CHRONIC LOW BACK PAIN, PHYSICAL ACTIVITY AND THE ROLE OF SHARED FAMILIAL FACTORS

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Publications and Presentations

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Zadro JR, Shirley D, Andrade T, Ferreira PH. The beneficial effects of physical activity: Is it down to your genes? A systematic review and meta-analysis of twin studies. *XIV International Back and Neck Pain Forum 2016; Buxton, Derbyshire, UK.*

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Preface

This thesis is organised into nine chapters, written so that each chapter can be read independently. The University of Sydney allows published papers that arise from the candidature to be included in the thesis. Chapters Two, Three, Four, Five, Six and Seven are the PDF files of the published papers and Chapter Eight is in thesis format.

Chapter One is an introduction that provides relevant background information on the topics that will be discussed in the remaining chapters of the thesis.

Chapter Two is a cross-sectional study that investigated the association between different presentations of chronic low back pain and meeting the World Health Organisation's Physical Activity Guidelines. The paper is presented as published in *The Spine Journal.* A summary of the media coverage this article generated is presented in Appendix 1.

Chapter Three is a cross-sectional study that investigated whether the built environment moderated the relationship between low back pain and different forms of physical activity. The paper is presented as published in *Preventive Medicine.*

Chapter Four is a longitudinal study that investigated whether educational attainment increased the risk of chronic low back pain, and whether this association was different for males and females. The paper is presented as published in *The Spine Journal.* A summary of the media coverage this article generated is presented in Appendix 2.

Chapters Two, Three & Four utilised a co-twin design to control for genetics and shared environmental factors. This contributed to a better understanding of the role of shared familial factors in the development of low back pain.

Chapter Five is a longitudinal study that investigated whether the familial aggregation of chronic low back pain impacted recovery. The paper is presented as published in *Spine.*

Chapter Six is a systematic review of twin and family studies that investigated how shared familial factors influenced the response to regular physical activity. The paper is presented as published in *Sports Medicine Open.* A summary of the media coverage this article generated is presented in Appendix 3.

Chapters Five and Six contributed to a better understanding of the role of shared familial factors in the recovery and management of chronic low back pain.

Chapter Seven describes a protocol for a randomised controlled trial that investigated the feasibility and clinical effects of a home-based video-game exercise program for older people with chronic low back pain. The paper is presented as published in *Physiotherapy.*

Chapter Eight is a randomised controlled trial that investigated a home-based video-game exercise program for older people with chronic low back pain. The paper is presented in the form it was submitted for publication in *Physical Therapy.*

Chapter Nine provides a discussion of the findings of the thesis, including implications for clinicians and recommendations for future research.

Each chapter contains its own reference list. Appendices that were published as online supplementary material are included at the end of the relevant chapter.

Ethical approval was obtained for the studies reported in Chapter Two, Chapter Three, and Chapter Five from the Human Research Ethics Committee of the University of Murcia – Spain, for the study reported in Chapter Four from the Washington State University Institutional Review Board, and for the study reported in Chapter Seven and Chapter Eight from the Human Research Ethics Committee of the Western Sydney Local Health District.

Abstract

Low back pain (LBP) is the leading cause of global disability, with the majority of disease burden accounted for by people with chronic LBP. Current intervention and prevention strategies are failing to reduce the substantial burden of LBP and there are numerous topic areas that warrant further investigation to increase our understanding of how to improve outcomes for this population. The broad aims of this thesis were to investigate the role of shared familial factors (including genetics) in the development, recovery and management of chronic LBP; and to investigate the feasibility and clinical effects of a novel home-based exercise program. Chapter Two showed that individuals with recent chronic LBP are less likely to be active compared to those without chronic LBP, while Chapter Three showed that the relationship between LBP and physical activity is moderated by the built environment. Chapter Four identified that females with low educational attainment are at increased risk of developing chronic LBP, but a co-twin control analysis suggested that these findings (like the findings in Chapter Two) are confounded by shared familial factors. Chapters Five and Six investigated factors influencing the recovery from chronic LBP and the response to increased physical activity, and showed that shared familial factors are an important contributor. Finally, Chapters Seven and Eight outlined the design and findings of a randomised controlled trial investigating the feasibility and clinical effects of home-based video-game exercises for older people with chronic LBP. High recruitment and response rates, and adherence to the intervention showcased trial feasibility, while home-based video-game exercises led to significant improvements in pain self-efficacy, pain and function compared to usual care. Home-based video-game exercises are therefore a promising self-management strategy for older people with chronic LBP that could improve outcomes and reduce health-care costs.

Thesis Overview

Low back pain (LBP) is the most prevalent and disabling musculoskeletal condition worldwide. The enormous costs resulting from health-care utilisation and lost work output due to LBP are primarily accounted for by individuals who develop chronic symptoms, particularly older people. Structured exercises programs (hereafter referred to as physical activity interventions) are strongly recommended for the management of chronic LBP, although only have modest effects for reducing pain and improving function. There is also conflicting evidence regarding the effect physical activity interventions have on reducing the risk of LBP, particularly chronic LBP. It is currently unclear why intervention and prevention strategies (particularly physical activity interventions) are failing to reduce the substantial disability and cost associated with chronic LBP. The aim of this thesis is to explore the following topic areas to better explain the ongoing burden of LBP: i) risk factors and factors associated with LBP and chronic LBP; ii) factors influencing the recovery and response to treatment for chronic LBP; and iii) a novel physical activity intervention targeting improvements in pain self-efficacy for older people with chronic LBP.

Chapters Two, Three and Four of this thesis explore the relationship between LBP, physical activity, the built environment and educational attainment, with the aim of providing guidance about management for populations with chronic LBP that would benefit from increased physical activity and for those at risk of developing chronic LBP. Furthermore, given the strong influence of genetics and shared environmental factors on the development of chronic LBP, physical activity engagement, residential selection, and educational attainment, it is important to adjust for these factors to minimise confounding and obtain more precise estimates of association. The studies reported in Chapters Two, Three, and Four employed a co-twin design to control for the confounding effects of genetics and shared

environmental factors (shared familial factors).

Evidence regarding physical activity levels in people with and without chronic LBP is inconclusive. This may be explained by existing studies using different methods to assess physical activity and recruiting samples with varying presentations of chronic LBP. The conflicting evidence also highlights a lack of understanding of what types and dosages of physical activity are the most beneficial for people with chronic LBP. Until the most beneficial form of physical activity for people with chronic LBP is known, research should determine whether people with chronic LBP are engaging in sufficient levels of physical activity for promoting optimal health, while investigating how different presentations of chronic LBP influence physical activity engagement. Chapter Two of this thesis presents the findings of a cross-sectional study demonstrating that individuals with a recent episode of chronic LBP are less likely to meet the World Health Organisation physical activity guidelines compared to those with no history of chronic LBP. On the other hand, individuals with persistent or previous chronic LBP are just as likely to meet these guidelines as individuals with no history of chronic LBP. These findings highlight that clinicians should incorporate specific strategies to encourage physical activity engagement into the management of individuals with a recent episode of chronic LBP. However, the association between recent chronic LBP and physical activity was no longer significant after controlling for the influence of shared familial factors. This suggests common genetic or shared environmental factors are influencing the development of both chronic LBP and physical activity, consistent with confounding, although we cannot rule out that a reduction in the sample size in the within-pair analysis was the reason these findings were no longer significant.

Individuals with chronic LBP should continue to be active following a physical activity intervention to ensure their symptoms continue to improve, or at least to maintain any improvements resulting from the physical activity intervention. However, existing physical activity interventions for people with chronic LBP only increase physical activity engagement in the short-term. This may be due to a lack of consideration for how the built environment influences physical activity engagement and long-term physical activity behaviour change. Chapter Three presents the findings of a cross-sectional study demonstrating that individuals with LBP are less likely to meet the physical activity guidelines, or walk more than 150 minutes per week, compared to those free of LBP if they live in an environment with short walkable distances to nearby amenities (high walkability). Furthermore, the strength of this association increased in magnitude after controlling for genetics and shared environmental factors. This increases our confidence in these findings as controlling for a greater number of confounding factors suggests the relationship between LBP and physical activity (for individuals living in an environment with high walkability) is independent of shared familial factors. The sample size in this study was over four-times greater compared to the study in Chapter Two so we can also be confident a reduction in the sample size during the within-pair analyses did not influence these findings. The findings of Chapter Three have important implications for targeting physical activity interventions towards individuals with LBP living in a neighbourhood with high walkability, as their environment could support long-term physical activity behaviour change. Future research investigating the association between LBP and physical activity, or the effectiveness of a physical activity intervention for people with LBP, must consider the influence of the built environment to build on these findings and better understand the facilitators and barriers to physical activity engagement in this population.

Another potential risk factor that has received little attention is educational attainment. A better understanding of how educational attainment increases the risk of developing chronic LBP could inform on which populations are at risk of developing chronic LBP. Cross-sectional studies have demonstrated a higher prevalence of chronic LBP in individuals with low educational attainment, with numerous studies highlighting gender differences in this relationship. Unfortunately, there are few longitudinal studies investigating educational attainment as a risk factor for developing chronic LBP, while also considering the influence of gender. Chapter Four presents the findings of a longitudinal study demonstrating a higher risk of developing chronic LBP in females with low educational attainment, and a lower risk in females with high educational attainment. There was no association between educational attainment and the risk of chronic LBP in males. These findings highlight the importance of targeting prevention strategies towards females with low educational attainment as they are at high risk of developing chronic LBP. In addition, health literacy education might be a key priority for females with chronic LBP as they are more likely to have lower educational attainment compared to females without chronic LBP. Further research is needed to explore the reason educational attainment affects the risk of chronic LBP in females but not in males. One hypothesis that deserves consideration is that shared familial factors could be confounding the positive association we found for females, since after controlling for genetics and shared environmental factors, educational attainment did not affect the risk of developing chronic LBP in females. Future studies exploring the relationship between education and chronic LBP must consider the influence of gender and shared familial factors to build on these results and inform on populations at risk of developing chronic LBP.

