the right hip (midaxillary line) during waking hours for 7 days. It has been suggested that 4 to 12 measurement days are needed for reliable accelerometer-based estimates of habitual daily PA levels (Berlin *et al*., 2006). A diary was provided to record non-wear time and encourage adherence. The monitor was set to record raw tri-axial acceleration at 30Hz. Following collection, data were downloaded to a computer using manufacturer software (ActiLife software version 6.13.3). The decision to analyse raw PA acceleration data over the more traditional 'count' based data was made because what corresponds as a 'count' is determined by the manufacturer and unknown to the researcher. Thus, by using the raw acceleration data you have more control over the analysis, which is hoped to enhance transparency. Compared to counts-based analysis, however, raw acceleration data analysis requires more time and training with specialist programmes (Van Hees *et al.,* 2013; GGIR). Furthermore, it is difficult to compare raw acceleration data to current PA recommendations and existing count-based findings. Thus, 'cut-points' are still applied to the outputs of raw acceleration data to present MVPA, for example.

Raw tri-axial acceleration values were converted into an omnidirectional measure of acceleration, referred to as Euclidian norm minus one (ENMO; Van Hees *et al*., 2013). Data were calculated per 5 second epochs via 1 minute windows with a minimum wear time of 10 hours per day and 3 days per week (including one weekend day) to be included in analysis (Matthews *et al*., 2012). Signal processing was done offline in R (http://cran.r-project.org/). The R package GGIR (Van Hees *et al*., 2013) facilitated data cleaning such as non-wear time (15-minute detection and 60-minute evaluation window) and extraction of user defined acceleration levels (moderate PA >69.1 g and vigorous PA >258.7 g; Hildebrand *et al*., 2014). These thresholds were selected because they were calculated based on raw acceleration data and allow for identification of Light to Vigorous-intensity PA. A key limitation is that there is limited calibration studies conducted in at-risk/low-fit. Thus, the intensity thresholds used in this thesis may underestimate the intensity of PA in low-fit populations.

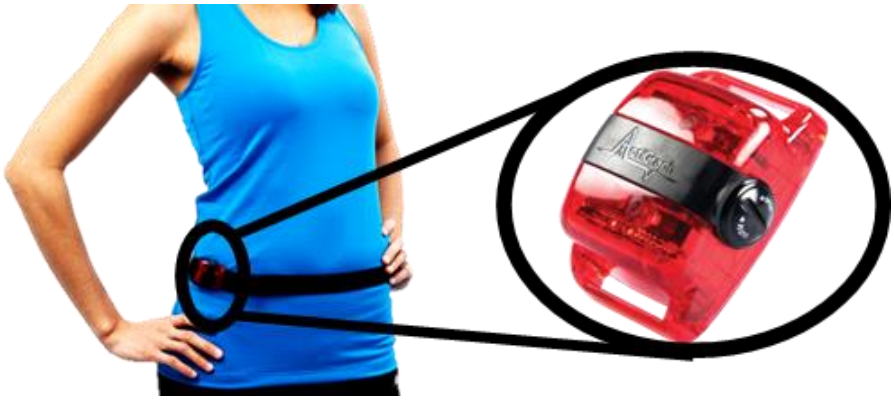


Figure 3-7. Activity monitor; Actigraph GT3x worn on the right hip.

3.5.2 Subjective Measurement: International Physical Activity Questionnaire

The International Physical Activity Questionnaire (IPAQ) was developed by a consensus group of PA assessment experts under the premise of creating a valid and reliable questionnaire to measure daily, health enhancing PA at the population level (Hagströmer *et al*., 2006; Bauman *et al*., 2009). The IPAQ has both a long and short version. The long version considers PA across four domains: during transportation, at work, during household and gardening tasks, and during leisure time. The short version of the IPAQ considers total time spent in vigorous and moderate-intensity PA, as well as time spent walking. These factors can then be transformed using IPAQ guidance to METS per day or week, as required, to give an indication of total PA level. Both short and long versions of the IPAQ have been deemed a valid and reliable measure of PA in a variety of populations (Craig *et al*., 2003). Overall, the IPAQ questionnaires produced repeatable data (Spearman's reliability coefficients (*p)* clustered around 0.8), with comparable data from short and long forms. Criterion validity had a median *p* of ~0.30, which was comparable to most other self-report validation studies (Craig *et al*., 2003). In addition, both the short and long versions of the IPAQ, participants are also instructed to recall the time they have spent sitting as a marker of sedentary behaviour. The sitting items on the IPAQ have been shown to be a valid and reliable assessment of sedentary behaviour (Rosenberg *et al*., 2008).

It is important to note, however, that the IPAQ was initially developed as a population level PA surveillance tool (Bauman *et al*., 2009). Research investigating the responsiveness to change i.e. ability to detect change over time is lacking (Van Poppel *et al*., 2010). Thus, to identify intervention effects, researchers have suggested IPAQ (or other self-report tools) should only be used in combination with accelerometery or when accelerometery is not possible, to reduce recall bias and improve precision (Limb *et al*., 2019). The IPAQ short form (7 items) was used throughout this PhD primarily to reduce participant burden in comparison to using the long form (27 items) and to compliment the device-based data.

3.6 Cardiorespiratory Fitness

Cardiorespiratory fitness (CRF) [Maximal oxygen consumption (VO_2max^{-2})] was estimated via the Astrand-Rhyming cycle ergometer protocol (Astrand *et al*., 1960). The protocol is a single-stage cycle ergometer test designed to elicit a steady-state heart rate over a period of 6 minutes. The initial workload was 60 (females) or 90 (males) watts, cadence remained constant (60-70 rpm), and heart rate was recorded at 1-minute intervals (Polar Oy, Kempele, Finland). Heart rate and loading wattage were noted at the end of each minute, with a target goal of obtaining two consecutive heart rate values between 125-170 bpm during the fifth and sixth minutes of work. In the case that heart rate failed to achieve the target zone by 6 minutes, 30 watts of resistance was added and the test was continued for a further 3 minutes. This was repeated until the desired heart rate was achieved. Oxygen uptake was estimated using the Astrand–Rhyming nomogram. CRF was chosen as a primary outcome measure as it has the strongest relationship with all-cause mortality (Kodama *et al*., 2009). Further, the Astrand submaximal test was selected due to its appropriateness with clinical populations. In light of using a submaximal test, however, it is important to consider measurement error, which is the difference between a measured quantity and its true value. This includes random (naturally occurring) and systematic (i.e. (mis)calibration) error. The Astrand Rhyming prediction of VO_2max has been shown to be sufficiently comparable to that of measured VO_2max scores (r =

.83 when presented as $ml.kg.^{-1}min^{-1}$; Cink & Thomas, 1981). Although deemed acceptable error, more recent work has suggested up to 15% SD from directly measured VO_2max (Rexhepi *et al*., 2011). Whilst differences between the Astrand-derived values and direct measurement were not statistically different (Hoehn *et al*., 2015), it needs to be acknowledged that the results may be somewhat influenced by error.

3.7 Psychological questionnaires

Mental wellbeing was measured via the Warwick-Edinburgh Mental Well-being Scale (WEMWBS, Tennant *et al.,* 2007). WEMWBS is a 14-item positively worded instrument containing items related to psychological functioning (e.g. "I've been thinking clearly") and subjective well-being (e.g. "I've been feeling cheerful"). Participants are asked to rate on a Likert scale of 1 (none of the time) to 5 (all of the time) how well each statement describes their experiences over the last two weeks. Evidence to support the construct validity of WEMWBS has been demonstrated with Cronbach's alpha values of 0.89 (student sample) and 0.91 (population sample; Tennant *et al*., 2007). Additional studies have demonstrated that WEMWBS scores are responsive to change in mental health interventions (Maheswaran, Weich, Powell, & Stewart-Brown, 2012).

Behavioural regulation was measured via the Behavioural Regulation in Exercise Questionnaire (BREQ-2; Markland & Tobin, 2004). Four additional items were included to assess integrated regulation (Wilson *et al*., 2006). The BREQ-2 plus integrated scale contains a total of 23 items, each answered on a Likert scale of 0 (not true for me) to 4 (very true to me). The scale includes items measuring amotivation (e.g. "I think exercising is a waste of time"), external regulation (e.g. "I exercise because other people say I should"), introjected regulation (e.g. " I feel ashamed when I miss an exercise session"), identified regulation (e.g. "it's important to me to exercise regularly"), integrated regulation (e.g., "I exercise because it is consistent with my life goals"), and intrinsic motivation (e.g. "I exercise because it's fun").

Cronbach's alpha values for BREQ-2 subscales have been shown to exceed .75 (Wilson *et al*., 2004).

Psychological needs satisfaction was measured via the Psychological Needs Satisfaction in Exercise Scale (PNSE; Wilson *et al*., 2006). The PNSE is an 18-item instrument designed to measure participants' perceived autonomy (e.g. "I feel free to exercise in my own way"), competence (e.g. "I feel capable of completing exercises that are challenging to me") and relatedness (e.g. "I feel connected to the people who I interact with while we exercise together") in an exercise context. Participants are asked to answer on a 6-point Likert scale (1 = false, 6 = true) to indicate how they typically feel when they exercise. Validation studies have provided support for interpreting scores from the PNSE in a manner consistent with SDT (e.g., Wilson, Rogers, Rodgers, & Wild, 2006; Wilson & Rogers, 2008). Cronbach's alpha values for perceived autonomy, competence and relatedness have been shown to exceed 0.7, 0.8 and 0.8, respectively (Mills *et al*., 2012).

Table 3-1 provides an overview of the role of the author through each research study within this complex PhD project.

Table 3-1. The author's role through each research study.

Research Study	Author's Role (Benjamin Buckley)
Study 1	**Design.** The author was involved throughout the iterative design of the co-production study with supervisors Dr Paula Watson, Prof Dick Thijssen, Dr Becky Murphy, and advisor Dr Lee Graves. **Selection of methods and measures.** Discussed and agreed between the author and Dr Paula Watson before receiving input from supervisors and the wider academic team (Prof Diane Crone, Dr Fiona Gillison, Prof Greg Whyte, and Prof Philip Wilson). **Data collection.** The author collected all of the data (audio recordings, pictures of meeting outputs, and researcher reflections). **Analysis.** The author completed the initial analyses before engaging in triangulation activities with Dr Paula Watson, Dr Becky Murphy, and Dr Lee Graves. **Write up.** The author led the writing process for the published manuscript then adapted the manuscript for the thesis chapter.
Study 2a	**Design.** The author was involved in the design of the study with Dr Paula Watson before receiving input from supervisors and the wider academic team. **Selection of methods and measures.** Discussed and agreed between the author and supervisory team. **Data collection.** The author collected all of the lab-based data. An MSc student (Daniel Hindley) collected participant interview data. **Analysis.** The author analysed all of the lab-based data. Daniel Hindley completed the preliminary analysis of the interview data. The author and Dr Paula Watson then participated in triangulation activities before the author made the final revision of the analyses. **Write up.** The author led the writing process for the published manuscript then adapted the manuscript for the thesis chapter.
Study 2b	**Design.** The author designed the study with Prof Dick Thijssen. **Selection of methods and measures.** Discussed and agreed between the author and supervisory team. **Data collection & analysis.** The author collected and analysed all of the data. **Write up.** The author led the writing process for the published manuscript then adapted the manuscript for the thesis chapter.
Study 3	**Design.** The author was involved in the design of the study with Dr Paula Watson before receiving input from the supervisory and wider academic teams. **Selection of methods and measures.** Discussed and agreed between the author and supervisory team. **Data collection.** The author collected all of the lab-based data. An MSc student (Bethan Price) collected participant focus group data. **Analysis.** The author analysed all of the lab-based data. Bethan Price completed the initial analysis of the focus group data and shared the preliminary data with the author, who further refined the analysis for presentation in the thesis chapter. **Write up.** The author led the writing process for the thesis chapter.

4 STUDY 1: CO-PRODUCTION

"*Human knowledge is never contained in one person. It grows from the relationships we create between each other and the world, and still it is never complete*."

(Paula Kalanithi, When Breath Becomes Air, 2016; p. 172)

4.1 INTRODUCTION

Physical activity as medicine is well-established, yet attempts to translate this evidence to practice have seen limited success (Pavey *et al*., 2011a). Findings of systematic review data have demonstrated many ERSs lack behaviour change components, fail to collect long-term outcome data, and report wide-ranging uptake and adherence rates (28-100% and 12-93%, respectively; Pavey *et al*., 2012). Consequently, evidence of effectiveness is scarce and systematic reviews have been deemed an unfair assessment of the *potential* of ERSs to impact public health (Beck *et al*., 2016).

This may, in part, represent a lack of practitioner and patient involvement in intervention development and implementation (Donaldson & Finch, 2012). Whilst highly-controlled efficacy trials represent the gold standard in academic research, they provide limited information for policy-makers and practitioners when implementing interventions in the real-world (Watson *et al*., 2012). If sport and exercise medicine is to inform the development of ecologically valid PA interventions, alternative research methodologies are urgently needed (Beedie *et al*., 2015).

To improve implementation and effectiveness of interventions to support long-term PA behaviour change, there is a need for ecologically valid, multi-stakeholder developed interventions that reflect the pragmatic needs of end-users (Harden *et al*., 2016; Gates *et al*., 2016; Farrance, Tsofliou, & Clark, 2016). The Medical Research Council recommends a phased approach to the development of complex interventions (Craig *et al*., 2015), starting with a

development phase, followed by piloting to ensure the intervention is refined sufficiently, before undergoing an effectiveness trial. Participatory research has been described as moving away from a 'them and us' mentality and involves actively engaging stakeholders from all levels (patients, practitioners, and policy-makers) alongside academics in the co-production of interventions (Glasgow, Lichtenstein, & Marcus, 2003). Multi-stakeholder involvement provides important insights into the feasible implementation of interventions in the real-world, in turn leading to interventions that are context-sensitive, effective, and sustainable within local infrastructures (Harden *et al*., 2016; Leask *et al*., 2017).

The purpose of this study was therefore to co-produce a *PA* referral intervention in a large city in the North-West of England (Liverpool). In doing so, two research questions were asked: a) factors that must be considered when translating evidence to practice in an exercise referral setting; and b) challenges and facilitators of conducting participatory research involving multiple stakeholders.

4.2 LOCAL CONTEXT

Liverpool was ranked the 4th most deprived local authority area on the Index of Multiple Deprivation (2015). As per the 2011 national consensus, the population of Liverpool was 466,415 (50.6% female, 86.2% White British and Irish). The gap in life expectancy between the highest and lowest areas within Liverpool was reported to be 10.5 years. Further, those with cancer are 3 times more likely to die in the area with lowest life expectancy compared to the highest (Healthy Liverpool Prospectus, 2014).

Currently, about half of the population within Liverpool do not participate in any form of PA and 86% of adults are not active enough to sustain good health, compared to the national average of 70%. If every adult in the city were to meet the PA guidelines, an estimated 424 premature deaths could be prevented each year (Healthy Liverpool Prospectus, 2014).

'Exercise for Health' is the local ERS for Liverpool, which has been running for 15 years. It is commissioned by Liverpool City Council Public Health and is provided by the 'Lifestyles' Sports and Leisure service. Exercise for Health consists of a 12-week scheme where eligible individuals are referred by an appropriate healthcare professional (e.g. GP) for an induction with a trained exercise referral practitioner, followed by 'prescription' of an appropriate exercise programme. There is no formal follow-up of participants following the initial induction. There is a cost to the participant of £7.50 for the induction session, and £1 for each subsequent session (Liverpool City Council, 2018).

Between April and December 2017, there were 1,305 referrals to Exercise for Health recorded (Mchale, 2018). An evaluation of the Exercise for Health scheme carried out in 2014-2015 revealed that, despite some patients reporting health benefits, there was limited contact from instructors (58% patients met their instructor once only) and few attempts to promote long-term PA behaviour change [Liverpool John Moores University, unpublished data].

4.3 METHODS

Participants

A purposive sampling approach was used to identify multi-level stakeholders who were involved with the current ERS in operation in the city. Potential stakeholders were contacted initially via email and some in person to discuss if they were interested in participating. A development group was consequently formed consisting of public health commissioners (*n*=4), a fitness centre area manager (*n*=1), general practitioner (GP; *n*=1), exercise referral practitioners (ERPs, *n*=2), health trainer (*n*=1), health trainer coordinator (*n*=1), patients (*n*=5), plus academic experts in exercise referral (*n*=1), exercise psychology (*n*=1,) and exercise physiology (*n*=1). The role of academic group members was to provide theoretical knowledge and scientific evidence, whilst local stakeholders contributed vital local knowledge and experiences to inform the pragmatic feasibility of the intervention (Beierle, 2002).

Participatory Research Process

The described methodology draws on a conceptual model of healthcare service co-production (Batalden *et al.,* 2016). Further, the pragmatic methods draw on previous experiences of complex intervention development (Stratton & Watson, 2009; Gillison *et al*., 2012), focus group facilitation (Kitzinger, 1994; Kidd & Parshall, 2000) and guidance on fostering autonomous motivation in others (Ryan & Deci, 2000).

Participatory meetings. Five development group meetings (2-3 hours) were organised between April and August 2016 to facilitate the iterative development of the intervention (Table 4-1). The overarching objectives were pre-determined for each meeting via discussions between the academic team (Benjamin Buckley, Dr Paula Watson, Prof Dick Thijssen, Dr Becky Murphy, and Dr Lee Graves) underpinned by findings from a previous evaluation conducted by our research group (see Figure 1-1). Specific content and timescales, however evolved based on discussions in preceding meetings. Each meeting was facilitated by a member of the research team, whose specialist area was not in exercise referral. Within each meeting, small-group activities (4-5 participants per subgroup) were used to facilitate collaboration and ensure all stakeholders were given a voice. Each subgroup was presented with open questions to discuss and asked to record their views on a flip chart. Following subgroup activities, a whole group discussion collated the issues raised in relation to each meeting's objectives. Efforts were made to facilitate co-development throughout by providing a clear rationale for decisions and tasks, and structuring activities to allow the development group to come up with their own solutions.

In addition to the core development meetings, e-mail correspondence facilitated preparations and planning for the development meetings, allowed the research team to clarify specific discussion points following the meetings, and provided evidence of commitment/agreement from specific individuals in writing. Once the intervention framework was agreed, continued liaison with group members (via e-mails, one-to-one and small group meetings) allowed the more detailed components of the scheme to materialise.

Online survey. To ensure stakeholder views had been accurately interpreted, participants were given the opportunity to complete an online survey to confirm their individual agreement of intervention components (e.g. aim, eligibility, exclusion criteria, outcome measures, behaviour change support; Batalden *et al*., 2016). Participants were also asked about their experiences of the process and to what extent they felt their views were valued and acted upon.

Table 4-1. Summary of co-production meeting content collected between April and August 2016 in Liverpool, UK.

Development Meeting	Objectives	Tasks / Key Questions
Needs analysis (April 2016)	To gather stakeholder views on strengths and areas for improvement of the current ERS in operation in the city (Exercise for Health (EFH)). To discuss potential aims and objectives for the new ERS.	"What should be the aim of a scheme?" "What positive factors of EFH would you like to keep?" "What issues with EFH would you like to change/develop?" "What changes could be made to address these issues?" "What needs to happen to enable these changes to take place? (E.g. training, resources, communication)".
Eligibility and referral (April 2016)	To attain preliminary thoughts from the stakeholders regarding eligibility for the scheme. To gain perceptions of what the referral pathway should look like (i.e. the professionals a patient will need to meet before they can uptake the scheme).	"Who is the scheme for?", "Who can refer?" "What will the referral pathway look like?" A summary of eligibility guidelines from NICE [34] was presented to the group to support discussion.
Intervention framework (stage 1) (May 2016)	To address the structural components of the referral scheme e.g. how much contact participants will have, how participants will be supported during the referral scheme, and who will deliver the behavioural change aspects of the programme.	Prior to the meeting, the PhD student and supervisors created a preliminary intervention framework based on discussions during meetings 1 and 2. The framework was then shared with the group to discuss issues of delivery and feasibility, and to inform further refinements to the proposed model.
Intervention framework (stage 2) and evaluation (May 2016)	To refine the intervention framework based on meeting 3 discussions. To determine how the intervention would be evaluated.	A refined intervention framework was developed by the research team based on meeting 3 discussions and presented to the group. To gain further feedback for the refined ERS framework from the development group. Discussions explored how the ERS would be evaluated and what outcome measures would be embedded into scheme delivery.
'*Follow-Up'* development Meeting (August 2016)	Primary objective: to summarise the outcome of the process thus far, check for consensus, and gather further comments prior to piloting the scheme. Secondary objective: to maintain contact and engagement with key stakeholders.	Discuss and check for consensus on data that had been analysed from the development meetings, online survey responses, and supplementary meetings. Make any necessary changes before piloting the intervention.

Data Collection and Analysis

Multiple qualitative methods were used to document the intervention development process and capture audio and visual data relevant to the research objectives. The primary researcher [BB] attended each meeting to collect data via audio recordings, observation, reflective notes, and photographs of white board and flip chart content (Bergold & Thomas, 2012). Reflective practice was used throughout the development process between the primary researcher and supervisory team (Knowles, Gilbourne, & Tomlinson, 2007). Since the iterative methods did not lend themselves to a traditional qualitative analysis, the analysis aimed to capture the processes the stakeholder group went through and the challenges that arose when translating evidence to practice in an ERS setting. Data from audio-recordings (verbatim transcriptions), visual records (e.g. white board notes) and researcher reflections were organised using NVivo-10 electronic software (QSR International 2002), then meaningful excerpts extrapolated relevant to the research questions (Ghaye *et al*., 2008). When analysing participant interaction, key principles of focus group analysis were followed to ensure interaction between group members was captured (Kitzinger, 1994; Kidd & Parshall, 2000). Primary analysis was conducted by the primary researcher [BB], with frequent debriefing sessions with the supervisory team to discuss and debate emerging data and inform the development of subsequent participatory meetings (Shenton, 2004). As details of intervention components emerged, they were iteratively mapped to the Template for Intervention Development and Replication (TIDieR) checklist (Hoffman *et al*., 2011). This was a systematic process to ensure the co-produced framework was evidence-based and mapped to local priorities.

4.4 RESULTS

Stakeholder responses to the preliminary framework informed an adapted intervention model (Figure 4-1; Table 3-3; Table 3-4). It was acknowledged (by both exercise referral practitioners and a fitness centre manager) that, with the appropriate training and support, practitioners *"could do more"* within their roles to support patient PA behaviour change. It was agreed that this approach was the most viable model for translating evidence to practice within local resources.

Fundamental adaptations from the existing ERS in operation included: a unified focus on lifestyle-based PA and not 'just exercise prescription' per se; additional consultations at week 4, 12 and 18; structured behaviour change support delivered by exercise referral practitioners; optional supplementary support from a Health Trainer service for additional health behaviours (e.g. nutrition, smoking, alcohol etc.); and collection of patient-determined evaluation data (e.g. PA, psychological wellbeing, body mass). The target population was inactive individuals with health-related risk factors or conditions, aligned with NICE (2014) recommendations. Behaviour change consultations were underpinned by SDT (Ryan & Deci, 2000) and included a range of behaviour change techniques. The detailed theoretical underpinning of the co-produced PA referral framework is described in Table 4-3 and the intervention components are described in detail in Table 4-4 (TIDieR checklist).

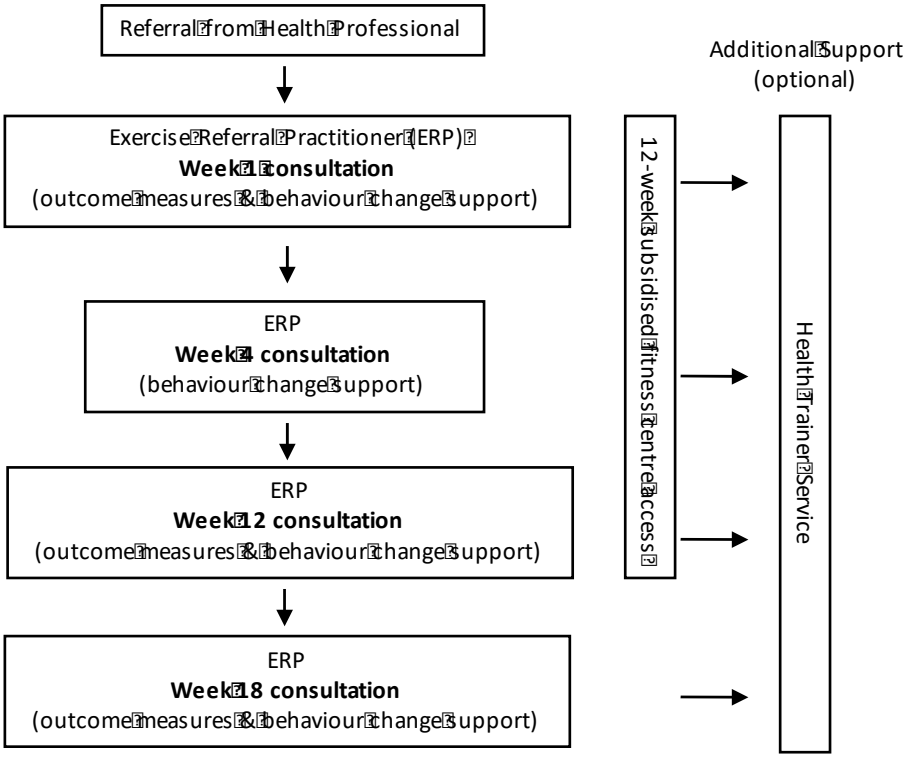


Figure 4-1. Overview of the PA referral scheme framework co-produced between April and August 2016 in Liverpool, UK.

Behaviour change theory underpinning the intervention. Physical inactivity is a complex public health issue and individuals face considerable barriers in trying to change such a complex behaviour. The field of PA and health research seems to be at the embryonic stage of a paradigm shift towards our understanding of complex behaviours and the application of ecological interventions (Buchan *et al*., 2012). As such, it is recommended that trials evaluating ERSs should be underpinned by behaviour change theory (Pavey *et al*., 2011b).

The intervention described in this study draws upon SDT (Ryan & Deci, 2000) previously described in detail (Chapter 2; Section 2.3) and elements of motivational interviewing (Miller & Rollnick, 2012). Strong evidence exists in support of SDT in diverse situations including: positive health behaviour change (Ng *et al*., 2012); weight loss (Silva *et al*., 2011; Williams *et al*., 1996); medication adherence and glycaemic control (Williams *et al*., 2007; 2009); and PA behaviour change (Biddle & Nigg, 2000; Edmunds, Ntoumanis, & Duda, 2006; Fortier *et al*., 2012; Teixera *et al*., 2012). Exercise referral practitioners were trained to deliver in a 'guiding'

style that maximises motivationally adaptive strategies (e.g. coming from the patient's perspective, offering meaningful choice) and reduces motivationally maladaptive strategies (e.g. imposing goals on participants, using commands/directives). Intervention strategies have been informed by previous SDT-based PA research (Kinnafick *et al*., 2014; Hancox & Quested, 2015; Ntoumanis *et al*., 2016) local evaluation data [Liverpool John Moores University, unpublished data] and motivational interviewing techniques (Milller & Rollink, 2013). Table 4-1 outlines the theoretical underpinning i.e. the behaviour change strategies used throughout the intervention. Whilst consideration was given to *what* behaviour change techniques (BCTs) were used, in accordance with SDT, the emphasis is placed on *how* these BCTs are delivered. It is possible the same BCTs could be delivered in either a motivationally adaptive (e.g. supporting the patient to set their own action plan that is congruent with their goals) or a motivationally maladaptive (e.g. imposing an action plan on the patient without taking their goals into consideration) manner. The design and integration of theoretical components was led by the primary supervisor who has expertise in SDT.

What factors must be considered when translating evidence to practice in an exercise referral setting?

Throughout the development meetings, debate among stakeholders raised three key issues that required consideration when translating evidence to practice in an ERS setting: 1. Current exercise referral culture; 2. Skills, safety and accountability; 3. Resources and capacity.

Current exercise referral culture

There was consensus among policy-makers, practitioners and patients that the ERS should have a *'person-centred'* approach, with a focus on improving *'whole person wellbeing'* through *'sustainable'* increases to PA. Yet, this emphasis on lifestyle PA behaviour change was not reflected in the current ERS culture, built around fitness centres and fixed-term exercise prescriptions (usually 12-16 weeks). Thus, it was deemed a cultural shift was required from the typical UK 'exercise referral' scheme to a more holistic 'PA referral' approach.

Skills, safety and accountability

Having established the importance of a PA behaviour change focus, consideration needed to be given to *how* such support could be embedded into a new PA referral intervention within existing resources. Initially, stakeholders agreed that a Health Trainer service [UK initiative that employs lay health workers to provide individualised behaviour change support for a broad spectrum of health issues] could act as the primary referral route and provide behaviour change support to patients. "*They* [health trainers] *are very skilled, they're very good at working with people and supporting them, so that makes a big difference, having the right type of people…*" (Exercise referral practitioner). Whilst health trainers have the requisite skills to provide such support, they are not qualified exercise professionals. This created a tension within the multi-stakeholder group to determine who could "sign patients off" to do lifestyle-related PA. Whilst the fitness centre manager reported a *"higher duty of care"* and emphasised a legal requirement for anyone prescribing PA to have an exercise referral qualification, others in the group took a "common sense" viewpoint:

> "*We don't need to get risk-averse here… we've got to give responsibility to the patient… otherwise it would become unworkable, and at what point is that realistic? Are you going to say to someone, 'you can't run for the bus once you leave here', clearly they can, it's up to them"* – GP and Public Health commissioner.

Due to a lack of clear guidance on this issue, the stakeholder group concluded that it was necessary for qualified exercise referral practitioners to assess all patients and provide appropriate PA advice. Consequently, ownership of the new PA referral intervention would remain with fitness centres.

Resources and capacity

Figure 4-2 demonstrates the preliminary PA referral framework that was presented to the development group in meeting 3, drawing on previous discussions about PA behaviour change and accountability. The framework involved baseline and post-ERS assessments with an exercise referral practitioner, followed by bi-weekly behaviour change support from a health trainer.

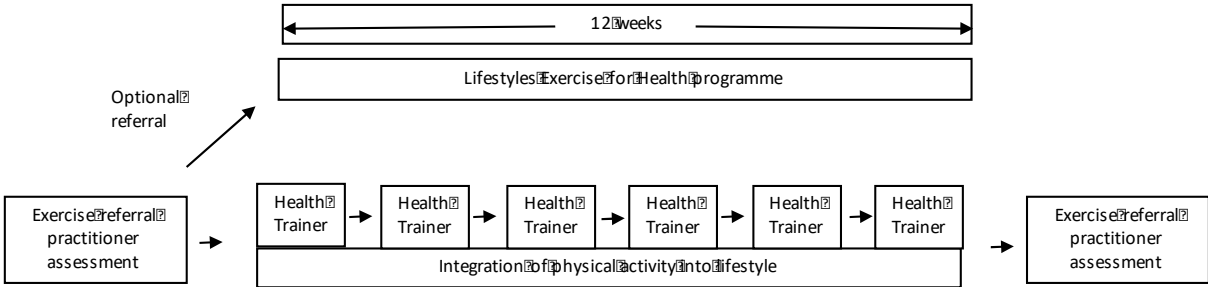


Figure 4-2. Flow diagram of a preliminary intervention framework for a PA referral scheme, co-produced from participatory meetings 1 and 2 (April 2016, Liverpool, UK). The framework was underpinned by the identified importance of focussing on PA and incorporating behaviour change support, the involvement of a health trainer service, and solving accountability concerns (i.e. exercise referral practitioner assessments pre-post intervention).

Whilst the preliminary PA referral framework was positively received by some stakeholders ("*It is easy to understand why this level of support would be beneficial for patients*"- Public health commissioner), patients felt the proposed level of bi-weekly support *"may not always be necessary and* [may be] *potentially intrusive"*. Furthermore, there were fears that the level of support proposed was time and resource intensive. It became apparent that the health trainer service would not have capacity to adopt the proposed role. Whilst the preliminary framework was evidence-based and co-produced by local stakeholders, subsequent discussions highlighted a lack of congruence between the perceived "ideal" (i.e. what would be delivered to produce optimal results) and the "real" (i.e. what could feasibly be delivered within current resources).

What are the facilitators and challenges of conducting participatory research involving multiple stakeholders?

Table 4-2 provides a summary of the perceived facilitators and challenges that arose during the co-production process of a PA referral intervention.

Table 4-2. Summary of pragmatic facilitators and challenges of a participatory research process (April-August 2016, Liverpool, UK)

Facilitators	Challenges
Using the first meeting as a 'needs analysis' allowed the stakeholders to share their perceptions of the existing scheme and expectations of the process.	Multidisciplinary group discussion meant that occasionally, different stakeholders had contrasting views on a topic that were not always resolved.
Open questions and use of sub-groups facilitated input and discussion from stakeholders ensuring that their knowledge and experience informed the intervention.	Irregular stakeholder attendance meant content had to be repeated for participants who missed previous meetings.
Multidisciplinary debate and problem solving allowed for various areas of expertise and experience to inform the intervention.	(Mis)perceptions of the evaluation process: Stakeholders may have initially seen evaluation as solely an academic agenda rather than an attempt to align the intervention to NICE exercise referral scheme guidance.
Reflective practice contributed to the iterative intervention development and facilitated knowledge translation.	

Commencing the development phase with a needs analysis allowed the stakeholders to share their perceptions of the existing scheme, ideas for change, and in turn, ensure the intervention development was stakeholder-driven. This sense of co-ownership was verified via online survey responses (n=11), whereby 100% respondents felt they had been given the opportunity to share their views and 89% respondents felt their views had been acted upon "very much" (the other 11% answering "somewhat"). Working with such a diverse group, however, exposed contrasting views, which required skilled facilitation (e.g. open questions, subgroup

discussions) and additional consultation procedures (e.g. email correspondence and one-to-one meetings) before a consensus could be reached. Stakeholder debate allowed an essential problem-solving process to occur, preventing unrealistic demands and enhancing potential for future implementation success.

During the participatory process, some stakeholders appeared to view evaluation as solely an academic agenda. When discussing how evaluation measures might be embedded within the intervention, a commissioner indicated that the primary purpose of collecting data was to meet academic requirements *("I think the point of the study is, you've* [research team] *got to get the data"*). In response, researchers highlighted the NICE (2014) guidance that stated ERSs should collect ongoing evaluation data beyond any research period.

Table 4-3. Theoretical underpinning of the PA referral scheme

Intervention component		(i) Autonomy	(ii) Structure	(iii) Involvement	(iv) BCTs	(v) PPOs*
Activities offered		Focus on integration of PA into individual lifestyles Patients can choose a combination of gym, class and external physical activities to suit their preferences	Activities tailored to participant ability Opportunities for progression	Include opportunities to exercise with similar others	n/a	3,8,12
Patient information (in patient logbook)		Clear information provided for patient to take away. Intervention information, benefits and guidelines for PA, options available	Frequently asked questions, testimonials from previous participants	Contact information for ERPs	Provide information (1)	1,5,7,8,9
Group Classes		Instructor gives clear explanations, creates opportunities for patients to have input/ make decisions about the workout, encourages patients to pace themselves, offers meaningful choice and variety	Instructor gives specific and constructive feedback, offers meaningful praise, offers opportunities for progression	Instructor learns names, interacts with all patients and responds to individual needs Opportunity to build relationships with other patients		2,3,11,12,15
Gym environment				Instructor present and interacts with patients		
ERP one-to-one support **ERPs will be provided with a template to guide each consultation**	Week 1 (induction)	Explains rationale for being physically active, explains recommended PA levels and options available within intervention; discusses what to expect from intervention; asks open questions to learn about patient, their preferences and potential barriers; emphasises meaningful choice; asks permission to provide advice Introduces patient log book	Collects PA, psychological wellbeing and body mass (optional) data and provides meaningful feedback; discusses long-term goals and sets action plan (guided goals) drawing on PA data; provides specific affirmations. Asks patient to complete log book to self-monitor progress.	For each patient, week 1, 4, 12 and 18 consultations will be conducted with the same ERP (where possible). Demonstrates empathy through voice tone and language; reflective listening; comes from patient's perspective. Considers referral to health trainer for support with other behaviours if appropriate.	Provide information (1,2) Action planning (7) Barrier identification/problem solving (8) Prompt self-monitoring of behaviour (16) Motivational interviewing (37)	1,2,4,5,6,7,8,9,10,11,14,15
	Week 4	Autonomy supportive communication (e.g. open questions, ask permission, explain rationale) Discusses options for progressing or changing action plan, emphasises choice	Provides positive feedback for attending consultation. Reviews action plan and discusses progression as appropriate, affirms progress.	Empathic communication (as per induction), shows interest in patient's life and	Action planning (7) Barrier identification/problem solving (8)	2,10,11,12,13,15

		Goes at the patient's pace, reassures patient it is ok if not achieved as much as expected – life sometimes gets in the way.	Discusses any challenges the patient is facing and how they might overcome these. Looks ahead to the end of the 12 weeks and discuss patient's thoughts on continuing beyond the subsidised sessions (if applicable).	tailors conversation to their needs. Considers referral to health trainer for support with other behaviours if appropriate	Prompt review of behavioural goals (10) Prompt self-monitoring of behaviour (16) Motivational interviewing (37)	
	Week 12	As per week 4	Provides positive feedback to patient for completing 12 weeks Collects PA, psychological wellbeing and body mass (optional) data and provides meaningful feedback; revisits long-term goals and action plan; provides specific affirmations. Discusses any challenges the participant is facing and how they might overcome these. Discusses plan for continuing PA now the 12-week subsidised sessions are finished (if applicable). Considers challenges that could arise and how these will be overcome.	As per week 4	Action planning (7) Barrier identification/problem solving (8) Prompt review of behavioural goals (10) Prompt self-monitoring of behaviour (16) Relapse prevention / coping planning (35) Motivational interviewing (37)	2,6,8,10,11, 12,13,15
	Week 18	As per week 4	Provides positive feedback to participant for attending Collects PA, psychological wellbeing and body mass (optional) data and provides meaningful feedback; revisits long-term goals and action plan; provides specific affirmations. Discusses any challenges the participant is facing and how they might overcome these. Discusses what behavioural strategies the participant plans to use to continue with their PA from this point.	As per week 4	Action planning (7) Prompt review of behavioural goals (10) Relapse prevention / coping planning (35) Motivational interviewing (37)	2,6,10,11,12,13,14, 15

PA = physical activity; **BCT** = behaviour change technique; **PPO** = proximal performance objective; ERP = Exercise Referral Practitioner; **IPAQ** = International Physical Activity Questionnaire; **WEMWBS** = Warwick-Edinburgh Mental Wellbeing Scale**.**
Numbers in column iv refer to the corresponding technique on the CALO-RE taxonomy (Michie *et al*., 2011).
Numbers in column v refer to the corresponding PPO in (Gillison *et al*., 2012).

Columns i-iii outline how activities will be carried out to foster an environment that is supportive of the patient's psychological needs of autonomy, competence (structure) and relatedness (involvement).
Column iv maps activities onto the CALO-RE taxonomy (Michie *et al*., 2011) to describe what behaviour change techniques (BCTs) will be used to support the client's PA behaviour change (where applicable).
Column v maps activities onto the Proximal Performance Objectives (PPOs) established by Gillison *et al.* (2012) to explain why each strategy is being used.

***PPOs**

Engagement

To perceive the programme as important
To engage openly with health professionals
To engage with the group

Increase physical activity

To accurately identify one's own baseline PA levels
To relate physical inactivity to health consequences (i.e. establish risk awareness)
To develop an awareness of personal risk (in relation to PA levels)
To establish realistic outcome expectancies for increasing PA
To identify acceptable opportunities within daily life/activities for increasing PA
To be motivated to initiate change
To plan specific changes in PA
To be able to act on personalised feedback in relation to PA
To develop self-motivation to continue with increased PA
To be able to cope with set-backs in achieving increased PA levels
To obtain social support from the home environment
To obtain social support from within the programme

Table and content created by Dr Paula Watson, Director of Studies and Health Psychologist on this PhD project.

Table 4-4. The Template for Intervention Description and Replication (TIDieR) checklist

Item Number	Item
Brief name	
1	Physical activity referral scheme
Why	
2	A holistic approach to change individual PA behaviour, with a view to improving patient wellbeing and quality of life (in addition to physiological health outcomes). The intervention aims to support patients to make gradual, sustainable changes to their PA levels through a series of one-to-one behaviour change consultations and provision of subsidised exercise access at a fitness centre. **Theoretical underpinning** The behaviour change element of the intervention will be underpinned by SDT (Ryan & Deci, 2000). There is a wealth of evidence supporting SDT in the context of PA behaviour change (Teixeira *et al*., 2012). Individuals who are autonomously motivated (i.e. make a volitional decision to be physically active) are more likely to adhere to PA than those who experience controlled motivation (i.e. feel coerced or pressured into being physically active). Practitioners can foster autonomous motivation in patients through supporting their psychological needs for autonomy (perceived volition), competence (perceived ability to overcome challenges) and relatedness (perceived connection with others). Self-Determination Theory-informed behaviour change training will be provided to exercise referral practitioners delivering the PA referral scheme. Self-Determination Theory will be combined with techniques from motivational interviewing (Miller & Rollink, 2012) to inform "how" exercise referral practitioners communicate with patients. Exercise referral practitioners will also be encouraged to use a range of behaviour change techniques from the CALO-RE taxonomy (Michie *et al*., 2011) such as action planning, self-monitoring and barrier identification. *Full details of the theoretical underpinning and behaviour change strategies used within the intervention are provided in Table 4-3.*
What	
3	**Training resources for Exercise Referral Practitioners** Slides – To facilitate education on the background and theory of physical activity behaviour change. Videos of directive and guiding techniques – Role play between a practitioner and a patient demonstrating two different delivery styles (directive and guiding). Workbook – A workbook for the exercise referral practitioners to use as a learning resource in physical activity behaviour change. Link to BMJ online learning motivational interviewing module - http://learning.bmj.com/learning/module-intro/.html?moduleId=10051582 **Intervention resources** Consultation log – A resource for exercise referral practitioners to use as a template to deliver the week 1 (induction), week 4, week 12 and week 18 consultations (4-page document provided for each patient). Templates prompt practitioners to collect appropriate information about physical activity levels, psychological well-being, patient preferences and barriers before setting an action plan with the patient. Patient log book – A resource to log physical activity and exercise sessions both in and outside of the fitness centre. The logbook also provides information about the intervention, physical activity benefits and guidelines, plus space to record individual action plans and consultation dates/times. Gym equipment – All end-users had 12-weeks access to a fitness centre (gymnasium equipment, exercise classes, swimming pool). Equipment for measuring height, body mass, and waist circumference.
4	**Overview of key components[a]:** **Eligibility criteria:** Aligned with NICE guidance (NICE, 2014) patients will be eligible if:

	They are inactive (not achieving the Public Health physical activity recommendations of 150 minutes of moderate or 75 minutes of vigorous physical activity, or a combination of the two). The patient will have a health condition (e.g. diabetes, cardiovascular disease, cancer, depression etc.) and/or risk factor(s) (hypertension, obesity, hyperglycaemia etc.). **Health Professional referral**: (GP, Physiotherapist, Exercise Physiologist, Nurse etc.). **Week 1 consultation (induction)**: Behaviour change support[b] (set action plan); introduction to fitness centre and gym induction (if patient wishes to use gym); data collection (physical activity levels, psychological wellbeing and body mass (optional)); 12-week subsidised access to classes, gym, and swimming at fitness centres begins. **Week 4 consultation**: Behaviour change support (review action plan). **Week 12 consultation**: Behaviour change support (review action plan, consider coping strategies moving forward); data collection (physical activity levels, psychological wellbeing and body mass (optional)); 12-week subsidised access to classes, gym, and swimming at fitness centres ends. **Week 18 consultation**: Behaviour change support (review action plan, consider coping strategies for maintenance); data collection (physical activity levels, psychological wellbeing and body mass (optional)). Throughout the intervention, there will be the opportunity to refer patients (as appropriate) to a Health Trainer service. This will be for additional support that includes a range of lifestyle behaviours (e.g. smoking cessation, alcohol consumption, weight loss etc.). [a]*See Figure 4-1 for a visual representation of the intervention components* [b]*See Table 4-3 for full details of the behaviour change support provided at each consultation.*
Who Will Provide	
5	**Referring professionals** (GP's, physiotherapists, nurses, clinical exercise physiologists etc.) will be fully qualified and already have capacity to refer to an exercise referral scheme. It was agreed that all patients would see a level 3 qualified exercise referral practitioner at the start of the intervention. It is part of the exercise referral practitioners' job role to check the appropriateness of the referral. If information is missing, the referral is too vague, or they are unsure of a medical condition or current health status, they should not accept responsibility for a referred patient (NICE, 2014). A referral should only be accepted if all necessary health status information is included on the referral. **Exercise referral practitioners** based at local authority fitness centres will provide all behaviour change consultations (week 1, 4, 12 and 18) and will set appropriate action plans for increasing physical activity with patients. All exercise referral practitioners will be registered on the Register of Exercise Professionals (REPs) with a level 3 exercise referral category of registration. Behaviour change training for these practitioners will be designed and delivered by a Registered Sport and Exercise Psychologist (Health Care and Professions Council), with the assistance of a Trainee Health Psychologist. **Health Trainers** will act as an optional support service for the patients who require support related to other lifestyle behaviours (i.e. smoking, alcohol, nutrition etc.) on the referral scheme. Health Trainers are already trained to provide lifestyle advice for numerous health-related behaviours (physical activity, weight loss, smoking cessation, nutrition etc.) as well as motivational interviewing and behaviour change support.
How	
6	12-week subsidised access to fitness centres (exercise classes, gym, and swimming) Week 1 consultation (induction): face-to-face and individual Week 4 consultation: face-to-face or via phone and individual Week 12 consultation: face-to-face and individual

	Week 18 consultation: face-to-face and individual
Where	
7	All consultations will take place at the patient's local fitness centre
When and How Much	
8	The scheme will support individuals to increase their PA levels over an 18-week period. The first 12 weeks will consist of subsidised fitness centre access, which is hoped will facilitate and motivate individuals to increase their lifestyle-based PA with the help of the one-to-one behaviour change consultations. Week 1 consultation (induction) will last approximately 1 hour. The subsequent consultations (Week 4, 12, and 18) will be allocated 30 minutes each. PA recommendations will be based on improving individual patients' baseline level in accordance with public health guidance (Department of Health, 2004). Activities offered will include use of a gym and swimming pool, as well as group activities organised at the fitness centre. In addition, behavioural changes may take place at home such as increased walking and/or cycling, climbing stairs and doing household chores etc. External PA initiatives of interest to individuals (e.g. walking/cycling groups etc.) will be encouraged.
Tailoring	
9	Each patient will be provided with individual guidance from an ERP who will assist the patient to create an individually tailored action plan. At each consultation, patient action plans will be reviewed and amended according to how the patient is progressing. The patient will be offered additional behaviour change support (optional referral to Health Trainer service) if deemed beneficial and the patient accepts/requests more support. It should be noted this additional support is for other health behaviours (i.e. smoking cessation, alcohol consumption, nutrition etc.). *For a full outline of the strategies used to support individual behaviour change please see Table 4-3.*
Modifications	
10*	Not yet applicable
How Well	
11	Adherence will be monitored by patient attendance at consultations (week 1, 4, 12 and 18) and patient logs of their physical activities (in patient log book). Ongoing training and support will be provided for exercise referral practitioners (via e-mail, one-to-one and group meetings) to review delivery challenges and enhance intervention fidelity. Intervention fidelity will be assessed by logging how many one-to-one sessions were offered and took place. Observations and interviews will be undertaken to explore to what extent exercise referral practitioners are practising in a needs-supportive style and adhering to consultation protocols.
12*	Not yet applicable
*If checklist is completed for a protocol, these items are not relevant to protocol and cannot be described until study is complete.	

4.5 DISCUSSION

Through this study a PA referral scheme was co-produced that focusses on facilitating long-term PA behaviour change. This study provides new insights into a) factors that must be considered when translating evidence to practice in a PA referral scheme, and b) facilitators and challenges of participatory research when co-producing a complex public health intervention with a multidisciplinary stakeholder group. Findings highlighted a need for a cultural shift to update ERS provision to a PA behaviour change approach, with stakeholder discussions identifying a number of issues that must be considered to enable this to happen.

It was noted that the aim of the PA referral scheme should be on changing individual *PA behaviour*. Whilst this aim was in line with the World Health Organization guidance (e.g. 150 minutes of moderate intensity PA per week; WHO, 2010) it meant a shift from "exercise prescription" to a focus on "PA behaviour change support". Despite the National Quality Assurance Framework (NQAF; Craig *et al*., 2001) advocating that ERSs should go beyond "*advice giving, recommending exercise, or offering patients vouchers to attend exercise facilities*" (p. vii), the majority of UK ERSs continue to offer 12-16 week exercise prescriptions and few exercise referral practitioners are trained to provide behaviour change support. Similarly, the existing local ERS (Exercise for Health) was also focussed on 'exercise prescription' within a leisure centre, with no formal practitioner contact following the initial induction. Consequently, exercise referral requires a cultural shift to align PA provision with World Health Organization guidance and consideration needs to be given to behaviour change training and education for ERS providers.

Given the lack of behaviour change expertise and limited staff capacity within local fitness centres, stakeholders within our co-production group proposed involvement from the health trainer service, who were deemed well placed to provide behaviour change support. This raised the issue of whether health trainers [who have no professional exercise qualification] could or should hold responsibility for providing PA advice to patients with health conditions.