Chapters Five and Six of this thesis explore factors influencing the recovery and response to treatment for chronic LBP, with the aim of improving clinicians' ability to identify patients at

risk of poor outcomes and predict their response to treatment. The role shared familial factors play in the recovery from chronic LBP and in the response to increased physical activity needs to be investigated if we are to better understand why some individuals have poor outcomes or fail to respond to a physical activity intervention. Shared familial factors have a strong influence on the development of chronic LBP, with the familial aggregation of chronic LBP increasing the likelihood of developing chronic LBP. Despite this, no studies have investigated the impact shared familial factors have on the recovery from chronic LBP. Understanding how the familial aggregation of chronic LBP impacts on the recovery from chronic LBP will help clinicians identify those at risk of poor outcomes and potentially inform the direction of treatment. Chapter Five of this thesis presents the findings of a longitudinal study demonstrating that the familial aggregation of chronic LBP significantly impacts on the recovery from chronic LBP. The likelihood of non-recovery was highest in identical twins with a family history of chronic LBP, suggesting that genetics play a strong role in the recovery from chronic LBP. With this in mind, future studies investigating the recovery from chronic LBP should control for shared familial factors (particularly genetics) to get more precise estimates of association. From a clinical perspective, the presence of chronic LBP within a family can inform clinicians on which patients are less likely to recover, and have implications for treatment strategies. Clinicians that identify a patient with negative beliefs and attitudes regarding their LBP that have further been reinforced amongst family members could intervene and educate about these beliefs to potentially improve this patient's recovery.

There is substantial individual variation in the responsiveness to regular physical activity in healthy adults and in people with chronic LBP. A better understanding of factors that influence the response to increased physical activity is warranted and may explain the modest

effects of physical activity interventions for chronic LBP. Shared familial factors appear to play a role in dictating how an individual will respond to increased physical activity. For example, identical twin pairs completing a standardized physical activity intervention demonstrate great variation for increases in maximal oxygen uptake between twin pairs, but only a small amount of variation within twin pairs. Chapter Six presents the findings of a systematic review demonstrating that genetics and shared environmental factors significantly influence the response of body composition and cardiorespiratory fitness following a physical activity intervention in healthy adults. Future studies should build on these results and investigate the role of shared familial factors in the response to a physical activity intervention for individuals with chronic conditions, such as LBP. If shared familial factors influence the response to physical activity in people with chronic LBP, this could have implications for adjusting modifiable intervention parameters (intensity, frequency, duration) to achieve a desired response, or for selecting alternative management strategies in the case of non-responders. Information about the response to physical activity could also be used by clinicians to guide treatment choices, decrease health-care costs, and reduce patient disappointment.

Chapters Seven and Eight of this thesis investigate the feasibility and clinical effects of a novel physical activity intervention targeting improvements in pain self-efficacy for older people with chronic LBP. A potential shortcoming of trials investigating physical activity interventions for older people with chronic LBP is an overemphasis on outcomes related to pain and function, while neglecting the important role of pain self-efficacy. Pain self-efficacy is an individual's ability to continue activities of daily living despite pain and is closely linked to self-management. Older people with poor physical functioning often prefer an exercise program that can be performed at home, reducing the need to travel to a clinic for

supervised exercise. However, poor adherence to home exercise highlights the need for an interactive physical activity intervention aimed at improving self-management in older people with chronic LBP. Chapter Seven outlines the protocol of a pilot randomised controlled trial investigating the feasibility and clinical effects of a home-based video-game exercise program in older people with chronic LBP. Chapter Eight details the results. Our trial had a high response rate (51%), a high recruitment rate in community-dwelling older people (11 participants per month), and high adherence to the intervention. No adverse events were reported. Participants completing video-game exercises demonstrated significantly higher pain self-efficacy in the long-term and significantly greater improvements in pain and function immediately post-intervention compared to a control group advised to maintain their usual activities. In addition, participants completing video-game exercises were significantly more likely to engage in flexibility exercises in the long-term, tended to be less likely to take pain medication in the long-term, and tended to have lower fear of movement immediately post-intervention. There were no significant between-group differences for the remaining physical activity and care-seeking variables, nor disability or falls-efficacy at any time point. The results of this pilot study support the feasibility and positive clinical effects of a home-based video-game exercise program for older people with chronic LBP. Considering the numerous benefits of physical activity for older people, a large randomised controlled trial is needed to build on these results. If home-based video-game exercises are shown to be effective, the intervention will be rolled out to community-dwelling older people and has the potential to reduce long-term health-care expenditure for chronic LBP by promoting self-management.

This thesis explored numerous issues not sufficiently addressed in the literature and will contribute to a better understanding of why current intervention and prevention strategies for

chronic LBP are failing to reduce the enormous personal and financial burden associated with the condition. In summary, clinicians need to incorporate physical activity promotion into the management of individuals with a recent episode of chronic LBP, and individuals with LBP who live in an environment with good walkable access to nearby amenities. Clinicians should also target prevention strategies towards females with low educational attainment, as these individuals are at an increased risk of developing chronic LBP. On the other hand, the relationships we found between chronic LBP and physical activity, and chronic LBP and educational attainment need to be interpreted with caution, since genetics and shared environmental factors appear to be confounding these associations. The co-twin study design should continue to be utilised when investigating risk factors for chronic LBP to control for the confounding effects of shared familial factors and obtain more precise estimates of association.

The thesis also highlighted the important role of shared familial factors in the recovery from chronic LBP, and in dictating the response to increased physical activity. Clinicians involved in the management of an individual with chronic LBP should consider the presence of chronic LBP within a family as a predictor of non-recovery, and use this information to better understand a patient's prognosis and guide treatment strategies. In addition, given the substantial role of shared familial factors in the response of body composition and cardiorespiratory fitness following a physical activity intervention, shared familial factors may also play a role in how an individual with chronic LBP responds to a physical activity intervention. Future studies should investigate the response to a standardised physical activity intervention in a sample of identical twin pairs with chronic LBP. A higher concordance in outcomes (e.g. pain and function) between identical twin pairs following the intervention would highlight a strong role of shared familial factors in dictating the response to a physical

activity intervention in people with chronic LBP. These findings would have implications for changing modifiable training parameters or selecting an alternative intervention to achieve a desired response, decrease treatment costs, and reduce patient disappointment.

Finally, this thesis highlighted the feasibility of a home-based video-game exercise program in community-dwelling older people with chronic LBP, while demonstrating positive clinical effects for pain self-efficacy, pain and function. Given the enormous benefits of increased physical activity in older people with chronic LBP, home-based video-game exercises are an innovative way to increase adherence to home exercise, support self-management, and reduce health-care expenditure for chronic LBP. However, before video-game exercises are recommended for older people with chronic LBP, an adequately powered randomised controlled trial is needed to confirm the efficacy of this novel self-management strategy.

CHAPTER ONE

Introduction

1.1. Epidemiology of non-specific low back pain

1.1.1. Introduction to non-specific low back pain

Low back pain (LBP) is the most prevalent and disabling musculoskeletal condition worldwide[1]. It is defined as pain which localises posteriorly within the region from the inferior border of the twelfth rib to the lower gluteal folds[2]. The majority of LBP cases presenting to primary care are classified as 'non-specific' (~85%)[3], with the remaining cases presenting with either spinal nerve or nerve root compression (~5-10%)[4, 5], or a serious pathology (e.g. malignancy, fractures, inflammatory conditions, cauda equina) (~1%)[6, 7]. This thesis will only consider non-specific LBP from this point onwards.

Although there are numerous pain-sensitive (nociceptive) structures within the spine, such as intervertebral discs, zygapophyseal joint capsules, synovia, muscles and spinal ligaments[8], classifying someone as having non-specific LBP reflects the complexity of determining which structures are responsible for the pain. Health-care professionals routinely use clinical examination findings to determine the source of nociception within the spine[9], while increasing rates of magnetic resonance imaging (MRI) for people with LBP likely reflect the desire to confirm a structural diagnosis[10]. Unfortunately, there are numerous issues with these approaches[9, 11], and solely focusing on a patho-anatomical source of nociception may neglect important psychological and social contributors to an individual's symptoms[12-14]. Numerous studies have investigated the diagnostic accuracy of clinical examination findings for identifying patho-anatomical sources of LBP. However, the lack of accurate reference standards limits our confidence in these findings[9]. For example, using medical imaging as a reference standard for determining the diagnostic accuracy of clinical examination findings has numerous issues. Structural abnormalities displayed on MRI, such as disc degeneration, facet joint arthropathy, and disc bulges are common in individuals without LBP[15, 16].

Furthermore, the prevalence of 'abnormal' findings (e.g. spondylolithesis) are often similar in people with and without LBP[17]. The presence of 'abnormal' imaging findings for an individual with LBP may also lead to pain catastrophising, increased health-care utilization[18], and worse outcomes compared to those who do not pursue medical imaging[18-20], especially if these individuals are not reassured that 'abnormal' findings are common in asymptomatic individuals[19]. Medical imaging is also costly[21], does not guide the choice of treatment[22], and does not predict treatment outcomes in individuals with LBP[23]. As a result, medical imaging is limited in ability to identify which spinal structure is responsible for pain and should not be routinely recommended for individuals with non-specific LBP[18]. Given the limited utility of clinical examination findings and medical imaging to diagnose a patho-anatomical source of LBP, a shift towards a biopsychosocial explanation of LBP – and away from the biomedical disease model – has been recommended to guide treatment[12]. This shift is supported by numerous studies identifying psychosocial factors in the development and prognosis of LBP[12-14] and highlights the importance of understanding how a variety of factors influence the development of LBP, the recovery from LBP and the response to treatment. Since the term non-specific LBP continues to be widely used in research and clinical practice – reflecting that pain may have a nociceptive origin but there are other factors contributing to the pain experience[24] – non-specific LBP will be referred to as LBP throughout this thesis.

1.1.2. Burden and cost of low back pain

The most recent Global Burden of Disease Study has ranked LBP as the leading cause of years lived with disability, in both developed and developing countries, ahead of other conditions including major depressive disorder, diabetes, and neck pain[1]. Furthermore, between 1990 and 2013, LBP rose from the twelfth leading cause of premature mortality and

non-fatal health loss (disability-adjusted life-years) to the fourth leading cause, only behind heart disease, cerebrovascular disease, and lower respiratory infections[25].

The economic cost of LBP is enormous across many countries[26, 27], and can be divided into the costs from direct or indirect sources. Direct costs refer to the utilisation of health services for LBP and include the cost of visiting health professionals (e.g. doctors, physiotherapists, and chiropractors), purchasing medications, or the costs of hospital admissions and surgical procedures. Indirect costs consist of lost work output resulting from decreased productivity and earnings, commonly accounting for the majority of the global economic burden of LBP[27, 28]. The costs of LBP also appear to be increasing. In 2001, the total yearly cost of LBP in Australia was approximately AU$9 billion, with direct costs estimated at AU$1 billion[28]. In 2012, direct costs alone were estimated at AU$5 billion[29]. Furthermore, the total yearly cost of LBP in 1998 was US$90 billion in the United States[30], with this figure increasing approximately 65% by 2005[31]. The total yearly costs of LBP are also substantial across other countries and have been estimated at £12 billion for the United Kingdom[32], and up to €300 billion for the whole of Europe[27].