The NQAF (Craig *et al*., 2001) stated that when an individual with health-related risk factors is specifically referred for an exercise intervention, *"responsibility for safe and effective design and delivery of the exercise programme passes to the exercise and leisure professionals"* (p.13). These exercise professionals should be registered with a national body (e.g. level 3 Register of Exercise Professionals qualification) and have indemnity in respect of their work. Conversely, NQAF also noted that *"recommendations to be habitually more active"* (p.11) may be provided by non-exercise professionals, a consensus supported in a recent Canadian position statement (Thornton *et al*., 2012). Where patients have conditions classified as high-risk, however, both the NQAF and Canadian position statement advocate referral to a qualified professional. This distinction creates a grey area for ERSs that are centred towards habitual PA recommendations, yet target at-risk populations (PA referral interventions). Such contradictions were represented between some of the stakeholder group. For example, the greatest public health gains may arise through small increases to daily PA (Wen *et al*., 2011). Yet, it is unviable and arguably unethical for professionals to control patients' habitual PA. Indeed, extensive evidence suggests that if patients feel autonomous in their PA, they are likely to have improved long-term adherence (Teixeira *et al*., 2012). Consequently, clearer guidance is needed to determine who holds responsibility for patient safety within PA referral interventions.

Co-production is a promising tool for public health services, however, associated challenges need to be considered. The inclusion of multiple levels of engagement is fundamental for a participatory development process (Glasgow *et al*., 2003). In practice, this requires leadership, a tolerance of messiness, and careful negotiation of group politics (particularly when the group involves natural power imbalances e.g. commissioners and service providers) to be able to have productive discussions that result in meaningful actions (Rycroft-Malone *et al*., 2016). It was found that commencing the co-production process with a 'needs analysis' was an important step to facilitate a consensus for an appropriate agenda and well aligned outcome objectives (Minkler *et al*., 2005). Multidisciplinary debate allowed diverse areas of expertise to

inform the intervention, whilst reflective practice enabled researchers to make sense of debate and inform the iterative development of the intervention (Ghaye *et al*., 2008; Bergold & Thomas, 2012). Finally, there may be times when a conceptual gap emerges between stakeholder and researcher desired outcomes. In the instance of disagreement, discussion of differences between stakeholders should be encouraged, and the involvement of the wider community should be viewed as a resource, not a threat (Rycroft-Malone *et al*., 2016).

Strengths & Limitations

Co-production methods have been advocated as a means of maximising the likely impact and sustainability of complex public health interventions (Batalden *et al*., 2016). Detailed reporting on intervention development is vital for the advancement of effective behaviour change initiatives (Neuhaus *et al*., 2014). Of note, inconsistent stakeholder attendance within this study meant that not all participants provided input to all meetings. Therefore, where individuals missed meetings, subsequent attempts were made to gather their views through meeting summary emails, informal conversations, and an online questionnaire. There is an urgent need for translational research methods that enable the development of evidence-based, yet ecologically valid referral schemes. The purpose of co-production is to establish a framework that has a high likelihood of success (due to the local multi-stakeholder input). Subsequent research is now required to explore the feasibility and effectiveness of the co-produced scheme in practice.

4.6 CONCLUSION

Systematic reviews have demonstrated that ERSs typically lack behaviour change components, fail to collect long-term outcome data, and report wide-ranging uptake and adherence rates (Pavey *et al*., 2011b; 2012). Yet, such conclusions have stemmed from interventions that have not been developed with local stakeholders to a point where they can be expected to have a meaningful public health impact (Craig *et al*., 2008). This is the first study to co-produce a PA

referral intervention for individuals with health conditions. This intervention is aligned with NICE (2011) guidance as well as a local evaluation study that fed into the development of the scheme [Liverpool John Moores University, unpublished data]. As the co-produced intervention was informed by both scientific-evidence and local stakeholder needs, it has potential to improve implementation success and thus, clinical effectiveness. Sequential chapters describe the pilot (5 & 6) and pragmatic evaluation (7) of this co-produced intervention.

5 STUDY 2a: PRELIMINARY EFFECTIVENESS AND ACCEPTABILITY

5.1 INTRODUCTION

The greatest public health gains can be realised by supporting those who are most inactive to engage in at least a low level of PA, even if the full recommended dose (i.e. 150 minutes per week) is not achieved (Department of Health, 2004; Ekelund *et al*., 2016). As previously discussed (Section 2.3), ERSs may provide a tool to facilitate PA behaviour change in at-risk populations. Evidence of their effectiveness is however uncertain (Pavey *et al*., 2011a). Focus continues to be on exercise prescription and few ERSs have been underpinned by behaviour change theory (Dugdill *et al*., 2005; Beck *et al*., 2016). Furthermore, the failure to involve service-users and other stakeholders in development phases may compromise intervention acceptability (Din *et al*., 2015; Beck *et al*., 2016).

To overcome such challenges, Study 1 involved the co-production of a PA referral intervention with multidisciplinary stakeholders (commissioners, practitioners, service-users and academics) that was evidence-based, drew on behaviour change theory, and deemed feasible to implement within local infrastructures (Chapter 4). Underpinned by Self-Determination Theory (SDT; Ryan & Deci, 2000), the co-produced PA intervention differed from the existing ERS in operation in Liverpool in its focus on PA behaviour change (rather than exercise prescription), and inclusion of frequent one-to-one consultations with exercise referral practitioners (rather than formal contact at induction only). Whilst the intervention framework was deemed feasible by multiple stakeholders in the co-production group, it was not yet known whether the intervention would be acceptable or effective when implemented in practice. Such evidence is crucial if we are to understand the relative value of co-production as a methodological approach. Yet, despite the growing popularity of co-production as a public health methodology (Batalden *et al*., 2016; Osborne *et al*., 2016; Rycroft-Malone *et al*., 2016), few reports are available documenting "what happens next". Feasibility work is important to

overcome teething problems, test research procedures and refine intervention components as documented by the MRC (2008).

The aim of this study was therefore to explore the preliminary effectiveness and acceptability of a co-produced PA referral scheme (Buckley *et al*., 2018), in participants with health conditions. This was conducted with a view to informing intervention refinement prior to a subsequent experimental trial. This phased approach is advocated by the Medical Research Council (MRC) to ensure complex interventions are developed to the point they can have a worthwhile effect, prior to investment in substantive trials (Craig *et al*., 2008).

5.2 METHODS

Study design

This pre-post study utilised outcome and process methods to explore preliminary effectiveness and acceptability of a co-produced PA referral intervention.

The co-produced intervention

Full details of the co-produced intervention are described in the previous chapter (Table 4-4 and Figure 4-1). In brief, the intervention aimed to support participants to make gradual, sustainable changes to their PA levels. Participants received 12 weeks subsidised access to a fitness centre (swimming baths, gymnasium, and group classes) plus a series of one-to-one behaviour change consultations (60-minute induction followed by 30-minute consultations at weeks 4, 12 and 18 (follow up)). A log book was provided for each participant to set action plans, log progress and facilitate consultation discussions. Consultations were delivered by exercise referral practitioners and underpinned by SDT (Ryan & Deci, 2000), with the aim of enhancing autonomous PA motivation. Practitioners received training in SDT-based communication strategies led by the researcher's primary supervisor, involving a group workshop plus ongoing one-to-one support.

Participants

Participants referred for PA by a health professional between January and March 2017 were invited to take part in the study. When potential participants arrived at the intervention leisure centre to book an initial induction, they were given a poster regarding the study and verbally consented for the researcher to contact them and discuss participation. Full written consent was obtained in person prior to testing at Liverpool John Moores University Laboratories. Inclusion criteria included: a) referral due to a health-related risk factor (e.g. hypertension, hyperglycaemia, obesity) and/or a controlled lifestyle-related condition (e.g. diabetes, cardiovascular disease, depression), and b) ≥18 years of age. A purposefully diverse (age, health condition, sex etc.) subsample of participants (*n*=12) took part in an interview. Participants were identified from baseline results and contacted via a letter of invitation.

Procedure

Data were collected at baseline and following week 12 consultations in university laboratories. Prior to testing, participants fasted for ≥6 hours, avoided consumption of alcohol for ≥12 hours and strenuous exercise for ≥24 hours. Upon the arrival at the laboratory, participants' anthropometrics were measured questionnaires were completed. Participants then took part in vascular ultrasound procedures, before undertaking a submaximal fitness test. Finally, an accelerometer was given to participants to record their PA levels for 7 days.

Outcome measures

Outcome measures were collected by the primary researcher and are described in detail in the General Methods section (Chapter 3) and in brief below:

Behavioural. PA levels were assessed via the commercially available tri-axial ActiGraph GT3x accelerometer (ActiGraph, Pensacola, FL, USA). Signal processing was done offline in R (http://cran.r-project.org/). The R package GGIR (Hees *et al*., 2013) facilitated data cleaning such as non-wear time (15-minute detection and 60-minute evaluation window) and

extraction of user defined acceleration levels (moderate PA >69.1 g and vigorous PA >258.7 g; Hildebrand *et al*., 2014).

Cardiometabolic and anthropometric. Cardiorespiratory fitness (CRF) [Maximal oxygen consumption (VO_2max^{-2})] was estimated via the Astrand-Rhyming cycle ergometer protocol (Astrand, 1960). Blood pressure was measured in the supine position following 20 minutes of rest using an automated blood pressure device (Omron Healthcare UK Limited, Milton Keynes, UK). Using standard techniques (Lohman *et al*., 1991) body mass index (BMI) was calculated as mass divided by stature (kg/m^2) and waist-to-height ratio was calculated as waist circumference divided by stature.

A clustered cardiometabolic risk score was calculated to minimise the impact of daily variation in individual risk markers (Wijndaele *et al*., 2006; Alberti *et al*., 2009). Standardised values for waist-to-height ratio, mean arterial blood pressure [(2(diastolic) + systolic)/3], and CRF (inverted) were calculated using baseline mean ± standard deviation. The sum of these standardised values was divided by the number of parameters included to give a clustered score. This approach has been used in a comparable adult sample (Knaeps *et al*., 2016).

Psychosocial. Behavioural regulation was measured via the Behavioural Regulation in Exercise Questionnaire (BREQ-2; Markland & Tobin, 2004). Psychological needs satisfaction was measured via the Psychological Needs Satisfaction in Exercise Scale (PNSE; Wilson *et al*., 2006).

Consultation attendance. Attendance at one-to-one consultations was logged by exercise referral practitioners.

Interviews

Semi-structured interviews (*n*=12; 8 female) lasted 30-60 minutes and were conducted at the intervention fitness centre following week 12. As participant perceptions of PA referral schemes have been frequently reported (Mills *et al*., 2012; Sharma *et al*., 2012), the aim of the interviews was to explore participant perceptions of the components of the intervention that

differed from usual care: a) the PA content of the intervention; and b) the individual progress support offered (via one-to-one consultations). Interviews were conducted by an MSc psychology student. Interviews also covered SDT concepts such as motivation, needs satisfaction and perceived needs support. To enhance depth and trustworthiness of the data, iterative questioning was used whereby the researcher used probes to elicit detailed data and returned to previously raised points by paraphrase participant answers or rephrasing the questions (Shenton *et al.,* 2004).

Statistical analyses

Data were analysed using SPSS version 23 (IBM, New York, USA) with alpha level set at $P \leq 0.05$. Intervention effects were compared at 12 weeks from baseline using paired samples T-tests and effect sizes (Cohen, 1988). Sample size estimations were not conducted for this study as its purpose was not to determine definitive effectiveness, but to explore potential health effects and intervention acceptability – informing the next evaluation phase (Study 3). Thus, inferential statistics were computed using a minimum clinically important difference method (Batterham & Hopkins, 2006; Hopkins et al., 2009). Briefly, the approach forms inferences based on clinically meaningful magnitudes, and is supported alongside hypothesis testing. A spreadsheet (http://newstats.org/generalize.html) was used to compute quantitative and qualitative probabilities that the true effects were beneficial, trivial, or harmful. A minimum clinically important difference for CRF was set at 2 $ml.kg.^{-1}min^{-1}$ based on previous epidemiological evidence (Simmons *et al*., 2009; Lee *et al*., 2010) and for MVPA was set at 10 minutes/day as identified by recent public health statistics (ONS, 2017) and magnitudes found in similar interventions (Gabrys *et al*., 2013). Minimum important differences for other variables were determined via previous epidemiological research and a small effect size.

Semi-structured interviews were transcribed and then analysed thematically using NVivo-10 software (QSR International Pty Ltd.) by the primary researcher and an MSc student who also conducted the interviews and was thus immersed in the data (Braun & Clarke, 2006). This method of analysis was chosen in order to identify positive aspects of the intervention as well

as areas requiring refinement. Methods to enhance trustworthiness included triangulation, participant choice whether to take part in the interview or not, and iterative questioning (Shenton *et al*., 2004). For example, several transcripts were read independently by three researchers (including the primary researcher) before meeting to discuss themes and any areas of disagreement. Final analysis and results were conducted and produced, respectively by the primary researcher.

5.3 RESULTS

Participant characteristics. Thirty-six participants were invited to take part in the study and 32 consented, 19 of whom provided data for at least one 12-week measure (figure 5-1). Incomplete datasets were due to inability to complete the CRF test (*n*=3), declining the blood pressure measure (*n*=1), and insufficient accelerometer wear time (*n*=5). Table 5-1 outlines baseline characteristics for the whole sample, complete cases and interview participants.

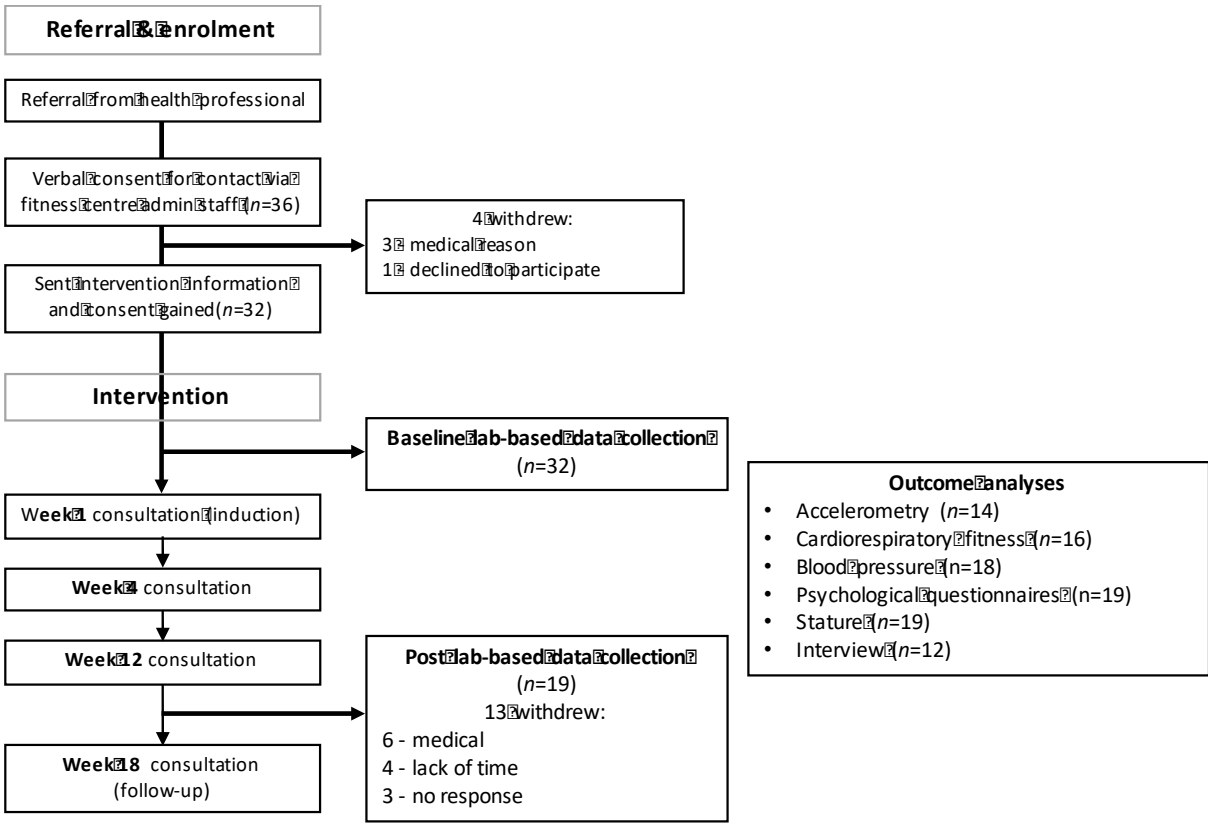


Figure 5-1. Flow diagram of intervention pathway.

Table 5-1. Baseline characteristics presented as Mean ± SD or % (n) of group.

	Participant characteristic (*n*=32)	Participant characteristics with pre-post data collected (*n*=19)	Interview participant characteristics (*n*=12)
Age (years)	53 ± 16	56 ± 13	52 ± 13
Female	63 (20)	58 (11)	66 (8)
White British	91 (29)	84 (16)	75 (9)
Full-time employment	16 (5)	16 (3)	17 (2)
Never smoked	53 (17)	25 (8)	58 (7)
Body mass (kg)	87.7 ± 20.5	87.1 ± 20.9	84.1 ± 21.0
Body mass index (kg/m^2)	31.2 ± 7	31.0 ± 5.9	30.6 ± 6.8
Systolic blood pressure (mmHg)	132 ± 17	134 ± 19	124 ± 16
Referral due to **>**1 CM risk factor and/or condition	68 (22)	74 (14)	50 (6)
Attendance at 0, 1, 2, 3, and 4 consultations %(*n*)	9 (3), 47 (15), 28 (9), 6 (2), 9 (3)	5 (1), 47 (9), 26 (5), 11 (2), 11 (2)	8 (1), 42 (5), 17 (2), 17 (2), 17 (2)

CM, cardiometabolic

Intervention effects

Cardiometabolic, PA, and psychological questionnaire results are displayed in Table 5-2. Statistically significant changes in CRF (3.6 ml.kg.$^{-1}$min^{-1}; benefit very likely), daily MVPA (12.6 minutes; benefit possible), systolic blood pressure (-9.8 mmHg; benefit very likely) and waist-to-height ratio (1; benefit unclear) were observed at week 12 compared to baseline. Correspondingly, a clustered cardiometabolic risk score demonstrated a significant reduction (benefit most likely) at week 12. No within-subject changes were observed from baseline to 12 weeks in psychological variables.

Table 5-2. Complete case analysis of changes in cardiometabolic, physical activity (PA) and psychological outcome variables.

Outcome measure (*n=sample)*	Baseline Mean (SD) or Median (IQR)	Week 12 Mean (SD) or Median (IQR)	Mean or Median effect (95 % CI, *p*-value)	Effect Size	Probability (%) the effect is beneficial / trivial / harmful	Qualitative inference
Physical activity						
MVPA (min.day)	27.2 (25.2)	39.7 (33.6)	12.6* (4.9 to 21.2, *p*=0.007)	0.44	74/26/0	Benefit possible
Cardiometabolic						
Estimated CRF ($ml.kg.^{-1}min^{-1}$)	21.1 (4.1)	24.7 (4.6)	3.6** (1.9 to 5.4, *p*<0.001)	0.84	96/4/0	Benefit very likely
MAP (mmHg)	95.1 (12.4)	88.5 (6.3)	-7.3** (-3.4 to -11.2, *p*=0.001)	0.68	99/1/0	Benefit very likely
Systolic blood pressure (mmHg)	134.4 (19.7)	126.6 (12.2)	-9.8** (-4.4 to -15.2, *p*=0.001)	0.48	97/3/0	Benefit very likely
Diastolic blood pressure (mmHg)	75.5 (11.1)	69.4 (6.7)	-6.4* (-2.4 to -10.4, *p*=0.004)	0.66	76/24/0	Benefit likely
CMRs	0.00 (0.6)	-0.4 (0.5)	-0.4** (-0.2 to -0.7, *p*<0.001)	0.77	100/0/0	Benefit most likely
Anthropometric						
BMI ($kg.m^2$)	31.1 (6.0)	30.9 (6.0)	0.3 (-1.1 to 1.6, *p*=0.652)	0.03	4/95/1	Very likely trivial
WHR	61.5 (7.5)	60.6 (6.7)	1.0* (0.9 to 1.9, *p*=0.033)	0.13	30/67/1	Unclear
BREQ-2						
Amotivation[b]	0.00 (0.38)	0.00 (0.25)	0.00 (-0.25 to 0.13, *p*=0.712)	0.08	-	-
External Regulation[b]	0.00 (0.5)	0.25 (0.5)	0.00 (-0.25 to 0.25, *p*=0.588)	0.14	-	-
Introjected Regulation[b]	0.33 (1.17)	0.67 (1.33)	0.17 (-0.65 to 0.65, *p*=0.260)	0.22	-	-
Identified Regulation[b]	2.25 (1.5)	2.75 (1.75)	0.19 (-0.25 to 0.63, *p*=0.390)	0.18	-	-
Integrated Regulation[b]	1.25 (1.25)	1.75 (2.13)	0.13 (-0.25 to 0.75, *p*=387)	0.19	-	-
Intrinsic Regulation[b]	2 (2.38)	2.5 (1.5)	0.25 (-0.25 to 1, *p*=0.183)	0.34	-	-
PNSE						
Autonomy	4.76 (0.88)	4.88 (0.99)	0.12 (-0.62 to 0.39, *p*=0.639)	0.13	-	-
Competence	4.01 (1.31)	4.18 (0.94)	0.17 (-0.72 to 0.38, *p*=0.531)	0.15	-	-
Relatedness	3.43 (1.56)	3.26 (1.64)	-0.17 (-0.54 to 0.88, *p*=0.625)	0.09	-	-

[a] Baseline and week 12 measures presented as mean (SD)

[b] Values presented as median and interquartile range due non-normally distributed data.

*P = <0.05 **P = ≤0.001

MVPA, Moderate-to-Vigorous Physical Activity; **CRF**, Cardiorespiratory Fitness; **MAP**, Mean Arterial Pressure; **CMRs**, Clustered Cardiometabolic Risk score; **BMI**, Body Mass Index; **WHR**, Waist-to-Height ratio; **BREQ-2**, Behavioural Regulation of Exercise Questionnaire; **PNSE**, Psychological Needs Satisfaction in Exercise scale.

For the cardiometabolic and PA variables, quantitative and qualitative magnitude-based inferences are reported. Due to the lack of agreement in what are meaningful / harmful changes in levels of motivation, magnitude based inferences were not calculated for psychological variables.

Process data

Three participants (9%) did not attend any consultations, 15 (47%) attended induction only, 9 (28%) attended induction plus one consultation, 2 (6%) attended induction plus two consultations, and 3 (9%) attended induction plus three consultations.

Interviews. Table 5-3 presents participant perceptions regarding a) PA content of the intervention, and b) Individual progress support.

Table 5-3. Qualitative findings from interviews. Under the table heading 'Subtheme' the following symbols refer to whether a theme was deemed positive (+), negative (-), or neither positive or negative (+/-). A participant identifier is included following each quote (Participant number; sex; age in years).

Theme	Subtheme	Descriptor	Exemplar Quote
Content of scheme	Log-book (+)	Most patients were in support of the use of a participant log-book.	*"I filled it in on a day-to-day basis including all my walking you know, I was taking my GPS thing out and logging it… I think it's pretty good, it gives people room to decide how they're going to do it themselves you know." (P20, Male, 76)*
	Narrow gym focus (-)	Several patients highlighted that the scheme was too gym focussed.	*"Maybe the induction shouldn't just focus on the gymnasium… Everyone's different so for some people it'd be fine just going to the gym… I'd rather go and get on a bike and cycle in the countryside…" (P7, Female, 51)*
Individual progress support	Frequent support (+)	Most patients identified that they felt they were well supported during the referral scheme.	*"I felt that it* [the induction] *focussed on my needs and I think it was a good programme to get me started. It was good having access to the practitioners throughout the scheme, having that review every four weeks" (P25, Female, 57)*
	Patient-centred support (+)	Many patients described examples of practitioners being autonomy supportive and not prescribing gym-based exercise per se.	*"They* [practitioners] *were really good because I just said I don't really feel like I belong here,* [practitioner] *said to me where do you gravitate towards, where do you feel you would like to start" (P7, Female, 51)*
	Patient centred support (+/-)	Some patients felt it was the exercise referral practitioners who controlled what activities were completed.	*"*[practitioner] *has decided* [my programme] *for me, I just kind of worked within those boundaries really", (P25, Female, 57).*
	Under-staffed (-)	Some patients felt they had little contact with the exercise instructors, potentially due to staff capacity.	*"I don't think for me personally there were enough staff… I was under the radar…" (P8, Female, 68)*
	"Choka" gym (-)	One patient highlighted that, sometimes, the gym was too busy for them.	*"I had one planned* [induction with a practitioner] *and because I suffer with depression and anxiety when I first went in and they were just absolutely chocka and I couldn't do it and walked out. I then went to see the health coach at the doctors and told him… he booked me in again but when it was going to be quiet for me." (P27, Female, 38)*

Overall perceptions of the intervention were positive. Most participants described meaningful health improvements (e.g. *"I've been off my anti-depressants…. I was on them for about eleven years and I tried several times to come off them"* P25, Jenny, 57) and participants described how the frequent support was tailored to their needs and kept them coming back (*"*[practitioner] *said I could see him every four weeks to see how I'm doing… which I think is very good"*, P19, Mark, 57). Some participants however felt the scheme was too gym-focussed, and the fitness centre was busy and under-staffed. It was not clear from the interviews how much autonomy participants felt in their PA behaviour change. Whilst some participants noted their exercise programmes were set by the practitioners, it was not specifically identified as positive or negative.

5.4 DISCUSSION

This study explored the preliminary effectiveness and acceptability of the co-produced PA referral intervention developed through Study 1. Findings demonstrated significant improvements in MVPA and clustered cardiometabolic health profile (CRF, waist-to-height ratio, blood pressure) from baseline to 12 weeks. There were no changes in psychological needs satisfaction or motivation towards exercise, although as 47% of participants attended only one of the four consultations offered, many did not receive the intended behavioural support. Whilst participants were positive about the support provided by exercise referral practitioners, some felt the intervention was too gym-focused and the fitness centre was under-staffed and too busy.

PA is recommended for maintenance of good health and as a treatment for individuals with health conditions. Despite UK PA referral schemes showing promise, systematic reviews have found they are not typically underpinned by theory and have reported a wide range of attendance rates (Pavey *et al.*, 2012; Campbell *et al*., 2015). The previously co-produced PA referral scheme was underpinned by behaviour change theory and deemed feasible to

implement in practice (study 1). It was not known, however, whether the intervention was acceptable or effective and what value co-production had for intervention success.

The magnitude of change observed in CRF (>3.5 $ml.kg.^{-1}min^{-1}$) has been linked to a 13% lower all-cause mortality risk (Lee *et al*., 2010). This may be particularly meaningful for the low-fit sample in this study (whereby 14/16 participants demonstrated CRF levels <27.7 $ml.kg.^{-1}min^{-1}$), given the most striking differences in mortality rates occur between the least-fit and next-least-fit quintiles. Thus, the greatest public health benefits may be realised by increasing PA levels among the least fit (Lee *et al*., 2010). Despite the low fitness levels of the study sample however, it is notable that 57% of participants were achieving the recommended 150 minutes of moderate-intensity PA per week at baseline. Such discordance demonstrates the importance of collecting both device-measured PA and objective CRF, whilst raising questions regarding the use of current PA guidelines (Department of Health, 2011) to assess eligibility for PA referral schemes (NICE, 2014).

The co-produced intervention aimed to support PA behaviour change within participants' daily lives, rather than focussing on exercise prescription. Whilst an increase in MVPA was noted, it is not clear what type of PA participants were involved in and qualitative accounts suggested some participants felt they were guided towards gym-based exercise rather than physical activity ("*the induction shouldn't just focus on the gym*…" P7, Kathy, 51). This perceived gym focus may have resulted from the intervention being delivered within a fitness centre, which was a co-produced decision driven by the need for accountability when working with individuals with health conditions (Study 1). Further research is needed to investigate whether similar interventions delivered in non-fitness environments are able to promote a more holistic PA focus.

The co-produced intervention was underpinned by SDT (Ryan & Deci, 2000) and intended to foster autonomous PA motivation through supporting the psychological needs of autonomy, competence and relatedness. No changes in psychological needs satisfaction or exercise

motivation regulation were however observed at 12 weeks. Participants' qualitative accounts suggested they may not have been exposed to the intended level of autonomy support, with some participants suggesting practitioners controlled their activity programmes. Participants also perceived the gym to be busy and understaffed, which may have impacted on practitioner ability to conduct consultations. Whilst this data do not allow conclusions to be drawn about the level of needs support provided by practitioners, challenges of implementing needs-supportive delivery within PA referral settings have been recognised elsewhere (Duda *et al*., 2014) and further work may be required to embed the intended level of behaviour change support.

There are several possible explanations for why changes in PA and CRF may have occurred in the absence of changes in psychosocial variables. Firstly, as it was not clear to what extent consultations were carried out as intended in the current study, it is possible the scheme that was actually delivered did not go much beyond the standard level of support typical of a standard exercise referral scheme (e.g. a 12-week gym programme). Whilst our data do not allow conclusions to be drawn about the level of needs support provided by practitioners, challenges of implementing needs-supportive delivery within PA referral settings have been recognised elsewhere (Duda *et al*., 2014). Therefore the short-term PA and CRF changes may have resulted from the more "typical" exercise referral factors such as subsidised gym access and attention from an instructor.

To our knowledge, however, no comparable evaluations of standard exercise referral have utilised device-measured PA, and only one study measured CRF. Isaacs *et al*. (2007) found an increase of 11% in CRF at 10-weeks following an ERS, which is less than the 17% increase in the present study. Comparison of the results from our co-produced intervention compared with *typical* exercise referral schemes is therefore limited. One study did however, use accelerometry to evaluate an exercise referral scheme with embedded PA counselling and found a significant increase in MVPA (9 minutes), which is slightly less than the 12.6 minute increase observed in the present study (Gabrys *et al.,* 2013). In addition, Sorenson *et al*. (2008)

measured CRF to evaluate a 4-month exercise referral scheme with motivational counselling and found an increase of 2.3 $ml.kg.^{-1}min^{-1}$, which is less than the 3.6 $ml.kg.^{-1}min^{-1}$ observed in the present study. More evaluation work is therefore needed that includes 'objective' health measures (i.e. device-measured PA and CRF) to better compare standard exercise referral schemes with adapted initiatives.

Other potential explanations for the lack of change in motivational variables relate to the sample's baseline profile and properties of the questionnaires used. It is noteworthy that participants did not have an "unhealthy" motivational profile to start with. In particular, the mean perceived autonomy satisfaction at baseline was 4.76 ± 0.88, indicating a positive level of perceived autonomy that we might not expect to change substantially (given the range is 1 to 6, and a score of 3.5 would be neutral). Finally, it must be acknowledged that the BREQ-2R and the PNSE both focus on exercise rather than PA. Therefore it is possible that changes in PA related to non-exercise domains of PA (e.g. walking, lifestyle activity) might not be reflected in changes in exercise motivation or related constructs. Due to the complex nature of PA however, it is challenging to measure specific motivation for the whole spectrum of PA (which may vary according to PA domain), nor are there current validated measures available.

The PA intervention in this study was previously co-produced by a team of commissioners, practitioners, service users and academics (Study 1). It is noteworthy that not all exercise referral practitioners delivering the intervention were involved in the co-production phase, which may have affected their sense of ownership of the scheme. The researcher and primary supervisor did however, meet regularly with the delivery team and developed a reciprocal relationship that facilitated a sense of shared ownership of the project and ensured teething problems were addressed promptly. Such observations highlight the benefits of co-production continuing beyond initial development throughout subsequent delivery and implementation (Craig *et al.*, 2008).

Strengths & Limitations

The intention of this study was not to determine definitive effectiveness, but to explore acceptability and estimate potential effects through magnitude-based inferences. As such, the sample size was small and there was no control group. The magnitude-based inference approach helps to prevent an over reliance on the *p* statistic, and instead facilitates the use of available evidence to infer meaningfulness. Further, this study did not include a measure of practitioner delivery during consultations, which makes it difficult to draw conclusions regarding intervention fidelity. Consultation documents completed by exercise referral practitioners demonstrated incremental dropout (3/32 participants attended all four consultations). Yet, 19 participants attended 12-week data collection at the university and anecdotal conversations with practitioners suggested attendance was higher than results implied. Therefore, it is not clear if missed consultations were due to failure on the part of the exercise referral practitioner to offer the consultation, failure on the part of the participant to attend, or poor attendance monitoring (i.e. the consultation did actually occur). Future research should include objective fidelity and attendance measures. In addition, the views of the exercise referral practitioners delivering the intervention would be beneficial from an acceptability perspective and complimentary to the participant qualitative data. Such feasibility work is vital to identify intervention components that need further refinement, prior to conducting a definitive trial to determine effectiveness. This phased approach thus enhances ecological validity and chances of future implementation success as recommended by the MRC guidance for complex intervention development and evaluation (Craig *et al*., 2008).

5.5 CONCLUSION

This study explored the preliminary effects and acceptability of a co-produced PA referral scheme. Following the 12-week intervention, improvements in device-measured MVPA and cardiometabolic health were observed. Process data suggested the focus on PA (rather than exercise) was not always achieved. Thus, further work may be required to embed the intended

holistic PA focus of the intervention and the level of needs support provided by practitioners, develop objective means of monitoring attendance and adherence, and improve the delivery and content of the behaviour change consultations, prior to conducting an experimental trial. The subsequent chapter (study 2b) describes the in-depth cardiovascular health implications of the findings within this study with the addition of a control arm. Whilst these results were positive, conclusions could not yet be drawn regarding intervention effectiveness until the PA referral scheme was further refined (as above) and compared to usual care and no-treatment comparisons. This was therefore the focus of study 3, the final study in this PhD.

Importantly, this study provides a novel insight into what happens beyond the co-production phase of a complex intervention. Findings highlight the challenges of implementing a complex PA referral scheme as intended and emphasises the importance of following MRC guidance (Craig *et al*., 2008), which advocates a phased approach to complex intervention development. Whilst it is not possible to know how the delivery of this intervention would have differed had it not been co-produced, the researcher wishes to emphasise the importance of an ongoing reciprocal relationship between commissioners, practitioners, service-users and academics to ensure congruence between the way interventions are planned, delivered and received.

6 STUDY 2b: PA REFERRAL & CARDIO-PROTECTION

6.1 INTRODUCTION

Study 1 involved the co-production of a PA referral intervention which was underpinned by multi-disciplinary stakeholder views and behaviour change theory. Study 2a then explored the preliminary health effects and acceptability of the co-produced intervention. This study will now provide an insight into the cardio-protective health benefits of the co-produced PA referral scheme, through an in-depth investigation of novel, vascular health outcomes, compared with control data from a comparable group of participants.

The sympathetic nervous system is an important regulator of central and peripheral blood flow. Previous work has found that sympathetic nervous system stimulation, via a cold pressor test (CPT; i.e. placing one hand in ice slush), leads to coronary (Monahan *et al*., 2013) and carotid artery (Rubenfire *et al*., 2000; Van Mil *et al*., 2017) vasodilation. In marked contrast, participants with cardiovascular risk factors and/or disease show an attenuated or even vasoconstrictive response (Monahan *et al*., 2013). The vasoconstrictive response in central arteries may have clinical relevance, since independent prospective studies have found that both coronary and carotid (Schächinger *et al*., 2000; Van Mil *et al*., 2017) vasoconstriction independently predicts disease progression and cardiovascular events.

Regular PA is a successful and potent stimulus that markedly reduces the risk for future cardiovascular events (Shiroma & Lee, 2010). However, no previous study has explored the impact of PA on carotid artery responses to sympathetic stimulation. This study, therefore, provides an in-depth investigation of cardiovascular health outcomes used in the pilot of the co-produced PA referral scheme (reported in chapter 5). The study hypothesis was that a 12-week PA intervention can reverse carotid artery vasoconstriction in response to sympathetic stimulation in participants with increased CVD risk.

6.2 METHODS

Participants

Thirty-two participants with increased CVD risk were recruited for this study. Nineteen patients (56 SD 13 years; Female (*n*=11); BMI 31 SD 6 kg.m^2) were referred by health professionals to a PA intervention, as presented in Study 2a. Twelve additional participants were recruited as a control group (49 SD 18 years; Female (*n*=8); BMI 29 SD 5 kg.m^2) to control for effect of time on vascular measures. Eligibility criteria included: completion of a Physical Activity Readiness Questionnaire (PARQ), increased CVD risk (e.g. high blood pressure, hyperglycaemia, obesity) and/or presence of lifestyle-related disease (e.g. CVD, diabetes, cancer, depression), and ≥18 years of age. Patient medications remained unchanged across the 12-week intervention period.

Design. This study used a non-randomised pre-post design to explore the effects of a previously co-produced PA scheme (described in chapter 5). Individuals were recruited based on a referral to the intervention leisure centre from a health professional (PA referral scheme) or by the primary researcher as a comparable control arm. All measurements were collected at baseline and 12 weeks.

Intervention. The co-produced intervention included 12 weeks of subsidised access to a fitness centre (swimming baths, gymnasium, and group classes) plus PA behaviour change consultations at weeks 1, 4, 12 and 18 (follow up). Participants were encouraged to use the fitness centre and increase their habitual PA levels relative to their own personal goals. A full intervention description and theoretical underpinning can be found in Chapter 4.

Measurements (general). Anthropometrics, blood pressure, and estimated CRF, and device-measured PA levels were examined as described in detail in Study 2a.

Vascular testing consistently started with the FMD (performed on the right arm). After a 10-minute period of rest in the supine position, carotid artery reactivity in response to sympathetic stimulus (CAR-test) was performed on the left common carotid artery.

Measurements (carotid and brachial artery vascular function).

These vascular measures are described in detail in the general methods section (Chapter 3). To investigate carotid artery health, carotid artery reactivity (CAR%) was examined, which is a measure of the carotid artery diameter response to sympathetic stimulation.

In brief, patients were positioned supine on a bed to facilitate movement of the left hand into a bucket of ice slush. A two-dimensional image of the left common carotid artery was obtained via a high-resolution ultrasound machine (Terason, 3300, Teratech) and a 10-12-MHz probe. After a 1-minute baseline, the patient immersed their hand (up to the wrist) in ice slush (~4.0°C) for 3 minutes. Following submersion, data were calculated as the mean value for 10-s intervals. Peak diameter change (CAR%, CAR_{mm}) and area-under-the-curve for diameter change (CAR_{AUC}) were calculated from the 10-s intervals. The peak diameter and CAR_{AUC} refers to a constriction or dilation.

Peripheral artery vascular health was also examined by measuring the brachial artery flow-mediated dilation (FMD%). Detailed description of procedures can be found elsewhere (Thijssen *et al*., 2011; Chapter 3). Briefly, a 1-minute baseline measurement was taken, then a pneumatic rapid cuff inflator (Hokanson, Bellevue, U.S.A.), fitted around the forearm distal to the humeral epicondyle, was inflated to 220 mmHg for 5 minutes. Recording continued for a period of 3 minutes post cuff deflation. Peak change in FMD from baseline (FMD%, FMD_{mm}) was calculated. Both CAR and FMD data were analysed using custom designed, validated automated edge-detection and wall-tracking software (described in Chapter 3).

Statistical analysis. Data were analysed using SPSS version 23 (IBM, New York, USA) with alpha level set at $P \leq 0.05$. Intervention effects were measured 12 weeks from baseline using

paired samples t tests (normally distributed) or related sample Wilcoxon Signed Rank test (non-normally distributed). Spearman's correlations were used to assess relationships between CAR%, FMD%, and CRF.

6.3 RESULTS

Baseline characteristics. Patients were referred for PA due to one of the following risk factors: obesity (*n*=3), hypertension (*n*=2), (pre) diabetes (*n*=5), CVD or event (*n*=3), hypercholesterolemia (*n*=2), poor mental health (n=2), or physical inactivity / low fitness capacity (*n*=2). The control group was recruited based on the presence of at least one cardiometabolic risk factor and/or disease (i.e. CVD or event, diabetes, cancer, obesity, hypertension, mental illness). Baseline-to-12-week change data is reported in Table 6-1. Due to health problems/contraindications the fitness test was not conducted on three individuals within the PA referral arm. No differences were found in baseline characteristics between the control and intervention group (Table 6-1).

Between Arm Effects. There was a significant difference in effects between the PA referral scheme and no-treatment control for CRF (p=0.023) and CAR% (p =0.02). There were no significant difference in effects between arms for MVPA (p =0.381), blood pressure (p =0.191), BMI (p =0.867), or FMD% (p =0.06).

PA Referral Scheme Effects. Following the 12-week PA referral scheme there were significant increases in CRF and MVPA, significant reductions in systolic and diastolic blood pressure, and no change in BMI (as described in Study 2a; Chapter 5). Of specific focus in this study, a significant increase in the carotid artery dilator response (CAR%, CAR_{mm}, and CAR_{AUC}) was observed following the PA referral scheme.

Prior to the intervention, six patients demonstrated carotid artery vasoconstriction during the CAR-test. At the 12-week post-intervention measure, this response was reversed to vasodilation in all six of these patients (Figure 6-1). Descriptive statistics revealed differences

between the patients that presented with carotid vasoconstriction (*n*=6) and vasodilation (*n*=13), with individuals demonstrating carotid vasoconstriction being older (11 years, SD 8), having a higher BMI (2.4 kg/m^2, SD 5) and higher systolic blood pressure (22 mmHg, SD 17), and lower CRF (-2.5 ml.kg.$^{-1}$min^{-1}, SD 2).

Brachial artery FMD% and FMD_{mm} significantly increased after the PA intervention, whilst no change was observed in brachial artery diameter (Table 6-1). No significant correlation was found between pre-intervention CAR% and FMD% (R=0.099; *P*=0.596) or baseline-to-12 week change in CAR% and FMD% (R=0.240; *P*=0.353). CAR% was not correlated with CRF (R=0.051; *P*=0.864).

No-Treatment Control Effects. In the control group, no changes were observed for CRF, BMI, FMD or CAR response. A significant reduction in diastolic blood pressure was found (Table 6-1).

Table 6-1. Carotid and peripheral vascular function and cardiometabolic risk factors.

	Control Group (*n*=12)			**Intervention Group** (*n*=19)		
Outcome measure	Baseline Mean (SD) or Median (IQR)	Week 12 Mean (SD) or Median (IQR)	*P*	Baseline Mean (SD) or Median (IQR)	Week 12 Mean (SD) or Median (IQR)	*P*
Vascular						
CAR%[b]	2.5 (2.9)	1.8 (2.2)	0.518	1.4 (4.5)	3.1 (3.1)	<0.001
CAR_{mm}[b]	0.18 (0.13)	0.17 (0.08)	0.591	0.1 (0.05)	0.20 (0.40)	0.001
CAR_{AUC}	0.7 (1.7)	1.1 (1.4)	0.815	0.5 (1.8)	2.2 (1.7)	<0.001
Carotid artery diameter (cm)	0.7 (0.1)	0.6 (0.1)	0.474	0.7 (0.1)	0.7 (0.1)	0.716
FMD%[b]	6.7 (2.3)	5.5 (2.1)	0.12	4.4 (4.7)	7.0 (4.4)	0.003
FMD_{mm}	0.23 (0.07)	0.19 (0.08)	0.079	0.18 (0.1)	0.25 (0.08)	0.007
Brachial artery diameter (cm)	0.4 (1)	0.4 (0.1)	0.288	0.4 (0.1)	0.4 (0.1)	0.860
SBP (mmHg)	121 (13)	117 (14)	0.063	134 (20)	126 (12)	0.001
DBP (mmHg)	72 (11)	66 (8)	0.011	76 (11)	69 (7)	0.004
MAP (mmHg)	88 (10)	83 (9)	0.007	95 (12)	88 (6)	0.001
Fitness & PA						
Estimated CRF ($ml.kg.^{-1}min^{-1}$)	31.2 (9.6)	30.6 (8.7)	0.479	21.1 (4.1)	24.7 (4.6)	<0.001
MVPA (min.day)	59.2 (31.3	64.8 (24.4)	0.471	27.2 (25.2)	39.7 (33.6)	0.007

CAR%, carotid artery reactivity (%); **CAR_{mm}**, carotid artery reactivity (mm); **CAR_{AUC}**, carotid artery reactivity (area under the curve); **FMD%**, flow mediated dilation (%); **FMD_{mm}**, flow mediated dilation (mm); **SBP**, Systolic blood pressure; **DBP**, diastolic blood pressure; **MAP**, mean arterial pressure; **CRF**, cardiorespiratory fitness; **BMI**, body mass index; **PA**, physical activity; **MVPA**, moderate-to-vigorous physical activity.
Baseline and week 12 measures presented as mean (SD) and compared via Paired Samples T test.
[b]Values presented as median and interquartile range due to significant skewness and/or kurtosis and compared via Wilcoxon Signed Rank test.

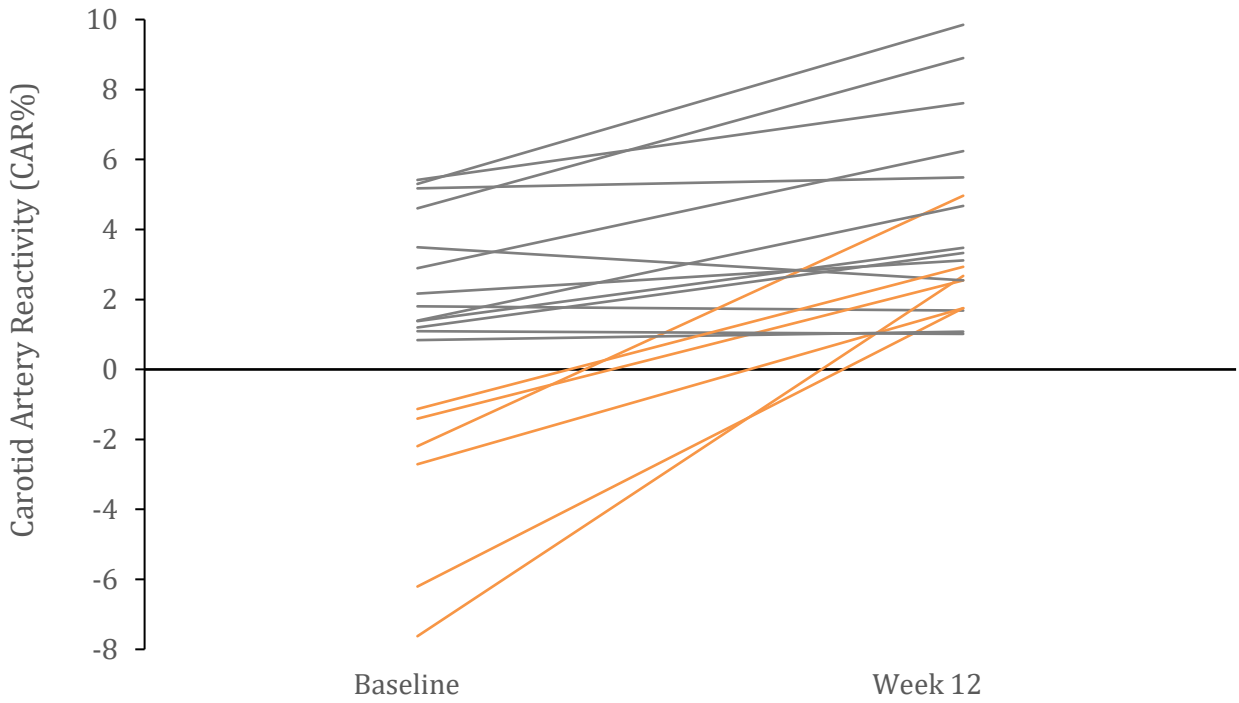


Figure 6-1. Individual patient carotid artery reactivity (CAR%) pre-post a 12-week physical activity referral scheme (*n*=19).

6.4 DISCUSSION

Several previous studies have demonstrated beneficial effects of PA and exercise (hemodynamic stimuli) on measures of vascular health, largely focusing on peripheral artery vascular health in response to increases in shear stress (see review for more information; Green *et al*., 2017). The novel finding of the present study is that following the 12-week co-produced PA referral scheme, vasomotor responses of the central carotid artery during sympathetic stimulation, using the CPT, improved. Specifically, carotid artery vasoconstriction in response to the CPT (a response linked to increased risk for cardiovascular events; Rubenfire *et al*., 2000), was found to be fully reversible following a 12-week PA intervention.

These altered vascular responses may, at least in part, contribute to the potent cardioprotective effects of regular PA in individuals with increased CVD risk.

Observations found in this study may also be relevant for coronary arteries, since previous work has highlighted the similarity between carotid and coronary artery function. For example, sympathetic stimulation is known to cause dilation in both the coronary and carotid arteries in healthy individuals, whilst this deteriorates to vasoconstriction in those with coronary artery disease (Rubenfire *et al*., 2000). Further, Hambrecht *et al.* (2000) demonstrated that 4 weeks of vigorous exercise training improved *coronary* endothelial function in response to acetylcholine infusion in patients with asymptomatic coronary atherosclerosis. The authors concluded that exercise had beneficial effects (partly attenuated artery constriction) on the endothelium of epicardial conduit vessels. Furthermore, they stated that exercise may have the most potent effects on vessels with endothelium dysfunction. Although, the 4-week exercise intervention did not restore endothelial function to normal (relative to a healthy individual). The authors proposed an extended stimulus may be required for such an effect. The potential link between coronary and carotid artery health was recently reinforced by Van Mil and colleagues (2017), who found moderate-to-strong correlation between carotid artery and coronary artery responses to sympathetic stimulation. Finally, one previous study found that 4-weeks of exercise training in patients with coronary atherosclerosis attenuated the coronary vasoconstrictive response to acetylcholine-infusion (Hambrecht *et al*., 2000). Collectively, these results highlight the ability of regular PA to reverse potentially detrimental vasoconstrictive responses of carotid arteries in humans with increased CVD risk.