1.1.3. Prevalence, incidence, and course of low back pain

The global point prevalence of LBP is estimated at 46.3%[1], with estimates for the lifetime prevalence being as high as 80% by 20 years of age[33]. These figures are typically higher in females[34-38]. The 1-year incidence of a first-ever episode of LBP ranges from 6.3-15.4%, with estimates for the 1-year incidence of any episode of LBP as high as 36%[39]. On average, individuals with LBP demonstrate substantial reductions in pain and disability within the first six weeks following an acute episode[40]. However, the rate of recurrence within the next year is estimated at 33%[41], and there is significant individual variation in the trajectory of

symptoms[42]. By examining individual data on pain intensity over time, a number of distinct pain trajectories describing the course of LBP have been identified[42]. Persistent or fluctuating pain can be used to describe an individual's pain variability, while different rates of improvement can describe how these symptoms change overtime[42]. The majority of people with LBP experience either persistent or fluctuating symptoms of mild to moderate intensity[42], with cases of severe or chronic LBP less common[43]. Nevertheless, individuals experiencing chronic LBP often have slower reductions in pain and disability[40], and are at greater risk of recurrence[41]. Individuals who go on to develop chronic LBP also account for the majority of the disability and cost resulting from LBP[26, 44, 45], with more than 75% of the costs associated with LBP accounted for by the 5% of individuals who develop chronic symptoms[44, 46]. Therefore, given that individuals with chronic LBP often fail to recover[43], research on these individuals is particularly important from a public health perspective and will be the focus of a number of chapters in this thesis.

Chronic LBP is most commonly defined as LBP lasting for more than 3 months[47]. However, there is inconsistency regarding this definition[48], with some sources defining chronic LBP as pain lasting for 6 months or longer, and others defining chronic LBP as the presence of pain for more than half the days in a year[39, 47, 49]. Given that LBP does not follow a linear course and individuals often have flare-ups and recurrent episodes[39, 41, 42], there is currently no consensus on which definition of chronic LBP is the most appropriate to use in research and clinical practice[2]. Therefore, because more than one database was used for the studies reported in this thesis, some studies define chronic LBP as symptoms lasting for at least 3 months, while others define chronic LBP as symptoms lasting for at least 6 months.

1.1.4. Chronic low back pain and older people

Chronic LBP has an enormous impact on older people, with older people commonly defined as individuals over 65 years old[50-52]. The 1-month prevalence of chronic LBP is estimated at 23.2% in the general population[53]. However, the prevalence of chronic LBP increases with age[52-55], with estimates being as high as 40% in males and 35% in females by 80 years old [53]. Chronic LBP also becomes more severe[52] and disabling with age[56], with the prevalence of disabling chronic LBP nearly three times higher in people over 90 years old (9.7%) compared to people between 75-80 years old (3.8%)[57], and the prevalence of severe chronic LBP nearly three times higher in people over 80 years old compared to people less than 60 years old[58]. The prevalence and financial burden of chronic LBP are increasing[45, 59], and individuals reporting high levels of disability and poor physical functioning spend up to five times more on health-care services compared to people with less disabling symptoms[45]. Furthermore, the likelihood of recovering from an episode of LBP decreases with age[60]. For example, older people tend to report smaller improvements in pain and disability over time[61], with older people reporting chronic or severe symptoms even less likely to recover[60].

Chronic LBP has a significant impact on physical functioning[62] and physical activity engagement in older people[63]. Older people with chronic LBP demonstrate significantly slower gait speed, stair descent time, and repeated sit-to-stand time compared to older people without LBP[64, 65], with worse physical functioning observed in individuals with longer duration of symptoms[60]. Older people with chronic LBP also demonstrate reduced overall levels of physical activity compared to pain-free individuals[63], with the duration of symptoms strongly associated with decreased physical activity engagement[66]. Decreases in physical functioning and physical activity engagement may explain why older people with severe LBP frequently experience difficulty with simple activities of daily living[67], are at high risk of falling[68], and have lower falls-related self-efficacy compared to older people without LBP[69].

Furthermore, the significant impact chronic LBP has on older people is highlighted by the fact that health-care costs associated with LBP increase with age and chronicity of symptoms[70]. This is particularly problematic given the global population of people over 60 years old is expected to triple by 2050[71]. However, despite the significant impact chronic LBP has on older people, they are commonly excluded from randomised controlled trials evaluating treatment options[72]. Therefore, chronic LBP in older people accounts for a substantial portion of the disability and cost resulting from LBP, and given the rapidly aging population[51, 71], more research on older people with chronic LBP is needed. Chapters Seven and Eight of this thesis will further explore this topic area.

1.2. Prevention and intervention strategies for low back pain

1.2.1. Prevention

Despite decades of research aimed at advancing our understanding of LBP, the prevalence and disability associated with the condition has failed to reduce since 1990[1]. This is likely reflecting a lack of research investigating appropriate prevention strategies to reduce the risk of developing LBP (particularly chronic LBP), and small effect sizes of current interventions for chronic LBP. In terms of prevention strategies, combining education with a structured exercise program can reduce the risk of developing a first-time episode of LBP by nearly 50%[73], while structured exercise programs in isolation are only effective at reducing recurrent episodes of LBP[74, 75]. Unfortunately, neither structured exercise programs nor education in isolation are effective at reducing the risk of a first-time episode of LBP[73, 76]. The content of structured exercise programs varies between studies but commonly includes one or more of the following: abdominal and lumbar muscle activation, strengthening or endurance exercises, lower limb muscle strengthening or stretching, or aerobic exercises[73]. Similarly, education commonly involves information regarding one or more of the following areas:

basic anatomy and pathophysiology of LBP, evidence-based information, lifting posture, ergonomic principles, or the benefits of increased physical activity[73]. Numerous other prevention strategies including lumbar supports, ergonomic modifications, and shoe insoles, are ineffective at reducing the risk of LBP[75, 77-79], and there is limited research on the prevention of chronic LBP. Graded activity[80] and pain education[81] are promising strategies for reducing the likelihood that individuals experiencing acute LBP will develop chronic symptoms, although more research in this area is needed before firm recommendations can be made. The lack of supporting evidence for many prevention strategies is likely be explained by a poor understanding of factors that increase the risk of developing LBP. This highlights the importance of first identifying risk factors for LBP, then targeting preventions strategies towards those at high risk. Identifying risk factors for LBP is a major component of this thesis and will be further explored in Chapters Two, Three and Four.

1.2.2. Intervention

Most evidence-based clinical practice guidelines recommend structured exercise programs for the management of chronic LBP[82-84]. These exercise programs are largely similar in content to those recommended for the prevention of LBP, although some additional forms of exercise have been recommended for the management of chronic LBP and include: yoga, pilates, and motor control exercises. Structured exercises programs are effective as a stand-alone intervention for chronic LBP[85], or can delivered alongside interventions such as spinal manipulative therapy[86], cognitive behavioural therapy[87, 88], education[83, 89], advice to remain active[89], and advice regarding the most appropriate physical activities to undertake to promote long-term self-management[83]. However, despite an abundance of research investigating different types and doses of the above-mentioned interventions for people with chronic LBP[90-92], the analgesic effects are small[93, 94]. For example, structured exercise

programs only result in a small decrease in pain and increase in function[91, 95, 96] and this is regardless of the exercise modality investigated (e.g. abdominal or lumbar muscle strengthening, aerobic exercise, pilates, etc.)[85, 97, 98]. Therefore, given the lack of evidence supporting the superiority of one exercise modality over another for the management of chronic LBP[85], and that physical activity encompasses all forms of bodily movements that result in energy expenditure[99], structured exercise programs will be referred to as physical activity interventions throughout this thesis.

1.2.3. Research priorities for low back pain

The ongoing disability and cost resulting from chronic LBP is a major concern[1, 100] and highlights that current intervention and prevention strategies are at best having a small impact on the burden of LBP. A major problem in the field of LBP is that most intervention and prevention strategies have been investigated without an adequate – let alone comprehensive – understanding of the range of factors that could influence the development of chronic LBP, the recovery from chronic LBP and the effects of treatment. Further, there is little-to-no research on interventions that facilitate self-management; an approach that could improve an individual's ability to manage their pain independently, reduce their reliance on the health-care system, and subsequently decrease the enormous burden of chronic LBP. These topic areas warrant further attention and will be explored in depth in this thesis.

1.3. Understanding risk factors and factors associated with low back pain and chronic low back pain

The majority of research on chronic LBP concerns therapy. However, a better understanding of factors increasing the risk of developing LBP (particularly chronic LBP) is essential to guide the design of more effective intervention and prevention strategies. A previous history

of LBP is the only strong and consistent risk factor for the development of LBP (including chronic LBP)[73, 101, 102]. Other factors that have been consistently shown to increase the risk of LBP only demonstrate small effects. For example, obesity[103], work-related physical activity[104], poor general health[105, 106], and low levels of job satisfaction[105] are consistently associated with a small increase in the risk of developing LBP, while high baseline pain intensity[102], low baseline function[106], obesity[103], poor general health[106], depression[107], and maladaptive coping behaviours[106, 107] are consistently associated with a small increase in the risk of developing chronic LBP. Despite this, there are other potential risk factors that demonstrate inconsistent effects (e.g. recreational physical activity[104, 105]), or that have not been investigated adequately to make definite conclusions regarding their effect (e.g. educational attainment, and the built environment). In addition, most studies investigating risk factors for LBP are cross-sectional, limiting their ability to determine which factors precede the development of LBP. Longitudinal studies overcome this limitation by identifying those at risk of developing LBP and subsequently those who might benefit from targeted prevention strategies. This thesis will aim to address some of the limitations and literature gaps regarding the relationship between recreational physical activity, the built environment, educational attainment and different presentations of LBP. A better understanding of risk factors and factors associated with LBP, and chronic LBP, will have implications for the future design of intervention and prevention strategies.

1.3.1. Physical activity

Physical activity is one of the most important factors for maintaining optimal health across numerous body systems, including the cardiovascular[108] and musculoskeletal system[109]. Throughout this thesis the following physical activity domains will be predominately referred to: i) recreational physical activity, which refers to any physical activity an individual

performs during their leisure time (e.g. sport, resistance training, flexibility exercises, etc.); and ii) work-related physical activity, which refers to any physical activity an individual does at work (e.g. lifting, bending, walking, etc.). Furthermore, structured exercise programs will be referred to as physical activity interventions as previously outlined.