One may question the potential mechanisms underlying such adaptations. In line with peripheral arteries, benefits of PA on carotid vascular health may be mediated through direct hemodynamic stimuli, leading to improvement in endothelial integrity and/or function (Thijssen *et al*., 2010; Green *et al*., 2017). Based on its ability to regulate vascular health, an intact endothelium protects against artery vasoconstriction to catecholamine release during sympathetic stimulation (Thijssen *et al*., 2010). Alternatively, training may elicit a shear stress-mediated upregulation of endothelium-derived nitric oxide synthase (eNOS), subsequently

leading to a larger NO availability (Deanfield, Halcox, & Rabelink, 2007). Repeated shear stress stimulation of eNOS bioactivity, e.g. via regular PA, facilitates radical homeostasis, leading to greater eNOS bioavailability (among other autacoids). Further, exercise training has been shown to reduce vasoconstrictive responses from endothelin-1 and angiotensin II in individuals with cardiovascular disease or risk (Adams *et al*., 2005; Van Guilder *et al*., 2007). Therefore, repeated shear stress stimulation of eNOS bioactivity during PA may improve endothelial integrity and/or function, contributing to the reversal of carotid artery vasoconstriction to a vasodilator response. It was also found that brachial artery vascular function improved following the PA referral. A change in FMD has prognostic value, since meta-analyses have shown that brachial FMD is inversely associated with CVD incidence (Inaba *et al*., 2010) and a 1% decrease in FMD is associated with a 13% higher risk of a future cardiovascular event (Inaba *et al*., 2010; Green *et al*., 2011). The improvement in FMD, however, was not correlated with the improvement in carotid artery function. Nor were the two measures of vascular health correlated with CRF. It may be that adaptation of the common carotid and brachial arteries do not occur in parallel within individuals, and may be driven through distinct processes. Somewhat in agreement with such a hypothesis, both measures of vascular health seem to be mediated through distinct processes. Previous work provided ample evidence that brachial artery dilation (i.e. brachial FMD) is mediated through elevated shear stress (Thijssen *et al*., 2010), whilst the carotid artery vasomotor response to the CPT is more likely linked to activation of the sympathetic nervous system (i.e. catecholamine release; Mueller *et al*., 1982). This observation suggests both tests of vascular health may provide complimentary information on the vascular system.

Clinical Relevance

Taken collectively, these results are encouraging for the utility of the CAR-test as a non-invasive marker of cardiovascular health. This study found a 12-week exercise referral scheme resulted in significantly increased CRF and reduced blood pressure. Correspondingly, our data is the first to show an increased CAR% elicited from a PA intervention for clinical populations.

More notably, this data is the first to suggest that carotid artery vasoconstriction (indicative of coronary artery dysfunction/disease) is potentially reversible. Interestingly, CAR% was not correlated with either CRF or FMD, despite similar directions of change, indicating that the CAR-test may provide independent information regarding the cardio-protective effects of PA.

Strengths & Limitations

The present study provides a novel in-depth investigation into the cardio-protective effects of a co-produced PA referral scheme. Whilst measuring CAR, however, end-tidal CO_2 was not controlled for, which is a known regulator of cerebrovascular function. Clear instructions were however, provided on breathing patterns and none of the participants hyperventilated, in addition to within-subject comparisons being conducted. It is therefore deemed unlikely that this impacted the main conclusions of this study. Also, some medications may have confounded patients' endothelial function, though any medications remained constant over the 12-week period in all individuals. A lack of objective attendance data is a limitation of this work, as it would have been interesting to see if attendance was related to health outcomes. A potential issue with this however, is that the intervention aimed to change lifestyle-based PA levels. Thus, poor attendance at the leisure centre may not mean the participant is not 'engaged' with the intervention. Therefore, future work should consider how best to monitor attendance, adherence, and engagement with such a complex intervention.

6.5 CONCLUSION

Following the co-produced 12-week PA referral intervention, carotid and brachial artery vascular health was significantly improved in a clinical population with increased risk for CVD. More importantly, this study demonstrated that carotid artery vasoconstriction, a vasomotor response strongly related to an increased CVD risk and a surrogate for coronary artery dysfunction, to be reversible following a real-world PA intervention. This highlights the potential of PA interventions to reduce risk for future cardiovascular events through systemic improvements in artery vascular health.

7 STUDY 3: PRAGMATIC EVALUATION

7.1 INTRODUCTION

Reviews and meta-analyses of the literature have revealed questionable and inconsistent evidence as to the effectiveness of ERSs on PA behaviour, mental well-being, quality of life, and physical health outcomes (Dugdill *et al*., 2005; Pavey *et al*., 2011b). Whilst categorised as ERSs, however, such initiatives are highly heterogeneous in both design and delivery (Craig *et al*., 2001), reflecting varying assumptions on how best to incite health behaviour change (Littlecott *et al*., 2014). Furthermore, outcome measures used in the studies and summarised by reviews and meta-analyses are often self-reported, with objective measures typically limited to blood pressure and body weight (Pavey *et al*., 2011b). It could be argued that such health measures, though important, are far removed from the true potential for ERSs to impact health. Effectiveness trials of ERSs are thus urgently needed that have high ecological validity (i.e. real-world relevance), yet still use relevant and objective outcome measures (Beedie *et al*., 2015).

As discussed previously in Chapter 4, co-production may improve intervention context-sensitivity and feasibility, meaning that there are improved chances of real-world effectiveness (Harden *et al*., 2016; leask *et al*., 2017). The PA referral intervention was co-produced with a multi-stakeholder group of academics, policy-makers, practitioners, and service-users that was deemed feasible to implement within local infrastructures (Study 1; Chapter 4). This co-produced PA referral intervention was subsequently piloted to explore preliminary impacts on participant health and acceptability (Study 2a and 2b; Chapters 5 and 6). Whilst clinically meaningful improvements on cardiometabolic health and PA behaviour were observed following the co-produced intervention, several 'teething problems' were noted that required further development. It was not known however, whether the intervention, following further iterative-co-development, was effective compared to usual care exercise referral or even no-treatment.

Thus, the aim of the final study of this PhD was to pragmatically investigate the effectiveness of the co-produced PA referral scheme in relation to a) usual care and b) a no-treatment control. In addition, an embedded process evaluation sought to explore who each intervention reached, participant adherence, intervention fidelity and acceptability.

7.2 METHODS

Study Design

A three-arm quasi-experimental trial involving: 1. the co-produced PA referral scheme (Co-PARS); 2. Usual care ERS; and 3. No-treatment control. Process evaluation was embedded to establish reach, adherence, fidelity and acceptability of the intervention and usual care conditions. Measures were collected at baseline and week 12.

Participants and Recruitment

Inclusion / Exclusion Criteria: Participants were aged ≥18 years with a health-related risk factor (e.g. hypertension, hyperglycaemia, obesity etc.) or a health condition (diabetes, cardiovascular disease, anxiety, depression etc.) that may be alleviated by increasing PA levels. Participant were not included if they had an uncontrolled health-condition (cardiac, metabolic, respiratory etc.) or a recent cardiovascular event (e.g. myocardial infarction, unstable angina or aortic stenosis) or severe psychological / neurological conditions (e.g. dementia, depression, psychosis etc.).

Eligible participants were recruited from the Co-PARS and usual care ERS after they were referred to the scheme by a health professional. The Co-PARS ran at the same centre that had been piloted in studies 2a & 2b. This decision was made as to continue the iterative work that had occurred with the exercise referral practitioners and manager at this centre as they had invested a lot of time and effort into this research. The usual care ERS ran at a similar centre and was chosen for its comparable size (e.g. number of referrals) and local demographic (e.g. socio-economic make-up of local population). For example, based on areas within Liverpool ranked from 1 (most deprived) to 30 (least deprived), Garston (Usual Care ERS) and Wavertree

(Co-PARS) were ranked respectively: 20th and 21st (income), 20th and 21st (employment), 22nd and 24th (Education) and 10th and 11th (living environment) (The Index of Multiple Deprivation, 2015). Participants in the no-treatment control arm were recruited via posters, electronic invitations, email communications, and via clinical trials registration (NCT03490747).

Study Arms

See Table 7-1 for a 'PaT Plot' of the intervention arm components.

Usual care exercise referral scheme (ERS). The usual care arm followed a standard ERS model of 12-week access to a fitness centre (as described earlier in Study 1; Section 4.2). Participants referred from a health professional met an exercise referral practitioner at the leisure centre for an initial induction (week 1). A 12-week exercise programme was provided for the participant based on their referral reason/health condition including subsidised access to the gymnasium and group classes. This system is already in place and is considered standard exercise referral care for the local area.

Co-produced PA referral scheme (Co-PARS). Both the Co-PARS and usual care ERS offered subsidised access to a fitness centre for 12 weeks. Compared to usual care, the Co-PARS was underpinned by SDT (Study 1; Figure 4-1; Table 4-3) and involved more individualised progress meetings (*n*=5), during which the exercise referral practitioner provided behaviour change support (Week 0, 4, 8, 12 and 18); this additional behaviour change support encouraged more PA-based options that included both daily opportunities to increase PA and activities available at the fitness centre; finally, at each consultation participants were offered (optional*)* additional support from a 'health trainer' service qualified to provide advice on multiple health-related behaviours. These intervention components have been described in detail previously (Study 1; Chapter 4; Table 4-3).

Based on the process findings of study 2a (and supplementary staff interviews conducted by the primary supervisor and MSc students), several refinements were made to the co-produced intervention that was piloted in study 2a. These refinements included: the inclusion of an additional consultation at week 8; enhanced focus on daily PA opportunities (rather than

focussing on activities offered at the fitness centre); adapted staff timetables to promote consistency of care and to allow participant one-to-one consultations to take place in a private room; and updated paperwork to make practitioner-collected data more user-friendly. The key aspect of the intervention was that the participant had autonomy over their activity but was supported through the process. These refinements were implemented (actioned) through an on-going co-production process that involved regular meetings between the primary supervisor, researcher, and delivery staff (over a ~6-month period).

No-treatment control. These participants received a lifestyle advice booklet only (provided to all study arms at baseline data collection, based on standard government guidance for nutrition, smoking cessation and alcohol consumption). Alternative options as an 'active control' group could have included a 'walking for health programme' or other existing community initiative. It was decided, however that we do not definitively know if UK exercise referral is better than nothing, thus a no-treatment control was the most appropriate.

Table 7-1. *'PaT Plot' of pragmatic evaluation describing intervention arm components.*

Timeline	Co-PARS	Usual Care ER	NTC
Staff Training	1		
	Baseline Data Collection		
Induction	2 A	3	
	4	4	
Week 4	5 A		
Week 8	5 A		
Week 12	5 A		
	Post Week-12 Consultation Data Collection		
Week 18	5 A		
	6 Month Data Collection (beyond the scope of this PhD)		

1	Substantial training delivered to Exercise Referral Practitioners in PA behaviour change by a trained HCPC-registered Psychologist. Training included: 1. Needs analysis (observation of current practices); 2. Education (Full day workshop); 3. Behaviour change support (one-to-one sessions over 4 weeks); 5. Ongoing support as required. See Buckley *et al*., (Under Review); Supplementary file 1 for more information.
2	Induction underpinned by behaviour change theory and focussed on facilitating participant autonomy, competence, and relatedness. Focussed on facilitating long-term PA behaviour change and agreeing a programme of activities and action plan (participant logbook) over the next 12 weeks.
A	Participant self-report PA logbook.
3	Usual care exercise referral induction focussed on prescribing an individualised 12-week exercise programme appropriate for the specific health condition.
4	12-week subsidised access to a fitness centre (swimming pool, gymnasium, group classes etc.).
5	Behaviour change consultation focussed on facilitating participant autonomy, competence, and relatedness with the aim of enhancing long-term PA behaviour change. Review of participant logbook, previous activities and agreeing future goals/action plans as appropriate.

Sample Size Estimation

Between-group effects (Co-PARS vs usual care ERS). Required sample size was estimated by using effect sizes of the previous pilot study (Chapter 5) that demonstrated a mean change in CRF 3.6±3.2 $ml.kg.^{-1}min^{-1}$ and existing epidemiological evidence. A 3.5 $ml.kg.^{-1}min^{-1}$ change in CRF has been deemed clinically meaningful with an associated reduction in all-cause mortality (13%) and cardiovascular disease risk (15%; Lee *et al*., 2010). Yet, it has also been demonstrated that substantially smaller magnitudes (Males: 0.5 $ml.kg.^{-1}min^{-1}$; Females 1.0 $ml.kg.^{-1}min^{-1}$) are associated with significant reductions in clustered-cardiometabolic risk in at-risk individuals (Simmons *et al*., 2008). Thus, it was deemed a moderate-large effect size (based on pilot baseline CRF SD of 3.2 $ml.kg.^{-1}min^{-1}$) equivalent to a change of 2 $ml.kg.^{-1}min^{-1}$, would be clinically meaningful. To detect a difference of 2 units ($ml.kg.^{-1}min^{-1}$) between groups, it was estimated that a total sample of 84 would be needed (f=0.25, p=0.05, power = 0.8).

Between-group effects (Co-PARS & ERS arms vs no-treatment control). It was estimated that a larger effect would occur between the intervention arms and the no-treatment control. To identify a difference of 3.2 units between the ERS arms and a no-treatment control arm, a sample of 17 would be required (f=0.5, p=0.05, power=0.8).

ERPs. All ERPs responsible for delivering the Co-PARS (n=4-5) and usual care ERS (n=2-3) were invited to take part.

Procedure

Quantitative data was collected at baseline and at week 12 in university laboratories. Prior to testing, participants fasted for ≥6 hours, avoided consumption of alcohol for ≥12 hours and strenuous exercise for ≥24 hours. Upon arrival at the laboratory, participants' consent was obtained and anthropometrics measured. Following questionnaire completion, participants took part in vascular ultrasound procedures, before undertaking a submaximal fitness test. Finally, an accelerometer was given to participants to record PA levels for 7 days.

Measurements

All measures were completed by the researcher [BB] apart from the focus groups which were completed by an MSc student.

Cardiorespiratory fitness (primary outcome). Cardiorespiratory fitness (CRF [Maximal oxygen consumption (VO_2max^{-2})]) was estimated via the sub-maximal Astrand-Rhyming cycle ergometer protocol (Astrand, 1960). This protocol is described in detail in the general methods (Chapter 3).

Physical activity. PA levels were measured for 7 days via the commercially available tri-axial ActiGraph GT3x accelerometer (ActiGraph, Pensacola, FL, USA), which has been validated in a comparable population (Kelly *et al*., 2013). This method and the raw analysis process is described in detail in the general methods (Chapter 3). Raw acceleration thresholds were defined as 5.9 to 69.1 mg for light-intensity PA (Bakrania *et al.,* 2016), 69.1 to 258.7 mg as moderate and >258.7 mg as vigorous-intensity PA (Hildebrand *et al*., 2014). Self-reported PA levels were assessed via the International PA Questionnaire (IPAQ; Craig *et al.,* 2003). The short-IPAQ is a 7-day recall self-administered tool that measures intensity, frequency and duration of PA and provides a total estimate of energy expenditure. Questions pertain to number of days, hours and minutes spent doing vigorous PA, moderate PA and walking. An unadjusted total score of MET-minutes/week was calculated according to the IPAQ scoring protocol, which is available to download from http://www.ipaq.ki.se/ipaq.htm.

Vascular function. Following 20 minutes of rest in the supine position, vascular health was assessed via brachial artery FMD and CAR. These measures are discussed in detail in the general methods (Chapter 3). Briefly, these techniques measure vascular endothelial function in a peripheral artery (FMD) and central artery (CAR), and have been demonstrated to independently predict future risk of cardiovascular events in humans (Chan *et al*., 2003; Green *et al.,* 2011; Van Mill *et al.,* 2017). Blood pressure was measured in the supine position using an automated blood pressure device (Omron Healthcare UK Limited, Milton Keynes, UK).

Anthropometrics. Body mass index (BMI) was calculated as mass divided by stature (kg/m^2). Waist-to-height ratio was calculated as waist circumference divided by stature.

Psychosocial. Mental wellbeing was measured via the Warwick-Edinburgh Mental Well-being Scale (WEMWBS, Tennant *et al.,* 2007). Behavioural regulation was measured via the Behavioural Regulation in Exercise Questionnaire (BREQ-2; Markland & Tobin, 2004). Four additional items were included to assess integrated regulation (Wilson *et al*., 2006). Psychological needs satisfaction was measured via the Psychological Needs Satisfaction in Exercise Scale (PNSE; Wilson *et al*., 2006). Further detail of these measures can be found in the general methods (Chapter 3).

Needs support was measured (at week 12 only) using a 15-item needs support tool developed by Markland and Tobin (2010) to measure the extent to which participants perceive their exercise instructors provide support for autonomy, structure (linked to competence) and involvement (linked to relatedness). The control group completed the questionnaire, only if appropriate i.e. attended exercise classes or received support from an exercise instructor or personal trainer.

Intentions to engage in PA was assessed via 3 items developed by Edmunds *et al*. (2007): "I plan to regularly engage in PA during the next 3 months"; "I intend to participate in physical exercise as much as I can every week during the next 3 months"; and "I intend to exercise at least three times per week over the next 3 months". Participants rate how true each statement is for them on a scale from 1 ("Strongly Disagree") to 7 ("Strongly Agree").

Process measures

Attendance at consultations (Co-PARS). The number of consultations offered (measured by appointment bookings), and the number of consultations conducted for each participant were collected by exercise referral practitioners at induction, 4,8,12 and 18 weeks.

Participant focus groups. Focus groups were conducted by an MSc student under supervision of the primary supervisor with a purposeful subsample of participants after approximately 6-12 weeks of attending the scheme (e.g. those with low attendance, high attendance, significant health changes, no change etc.). Two focus groups were conducted with participants attending the Co-PARS centre and one focus group was conducted with participants attending the usual care ERS centre (4 participants per group). Focus groups were conducted at the individual fitness centres and lasted approximately 60 minutes. Discussions focussed on the extent to which, and how, participants felt each scheme was facilitative (or not) in helping them to become more physically active, with questions regarding staff interaction, available activities, and the impact of the scheme on their continuation of PA. Focus groups were chosen over interviews to obtain detailed information about personal and group feelings, perceptions and opinions of the different referral schemes. In addition to pragmatic reasons such as reduced time burden and more cost efficient compared to individual interviews i.e. allowing data to be collected from a larger number of participants. Focus group questions were generated by the research team, based on the findings of Study 2 and the need to investigate how the novel aspects of the Co-PARS were received. Transcripts were read by multiple researchers, including the primary author to check they were delivered as intended and to immerse themselves in the data.

Statistical analyses

Quantitative data were analysed using SPSS version 25 (IBM, New York, USA) with alpha level set at $p \leq 0.05$. An intention-to-treat approach was undertaken assuming no change in non-respondents (last observation taken forward) to produce a conservative estimate of intervention effects, as in Duda *et al*. (2014). Change in primary and secondary outcomes were examined using repeated-measures linear mixed models with fixed effects for study arm (Co-PARS, usual care ERS, no-treatment control), time (pre *versus* post-intervention) and a study arm*time interaction, with subjects included as random effects. Variable residuals were checked for normality. For non-normally distributed data, median and interquartile range is

presented and within group median change was calculated via Wilcoxon signed-rank tests. Linear mixed models were also used to check for any baseline differences between groups to explore comparability between arms.

Linear mixed models are robust to the biases of missing data at random, provide appropriate balance of Type 1 and Type 2 error, and can handle baseline differences between groups (Connell *et al*., 2017). Testing for baseline differences to identify covariates was avoided, as this method has been demonstrated to inflate bias (De Boer *et al*., 2015). Instead, covariates were pre-determined (baseline score) with consideration given to power limitations (Raab, Day, & Sales, 2000). All linear mixed model analyses were repeated with age and employment as covariates as a comparison to the results presented in this study (with baseline score as a covariate) due to their known prognostic value. For example risk of ill health increases with age (Yashin *et al*., 2007) and employment status is a well cited social determinant of health, associated with numerous negative health consequences (Wilkinson & Marmot, 2003). Using age and employment as covariates resulted in no change in inferences presented in this study.

P-statistic inferences were supported using a minimum clinically important difference approach (Batterham & Hopkins, 2006; Hopkins *et al*., 2009) described in detail Study 2a (Chapter 6). Briefly, the approach forms inferences based on clinically meaningful magnitudes, and is supported alongside hypothesis testing. A spreadsheet (http://newstats.org/generalize.html) was used to compute qualitative probabilities that the true effects were beneficial, trivial, or harmful. A minimum clinically important difference for CRF was set at 2 $ml.kg.^{-1}min^{-1}$ based on previous epidemiological evidence (Simmons *et al*., 2009; Lee *et al*., 2010) and for MVPA was set at 10 minutes/day as identified by recent public health statistics (ONS, 2017) as well as magnitudes found in similar interventions (Gabrys *et al*., 2013). Minimum important differences for other variables were determined via previous epidemiological research and/or a small effect size (Cohen, 1988). Due to a lack of agreement in what are meaningful/harmful changes, magnitude based inferences were not calculated for

BREQ-2, PNSE, Needs Support or Exercise Intention variables. Instead, change scores and effect sizes are reported for these variables.

Focus groups were analysed thematically in a deductive manner (Braun & Clarke, 2006) using NVivoPro-11 software (QSR International Pty Ltd.) by the MSc student who collected the data. The deductive themes consisted of the three psychological needs of SDT (Ryan & Deci, 2000); autonomy, competence, and relatedness. Methods to enhance trustworthiness included triangulation (including regular review meetings with the primary supervisor), participant choice whether to take part in the focus group or not, and iterative questioning (Shenton, 2004). The primary researcher then reviewed themes and adapted the narrative in order to explore who each intervention reached, participant adherence, intervention fidelity and acceptability.

As participant perceptions of exercise referral have been reported (Mills *et al*., 2012; Sharma *et al*., 2012). A deductive approach was chosen to more specifically explore whether SDT components (autonomy, competence, and relatedness) are important for participant uptake, adherence, intervention fidelity/acceptability, and likelihood of long-term PA behavior change. More inductive methods may have revealed different information, but would not have highlighted the importance (or not) of the behavior change theory underpinning the intervention. This work also extends the qualitative approach taken in Study 2, which aimed to explore participant perceptions of the *novel* intervention components of the Co-PARS.

7.3 RESULTS

Participants. One-hundred participants were invited to take part in the study, 68 of whom consented. All participants who provided baseline data were included in the analysis for that variable (with baseline data carried forward if 12-week data were missing; n=12). If a participant did not provide CRF data at baseline, they were still included for other analyses for which baseline data were provided. Missing data was due to inability to complete the CRF test (n=12), inability to complete the vascular ultrasound protocols (n=4), insufficient accelerometer wear time or non-return (n=10), and 10 participants from the no-treatment

control arm felt the Needs Support questionnaire was not relevant to them. Figure 7-2 depicts a participant flow diagram for the primary outcome, CRF. Based on the sample size estimations, the desired number of participants was not reached (42 per intervention arm; 17 per no-treatment control arm). This was due to pragmatic limitations such as reception staff at the leisure centres struggling with the recruitment procedures, participants not wanting to travel to the laboratories for testing, PhD time constraints to collect the number of participants needed (which took longer than anticipated), and participant drop-out.

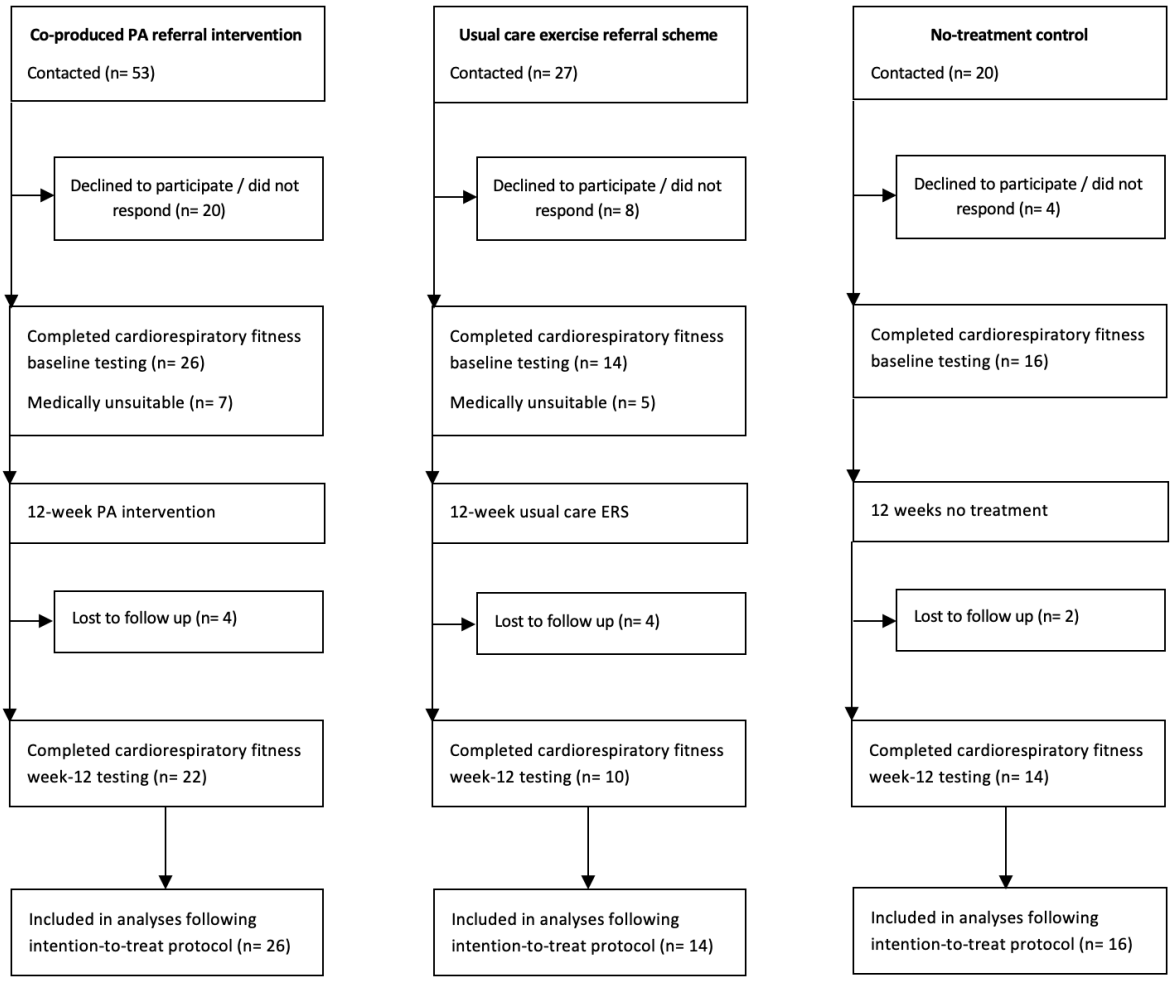


Figure 7-2. Participant flow diagram for cardiorespiratory fitness (primary outcome) for the three study arms.

Baseline characteristics. At baseline, significant differences were noted between study arms for employment and smoking status, as well as systolic blood pressure (Table 7-1). Full-time employment was significantly more common in the no treatment control compared to the intervention and usual care arms. Systolic blood pressure was significantly higher in the intervention and usual care arms compared to the no treatment control. The usual care arm included significantly more participants who had smoked compared to the intervention and no-treatment control arms. No other baseline differences existed. Focus group participant characteristics are presented in Table 7-2.

Table 7-1. Baseline characteristics presented as Mean ± SD or % (n) of group.

	Co-produced PA referral (*n*=33)	Usual care ERS (*n*=19)	No-treatment control (*n*=16)	Between arm *p*-value
Age (years)	57 ± 12	53 ± 16	48 ± 15	*p*=0.319
Female (% of sample)	58 (19)	47 (9)	56 (9)	*p*=0.774
White British (% of sample)	82 (27)	95 (18)	75 (12)	*p*=0.132
Full-time employment (% of sample)	18 (6)	26 (5)	62 (10)	*p*=0.001
Never smoked (% of sample)	73 (24)	37 (7)	81 (13)	*p*=0.002
Body mass index (kg/m^2)	31 ± 7	33 ± 6	29 ± 6	*p*=0.226
Systolic blood pressure (mmHg)	131 ± 11	138 ± 18	123 ± 12	*p*=0.010
CRF (ml.kg.mim^{-2})	22.2±7	23.3±6.6	29.6±9.2	*p*=0.015
Primary referral reason / health concern (control)				*p*=0.132
Cardiometabolic	67 (22)	43 (8)	62 (10)	-
Cancer	6 (2)	5 (1)	6 (1)	-
Mental Health	18 (6)	26 (5)	19 (3)	-
Musculoskeletal	9 (3)	26 (5)	13 (2)	-
Comorbidity (% of sample)	85 (28)	100 (19)	81 (13)	*p*=0.166

Table 7-2. Focus group participant characteristics

Focus group	Study arm	Participants (*n*=)	Age (years) Mean±SD	Sex ratio Male:Female
1	Usual care ERS	4	61.5±11.21	1:1
2	Co-PARS	4	58±4.76	1:1
3	Co-PARS	4	65.5±11.70	3:1

Raw outcome values are presented for baseline and week-12 in Table 7-3 (cardiometabolic and PA outcome measures) and Table 7-4 (psychosocial outcome measures) with between arm difference in change scores (*p*-statistic). Within arm effects (change score) are reported in Table 7-5 and Table 7-6. Figure 7-3 depicts individual participant change scores for CRF, WEMWBS, CAR%, and FMD% for the three study arms.

Baseline values. No significant differences were noted between arms for age, sex, ethnicity, BMI, or referral reason (P>0.05). Differences were noted, however, for employment, smoking status and CRF. Full-time employment status was significantly higher in the control group compared to usual care ERS and Co-PARS (p=0.001). Smoking status was significantly higher in the usual care ERS compared to Co-PARS and control arms (p=0.010). CRF was significantly higher in the control compared to Co-PARS and usual care ERS (p=0.015).

Cardiorespiratory fitness (CRF; primary outcome). There was a significant effect for study arm in change in CRF (p=0.002). Post-hoc testing revealed that the change in CRF was significantly higher in the Co-PARS (p<0.001) compared to ERS (p=0.021) and control (p=0.001). There was no difference between the ERS and control for change in CRF (p=0.314). Within arm magnitudes for CRF demonstrated a very likely benefit in the Co-PARS and trivial benefit in the ERS and control arms.

Physical activity. There were no study arm effects for change in any of the device-measured or self-reported PA outcome variables (p>0.05). Within arm magnitudes for device-measured data demonstrated a likely benefit for an increase in light-intensity PA for the Co-PARS only. All other changes in PA variables for the three study arms were deemed 'benefit unclear'.

Vascular function. No study arm effects were noted for change in CAR% (p=0.073). Within arm magnitudes demonstrated a possible beneficial increase in the Co-PARS and ERS with a trivial change in the control. The number of participants presenting with carotid artery vasoconstriction at baseline to week 12 was reduced in the Co-PARS (6 to 3) and ERS (3 to 1) and increased in the control (2 to 3).

A significant effect for study arm was found in change in FMD% (p=0.002). Post-hoc testing revealed that the change in FMD% was significantly higher in the Co-PARS compared to control (p=0.001) but not the ERS (p=0.099). The change in FMD% was not significantly different between the ERS arm and control (p=0.71). The magnitude of change in the Co-PARS was deemed very likely beneficial.

No significant differences were observed for change in blood pressure or resting HR between any of the study arms (p > 0.05). Within arm magnitudes demonstrated a possible benefit for all study arms for change in systolic blood pressure, and a possible benefit for diastolic blood pressure for the control only. Change in resting HR demonstrated a possible benefit for the Co-PARS only.

Anthropometrics. No significant differences were observed in change in BMI or WHR between any of the study arms (p>0.05). Magnitude based inferences demonstrated trivial effects for BMI and WHR for all study arms.

Mental wellbeing. No study arm effects were noted for change in WEMWBS (p=0.417). Within arm magnitudes demonstrated a likely, possible, and trivial benefit for the Co-PARS, ERS, and control arms, respectively.

Motivational Variables and Referral Interventions. There were no study arm effects for change in any of the self-reported behavioural regulation variables, needs satisfaction variables, or exercise intentions variables (p>0.05).

Needs Support. No significant differences were observed in Needs Support between any of the study arms (p>0.05).

Table 7-3. Cardiometabolic health outcomes and PA levels at baseline, week 12, and between arm baseline-to-week 12 effects (*p*-value).

	Co-PARS		Usual Care ERS		No-Treatment Control		
Outcome measures	**Baseline**	**Week 12**	**Baseline**	**Week 12**	**Baseline**	**Week 12**	**Between arm effect *p*-value[(a)]**
Fitness *(n=56)*							
CRF ml.kg.-1min-1	22.2±7	24.6±7**	23.3±6.6	23.6±7	29.6±9.2	28.9±8.7	*p*=0.002
Physical activity							
GT3x *(n=58) Mins.day*							
Light-intensity PA	443±188	483±191	401±101	411±116	424±103	461±98	*p*=0.573
Moderate-intensity PA	44±32	42±29	42±27	42±32	60±31	63±25	*p*=0.732
Vigorous-intensity PA	1±3	1±2	1±2	1±1	2±5	2±3	*p*=0.945
IPAQ *(n=68) MET.mins.week*							
Walking	594±1881	660±644	792±1138	1040±1172	594±1350	1287±2099	*p*=0.195
Moderate PA[b]	0±240	460±720	320±1260	720±1680	200±585	180±720	*p*=0.850
Vigorous PA[b]	0±80	0±960	0±400	360±1200	400±960	400±900	*p*=0.858
Total PA[b]	990±2536	1653±1878	1455±2424	2772±3058	1899±1350	2098± 2162	*p*=0.347
Sitting[b] mins.weekday	420±240	360±300	360±360	270±308	480±240	363 ± 285	*p*=0.973
Vascular *(n=64)*							
CAR%	1.7±2.7	2.8±2.2*	2.7±1.8	3.9±2.8*	2.5±2.7	1.7±2.7	*p*=0.073
CAR Baseline cm	0.69±0.07	0.69±0.06	0.69±0.08	0.7±0.09	0.65±0.07	0.64±0.06	*p*=0.130
FMD%	4.4±2.3	6.8±2.7**	4.2±2	5±2.1*	6.2±2.1	5.2±2.8	*p*=0.002
FMD Baseline cm	0.39±0.07	0.38±0.06	0.39±0.09	0.41 0.08	0.38±0.08	0.37±0.06	*p*=0.728
Cardiometabolic *(n=68)*							
BMI kg.m2	31±7	30±7	33±6	32±6	29±6	29±6	*p*=0.323
WHR	62±9	61±10*	64±8	63±8*	56±9	56±9	*p*=0.261
SBP mmHg	131±11	127±12*	138±18	132±15*	123±12	118±13	*p*=0.937
DBP mmHg	73±7	71±8	73±9	71±11	72±11	68±10*	*p*=0.584
RHR bpm	70±10	65±10*	70±12	68±11	66±12	63±9	*p*=0.540

Baseline and week 12 measures presented as mean ± SD
[b] Values presented as median ± interquartile range due non-normally distributed data
(a) p-statistic for between group difference in change scores
Within arm change; **p* = ≤0.05 ***p* = ≤0.001

Co-PARS, Co-produced PA referral scheme**; ERS,** Exercise referral scheme**; PA,** Physical Activity; **CRF**, Cardiorespiratory Fitness; **GT3x**, Device-measured physical activity monitor worn on the hip for 7 days; **MET**, Metabolic equivalent (3.5 ml.kg.min = 1 MET); **IPAQ**, International Physical Activity Questionnaire; **SBP**, Systolic Blood Pressure; **DBP**, Diastolic Blood Pressure; **BMI**, Body Mass Index; **WHR**, Waist-to-Height ratio; **RHR**, Resting Heart Rate.

Table 7-4. Psychosocial health outcomes presented at baseline and week 12 and between arm baseline-to-week 12 effects (*p*-value).

	Co-PARS		Usual Care ERS		No-Treatment Control		
	Baseline	**Week 12**	**Baseline**	**Week 12**	**Baseline**	**Week 12**	**Between arm effect *p*-value[(a)]**
WEMWBS (*n*=68)							
Mental Wellbeing	46±9	51±10**	49±10	52±11*	53±9	56±9	*p*=0.417
BREQ-2 (*n*=68)							
Amotivation[b]	0±1	0±0.25	0.25±0.63	0±0.63	0±0	0±0	*p*=0.270
External Regulation[b]	0±1.25	0.25±1.25	0±1	0.5±0.75	0.25±0.5	0.25±0.81	*p*=0.478
Introjected Regulation[b]	1.33±2.67	1.33±2.33	1.33±1.83	1±2	0.5±1	1.33±1.75*	*p*=0.497
Identified Regulation[b]	2.5±1.25	2.75±1.25*	2.25±1.25	2.75±1.5*	3.13±1.06	3.13±1.06	*p*=0.146
Integrated Regulation[b]	1.25±1.5	1.75±1.75	1±2	1.5±2.5*	2.25±1.38	2.13±1.63	*p*=0.180
Intrinsic Regulation[b]	1.75±2.25	2.5±2*	2.25±1.25	3±1.38*	3±0.88	3±1.38	*p*=0.097
PNSE (*n*=68)							
Autonomy[b]	4.5±2	5.17±2*	4.5±1.08	5.5±1.42*	5.58±0.88	5.92±0.88	*p*=0.139
Competence[b]	3.17±2.17	4±1.17*	3.33±2.33	4.33±2.08*	4.33±1.54	4.67±1.04	*p*=0.629
Relatedness[b]	2.83±3.17	3.67±2.67	3.33±1.58	3.33±2.5	3.75±1.38	4.08±2.79	*p*=0.703
Exercise Intentions (*n*=68)							
Q1	6.15±1.42	5.88±1.49	6.42±1.5	5.68±1.52*	6.25±1.03	6.56±0.7	*p*=0.076
Q2	6.18±1.34	6±1.39	6.37±1.56	5.68±1.45*	6±1.06	6.25±0.9	*p*=0.074
Q3	5.88±1.82	5.58±1.72	6.16±1.56	5.21±1.91*	5.63±1.87	6±1.66	*p*=0.084
Psychological Needs Support (*n*=45)							
Needs Support[b]	-	6.33±1.4	-	5.47±1.47	-	5±2.27	*p*=0.441
Autonomy[b]	-	6.2±1	-	5.6±1.4	-	5±3.25	*p*=0.082
Structure[b]	-	6.4±1.2	-	5.8±1.8	-	6.3±2.1	*p*=0.661
Involvement[b]	-	6±2	-	5.4±1.8	-	4.4±3.8	*p*=0.453

Baseline and week 12 measures presented as mean ± SD

[b] Values presented as median ± interquartile range due non-normally distributed data

(a) p-statistic for between group difference in change scores

Within arm change; **p* = ≤0.05 ***p* = ≤0.001

Co-PARS, Co-produced PA referral scheme**; ERS,** Exercise referral scheme**; WEMWBS,** Warwick-Edinburgh Mental Wellbeing Scale**; BREQ-2**, Behavioural Regulation of Exercise Questionnaire; **PNSE**, Psychological Needs Satisfaction in Exercise scale. Q1, 'Intentions to exercise regularly over the next three months'; Q2, 'Intentions exercise as much as I can over the next three months'; Q3, 'Intentions to exercise at least 3 times per week over the next three months'.

Table 7-5. Within arm effect (95% confidence interval) and colour coded qualitative magnitude based inference.

	Co-PARS	Usual Care ERS	No-Treatment Control
	Fitness *(n=56)*		
CRF $_{ml.kg.^{-1}min^{-1}}$	2.4 (1.3 to 3.4)**	0.3 (-1.1 to 1.7)	-0.6 (-1.9 to 0.7)
	WEMWBS (n=68)		
Mental wellbeing	5 (3 to 8)**	3 (0 to 6)*	3 (-1 to 6)
	Physical activity		
GT3x *(n=58)* $_{Mins.day}$			
Light-intensity PA	40 (-7 to 87)	3 (-66 to 71)	39 (-29 to 109)
Moderate-intensity PA	-2 (-13 to 8)	0 (-16 to 16)	4 (-11 to 20)
Vigorous-intensity PA	0 (-1 to 1)	0 (-2 to 2)	0 (-1 to 1)
IPAQ *(n=68)* $_{MET.mins.week}$			
Walking[b]	-58 (-396 to 190)	66 (-165 to 446)	347 (-347 to 1634)
Moderate PA[b]	120 (0 to 340)	120 (0 to 720)	0 (-240 to 200)
Vigorous PA[b]	40 (0 to 480)	240 (0 to 720)	120 (-240 to 1680)
Total PA[b]	71 (-188 to 650)	701 (-75 to 1752)	335 (-518 to 2454)
Sitting[b] $_{mins.weekday}$	-30 (-60 to 15)	-60 (-180 to 0)	-60 (-180 to 30)
	Vascular *(n=64)*		
CAR%	1.1 (-0.1 to 2.2)*	1.2 (-0.2 to 2.6)*	-0.8 (-2.3 to 0.7)
FMD%	2.4 (1.3 to 3.5)**	0.8 (-0.6 to 2.3)	-1.1 (-2.6 to 0.4)
	Cardiometabolic *(n=68)*		
BMI $_{kg.m2}$	-0.3 (-1 to 0)	-0.6 (-1 to 0)	0 (-1 to 0)
WHR	-1 (12 to 0)*	-1 (13 to 0)*	0 (-1 to 1)
SBP $_{mmHg}$	-5 (-8 to -1)*	-6 (-10 to -1)*	-4 (-9 to 0)
DBP $_{mmHg}$	-2 (-4 to 1)	-3 (-6 to 1)	-4 (-8 to -1)*
RHR $_{bpm}$	-5 (-8 to -2)*	-2 (-6 to 2)	-3 (-7 to 2)

Baseline-to-week 12 change presented as mean (95% CI)
[b] Median change (95% CI) due to non-normally distributed data
Within arm change; **p* = ≤0.05 ***p* = ≤0.001

Co-PARS, Co-produced PA referral scheme**; ERS,** Exercise referral scheme**; CRF**, Cardiorespiratory Fitness; **WEMWBS,** Warwick-Edinburgh Mental Wellbeing Scale**; GT3x**, ;**IPAQ**, ' **SBP**, Systolic Blood Pressure; **CMRs**, Clustered Cardiometabolic Risk score; **BMI**, Body Mass Index; **WHR**, Waist-to-Height ratio.

Colour coded qualitative magnitude-based inference:

Benefit Likely	Benefit Possible	Trivial / Unclear	Possibly Harmful

Table 7-6. Within arm effect (95% confidence interval) and colour coded effect size

	Co-PARS	Usual Care ERS	No-Treatment Control
	BREQ-2 (*n*=68)		
Amotivation[b]	0 (-0.5 to 0)	0 (-0.13 to 0)	0 (0 to 0)
External Regulation[b]	0 (-0.17 to 0.13)	0 (-0.13 to 0.25)	0 (0 to 0.25)
Introjected Regulation[b]	0 (-0.17 to 0.34)	0.09 (-0.34 to 0.59)	0.33 (0 to 0.67)*
Identified Regulation[b]	0.25 (0 to 0.5)*	0.38 (0 to 1.13)*	0 (-0.25 to 0.25)
Integrated Regulation[b]	0.25 (0 to 0.38)	0.44 (0 to 1)*	0.25 (-0.5 to 0.5)
Intrinsic Regulation[b]	0.38 (0 to 0.75)*	0.5 (0 to 1.13)*	-0.13 (-0.38 to 0.13)
	PNSE (*n*=68)		
Autonomy[b]	0.5 (0.09 to 0.84)*	0.83 (0.33 to 1.3)*	0.17 (-0.09 to 0.42)
Competence[b]	0.42 (0.09 to 0.75)*	0.59 (0.33 to 1.09)*	0.25 (0 to 0.67)
Relatedness[b]	0.25 (0 to 1)	0 (-0.67 to 0.67)	0 (-0.51 to 0.67)
	Exercise Intentions (*n*=68)		
Q1	-0.27 (-0.74 to 0.19)	-0.74 (-1.35 to -0.13)*	0.31 (-0.35 to 0.98)
Q2	-0.18 (-0.6 to 0.23)	-0.68 (-1.23 to -0.14)*	0.25 (-0.34 to 0.84)
Q3	-0.30 (-0.9 to 0.29)	-0.95 (-1.73 to -0.16)*	0.38 (-0.48 to 1.23)

Baseline-to-week 12 change presented as mean (95% CI)
[b] Median change (95% CI) due to non-normally distributed data.
Within arm change; **p* = ≤0.05 ***p* = ≤0.001

Co-PARS, Co-produced PA referral scheme**; ERS,** Exercise referral scheme**; BREQ-2**, Behavioural Regulation of Exercise Questionnaire; **PNSE**, Psychological Needs Satisfaction in Exercise scale. **Q1**, 'Intentions to exercise regularly over the next three months'; **Q2**, 'Intentions to exercise as much as I can over the next three months'; **Q3**, 'Intentions to exercise at least 3 times per week over the next three months'.

Colour coded effect size:

Moderate-Large Effect	Small-Moderate Effect	≤ Small Effect

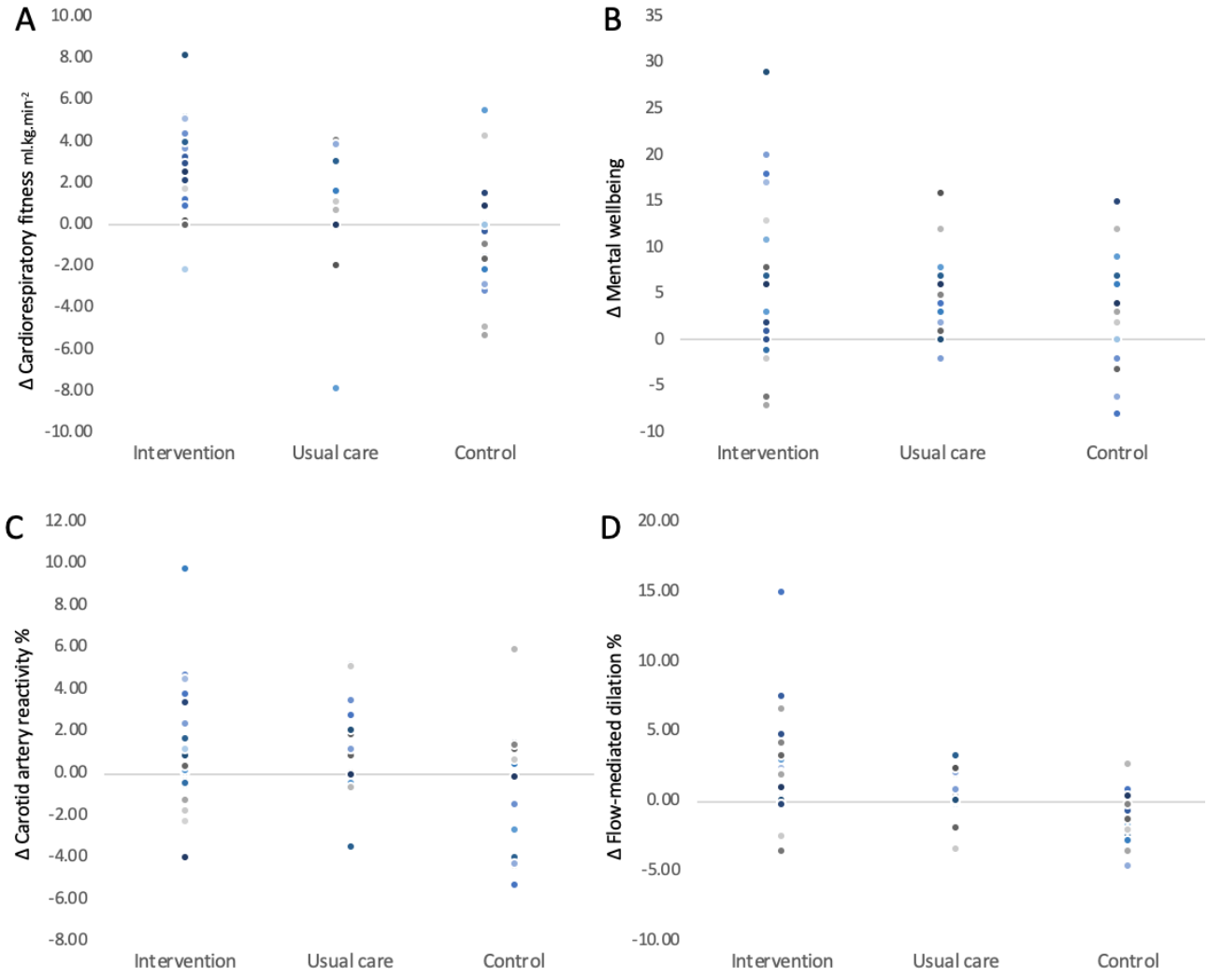


Figure 7-3. Comparison of intervention, usual care, and no-treatment control effects for **A**) Cardiorespiratory fitness **B**) Mental wellbeing via Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS), **C**) Carotid artery reactivity (CAR), and **D**) Flow-mediated dilation (FMD).