Physical activity interventions are commonly recommended for the management of chronic LBP[83], although they only provide modest improvements for pain and function[93]. A possible explanation for these modest results could be that these interventions are implemented in populations that already achieve adequate levels of physical activity[63, 104]. Despite an abundance of research investigating physical activity levels in people with chronic LBP, it is not clear whether individuals with chronic LBP have reduced physical activity levels compared to those without chronic LBP[63, 104], or that a lack of or excessive amount of physical activity increases the risk of developing LBP or chronic LBP[104, 110]. Some studies report that individuals with chronic LBP have reduced levels of recreational physical activity (e.g. sports participation) compared to people without LBP[111-113], while others report that individuals with chronic LBP have either greater[114, 115], or similar physical activity levels compared to people without LBP[116-118]. These conflicting findings are likely explained by different methods of assessing and defining chronic LBP and physical activity, and highlight a lack of understanding of what types and dosages of physical activity are the most beneficial for people with chronic LBP. With this in mind, it would be beneficial to assess physical activity in light of promoting optimal health across a variety of body systems, and investigate how different presentations of chronic LBP influence the engagement in sufficient levels of physical activity. The 2010 World Health Organisation (WHO) Physical Activity Guidelines recommends a minimum of either 150 minutes moderate-intensity physical activity, 75 minutes of vigorous-intensity physical activity, or a combined 150 minutes of moderate or

vigorous-intensity physical activity per week, accumulated in multiple bouts of at least 10 minutes[50]. Therefore, until it is clear what types and dosages of physical activity are the most beneficial for people with chronic LBP, research should focus the prescription of physical activity according to the WHO physical activity guidelines to ensure people with chronic LBP are sufficiently active for improving or maintaining their overall health. In addition, understanding the relationship between different presentations of chronic LBP (e.g. time since last episode, persistence) and physical activity engagement will help clinicians and policy makers better determine which populations with chronic LBP would benefit the most from increased physical activity. The second chapter of this thesis presents the findings of a cross-sectional study investigating what proportion of individuals with various presentations of chronic LBP are meeting the physical activity guidelines, and whether there is an association between various presentations of chronic LBP and meeting the WHO physical activity guidelines.

1.3.2. The built environment

Physical activity interventions are commonly recommended for individuals with chronic LBP to reduce pain and improve function[83], and primarily consist of structured exercise programs implemented over a certain timeframe[74, 85]. However, it is important that individuals with chronic LBP continue to be physically active following the completion of a physical activity intervention. This is to ensure their symptoms continue to improve, or that any improvements resulting from the physical activity intervention are maintained. Despite this, current physical activity interventions only increase physical activity engagement in the short-term[119, 120], and fail to result in long-term physical activity behaviour change[121-124]. Understanding factors that influence long-term engagement in physical activity following a physical activity intervention is important. A shortcoming of current physical activity interventions may be a lack of

consideration for the influence of external environmental or community-level factors, such as the built environment. By incorporating information on environmental characteristics such as the continuity of sidewalks, variety of land-uses in a neighbourhood (e.g. residential, business, and entertainment), and walkable distance to nearby amenities (e.g. parks, shops, restaurants, etc.), walkability can be used to objectively quantify the extent the built environment in a neighbourhood promotes physical activity[125-127]. Walkability is high in cities where residents are within walking distance of work, public transportation, and shopping centres, but is generally lower in suburbs or rural areas where the distance to nearby amenities is greater[125]. However, it is currently unclear how walkability impacts physical activity levels in people with LBP. Individuals who live in a neighbourhood with low walkability and experience LBP may be less likely to practice regular physical activity compared to those free of LBP. On the other hand, those suffering LBP may be less likely to engage in physical activity despite living in an environment which promotes it (high walkability). A better understanding of the relationship between LBP, physical activity, and walkability may serve to explain why current physical activity interventions fail to demonstrate long-term physical activity behaviour change in people with LBP. The third chapter of this thesis presents the findings of a cross-sectional study investigating whether walkability moderates the association between LBP and physical activity.

1.3.3. Educational attainment

Despite conflicting evidence regarding levels of recreational physical activity in people with and without chronic LBP[63], the exposure to physically demanding work-related physical activities, such as awkward or prolonged postures, and heavy lifting, is consistently more common in people with LBP[104, 128, 129] and chronic LBP[130, 131], compared to those without LBP. In addition, exposure to physically demanding work-related physical activities has been

associated with an increased risk of severe LBP[132], and the development of chronic LBP[130, 133]. These work-related physical activities are primarily influenced by an individual's occupation, a common indicator of socioeconomic status, and may highlight the importance of considering other socioeconomic risk factors for chronic LBP, such as educational attainment. The prevalence of LBP[39, 134], and chronic LBP[131, 135] are higher in individuals with low educational attainment, with these individuals experiencing greater severity[136, 137] and frequency of symptoms[138], longer symptom duration[134], and a less favourable prognosis[134]. Only a few studies have investigated educational attainment as a risk factor for LBP, demonstrating that having a higher education reduces the risk of developing activity limiting LBP[139, 140], but no studies have investigated whether educational attainment increases the risk of developing chronic LBP. Furthermore, a number of observational studies have highlighted potential gender differences in the relationship between educational attainment and LBP[141-143], and chronic LBP[135], although further research is needed to build on these findings. People with low educational attainment might be at increased risk of developing chronic LBP because they are more likely to engage in strenuous work-related physical activity[104] and have lower job satisfaction[105]. Further, gender differences in the relationship between educational attainment and the development of chronic LBP might be explained by occupational factors. For example, work-related physical activity appears to have a larger influence on the risk of LBP-related disability in males[140], while high emotional demands are stronger predictors of LBP in females[144]. A better understanding of the relationship between educational attainment and chronic LBP may assist clinicians more appropriately target intervention strategies towards individuals at risk of developing chronic LBP. The fourth chapter of this thesis presents the findings of a longitudinal study investigating how gender influences the relationship between educational attainment and the prevalence and risk of chronic LBP.

1.3.4. Heritability and shared familial factors

When investigating risk factors or factors associated with LBP (particularly chronic LBP) the potential confounding effects of shared familial factors, including genetics, need to be considered. Twin studies are frequently used to quantify the extent genetics and shared environmental factors contribute to a particular trait (classical twin study), such as the presence of LBP. It is known that non-identical twins (dizygotic – DZ) twins share approximately 50% of their genes while identical twins (monozygotic – MZ) twins share approximately 100%[145]. It is also assumed that both DZ and MZ twins were exposed to the same environment when growing up[145]. If genetics influence a particular trait, MZ twin pairs would demonstrate a greater concordance (or similarity) for the trait compared to DZ twin pairs, and the heritability estimate would be high. If genetics were the only influence on a trait, the ratio of concordance between MZ and DZ twin pairs would be 2:1, with a heritability estimate of 100%. On the other hand, if concordance for a trait was similar between MZ and DZ twin pairs, shared environmental factors would be an important contributor to the trait. Examples of environmental exposures during childhood include physical activity levels, educational development, socioeconomic status, and parental role modelling. Genetics play a strong role in the development of LBP, with heritability estimates as high as 67% for cases of chronic or disabling LBP[146]. Furthermore, genetics and shared environmental factors substantially influence the engagement in physical activity[147], educational attainment[148], and residential selection[149]. Therefore, when investigating risk factors for LBP, it is important to account for genetics and shared environmental factors.

Twin studies provide a unique opportunity to control for the confounding effects of genetics and shared environmental factors and over the past two decades there has been increasing recognition of their utility in research investigating risk factors for LBP[150-153]. Leboeuf-Yde

and colleagues (1998) demonstrated that the association between smoking and LBP disappeared after controlling for the confounding effects of genetics and shared environmental factors[153], while Hestbaek and colleagues (2006) found that controlling for these factors didn't influence the association between obesity and LBP[150]. More recently, numerous publications from our research group have supported the utility of twin studies in better understanding risk factors and factors associated with LBP[154-156]. For example, a systematic review and meta-analysis by Dario and colleagues (2015) showed that the association between obesity and LBP disappeared when pooling results from studies that had adjusted for the confounding effects of genetics and shared environmental factors[154]. This suggests common genetic and shared environmental factors may be responsible for the presence of both obesity and LBP, and are confounding this relationship. In addition, another study within our research group demonstrated that the association between physical activity (recreational and work-related) and LBP increased in magnitude after adjusting for shared familial factors[155], suggesting a more direct relationship between physical activity and LBP. The findings of twin studies have important implications for the design of intervention and prevention strategies for LBP. For example, if genetics and shared environmental factors are driving the relationship between obesity and LBP, this could explain why weight loss interventions are ineffective for people with LBP[157]. Therefore, if researchers plan to use knowledge of risk factors, and factors associated with LBP, to guide intervention and prevention strategies, a robust method of adjusting for the confounding effects of genetics and shared environmental factors is required to obtain more precise estimates of association. Unfortunately, the majority of observational studies investigating risk factors or factors associated with LBP have unknowingly neglected the potential confounding effects of shared familial factors. This thesis builds on the body of evidence from within and outside our research group by utilising the twin study design to investigate a few precise risk factors for

LBP. Overall, this work contributes to a larger body of twin research that aims to better understand how shared familial factors influence the risk of developing LBP.

1.3.5. Twin study design to control for shared familial factors

There are numerous ways to control for shared familial factors when analysing twin data[150-152] but this thesis will predominately focus on the co-twin control design as this approach has been utilised extensively in the field of LBP[150, 154-156]. Considering complete twin pairs discordant for LBP (i.e. one twin reported LBP but the co-twin did not) allows researchers to control for the effects of genetics and shared environmental factors, and can be achieved through the following steps. First, considering only DZ twin pairs allows the researcher to adjust for 50% of genetics, while considering only MZ twin pairs in the next step allows the researcher to adjust for almost 100% of genetics. Since it can be assumed both DZ and MZ twin pairs were exposed to similar environmental factors during childhood, both analyses are adjusted for shared environmental factors. In theory, when the association between two variables remains or increases in magnitude as we adjust for a greater proportion of genetics (particularly in the analyses of MZ twins where the highest level of adjustment is achieved), this is likely to be consistent with a more direct association between the two variables. Conversely, if the magnitude of the association decreases, this is more likely consistent with confounding[158]. Confounding would suggest that genetics and/or shared environmental factors are driving the relationship between the two variables, or that common genetic and/or shared environmental factors are responsible for the development of both traits (such as LBP and physical activity engagement). Therefore, to get a clearer understanding on factors that increase the risk, or that are associated with LBP, we need to control for the influence of genetics and shared environmental factors. Chapters Two, Three, and Four present the findings from three studies that utilised a co-twin control design to adjust for shared familial

factors. This allowed us to obtain more precise estimates of investigated risk factors (educational attainment) and factors associated with LBP (physical activity and the built environment). The findings presented in these chapters will likely inform on the design of future prevention and intervention strategies.