Consultation fidelity (Co-PARS only). Out of an initial 33 participants, 30 (91%) inductions, 27 (82%) week-4, 22 (67%) week-8, 21 (63%) week-12, and 18 (55%) week-18 consultations were booked by exercise referral practitioners. Of the 33 participants, 5 (18%) did not attend any consultations, 6 (18%) attended induction only, 2 (6%) attended induction plus one consultation, 2 (6%) attended induction plus two consultations, 10 (30%) attended induction plus 3 consultations, and 8 (24%) attended induction plus four consultations. At the time of writing, eight (24%) participants had signed up to a fitness centre membership following the Co-PARS. Table 7-7 presents both the participant consultations booked and the consultations attended.

Table 7-7. Behaviour change consultation fidelity.

Consultation	*n* Booked (/33)	*n* Attended
Induction	30	28
Week 4	27	21
Week 8	22	20
Week 12	21	17
Week 18	18	9

Focus groups. Focus group results are presented within the SDT (Ryan & Deci, 2000) themes of autonomy, competence, and relatedness for the Co-PARS and usual care ERS, respectively. Participants are identified by a participant number (1-12), referral arm (Co-PARS or ERS), and if Co-PARS, the focus group number (1 or 2).

Co-PARS

Autonomy. Intervention participants reported feeling in control over their own exercise programmes and were given choice as to how and where they could increase their PA levels. For example, the practitioner acknowledged the fact they may prefer to increase their PA levels elsewhere (outside the fitness centre) and were encouraged to do so. When discussing the amount of control participants had over the activities they were doing, responses included '*it was entirely up to us*' (Participant 7, Co-PARS, focus group 1); and '*it was equal, I think* [the practitioner] *suggested stuff but then you could say well can I do this or that*' (Participant 11, Co-PARS, focus group 2). It was apparent that some participants within Co-PARS had increased the amount of PA they underwent outside of the fitness centre; '*I cycle to work anyway but what I've been doing is going a longer way home doing a couple of extra miles that way so I haven't been going to the gym quite as much*' (Participant 6, Co-PARS, focus group 1). Such activities seem to be encouraged by the Co-PARS practitioners; '*when* [the practitioner] *saw me the first time she asked what are you doing already and then she does say to add it* [further activities] *on rather than do it instead*' (Participant 9, Co-PARS, focus group 2).

Competence. Co-PARS participants generally expressed positive changes in their PA ability; e.g. '*when I first started… I was doing 100 steps and it was killing me but I'm doing 700 now and it's not bothering me at all*' (Participant 8, Co-PARS, focus group 1). An improvement in participant confidence was also noted; '*I would never have gone on a cross trainer before I used to look at people on that and thought I couldn't have that… but I've been going on it regularly the last 4 weeks and it doesn't bother me now, it has brought my confidence up*' (Participant 8, Co-PARS, focus group 1). Generally, Co-PARS participants seemed confident in continuing with PA following the PA referral intervention. Some described how they used goal setting to increase their PA behaviour outside of the fitness centre; '*my goal for the next four weeks is I normally*

park at the other side of the park before I do aqua fit' – ' *but now I've got to walk all the way back home'* (Participant 7, Co-PARS, focus group 1).

Relatedness. In general, participants seemed well-supported by the practitioners within the Co-PARS arm; '*I found [*Practitioner*] really easy to talk to I thought she was a very positive person so even if you sort of admitted that you didn't do very much she was very encouraging about the little bit that you did do*' (Participant 12, Co-PARS, focus group 2). Although, participants typically did not feel like they had contact with other participants on the scheme, despite the majority of participants indicating they would like interaction with others; '*I think it would be good to see different people who have been referred and why they've been referred well ill meet you there at such a time I think it would have been better'* (Participant 10, Co-PARS, focus group 2).

Usual Care ERS

Autonomy and Competence. Some participants reported a lack of autonomy over their PA choices; when asked about whether ERS participants were encouraged to exercise outside the centre responses included '*no they encouraged me to use the equipment*' (Participant 4, ERS). Whilst others seemed to have more choice in the activities they did. For example, a participant expressed that she had been walking consequently more. Although when asked if this was a result of the ERS she responded '*well you can't really say, I think it's because of the weather*' (Participant 3, ERS). There was, however, evidence that ERS participants did have a say in what activities they participated in, as well as demonstrating a high level of competence; '*I just tailor the plan every day to what I think is necessary*' (Participant 2, ERS).

Relatedness. ERS participants made numerous references to instructors being '*too busy*' (Participant 2, ERS) to regularly discuss the programme and longer-term PA plans. Similar to the Co-PARS groups, ERS participants expressed that there were limited opportunities to socialise with other participants on the scheme. Although, whereas the majority of participants

from the Co-PARS centre said they would benefit from opportunities to meet others, this was not replicated among the ERS participants; '*I'm okay*' (Participant 4, ERS), *'I like it the way I am*' (Participant 2, ERS).

7.4 DISCUSSION

This study sought to pragmatically test the effectiveness of the co-produced PA referral scheme (Co-PARS), which was co-produced through study 1 and piloted through Study 2. Primarily, findings demonstrated significant improvements in CRF and FMD for the Co-PARS (intervention) compared to the usual care ERS and no-treatment control arms. No other effects in health measures were statistically different between arms. Within-arm effects, however, demonstrated that mental wellbeing and device-measured light-intensity PA were deemed clinically meaningful for the Co-PARS. No between arm differences were observed for psychological needs satisfaction (PNSE), motivations for exercise (BREQ-2) or intentions to engage in exercise.

Embedded process evaluation demonstrated that 54% of the Co-PARS participants attended an induction plus 3 or 4 behaviour change consultations. Despite some similarities between the Co-PARS and usual care ERS in terms of perceived autonomy, competence, and relatedness, autonomy was more consistently supported within the Co-PARS arm. Furthermore, relatedness with practitioners appeared to be better facilitated within the Co-PARS compared to the usual care ERS. Both arms, however, identified a lack of relatedness with other referral participants. These findings seem to support the co-produced changes made to the Co-PARS, since it has demonstrated improved intervention fidelity (consultation attendance) and acceptability (interview data) compared to Study 2. In addition, there seems to be enhanced facilitation of autonomy and practitioner-participant relatedness in the Co-PARS compared to usual care.

According to Clausen *et al*. (2018) the participants in the present study (both the Co-PARS and usual care ERS) were below the lower limit of normal for CRF. This has important implications, as low CRF is associated with a substantially elevated risk of all-cause mortality. The magnitude of change within the Co-PARS was 2.4 $ml.kg.^{-1}min^{-1}$, which could be deemed clinically meaningful, as it has been demonstrated that an increase of 1 $ml.kg.^{-1}min^{-1}$ can increase longevity by 45 days (Clausen *et al*., 2018). Though, in at-risk populations, even smaller magnitudes of 0.5 (male) and 1 $ml.kg.^{-1}min^{-1}$ (female) have been shown to significantly reduce clustered cardiometabolic risk (Simmons *et al*., 2008).

Change in device-measured PA levels were not statistically different between study arms, despite an increase in CRF for the Co-PARS. When observing magnitudes of change for the accelerometer-derived data, however, both the Co-PARS and no-treatment control arm increased in light-intensity PA by ~40-minutes per week (Figure 7-5). The no-treatment control arm, however, did not demonstrate any change in CRF, as in the Co-PARS. It is of note that device-measured PA (via accelerometer) is absolute e.g. via fixed intensity 'cut-points' for all participants (regardless of fitness). One potential explanation for the increase in CRF is that the Co-PARS participants were working at a *relatively* higher intensity, despite the same *absolute* intensity compared to the no-treatment control arm. For example, Kujala *et al*. (2017) found that compared with low-fit individuals, it is easier for high-fit individuals to reach MVPA intensity levels according to *absolute* criteria. To test this hypothesis, a suitable measure of relative PA intensity is required. The issue of measuring relative PA intensity (for fitness) has been previously discussed (Miller *et al*., 2010) and despite some promising work (Kujala *et al*., 2017) further research is needed.

Despite low CRF and in agreement with the previous pilot findings (Study 2; Chapter 5), a substantial percentage of the Co-PARS (73%) and usual care ERS (71%) participants were meeting the recommended 150-minutes of moderate-intensity PA per week at baseline, based

on device-measured data. This reinforces the question as to the use of current PA guidelines (Department of Health, 2011) to assess eligibility for PA referral schemes (NICE, 2014). Such health status discordance between device-measured PA and objective CRF measures demonstrates the importance of collecting both in PA behaviour change interventions.

Brachial artery FMD was significantly improved in the intervention compared to the usual care and control arms. Whereas, CAR was not statistically different between arms, though the Co-PARS and usual care ERS arms demonstrated a potentially meaningful within-subjects improvement compared to the no-treatment control, which exhibited a potential deterioration for both vascular measures (FMD and CAR). Such improvements in vascular measures may have prognostic implications. For example, a 1% increase in FMD has been suggested to reduce the future risk of CVD events by 13% (Yeboah *et al*., 2007; Inaba *et al*., 2010; Green *et al*., 2011). The findings of this study support that of Study 2b (Chapter 6), which demonstrated carotid artery vasoconstriction could in fact be reversed following a PA intervention. In the present study, it was found that the number of participants exhibiting carotid artery vasoconstriction (a response linked to increased CVD risk; Rubenfire *et al*., 2000; Van Mil *et al*., 2017) was reduced in the Co-PARS (50%) and usual care ERS (33%), yet increased in the control arm (33%).

In addition to physiological health measures, a number of psychosocial variables were tested. Despite no significant difference in change in mental wellbeing between arms, magnitudes of within-subjects effect were deemed likely, possible, and trivially beneficial for the Co-PARS, usual care ERS, and no-treatment control arms, respectfully. The Co-PARS was underpinned by SDT (Ryan & Deci, 2000) and intended to foster autonomous PA motivation through supporting the psychological needs of autonomy, competence and relatedness. No changes were found, however, in psychological needs satisfaction, exercise motivation regulation, or exercise intentions at 12 weeks. Challenges of implementing needs-supportive delivery within

PA referral settings have been previously recognised (Duda *et al*., 2014). A lack of fidelity was one explanation the authors proposed for a lack of between-group differences in psycho-social measures between a usual care and a needs supportive ERS (Duda *et al*., 2014). Ongoing work (outside of the remit of this PhD) involved audio-recording consultations within the Co-PARS and usual care ERS to explore the extent to which consultations were being delivered as intended. Findings from this work may shed some light on the mechanisms through which behaviour change was (or was not) occurring within each condition. In the previous pilot work (Study 2a; Chapter 5) no changes for needs satisfaction or exercise motivation were observed following the intervention. It is of note that these measures are *exercise* focussed, whereas the Co-PARS aimed to facilitate *PA* behaviour change, and thus these measures may not be sensitive to changes in motivation for lifestyle-based PA.

Whilst there were no between group differences in the intended mechanisms of change (i.e. SDT constructs & PA), there was a significant effect on the primary outcome of CRF. It may be that the mechanisms were not what were hypothesised and perhaps it was simply that someone was tracking participant progress regularly, and talking to them about broader PA, even if participants did not feel more autonomous, competent, or related in the process. Longer-term, 6-month follow up data may elucidate these potential mechanisms. As it is hypothesised that because of the way the Co-PARS was delivered, it would be expected that the Co-PARS participants are more likely to adhere to PA. Subsequently, it is likely the Co-PARS participants will have enhanced autonomous motivation and needs satisfaction, whilst in the usual care ERS, it is expected participants are more likely to deteriorate back to baseline levels of PA and psychosocial measures. It is therefore possible between-group differences will emerge at 6-months follow-up. This data collection is ongoing, and thus outside the remit of this PhD.

Despite no change in the self-reported psychosocial measures, focus group data suggested a positive impact on SDT components; autonomy, competence, and relatedness (Ryan & Deci, 2000). A shift in PA focus and practitioner-delivered autonomy support seemed apparent when comparing the interviews of the previous Study 2 (Chapter 5) to the findings within this study. For example, rather than references to an under-staffed and busy centre (as in Study 2; Chapter 5), the Co-PARS participants in this study noted various changes to PA behaviour supported by practitioner meetings. Thus, relatedness seemed well supported by practitioners in both the PA intervention and usual care centres. Of interest, however, relatedness from other referral participants was limited for both arms. This is therefore a potential development point for the intervention going forward. As social support has been shown to be an important correlate of PA (Carron *et al*., 1996) and in a review of ERSs, Williams *et al*. (2007) demonstrated that intervention participation prompted social benefits, whilst poor social support was related to non-adherence. More recently, Littlecott *et al*. (2014) in a secondary analysis of an RCT investigating the effectiveness of an ERS (Murphy *et al*., 2012), identified significant effects of autonomous motivation and social support for exercise at 6-months follow-up.

Strengths & Limitations

Due to pragmatic challenges, this study was not sufficiently powered, thus inferences of effectiveness need to be taken with caution. Magnitude-based inferences were however, computed to determine clinical meaningfulness, and to avoid complete reliance on *p*-statistics. The tables and figures presented have also been produced to facilitate data transparency.

It is of note that there was evidence of how participation in the laboratory testing may have contaminated the data (i.e. Hawthorne effect: we may not be getting a true picture of the usual care ERS experience, since participants' behaviour were potentially affected by testing); '*I thought well I've got to show something for Ben's* [researcher] *sake'* (Participant 4, usual care

ERS). Previous research has attempted to investigate the unintended impact of research participation (MacNeill *et al.*, 2016). Trying to unpick the effects of research participation from the effects of a behaviour change intervention compared to usual care and a no-treatment control, however, remains problematic.

Exercise referral practitioner (staff delivering the intervention) views were not presented in this thesis as it was beyond the scope of the PhD. Staff perceptions of the intervention would have complimented the participant data presented in this chapter. To better explore intervention acceptability, future research should include process evaluation involving those receiving and delivering the intervention. A number of activities were undertaken in order to reduce researcher bias in the qualitative participant data including: 1. transcripts were professionally transcribed and anonymised; 2. initial data analysis was conducted by an MSc student who was not involved in the direct PhD project (i.e. more independent than the primary researcher); 3. data were analysed drawing on thematic analysis using NVivo electronic software; and 4. triangulation activities involved several researchers cross-referencing the findings to improve trustworthiness.

Finally, this study provides the 12-week outcomes of a co-produced PA intervention (Co-PARS), however, the Co-PARS intervention provided behaviour change support for up to 18 weeks. Longer-term outcome measures are therefore needed to provide better insight into intervention effectiveness for CRF, PA behaviour change, and psychosocial measures. It is hypothesised that any differences between the Co-PARS and usual care ERS arms will be enhanced at 6-month compared to week-12 due to the incorporated behaviour change support of the Co-PARS.

7.5 CONCLUSION

This study sought to explore the effectiveness of the co-produced PA referral scheme, previously piloted in study 2a. Following the intervention, CRF was significantly enhanced compared to usual care and a no-treatment control arm. In addition, clinically meaningful improvements in vascular health and mental wellbeing were observed. Despite no significant changes in psychosocial measures, focus group data suggested that autonomy, competence, and components of relatedness were well supported, though for both the Co-PARS and usual care ERS. Further, intervention fidelity (consultation delivery) and participant attendance appeared to be improved compared to the previous pilot study (Chapter 5). Findings emphasise the importance of following MRC guidance (Craig *et al*., 2008), which advocates a phased approach to complex intervention development and evaluation. This approach has facilitated multiple-stakeholder input into the iterative intervention development, allowing for ongoing refinements to be made.

Through co-production and piloting, this PhD has iteratively developed an intervention that appears to be effective at improving participant health and importantly, is deemed feasible to implement in practice. Whilst a meaningful improvement in the primary outcome was noted, the hypothesised mechanisms did not change. Thus, ongoing 6-month follow-up data collection may provide some clarity, though further research might be required to understand what it was that led to the improvement in health outcomes.

8 SYNTHESIS OF FINDINGS

8.1 Aims and Objectives

The aim of this thesis was to present the iterative process of the co-production, pilot, and evaluation of an evidence-based PA referral intervention. The overarching hypothesis was that this phased approach would result in an initiative with improved effectiveness compared to usual care and was feasible to implement in practice. In addition, embedded process evaluation sought to identify potential active ingredients and any areas that needed further development.

This synthesis first briefly summarises the findings of the three research studies, presented over four chapters (4-7) within this thesis. It then draws on the collective findings of the three studies to discuss: a) making the case for co-production and a mixed methods phased approach to intervention development and evaluation; and b) factors that constitute success in a PA referral scheme. Implications for policy, practice, and future research are then outlined.

8.2 Summary of Findings

Study 1 involved the co-production of a PA referral scheme aimed at improving long-term PA adherence via a multi-disciplinary stakeholder group including academics, public health commissioners, practitioners and service-users. This process involved several iterative development workshops, which resulted in an intervention framework that was deemed appropriate for the local needs and feasible to implement in practice. The key components of the PA referral scheme included underpinning by SDT, a focus on changing PA behaviour, and behaviour change consultations at 1, 4, 12 and 18 weeks.

Study 2 (a and b) piloted the co-produced PA referral scheme developed through Study 1. This work sought to explore preliminary health effects and real-world acceptability of the intervention. Whilst findings provided promising effects of the PA referral scheme on

participant cardio-metabolic health and PA behaviour, some teething problems were noted. These problems (e.g. not achieving the intended intervention PA focus and overloading the practitioners with data collection procedures) required further refinement prior to conducting a more definitive trial (Study 3).

Study 3 involved the pragmatic evaluation of the co-produced PA referral scheme, following further refinements as recommended in study 2 (e.g. the addition of a consultation at week 8 resulting in participant behaviour change support at 1, 4, 8, 12, and 18 weeks, reduced data collection procedures for practitioners, and further training with practitioners to improve the intended PA behaviour change focus). Findings highlighted significant and clinically meaningful improvements in CRF, vascular health, and mental wellbeing at week 12 compared to a usual care ERS and no-treatment control. Further (ongoing) work is required to explore longer-term intervention effects, and 'active ingredients' leading to any positive health impact.

Table 8-1 provides a summary of the collective contribution of this work to practice, policy and research. Primarily, this body of work has addressed key research gaps by undertaking a co-production approach via a multi-disciplinary team of academics, public health commissioners, service-providers, and service-users, to develop a PA referral scheme that was evidence-based and appropriate for the local context. Iterative development phases have then allowed for teething problems to be refined, prior to conducting a more definitive trial. This body of work has therefore extended the exercise referral evidence-base, which represented minimal reference to behaviour change theory, lacked focus on lifestyle-based PA, and represented interventions that were not developed to the point where they were deemed to have a worthwhile effect (NICE, 2014; Craig *et al*., 2008). Furthermore, this work is the first to utilise 'objective' health outcome measures such as device-measured PA, CRF, and vascular function to evaluate a PA referral scheme. The detailed contributions of this work for practice, policy and future research are described later in section 8.6.

Table 8-1. Collective contribution of this PhD work.

Practice	This work has demonstrated that an iterative, co-production approach may enhance the likelihood of producing interventions that are ecologically valid and effective. This co-produced intervention is being delivered in one centre in Liverpool. Further work is underway to improve exercise referral provision across Liverpool (See Policy and Research sections below).
Policy	The findings of this PhD were presented to a Physical Activity Strategy (PAS) Board involving representatives from Liverpool city council (LCC), clinical commissioning group (CCG), and Lifestyles fitness centres, including the Director of Public Health and Director of Community Services. Discussions between the academic team and PAS board covered how this work will contribute to improving exercise referral provision across Liverpool. In brief, next steps will involve embedding the 'active ingredients' of this PhD work within a more 'systems-based approach' to improve PA provision across the city.
Research	This work has extended the current evidence-base by: 1. Identifying a) factors that must be considered when translating evidence to practice in an exercise referral setting; and b) challenges and facilitators of conducting participatory research involving multiple stakeholders (Study 1). 2. Investigating what happens after co-production, by exploring preliminary health impacts and intervention acceptability (Study 2a & 2b). 3. Investigating the effectiveness of a co-produced referral scheme that is underpinned by psychological theory and focusses on PA behaviour change (rather than exercise prescription) compared to usual care and a no-treatment control (Study 3). *N.B.* The 6-month patient outcome data analysis is currently underway (beyond the scope of this PhD) and will determine sustained health impacts of the PA referral scheme. This PhD work has underpinned an additional study that will explore GP perspectives of the referral system, and determine how this component can be improved. Collectively, plans for the implementation of the most promising components of the intervention across Liverpool are underway with support from the LCC and CCG.

8.3 Making the case for co-production

"Qualitative researchers can and do sometimes come across as being problem-rich but solution-poor. That said… solutions proposed by exercise scientists and policy-makers are often ignorant or wilfully neglectful of social inequalities and inequitable interventions."

(Williams & Gibson, 2017; p. 13).

The process in this PhD highlights some of the challenges of implementing a complex PA referral scheme as intended, and how these may be overcome. The phased research approach presented in chapters 4-7 illustrates a collaborative effort between a multi-disciplinary group of academics and local-stakeholders with a shared goal of improving exercise referral provision in Liverpool.

The importance of trans-disciplinary partnerships has long been recognised in public health (Roussos & Fawcett, 2000). There has been recent renewed interest in and advocacy for the adoption of co-production as a means of co-creating value across the public sector (Clarke *et al*., 2017). The concept was first coined in 1970 when social policy recognised the benefits of including service-users in the delivery of their own public services (Realpe & Wallace, 2016). In a healthcare context, such participatory, co-production methods should draw on stakeholder knowledge in addition to the available scientific evidence in both the design, and crucially, the delivery of services (Hunter & Visram, 2016; Batalden *et al*., 2016).

The initial co-production phase (Study 1) is the first study to bring together a variety of local stakeholders to ensure a PA referral scheme was appropriate for the available resources and local infrastructure. This approach also gave practitioners a sense of ownership of the intervention. Then through the subsequent pilot (Study 2), the research team worked closely with practitioners to identify teething problems and iteratively adapt the intervention as appropriate. Through this iterative work with the practitioners delivering the intervention, it was possible for improvements to be made prior to conducting a more definitive evaluation

(Study 3). For example, poor adherence is a primary problem cited in the exercise referral literature (Pavey *et al*., 2012; Rowley *et al*., 2018). The pilot findings demonstrated participant adherence was poor with only 9% of participants attending an induction plus 3 behaviour change consultations, whereas in study 3, 54% of Co-PARS participants attended an induction plus 3 or 4 behaviour change consultations. Similarly, qualitative participant reports of instructor support were more positive for the Co-PARS group in study 3 than in study 2. It is possible that these improvements resulted from refinements to the intervention, identified by the qualitative data and continued work with the practitioners between study 2 and 3. Such intervention refinements included making sure consultations were carried out in a separate room, instructors being given the time to follow up consultations and make participant phone calls if appropriate. In addition, iterative work with the instructors involved the presentation of pilot findings and behaviour change 'refresher' sessions.

Despite increasing interest in and advocacy for co-production, there is a lack of rigorous evaluation in healthcare settings (Clarke *et al*., 207). The results presented in this thesis demonstrate that an iterative, co-production approach may provide a potential process of how intervention delivery and acceptability can be improved. It is not known however, how the delivery of the PA referral scheme would have differed had it not been co-produced. Nonetheless, the researcher wishes to re-emphasise the importance of an ongoing reciprocal relationship between commissioners, practitioners, service-users, and academics to ensure congruence between the way interventions are planned, delivered, and received. This process has demonstrated that improvements in intervention acceptability can be improved if given the time and resources to refine intervention components. Ultimately, these findings emphasise the importance of following the MRC guidance (Craig *et al*., 2008), which advocates a phased approach to complex intervention development and evaluation.

A primary problem for the public health sector is a lack of successful implementation of research findings into community settings where it can have the most impact (Nutbeam, 1996; Brownson *et al*, 2006). Furthermore, it has been loosely accepted that when successful, the process of translation of traditional evidence to real-world practice takes an estimated 17 years, on average (Westfall *et al*., 2007). Though a crude estimate (Morris, Wooding & Grant, 2011), it highlights a clear gap in the transition from research evidence to evidence-based practice. More translational research is necessary, that involves continuous improvement approaches, to better translate evidence to interventions that are feasible, sustainable, and have public health needs at the forefront (Watson *et al*., 2012).

8.4 Determining success in PA referral interventions

Despite promising potential, systematic-analyses and review literature have demonstrated uncertainty as to the effectiveness of ERSs to improve health (Dugdill *et al*., 2005; Pavey *et al*., 2011a). Such findings, however, have been underpinned by studies primarily using self-reported outcome measures (e.g. PA), and typically have not been underpinned by behaviour change theory (Pavey *et al*., 2011b; Campbell *et al*., 2015). The few evaluations that have included objective measures were limited to blood pressure and/or body mass (Rowley *et al*., 2018), arguably removed from the potential of a PA intervention to impact health. The findings within this thesis have demonstrated that clinically meaningful health changes (i.e. device-measured PA, objective CRF, and self-reported mental wellbeing) were observed following a PA referral scheme underpinned by behaviour change theory. Furthermore, meaningful changes in mental wellbeing and objective measures of vascular health were even observed in a usual care ERS. Whilst the magnitudes of change in the usual care ERS were smaller than that of the Co-PARS, these findings indicate that the potential of ERSs to impact public health may be realised, if the appropriate outcome measures are utilised.

NICE (2014) recommends that ERSs should only be funded for individuals who are sedentary or inactive and have a health condition. This recommendation came from the limited evidence of effectiveness for these interventions to impact public health (Pavey *et al*., 2011a; Campbell *et al*., 2015). The findings of studies 2 and 3 demonstrated that a high percentage (57% and 73%, respectively) of the PA referral samples were already meeting the recommended 150-minutes of weekly MVPA, based on device-measured data. Despite this, baseline CRF levels exhibited a high percentage (88% and 85%, respectively) of participants were at a substantially elevated risk of all-cause mortality. Such discordance between the health representation from device-measured PA and objective CRF raises questions as to the suitability of using inactivity as an eligibility criterion, as is currently the case (NICE, 2014). Based on these findings, it would seem that CRF would be a more suitable eligibility measure, though the viability of measuring every participant prior to commencing a referral scheme is unknown. Indeed, many participants report important social benefits of attending a referral scheme, whom may already be active but suffer from social-isolation, for example (Stathi *et al*., 2004; Markland & Tobin, 2010). Thus, a more holistic approach may be required, one where the healthcare professional and participant both discuss potential benefits from attending a referral scheme. It is noteworthy, however, that previous research has questioned whether ERS eligibility should in fact be tapered to those most likely to benefit/adhere i.e. older participants (Hanson *et al*., 2013). Further research is therefore required to determine the most suitable way to update PA referral eligibility criteria.

Figure 8-1 illustrates the proposed causal pathway of intervention effects adapted from Fortier *et al*. (2012). It was hypothesised that the PA referral scheme would facilitate enhanced motivation towards being more physically active, leading to increased PA levels, which would result in improved physiological and psychological health markers. Whilst there were significant and clinically meaningful changes in MVPA (Study 2a; Chapter 5), vascular health

(Study 2b; Chapter 6), and CRF (Study 3; Chapter 7), there were no notable changes for exercise motivation measures in either of these studies.

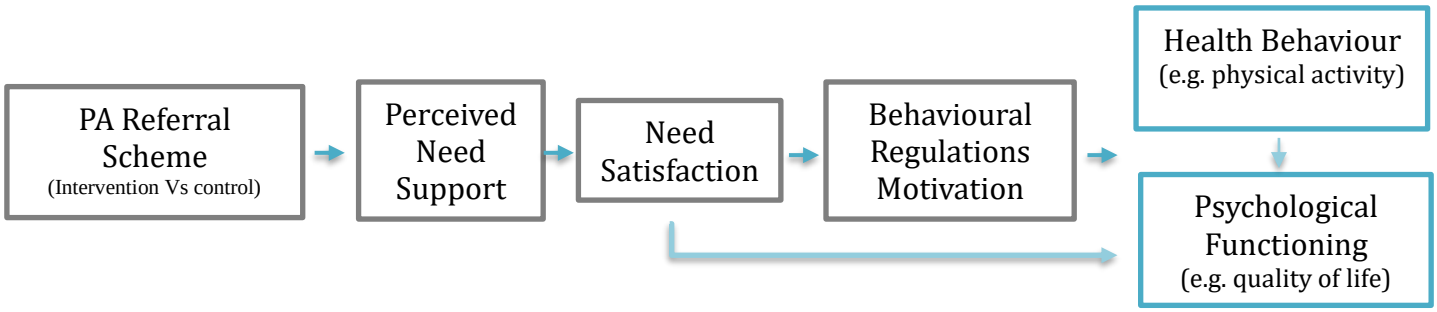


Figure 8-1. Proposed causal pathway of intervention effects adapted from the SDT process model for health behaviour change in intervention research (Fortier *et al*., 2012).

Data from Study 3 demonstrated that when the Co-PARS and usual care ERS were grouped, significant correlations were found for change in mental wellbeing and change in identified, integrated and intrinsic motivation. This supports the notion of a relationship between autonomous motivation and wellbeing (Ryan & Deci, 2000). The qualitative findings of Kinnafick *et al*. (2014), however, suggested that competence and relatedness are most important for exercise adoption. Whilst, it has been suggested that satisfying all three needs of autonomy, competence, and relatedness is better related to ERS adherence (Eynon *et al*., 2017).

An important caveat regarding the measures of motivation used throughout this PhD (e.g. BREQ-2R and PNSE) is that they are *exercise* focussed, whereas the co-produced intervention aimed to enhance *PA* behaviour change. Thus, these measures may not be sensitive or specific enough to identify changes in PA motivation. As of yet, there are no known measures of PA-specific changes in motivation. In addition, the conservative Intention-To-Treat approach utilised in the evaluation study (Chapter 7), may have resulted in reported magnitudes that underestimated the true intervention effects.

The change in CRF suggested that the Co-PARS was more effective than usual care. The magnitude of change (2.4 $ml.kg.^{-1}min^{-1}$) in study 3 was comparable to that of Sorenson *et al.* (2008) who demonstrated a comparable magnitude of change following a Swedish physical activity on prescription scheme. It is unfortunately not possible to compare the magnitude of change in CRF to comparable UK exercise referral, as no known studies have measured or presented CRF in a comparable way. The magnitude of change within the Co-PARS was 2.4 $ml.kg.^{-1}min^{-1}$ (Study 3), which could be deemed clinically meaningful, as it has been demonstrated that magnitudes of 0.5 (male) and 1 $ml.kg.^{-1}min^{-1}$ (female) have been shown to significantly reduce clustered cardiometabolic risk (Simmons *et al*., 2008). Further, it was demonstrated in Study 2b, that following the Co-PARS, carotid artery vasoconstriction, a response related to substantially elevated CVD and stroke risk, was reversed. The participants that demonstrated vasoconstriction at baseline were typically, older, and more likely to be obese and hypertensive than the rest of the sample, highlighting the potential of the Co-PARS to reduce PA-related health inequalities.

Despite enhanced CRF, there were no significant changes in PA (both device-measured and self-report) were noted in the Co-PARS, usual care ERS or no-treatment control (Chapter 7). Despite recent advances, accelerometers poorly identify cycling, swimming, and resistance-based activities (Kozey *et al*., 2010; Broderick *et al.,* 2014), which are commonly offered within referral schemes. In addition, a substantial number of baseline PA data were carried forward (Intention-To-Treat approach) and may have underestimated the true effects. Of note, the studies within this PhD were not powered for PA evaluation, which requires a large sample size due to the high variance associated with the data. When observing the within-arm magnitudes of change, however, both the Co-PARS and no-treatment control demonstrated increased light-intensity PA by ~40-minutes per week. The no-treatment control arm, however, did not demonstrate an improved CRF, as in the Co-PARS. One potential explanation for the increase in CRF in the Co-PARS is that participants were working at a *relatively* higher

intensity, despite the same *absolute* intensity compared to the no-treatment control arm (as the control demonstrated a substantially higher CRF level at baseline). For example, Kujala *et al*. (2017) found that compared with low-fit individuals, it is easier for high-fit individuals to reach *absolute* MVPA intensity levels.

Combining both outcome and process findings produces more complete knowledge, which is more likely to inform both research and practice (Creswell & Plano Clark, 2007). In Study 3, focus group data indicated similarities between the Co-PARS and the usual care ERS for satisfying autonomy, competence, and relatedness (Study 3; Chapter 7). It is possible that there were other mechanisms (beyond the hypothesised SDT constructs; Figure 8-1) that influenced the intervention outcomes. Similarly, Duda *et al*. (2014) found no difference in measures of SDT when comparing a usual care ERS to an ERS underpinned by SDT. There process model did however, support SDT and enhanced PA levels. They suggested that pragmatic issues such as limited staff time and access to communications from the research team negatively influenced staff training. In addition, Duda and colleagues noted some practitioners in the usual care arm were naturally autonomy supportive, which could have been an influencing factor in the present research.

A pragmatic randomised trial of the Welsh NERS demonstrated promising effects on PA levels and markers of mental wellbeing (Murphy *et al*., 2012). A subsequent process evaluation however, identified that the intervention was delivered poorly (Moore *et al*., 2012). Qualitative data highlighted that professional support from practitioners positively influenced patient confidence, and that patient-only classes provided important social contacts. It was noted that NERS was 'completed' by 44% of participants (Moore *et al*., 2012). Compared to the findings in this thesis, it is higher than that reported in study 2, but lower than that reported in study 3. This demonstrates a fundamental advantage of following an iterative research approach, which allows for intervention refinement prior to definitive evaluations, as recommended by

the MRC (Craig *et al*., 2008). As previously discussed, the pilot findings (Study 2) demonstrated participant adherence was poor with only 9% of participants attending an induction plus 3 behaviour change consultations. Whereas in study 3, 54% of Co-PARS participants attended an induction plus 3 or 4 behaviour change consultations. Correspondingly, qualitative participant reports of instructor support were more positive for the Co-PARS in study 3 than in study 2. These findings are important because attendance and adherence data is a central outcome for public health commissioners and managers interested in intervention reach and cost-effectiveness.

8.5 Strengths & Limitations

Key strengths of this PhD work include the interdisciplinary combination of objective health outcome measures (i.e. device-measured PA, CRF, and vascular function) and psychosocial, behavioural and process measures. In addition, it is the first body of work to present a phased co-production approach to develop and evaluated a PA referral intervention deemed ecologically valid by a multidisciplinary team of local stakeholders and academics. It is important, however, to acknowledge key limitations that can help inform future research.

Long-term follow up. There is a paucity of long-term behaviour change follow-up in ERS evaluations (NICE, 2014). Existing research has demonstrated the ability of short-term intensive interventions to elicit a myriad of health effects (Lin *et al*., 2015), yet these are predictably lost when the intervention is over. A limitation within the work presented in this thesis is a lack of longer-term follow-up. It is important to explore whether the Co-PARS has any longer-term effects to determine clinical and cost-effectiveness. It is hypothesised that any differences between the Co-PARS and usual care ERS arms will be enhanced at 6-month compared to week-12 due to the incorporated behaviour change support of the Co-PARS (Focussed on promoting long-term engagement with PA). Ongoing work, beyond the scope of this PhD is underway to collect and analysis 6-month patient follow-up data.

Sample size. Sample size calculations were not done for study 2, as the purpose of this phase was to determine intervention acceptability and highlight any adaptations that were needed prior to conducting a more definitive trial. Instead, potential effects on health outcomes were explored via a magnitude based inference approach, whereby minimum clinically important differences are determined for each output. Therefore, the sample was small and the results are not appropriate for determining 'effectiveness'. A sample size estimation was determined for study 3, however, which sought to determine the effectiveness of the Co-PARS to increase CRF compared to usual care ERS and a no-treatment control. The required sample was not achieved for this study due to pragmatic challenges. The main reasons for not have the required power included the intervention centre undergoing renovation work and staff training/holidays, which resulted in reduced ER provision and less time for recruitment. There were also issues with staff turnover and recruitment procedures (i.e. poor fidelity of the recruitment procedure used by fitness centre reception staff. Thus inferences need to be taken with caution as the small sample size increases the chances of missing an effect, although observed effects in Chapter 7 were promising. Future evaluation work is therefore warranted to substantiate the results presented in this thesis.

Randomisation. As the focus of Study 2 was to explore the Co-PARS acceptability, it was deemed unnecessary to include a control group. Chapter 2 does not, therefore, provide information on the effectiveness of the Co-PARS compared to usual care, but highlighted components needing refinements prior to a more definitive trial. Study 3 did however, involve a three-arm quasi-experimental trial comparing the Co-PARS to a usual care ERS and a no-treatment control. As participants were not randomised to the intervention arms, the quality of evidence is not as high as it would have been if it was an RCT, for example. Key limitations within Study 3 were uneven sample numbers between intervention arms, and a relatively healthier (e.g. higher CRF and lower blood pressure) no-treatment control arm compared to the two ER arms. This may have limited the ability to observe effects between groups. Reasons

for not randomising participants were practical. For example, it was not possible to randomise at the GP level (i.e. when participants were referred) as participants need to be able to choose their intervention centre, if centre location was pre-selected, this could have influenced the results. It was also decided that it was not yet appropriate to conduct a cluster RCT. It was decided following study 2, that the PA referral scheme was not yet being delivered as intended (poor intervention fidelity) and more work was required to have a worthwhile effect in practice. If the decision was made to randomise at the fitness centre level, our research group would not be able to continue the work at the co-produced intervention centre. Thus, the findings are not definitive (with larger scale evaluations needed), but supportive of the local implementation of active components of the scheme.

Narrow focus on fitness centre provision. Through this PhD work, we only had capacity to focus on the ERS from the point participants arrived at the fitness centre. As such we were not able to investigate any processes that occurred at the health professional referral stage Therefore, our efforts were focussed on the more motivated participants, which may have biased our results by inflating intervention effects. We also did not communicate with referring practitioners to change promotion messages to a PA behaviour change scheme, so participants arrived at the centre expecting a more traditional exercise prescription. Exercise (or PA) referral is a complex system and further work is needed to understand optimum referral pathways and factors that influence uptake and adherence. Finally, this work has focussed primarily on individual-level factors. A socio-ecological perspective, which emphasises the need to understand how influences beyond the individual (e.g. organisational, community, or policy-level factors), lead to patterning in responses to individual-level interventions would be an interesting area of investigation (Littlecott *et al*., 2014).

8.6 Implications for Policy, Practice, and Future Research

8.6.1 Implications for Policy

The 'WHO Global Action Plan on Physical Activity 2018-2030 More Active People for a Healthier World' marks a critical milestone for the global recognition of the PA pandemic. More locally, 'Liverpool Active City' is the PA and sport strategy for Liverpool. It outlines the vision for the transformation and continued investment in sport and active recreation in the city. The development of an integrated universal offer for health and wellbeing is a priority for tackling health inequalities. A coordinated approach to promoting and enabling PA and sport in the city will be a key step in helping to achieve this. Exercise referral initiatives provide one potential tool to facilitate PA behaviour change in some of the most at-risk populations (Sowden *et al*., 2008; Craike *et al*., 2018). Due to a lack of evidence of effectiveness, NICE (2014) recommendations note that policy makers and commissioners should only fund ERSs for people who are sedentary or inactive and have existing health conditions. In addition, it called for such schemes to be evaluated (both impact and process) to inform future practice. The research presented within this thesis sought to co-produce, pilot and evaluate an evidence-based PA referral initiative with embedded process evaluation.

As stated at the end of Chapter 2, a complex systems approach is needed to address numerous public health issues. A shift in thinking is required, away from simple, linear, causal models, to consideration of the ways in which processes and outcomes at all points within a system drive change. Thus, instead of asking whether the intervention works to fix a problem, this PhD will identify if and how it contributes to reshaping the PA referral system in favourable ways (Rutter *et al*., 2017).

Similarly, it is important to think about how different types of interventions work together. Rather than taking an 'either/or' lens, some combinations of interventions may have synergistic effects. Thus, rather than falling into ideological camps, if the public health

community really wants to effect change, they need to find ways to transcend ideological debates and acknowledge the potential value of many different approaches, ideally in collaboration (Adams, 2018).

In light of the findings presented within this thesis, the following recommendations are made for improving the provision of such initiatives:

- Organisations and commissioners must recognise the value of multi-stakeholder engagement including the views and experiences of those delivering and using a service.
- The resources and time required to competently co-produce and pilot interventions, prior to evaluation and implementation phases needs to be appreciated if it is to be used as an approach to improve chances of effectiveness.
- The most appropriate physical, behavioural, and psycho-social health outcomes should be encouraged, with consideration given to ecological validity and scientific rigour.
- Reconsideration of the eligibility of referral initiatives is warranted, given findings regarding a discordance between CRF and PA health status inferences, in addition the large heterogeneity in service-user characteristics.

8.6.2 Implications for Practice

The research presented in this thesis has focussed on exploring what works in practice for a PA referral scheme. This approach was iterative in nature, following a translational approach which allowed for ongoing intervention refinement as available evidence emerged (Koorts *et al.,* 2018). The following bullet points list key changes made to the intervention as a result of the co-production and pilot work, which were deemed useful in improving the intervention, and provide practical recommendations for others in implementing PA behaviour change schemes:

- **Additional behaviour change support**. Behaviour change consultations at the initial induction, week 4, 8, 12, and 18 compared to usual care which included an induction only. Within these consultations, the practitioner-collected data was also refined to reduce practitioner-burden and simplify the process.
- **Practitioner training.** Ongoing behaviour change training sessions were delivered to practitioners in an effort to improve their knowledge and ability to facilitate participants' autonomous motivation to be more physically active. It is important to acknowledge this was an ongoing process, and practitioner training needs to be considered as behaviour change in its own right.
- **Physical activity focus.** A primary aim of the intervention was to facilitate PA behaviour change. Thus, the goal was to provide support to encourage participants to increase both structured exercise (using the fitness centre facilities) and other lifestyle-based PA initiatives. If the fitness centre was not appropriate for an individual, however, the idea was that they could be made aware of other potential initiatives in the local area and still attend the behaviour change consultations.
- **Participant logbook.** A participant logbook was used as a behaviour change tool, encouraging participants to log their activities. It was also used as a discussion point during behaviour change consultations i.e. agreed action plans and goals, as well as allowing practitioners to review participant progress.
- **Peer support.** Whilst this was not a focus within the PA referral scheme, the importance of peer support arose from the qualitative participant data in Study 3. It is therefore an important intervention component to consider.

As a result of the research study findings described in this thesis, the following recommendations for PA referral initiatives are made:

- Incorporating a multidisciplinary group of local stakeholders and academics in the co-production of an intervention from its conception may facilitate the creation of interventions that are both evidence-based and feasible to implement in real-world practice.
- If UK exercise referral is to evolve from an 'exercise prescription' to a 'PA behaviour change' focus, consideration must be given to participant safety and accountability, provision of behaviour change support, as well as feasibility within available resources.
- A phased developmental approach, that allows for intervention refinement may facilitate the translation of scientific-evidence to practice, in turn, producing interventions that are more likely to be implemented successfully.
- It is important to consider co-production, not just in early developmental phases, but through pilot and evaluation work in order to improve intervention acceptability and context sensitivity.

8.6.3 Recommendations for Future Research

Given Liverpool's high preventable mortality (PHE, 2018), there is an urgent need for effective mechanisms to help at-risk individuals make healthy changes. The referral scheme in Liverpool, "Exercise for Health" (E4H) aims to reduce health inequalities through 12-week exercise referrals for inactive, high-risk individuals. However, drop-out is high and E4H effectiveness is unclear (Mchale *et al*., 2018).

Whilst this PhD has made some progress with the PA referral system in Liverpool, it is important to note that such referral initiatives are multilevel interventions. These initiatives require a joined-up transition from health professional referral to intervention delivery, and finally to long-term behaviour change. Thus far, this research has focussed primarily on the intervention delivery aspect of the referral process. It is therefore crucial that research is

undertaken to explore the entire referral process and long-term effects. Specifically, further research is needed to investigate:

1. What happens before the PA referral scheme, as input from referring GPs is crucial to inform improvements to the referral process;

General Practitioners are an integral component of the PA referral system as they see at-risk patients from diverse socio-economic backgrounds (Hutt & Gilmour, 2010). Staff interview data (beyond the scope of this PhD) has eluded to a) Potential communication issues between GP practices and the referral scheme; and b) A lack of systematic referral across different practices in Liverpool. There is limited evidence relating to these issues or solutions to overcome them. Further research is therefore needed to explore GP perceptions of the current PA referral system, which would allow the identification of facilitators and barriers for referring at-risk patients.

2. What happens after the PA referral scheme, as public health benefits will only be realised if change in PA/health is sustained;

It is important to measure whether 12-week effects are maintained at 6 months and beyond. It has been observed that patients living in areas of greater disadvantage utilise ERS services at a higher rate and pay lower out-of-pocket fees than those living in more affluent areas (Craike *et al*., 2018). Consequently, if PA referral as a whole system can be improved, it has real potential to contribute to the alleviation of PA-associated health inequalities. In addition, it is crucial to understand the long-term effects of the Co-PARS, as evidence suggests individuals who engage in a behaviour for ≥6-months are more likely to sustain the new behaviour in the long-term (Fortier *et al*., 2012). This long-term data is also important for our understanding of any effect on health inequalities, as it will reveal the extent to which the PA referral scheme is having a sustainable impact for the most at-risk members of our communities.

3. Finally, a better understanding is needed of the important factors for change (i.e. 'active ingredients').

Additional process data (consultation delivery fidelity and staff interviews; beyond the scope of this PhD) could improve clarity, though further research might be required in order to identify important intervention components. Then, when the active ingredients are better understood, the evaluation of the implementation of this work over a broader scale of delivery centres is required. This would allow for learnings regarding scalability and could highlight the importance of this work for a broader public health perspective.

8.7 Reflections and Summary

From a personal perspective, this research process has been an immeasurable learning experience. I have had the opportunity to work with both a multidisciplinary academic and local stakeholder team. Consequently, I have been immersed in a variety of outcome and process research methods. These have included co-production, lab-based testing (anthropometry, cardio-respiratory fitness testing, vascular ultrasound, phlebotomy, questionnaires, log-books, accelerometry), as well as focus groups and interviews. I have developed a broader, more critical outlook of the importance of scientific rigour balanced with the necessity of ecological validity. Further, I have a new found appreciation for the complexity of PA behaviour change, and the different circumstances that 'we' find ourselves in. For this I am forever thankful.

In a time where the differentiation between *efficacy* and *effectiveness* has never been more important, this research has extended the exercise referral evidence base. Specifically, chapter 4 described the first co-production approach of an evidence-based PA referral scheme, deemed feasible to implement in practice by a multidisciplinary stakeholder group. Chapters 5 and 6 document the piloting of the Co-PARS to explore acceptability and preliminary health impact.

Importantly, this pilot phase identified a number of teething problems requiring refinement, prior to a definitive trial. Following these refinements, chapter 7 then sought to test the effectiveness of the Co-PARS compared to usual care and no-treatment. Findings demonstrated that the Co-PARS was more effective in terms of enhanced CRF, vascular health, and mental wellbeing compared to usual care and no treatment (Chapter 7). Embedded process evaluations demonstrated that intervention acceptability and participant adherence was improved from the pilot (Study 2) to the quasi-experimental evaluation (Study 3).

Collectively, this research has demonstrated that by following a phased approach, whereby a PA referral scheme was co-produced and iteratively adapted, real-world *effectiveness* can be achieved. Importantly, the Co-PARS was developed by a multidisciplinary stakeholder group, who had a valued interest in its success. The intervention was underpinned by SDT and motivational interviewing and focussed on changing long-term PA behaviour. It was therefore co-produced in line with scientific evidence and available local resources.

Finally, it is hoped that these findings have demonstrated the potential of a phased, co-production process for not only a PA referral scheme, but as a potential approach to tackle complex public health problems more generally. Learnings and subsequent recommendations as a result of this work have been made for policy, practice, and future research (Chapter 8). It is now crucial that policy-makers, practitioners, researchers, and service users continue to work together to ensure complex public health initiatives are developed, refined, and implemented appropriately for the local needs and available resources.

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Appendices

1 - **Buckley, B.J.R**. Watson, P.M. Murphy, R.C. Graves, L.E.F. Whyte, G. & Thijssen, D.H.J. (2019). Carotid artery function is restored in subjects with elevated cardiovascular disease risk following a 12-week physical activity intervention. *Canadian Journal of Cardiology*, 35, 23-26. doi: 10.1016/j.cjca.2018.10.015.

2 - **Buckley, B.J.R**. Thijssen, D.H.J. Murphy, R.C. Graves, L.E.F. Whyte, G. Gillison, F.B. Crone, D. Wilson, P.M. & Watson, P.M. (2018). Making a move in exercise referral: co-development of a physical activity referral scheme. *Journal of Public Health,* Advance online publication. doi: 10.1093/pubmed/fdy072.

3 - Rigby, B.P. **Buckley, B.J.R**. Kelly, M.C. & Hanson, C.L. (2017). Exercise on Referral – Symposium hosted by the Physical Activity Special Interest Group of the Wolfson Research Institute for Health and Wellbeing, Durham University. *Sport and Exercise Psychology Reviews*, 13;2.

4 – Ethics approval certificates for Studies 1-3.