1.4. Factors influencing the recovery and response to treatment for chronic low back pain

1.4.1. Environmental influences on recovery

Understanding a range of factors that influence recovery and the response to treatment for chronic LBP may help to explain why current interventions are failing to reduce the prevalence and disability resulting from the condition[100]. Numerous factors have been investigated in the recovery from chronic LBP[159, 160], with only a few demonstrating a consistent negative impact, including recurrent episodes of LBP or longer symptom duration[161, 162], high initial pain intensity[163, 164], longer work absence[165], negative expectations about recovery[166, 167], pain catastrophising[13], and symptoms of depression[14, 164]. Negative expectations about recovery can increase the risk of persistent symptoms by approximately 2.5 times[166], while pain catastrophising has been shown to negatively influence the prognosis in all types of LBP (e.g. acute, sub-acute, and chronic)[13]. Furthermore, symptoms of depression in people with chronic LBP appear to predict worse pain, disability, and a reduced likelihood of returning to work[14]. Numerous other factors have been investigated in the recovery from chronic LBP and include gender[160], recreational physical activity[168], fear-avoidance beliefs[169], and clinical examination findings (e.g. lumbar spine range of motion, hip range of motion, pain provocation tests, lumbar muscle strength and lumbar muscle endurance)[159], although their effects are less consistent.

1.4.2. Shared familial factors and recovery

Although a number of the above-mentioned factors are important, they only consider the individual, without consideration of external or familial factors. Genetics account for up to 67% of chronic and disabling LBP cases[146], with the family environment accounting for up to 48% of LBP cases in children[170, 171]. Therefore, it may be important to extend our understanding of factors impacting the recovery from chronic LBP beyond the individual and into the family environment. Among familial factors that could influence recovery, the familial aggregation of chronic LBP – where multiple family members report a history of chronic LBP – is likely to be relevant. Familial aggregation of chronic LBP is associated with the presence of chronic LBP[172], while having family members suffering from chronic LBP increases the likelihood of developing chronic LBP[173, 174] or chronic LBP with high fear avoidance beliefs[175]. Further, both children and adults are at increased risk of seeking care for their LBP if they have family members seeking care for LBP[176, 177]. Despite this, familial aggregation of chronic LBP is yet to be investigated in the recovery from chronic LBP. A broader understanding of the factors associated with persistent pain and disability will assist clinicians to identify those at risk of non-recovery and better target treatment. The fifth chapter of this thesis presents the findings from a longitudinal study investigating the impact familial aggregation of chronic LBP has on the recovery from chronic LBP, while gaining insights into the influence of shared familial factors.

1.4.3. Environmental influences on the response to treatment

A better understanding of the factors that influence how an individual responds to an intervention may explain the modest treatment effects of current interventions for chronic LBP and guide a more tailored approach to therapy. Some research has focussed on identifying factors that predict a favourable response to an intervention in people with

chronic LBP, such as lower baseline pain levels, younger age, and increased adherence[178]. Alternatively, others have focused on identifying sub-groups of patients who demonstrate a more favourable response to a particular intervention over another[179-181]. Numerous studies have attempted to use a patient's history and clinical examination findings[182-184], or the presence of impaired trunk movements[185, 186], to guide the choice of treatment. However, despite on-going enthusiasm for the use of treatment-based sub-grouping, strong evidence supporting outcomes for individuals managed using these approaches is lacking[187, 188]. This is partly due to the fact that conclusions from existing sub-group studies are not appropriate given their poor methodological quality, and it is recommended that future studies be conducted in a step-by-step and rigorous manner[179, 189]. In addition, existing sub-group studies have only focused on how patient characteristics can be used to guide treatment, neglecting the potentially important role of shared familial factors (including genetics).

1.4.4. Shared familial factors and the response to increased physical activity

Understanding how shared familial factors influence the response to treatment for individuals with LBP, particularly chronic LBP, might explain why some individuals fail to respond to a particular intervention and could even influence the direction of treatment. For example, if shared familial factors dictate how individuals with chronic LBP respond to increased physical activity this would have implications for changing modifiable training parameters (e.g. frequency, intensity, duration) or for selecting alternative management strategies in scenarios where an individual fails to respond. Using an individual's response to treatment to modify therapy accordingly could be considered a flexible approach to the management of chronic LBP, and may be more beneficial than basing the management of an individual's LBP on a rigid treatment protocol. Currently, no research has investigated how shared familial factors influence the response to treatment in people with chronic LBP, although

there is research suggesting the responsiveness to regular physical activity is partially influenced by shared familial factors in healthy adults[190]. Identical female twin pairs performing an identical physical activity program demonstrate great variation in the amount of weight lost between twin pairs but only a small amount of variation within twin pairs[191]. Similarly, individual differences in the response of maximal oxygen uptake following an exercise program is more variable between families than within families[192]. These results suggest that factors shared within families, including genes, play a role in the response to a physical activity intervention. However, prior to investigating whether the response to increased physical activity for individuals with chronic LBP is influenced by shared familial factors, we plan to evaluate the available evidence on how shared familial factors influence the response to a physical activity intervention in healthy individuals. The sixth chapter of this thesis presents the findings of a systematic review investigating the role of shared familial factors (including genetics) in the response of body composition and cardiorespiratory fitness following a physical activity intervention.

1.5. Physical activity interventions targeting pain self-efficacy for older people with chronic low back pain

1.5.1 Importance of assessing pain self-efficacy

A potential shortcoming of trials investigating physical activity interventions for chronic LBP is an overemphasis on outcomes related to pain and function[74, 85, 91], while neglecting the important role of pain self-efficacy. Pain self-efficacy is defined as an individual's ability to continue activities of daily living despite pain[193] and has been shown to significantly influence treatment outcomes in people with chronic pain[194]. Pain self-efficacy is closely related to an individual's ability to self-manage their pain, and given the importance of self-management for people with chronic LBP[83], targeting improvements in pain self-efficacy is

an important consideration. Pain self-efficacy is also a strong mediator accounting for how pain leads to disability in people with LBP[195]. Therefore, given that people experiencing high levels of disability are more likely to seek care for their LBP[196], identifying interventions that improve pain self-efficacy has the potential to support self-management in people with chronic LBP and reduce the enormous financial burden of the condition[29, 197].

1.5.2. Physical activity interventions for older people

The health benefits of physical activity for older people are enormous, with regular moderate-intensity physical activity reducing the risk of mortality, coronary heart disease, stroke, type 2 diabetes, and falls[198]. Physical activity also has positive effects on musculoskeletal and psychosocial health, and can help to preserve independence and quality of life as people age[109]. Despite this, older people with chronic LBP have lower levels of overall physical activity and are less likely to engage in regular strengthening exercise compared to pain-free older people[63, 114]. Therefore, in light of the importance of targeting physical activity interventions towards this population, it is inappropriate that older people are commonly excluded from randomised controlled trials evaluating treatment options for chronic LBP[72]. This is despite a rapidly aging population and evidence that the prevalence and disability resulting from chronic LBP are the greatest amongst older people[52, 53, 56, 71].

Physical activity interventions can reduce pain and increase function in older people with chronic LBP, particularly interventions involving strengthening exercises[94, 199]. However, poor adherence to unsupervised exercise programs[85] has increased the need for these programs to be supervised[94, 200], which presents its own issues. Supervised exercise programs are superior to unsupervised home exercises for improving pain and function in people with chronic LBP[94]. However, attending supervised exercise programs can be problematic for

older people with disabling chronic LBP, who prefer a home-based exercise program that does not require transport[201]. In addition, the need for on-going supervision will increase the already enormous health-care costs accounted for by older people suffering chronic LBP[70]. As one might suspect, increased adherence to a physical activity intervention is associated with a more favourable outcome in people with chronic LBP[178], and may explain why supervised exercise programs are superior to unsupervised home exercise programs for improving pain and function[94]. However, there are numerous factors that can improve adherence to an unsupervised home-based exercise program, and these factors need to be considered when designing physical activity interventions targeting self-management in older people with chronic LBP. Adherence to an unsupervised home-based exercise program can be improved in people with chronic LBP if they have a better understanding of their condition, and the potential beneficial effects of home exercise[202-204]. In addition, people with chronic LBP prefer a home-based exercise program that is simple, time-efficient, and provides motivation to engage in exercises through video or audio instructions, real-time feedback, and feedback on overall exercise performance[203, 205]. Incorporating this information into the design and implementation of a physical activity intervention for people with chronic LBP (particularly older people) has the potential to increase the capacity of this population to manage their condition independently, and ultimately increase their pain self-efficacy. Self-management is an on-going health-care priority for the management of chronic diseases and has the potential to reduce health-care utilisation in older people with chronic LBP[206]. Therefore, more research is needed on physical activity interventions that aim to increase adherence to an unsupervised exercise program and improve pain self-efficacy through self-management.

1.5.3. Video-game exercises targeting pain self-efficacy

Video-game exercises have been shown to increase adherence to unsupervised home-based physical activity interventions[200], and are already widely utilised in the management of some neurological and musculoskeletal disorders[207-209]. Increased adherence is likely due to improvements in patients' motivation levels to complete the video-game exercises, which may be due to video and audio instructions, real-time feedback, or feedback on overall exercise performance[203, 205]. In addition, the ability to perform video-game exercises at home reduces the need to travel to clinics and is more time-efficient[203]. With this in mind, tailored video-game exercises could be particularly useful for older people with chronic LBP as they can be implemented at home and allow patients to more effectively self-manage their condition. This has the potential to improve pain self-efficacy and reduce care seeking behaviours in this population. The use of video-game exercises for the management of chronic LBP is promising, with working-age adults demonstrating improvements in pain, disability, fear avoidance, and quality of life following a video-game exercise program[210, 211]. However, no randomised controlled trial has investigated changes in pain self-efficacy and other clinical outcomes (e.g. pain and function) following an unsupervised video-game exercise program in older people with chronic LBP. The seventh chapter of this thesis outlines the protocol for a pilot randomised controlled trial investigating the feasibility of a home-based video-game exercise program aimed at improving pain self-efficacy in older people with chronic LBP. The eighth chapter of this thesis presents the results of this study.

1.6. Aims of thesis

The broad aims of this thesis are to investigate the role of shared familial factors in the development of LBP, and in the recovery and management of chronic LBP; and to investigate

a novel home-based exercise program for older people with chronic LBP. The specific aims of this thesis are to:

i) Investigate the relationship between LBP and educational attainment, physical activity, and the built environment, while using a co-twin design to control for the confounding effects of genetics and shared environmental factors

ii) Investigate the role of shared familial factors in the recovery from chronic LBP

iii) Investigate the role of shared familial factors in the response to increased physical activity in healthy adults

iv) Investigate the feasibility and clinical effects of a home-based video-game exercise program for older people with chronic LBP

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CHAPTER TWO

Are people with chronic low back pain meeting the physical activity guidelines? A co-twin control study

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Clinical Study

Are people with chronic low back pain meeting the physical activity guidelines? A co-twin control study

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Abstract

BACKGROUND: Despite a large amount of research investigating physical activity (PA) levels in people with chronic low back pain (LBP), no study has investigated whether people with chronic LBP are meeting the World Health Organization (WHO) PA guidelines. Furthermore, with genetics and the early shared environment substantially influencing the presence of LBP and PA engagement, these factors could confound the association between LBP and PA and need to be controlled for.
PURPOSE: This study aimed to investigate the association between chronic LBP and meeting the PA guidelines, while controlling for the effects of genetics and early shared environment.
DESIGN: This is a cross-sectional co-twin control study.
PATIENT SAMPLE: A cross-sectional analysis was performed on 1,588 twins from the Murcia Twin Registry in Spain with available data on LBP and PA from the 2013 data collection wave.
OUTCOME MEASURES: The exposure and outcome variables in our study were self-reported. Twins reporting a history of chronic LBP were asked follow-up questions to inform on the presence of recent LBP (within the past 4 weeks), previous LBP (no pain within the past 4 weeks), and persistent LBP (no pain-free month in the last 6 months). These were our exposure variables. Our outcome variable was meeting the WHO PA guidelines, which involved at least 75 minutes of vigorous-intensity PA, or at least 150 minutes of moderate-intensity PA per week.
METHODS: To investigate the association between chronic LBP and meeting the PA guidelines, we first performed a multivariate logistic regression on the total sample of twins. Co-variables entered the model if the univariate association between the co-variable, and both the exposure and the outcome reached a significance of p<.2. Second, to adjust for the influence of genetics and early shared environment, we performed a conditional multivariate logistic regression on complete twin pairs discordant for LBP. The Murcia Twin Registry is supported by Fundación Séneca, Regional Agency for Science and Technology, Murcia, Spain (08633/PHCS/08 and 15302/PHCS/10) and the Ministry of Science and Innovation, Spain (PSI11560-2009). Funding for this project has also been received from Fundación MAPFRE (2012). The authors declare that there are no conflicts of interest.
RESULTS: There was a significant inverse association between recent LBP and meeting the PA guidelines (odds ratio [OR]=0.71, p=.034). When controlling for genetics and early shared environment, this association disappeared. There was no association between previous (OR=0.95, p=.779) or persistent LBP (OR=0.78, p=.192) and meeting the PA guidelines.

FDA device/drug status: Not applicable.

Author disclosures: ***JRZ:*** Nothing to disclose. ***DS:*** Nothing to disclose. ***AA:*** Nothing to disclose. ***FP-R:*** Nothing to disclose. ***JRO:*** Nothing to disclose. ***PHF:*** Nothing to disclose.

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CONCLUSION: Twins with recent LBP are less likely to meet the PA guidelines than those with no history of chronic LBP, highlighting the importance of incorporating PA promotion in the treatment of these individuals. Genetics and early shared environment appear to be confounding the association between LBP and PA, although this needs to be further tested in larger twin samples.

Keywords: Early shared environment; Genetics; Low back pain; Murcia Twin Registry; Physical activity guidelines; Twin study

Introduction

Low back pain (LBP) is a worldwide problem, contributing to the highest number of years lived with disability among all musculoskeletal conditions [1]. LBP has a large financial impact, significantly burdening economies throughout the world [2,3], with the estimated cost being as high as €300 billion for Europe [2]. Physical activity (PA) is one of the most important aspects for maintaining optimal health [4–6] and is also recommended in evidence-based clinical guidelines for the management of chronic LBP [7]. Recent guidelines outline PA recommendations to improve cardiorespiratory fitness and reduce the risk of non-communicable diseases (eg cardiovascular disease) [8]. These guidelines recommend a minimum of 150 minutes of moderate-intensity PA, or 75 minutes of vigorous-intensity PA per week, accumulated in multiple bouts. However, an astonishing one in four adults worldwide are failing to meet these guidelines [8], with individuals experiencing chronic conditions, such as knee and hip osteoarthritis, even less likely to meet the guidelines [9]. Considering the high prevalence and associated disability of chronic LBP [1], it is important to determine what proportions of individuals with chronic LBP are meeting these guidelines. This information will have important implications for incorporating PA promotion into the treatment of these individuals.

Despite numerous studies investigating the relationship between LBP and PA, no study to date has investigated whether individuals with chronic LBP are more or less likely to meet the PA guidelines than the pain-free population [10]. Furthermore, there appears to be a considerable amount of confusion in the literature regarding activity levels in individuals with chronic LBP. Some studies report that individuals with chronic LBP have reduced levels of PA (eg sports participation, recreational exercise) compared with the pain-free population [11–13], whereas others found that both groups have either greater [14,15] or similar levels of PA [16–18]. Taking into account the different presentations of LBP is important and may help to explain some of these inconsistencies (eg chronicity, time since last episode, persistence); however, it may also be helpful to use a well-recognized definition of sufficient levels of activity (PA guidelines) to better understand whether individuals with different presentations of chronic LBP are sufficiently active for the purpose of health promotion.

To get the clearest understanding of the relationship between chronic LBP and meeting the PA guidelines, it is important to consider the effects of genetics and early shared environment. Genetics substantially contributes to the variance of LBP and PA, with heritability estimates being as high as 67% for the presence of chronic and disabling LBP [19], and 85% for the engagement in PA [20]. In addition, the importance of adjusting for genetics and early shared environment has been highlighted in a previous study investigating the relationship between LBP and PA [16].

The aim of this cross-sectional study is to investigate what proportion of individuals with various presentations of chronic LBP are meeting the PA guidelines, and to investigate the association between these variables using a co-twin control design to adjust for the effects of genetics and early shared environment.

Methods

Participants and data collection

Data for this study were derived from a sample of adult twins born between 1940 and 1966 from the Murcia Twin Registry (MTR). The MTR has gathered information from the twins in three waves: 2007, 2009–2011, and 2013. Detailed information regarding the data collection procedures and registry characteristics can be found elsewhere [21]. Participants completed a health-related questionnaire via face-to-face or telephone interview, capturing information on anthropometrics, demographics, health history, and health behaviors (eg PA, smoking).

Of the 2,148 adult twins registered in the MTR, there were 1,613 twins who participated in the 2013 data collection wave, which included a detailed assessment of LBP and PA. Of these twins, 1,588 (98.5%) provided data on LBP and PA and were included in our cross-sectional analyses. Assessors were blinded to the exposures and outcome of this study, and the Committee of Research Ethics of the University of Murcia approved all registry and data collection procedures used in the MTR.

Zygosity ascertainment

When DNA testing was not performed, twin zygosity was ascertained through a 12-item questionnaire focusing on the similarities between twins' eye color, hair color, face color, and face form, as well as mistaken identity between twins. This questionnaire has demonstrated agreement with zygosity determined through DNA testing in nearly 96% of cases [21].

EVIDENCE & METHODS

Context

Physical activity is recommended for persons with chronic low back pain, yet the prevalence of engaging in recommended levels of activity overall and in comparison to pain-free populations is largely unknown.

Contribution

The authors analyzed data from Spain's Murcia Twin Registry to estimate crude and adjusted cross-sectional associations between self-reported chronic low back pain and meeting the World Health Organization's physical activity guidelines (150 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity per week), finding similar guideline adherence for individuals with low back pain histories but without current pain and those with no pain histories, but relatively less adherence for those with chronic low back pain. This latter association attenuated when adjusted for genetics and early shared environment.

Implications

Although the findings suggest that genetics and shared early environment may be confounders of the back pain – physical activity association, the measures are self-reported, estimates imprecise, and the authors were not able to consider pain intensity and many other factors likely related to physical activity and pain.

Assessment of LBP

A comprehensive self-reported assessment of LBP was conducted in 2013 with questions regarding LBP derived from standardized definitions aimed to facilitate uniformity across observational studies [22]. The presence of activity limiting chronic LBP was assessed by the following questions. First, participants were asked: "Have you ever suffered from chronic LBP?" Chronic LBP was described to participants as pain in the lower back lasting for 6 months or longer, including seasonal and recurrent episodes. Participants responding "yes" were asked a follow-up question: "Was this pain bad enough to limit your usual activities or change your daily routine for more than 1 day?" There were 442 twins who responded "yes" and 1,146 twins who responded "no" (total n=1,588). Participants responding "yes" were considered to have experienced activity limiting chronic LBP (hereafter referred to as chronic LBP), and were asked additional follow-up questions, forming the LBP variables for this study.

Recent LBP

"When was the last time you experienced LBP?" Participants selecting the response "within the past 4 weeks" were considered to have recent LBP.

Previous LBP

Participants who did not experience LBP "within the past 4 weeks" were considered to have previous LBP.

Persistent LBP

"How long has it been since you have had a whole month pain free?" Participants selecting the response "7 months to 3 years," or "greater than 3 years" were considered to have persistent LBP.

These variables were dichotomized with the comparison being twins who had never experienced any chronic LBP (n=1,005).

Assessment of meeting the physical activity guidelines

The World Health Organization PA guidelines for adults aged 18–64 (at the time data were collected for this study) recommend a minimum of either 150 minutes of moderate-intensity PA, 75 minutes of vigorous-intensity PA, or a combined 150 minutes of moderate or vigorous-intensity PA per week, accumulated in multiple bouts lasting at least 10 minutes [8]. A detailed assessment of PA for this study was conducted in 2013, with questions adapted from the Active Australia Survey [23]. Engagement in vigorous-intensity PA was determined by participants' response to the following questions: "In the last week, how many times did you do any vigorous PA for at least 10 minutes which made you breathe harder or puff and pant? (eg running, cycling)" and "what do you estimate was the total time that you spent doing this vigorous physical activity in the last week?" Engagement in moderate-intensity PA was determined by participants' response to the following set of questions: (1) "In the last week, how many times have you walked continuously, for at least 10 minutes (to get to or from places, for recreation or exercise)?" and "what do you estimate was the total time that you spent walking in this way in the last week?"; (2) "In the last week, how many times did you do any other more moderate physical activities for at least 10 minutes that you have not already mentioned? (eg gentle swimming, social tennis, golf)" and "what do you estimate was the total time that you spent doing these activities in the last week?" The order in which participants were asked these questions indicates "moderate physical activities" would exclude walking, as this was asked in a prior question. Because it is likely walking is a common form of exercise in the Spanish population of this age, we included walking as a type of moderate-intensity PA despite being unable to assess intensity. Participants who engaged in at least 75 minutes of vigorous-intensity PA, or at least 150 minutes of moderate-intensity PA, or at least 150 minutes of combined moderate and vigorous-intensity PA per week, on at least two separate occasions, were considered to have met the PA guidelines.

Assessment of co-variables

We investigated potential confounding variables based on previous studies in the field and data availability. The

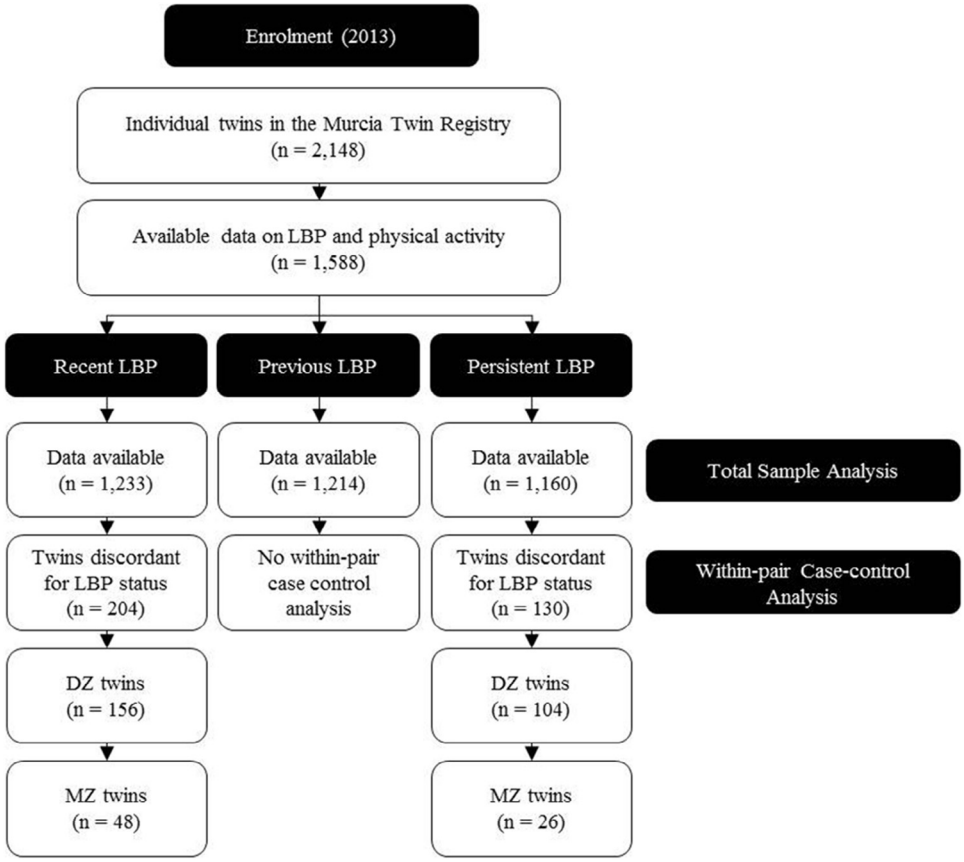

Fig. 1. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) flow diagram. LBP, low back pain; DZ, dizygotic; MZ, monozygotic; n, number of individual twins.

co-variables included age, gender, zygosity, body mass index (BMI), smoking, and symptoms of depression or anxiety. Data on BMI were based on self-reported height and weight. Data on smoking were based on the Spanish National Health Survey Questionnaire [21] and was dichotomized as (1) ex-smoker or never smoked or (2) current smoker. Symptoms of depression or anxiety were based on the depression or anxiety domain of the EuroQol-5 dimension and were assessed by participants selecting one of the following options: (1) I am not anxious or depressed; (2) I am moderately anxious or depressed; and (3) I am extremely anxious or depressed. Responses were dichotomized as not depressed or anxious (1) and moderately or extremely depressed or anxious (2 and 3).

Analysis

We conducted descriptive analyses for all study variables, describing continuous variables with means and standard deviations (SD), and nominal variables with percentages. The exposure variables were recent LBP, previous LBP, and persistent LBP, whereas the outcome variable was meeting the PA guidelines (Fig. 1).

Total sample analysis

We conducted univariate and multivariate logistic regression analyses in the following sequence. First, we performed an unadjusted total sample analysis, including all complete and incomplete twin pairs, to explore the univariate associations between LBP and meeting the PA guidelines. To determine which co-variables should be included in the adjusted total sample analysis (multivariate model), we performed a univariate logistic regression between the co-variables, and both the exposure and the outcomes. If the univariate association between co-variables, and both the exposure and the outcomes reached a significance level of $p<.2$, these variables were adjusted for in the multivariate logistic regression models. This is a widely used method to identify confounding variables for inclusion in the multivariate models [24–26]. Age and gender were forced into the multivariate models to facilitate comparison between the total sample analysis and the within-pair case-control analysis, in which age (all case-control analyses) and gender (analysis of identical twins only) are naturally adjusted for. To account for the non-independence of twins, we used a robust sandwich estimator (*cluster* command in STATA), allowing us to control for observations that are independent across groups, but not necessarily within groups.

Within-pair case-control analysis

If the association from the adjusted total sample analysis reached a significance level of <.2, we performed a within-pair case-control analysis to adjust for the influence of genetics and early shared environment. The within-pair case-control analysis included complete twin pairs discordant for LBP status (ie one twin reported LBP but the co-twin did not). We adjusted for potential confounding variables as described above, with gender forced into analyses including only dizygotic (DZ) twins. The adjustment for confounding variables determined whether the analysis was univariate or multivariate. Because it is assumed twin pairs share similar environments during childhood, all within-pair case-control analyses allow us to adjust for early shared environmental factors. First, we considered DZ and monozygotic (MZ) twin pairs in the same analysis, to adjust for the influence of genetics and early shared environment. Second, to better understand the role of genetics, we stratified analyses by zygosity. DZ and MZ twin pairs share approximately 50% and 100% of their segregating genes, respectively [27]. Therefore, considering only DZ twins allows us to adjust for 50% of genetics, whereas considering only MZ twin pairs allows us to completely adjust for genetic factors. In theory, when the association between two variables (LBP and PA) maintains or increases in magnitude as we adjust for a greater proportion of genetics (particularly in MZ twins where the highest level of adjustment is implemented), this is likely consistent with a more direct association between the two variables. Conversely, if the magnitude of the association decreases, this is more likely consistent with confounding. Analyses were conducted using STATA statistical software (StataCorp. 2013, Stata Statistical Software: Release 13, Version 13.1, StataCorp LP, College Station, TX, USA) with the significance level set at .05. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from the regression models.

Results

There were 1,588 twins with data available on LBP and PA from the 2013 data collection wave. Of these twins, there were 442 twins who reported chronic LBP at some point in their life that limited their daily activities for more than 1 day (27.8%), with 228 twins experiencing recent LBP (pain with the past 4 weeks) and 209 twins reporting previous LBP (no pain within the past 4 weeks). Five twins failed to report when they experienced their most recent episode of LBP. There were 155 twins who reported having persistent LBP (no pain-free month for 7 months or longer). All of them had recent LBP. On the other hand, 73 twins experienced recent but not persistent LBP. The mean age (SD) of twins included in this study was 56.7 (7.1), with 877 females (55.2%) and 554 MZ twins (34.9%). Further details regarding sample characteristics can be found in Table 1. Zygosity was not adjusted for in any analysis as it was not identified as a confounding variable using the methods previously described (see Assessment of co-variables section).

Meeting the PA guidelines

There were 962 twins (60.6%) who met the PA guidelines, which is comparable with the estimate from the Spanish population in 2011–2012 for adults aged between 18 and 69 years (66.4%) [28]. There were 243 twins (55.0%) who reported a history of chronic LBP and met the PA guidelines (Table 2). When we considered the various phenotypes of chronic LBP, there were 111 twins with recent LBP (48.7%), 128 twins with previous LBP (61.2%), and 79 twins with persistent LBP (51.0%) who met the PA guidelines (Table 2).

Table 1
Sample characteristics of twins who met the PA guidelines

	Met the PA guidelines		Did not meet the PA guidelines	
Variables	Mean (SD) or n (%)	Total	Mean (SD) or n (%)	Total
Confounding variables				
Age (y)	56.9 (7.2)	961	56.4 (6.9)	627
BMI	27.0 (4.0)	902	27.6 (4.7)	571
Males	481 (49.9%)	961	231 (36.8%)	627
Females	480 (50.1%)	961	396 (63.2%)	627
Smoking*	305 (31.7%)	961	269 (42.9%)	627
Depression†	203 (21.1%)	961	206 (32.9%)	627
Outcome variables (percentages are based on twins with available data on each variable)				
Recent LBP‡	111 (15.0%)	739	117 (23.7%)	494
Previous LBP§	128 (16.9%)	756	81 (17.7%)	458
Persistent LBP‖	79 (11.2%)	707	76 (16.8%)	453

LBP, low back pain; PA, physical activity; SD, standard deviation; MZ, monozygotic; DZ, dizygotic; n, number of individual twins; BMI, body mass index.

* Current smokers.

† Moderately or very depressed or anxious.

‡ Those who have had symptoms of LBP within the past 4 weeks.

§ Those who have a previous history of chronic activity limiting LBP without symptoms in the past 4 weeks.

‖ Those who have not had a pain-free month in the last 6 months.

Table 2
Number and proportion of twins who met the PA guidelines

	Subjects meeting the PA guidelines (%)
Total sample (n=1,588)	962 (60.6)
Chronic LBP (n=442)	243 (55.0)
Chronic LBP phenotypes	
Recent LBP (n=228)	111 (48.7)
Previous LBP (n=209)	128 (61.2)
Persistent LBP (n=155)	79 (51.0)

LBP, low back pain; PA, physical activity; n, number of individual twins.

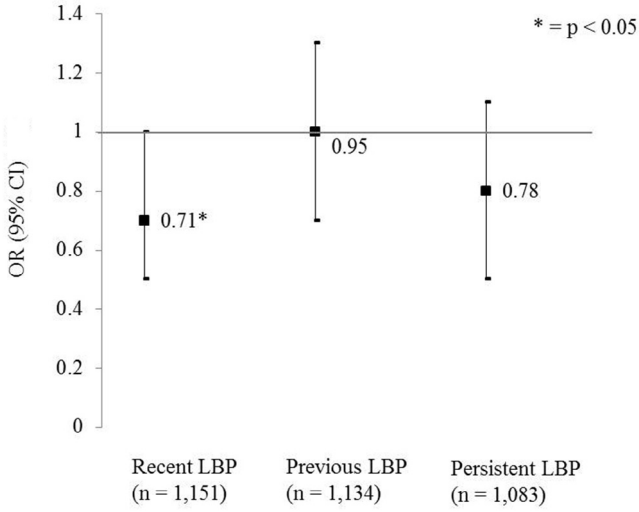

Fig. 2. Meeting the physical activity guidelines (adjusted total sample analysis). OR, odds ratio; CI, confidence interval; LBP, low back pain; n, number of individual twins.

Recent LBP

Individuals reporting a history of chronic LBP, and experiencing LBP within the past 4 weeks (n=228), were significantly less likely to meet the PA guidelines (compared with those with no history of chronic LBP, n=1,005) in the unadjusted total sample analysis (OR=0.57, 95% CI: 0.42–0.76, p<.001), and analysis adjusted for age, gender, BMI, and depression (OR=0.71, 95% CI: 0.52–0.97, p=.034) (Table 3) (Fig. 2). When we adjusted for the influence of genetics and early shared environment in the within-pair case-control analysis of DZ and MZ twins, the association between recent LBP and meeting the PA guidelines was no longer statistically significant (OR=0.71, 95% CI: 0.34–1.51, p=.379) (Table 3). In addition, there was no significant association when the within-pair case-control analysis was performed separately for DZ (OR=0.93, 95% CI: 0.37–2.34, p=.875) and MZ twins (OR=0.43, 95% CI: 0.11–1.66, p=.220) (Fig. 3). The analyses of DZ and MZ twins, and DZ twins only were adjusted for gender.

Previous LBP

Individuals reporting a history of chronic LBP, but without symptoms over the past 4 weeks (n=209), were not less likely to meet the PA guidelines (compared with those with no history of chronic LBP, n=1,005) in the unadjusted total sample analysis (OR=0.94, 95% CI: 0.70–1.28, p=.713), and analysis adjusted for age, gender, BMI, and depression (OR=0.95, 95% CI: 0.69–1.33, p=.779) (Table 3) (Fig. 2). Because the p-value of the association in the adjusted total sample analysis was not <.2, we did not proceed with a within-pair case-control analysis.

Persistent LBP

Individuals reporting a history of chronic LBP, without a pain-free month in the past 6 months (n=155), were significantly less likely to meet the PA guidelines (compared with those with no history of chronic LBP, n=1,005) in the

Table 3
Logistic regression analyses reporting the association between chronic LBP phenotypes and meeting the PA guidelines

Outcome	Analysis	Sample	OR	95% CI	p	n
Recent LBP	Total sample analysis	Unadjusted	0.57	0.42–0.76	**<.001**	1233
		Adjusted*	0.71	0.52–0.97	**.034**	1151
	Within-pair case-control analysis	DZ and MZ twins†	0.71	0.34–1.51	0.379	204
		DZ twins†	0.93	0.37–2.34	0.875	156
		MZ twins	0.43	0.11–1.66	.220	48
Previous LBP	Total sample analysis	Unadjusted	0.94	0.70–1.28	0.713	1214
		Adjusted*	0.95	0.69–1.33	0.779	1134
	No within-pair case-control analysis owing to the association in the adjusted total sample analysis failing to reach a significance of <.2					
Persistent LBP	Total sample analysis	Unadjusted	0.62	0.44–0.88	**.008**	1160
		Adjusted*	0.78	0.53–1.14	0.192	1083
	Within-pair case-control analysis	DZ and MZ twins‡	0.92	0.37–2.26	0.848	130
		DZ twins†	1.44	0.49–4.24	0.505	104
		MZ twins	.25	.03–2.24	.215	26

LBP, low back pain; PA, physical activity; OR, Odds ratio; CI, confidence interval; n, number of individual twins that entered the analysis.

Notes: This value includes the number of twins with each subtype of LBP (incident cases), plus the number of twins who have never experienced chronic LBP (comparison). Statistically significant results (p<0.05) are in bold.

* Adjusted for age, gender, BMI, and depression.

† Adjusted for gender.

‡ Adjusted for gender and smoking.

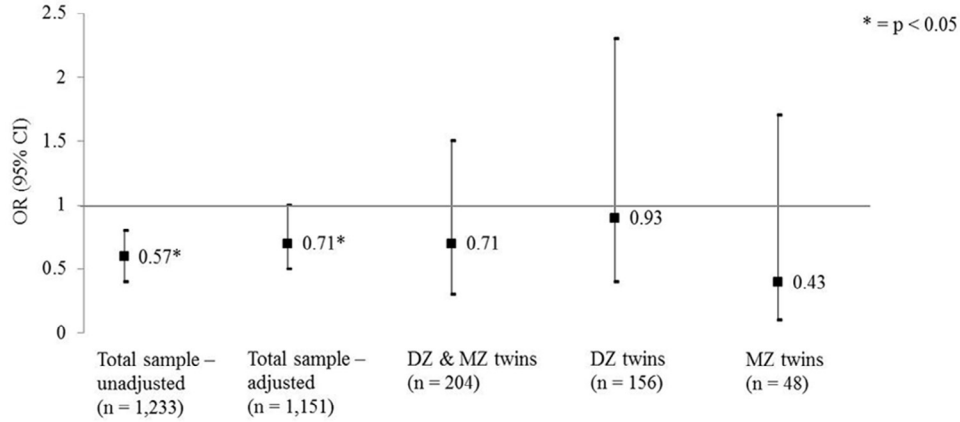

Fig. 3. Total sample and within-pair case-control analysis for recent low back pain and meeting the physical activity guidelines. OR, odds ratio; CI, confidence interval; DZ, dizygotic; MZ, monozygotic; n, number of individual twins.

unadjusted total sample analysis (OR=0.62, 95% CI: 0.44–0.88, p=.008) (Table 3). The magnitude of this association was similar when adjusting for age, gender, BMI, and depression (OR=0.78, 95% CI: 0.53–1.14, p=.192) (Table 3) (Fig. 2), although not statistically significant. When we adjusted for the influence of genetics and early shared environment in the within-pair case-control analysis, there were no statistically significant results (Table 2) (Fig. 4). The analyses of DZ and MZ twins, and DZ twins only were also adjusted for gender and smoking.

Discussion

Our results show that 55% of individuals with chronic LBP met the PA guidelines, although this varies depending on the phenotype of chronic LBP assessed. Individuals with recent LBP were significantly less likely to meet the PA guidelines compared with those with no history of chronic LBP. After adjusting for the influence of genetics and early shared environment, the association between recent LBP and meeting the PA guidelines was no longer statistically significant despite remaining in the same direction. This suggests that the effects of genetics and early shared environmental factors may be confounding the association between LBP and PA.

Proportion of individuals with chronic LBP meeting the PA guidelines

The proportion of individuals who met the PA guidelines in this study (60.6%) was similar to the estimate for adults aged between 18 and 69 years old from the Spanish National Health Survey (66.4%) [28]. Although the sample of twins in our study was older (mean age [SD]: 56.7 [7.1]) compared with the overall Spanish population (median age: 41.8), it is unlikely age would significantly affect our estimate because approximately 68% of the Spanish population between 60 and 69 years old met the PA guidelines [28]. Questions regarding PA in our study were adapted from the Active Australia Survey, whereas data from the Spanish population were captured through the International Physical Activity Questionnaire [29]. These questionnaires capture very similar PA data so are unlikely to impact the comparison between estimates.

Our results showed that 55.0% of individuals with chronic LBP met the PA guidelines, which does not appear to be

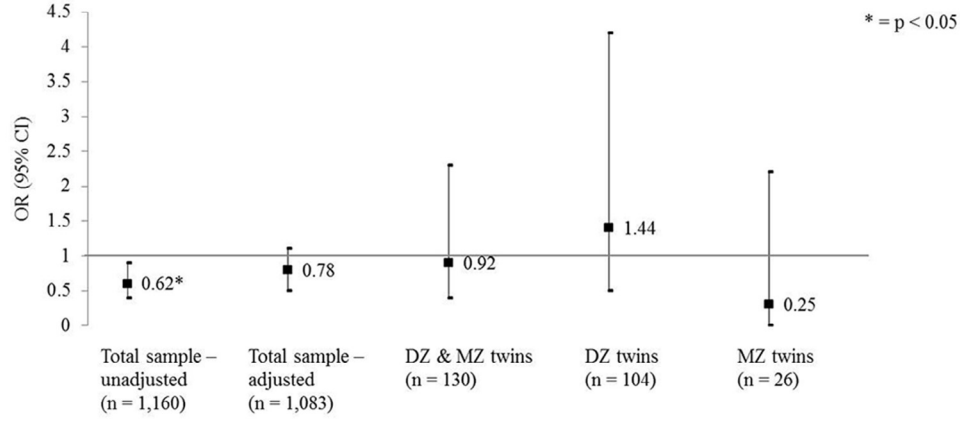

Fig. 4. Total sample and within-pair case-control analysis for persistent low back pain and meeting the physical activity guidelines. OR, odds ratio; CI, confidence interval; DZ, dizygotic; MZ, monozygotic; n, number of individual twins.

significantly lower than the total sample (60.6%). However, a lower proportion of individuals met the PA guidelines if they reported recent LBP (48.7%) (Table 2). Furthermore, individuals with recent LBP were significantly less likely to meet the PA guidelines compared with those with no history of chronic LBP (OR=0.71, p=.034), whereas there was no association between LBP and PA for those with persistent (OR=0.78, p=.192) or previous LBP (OR=0.95, p=.779). This suggests that once an individual recovers from a recent episode of LBP, he or she is just as likely to meet the PA guidelines as the pain-free population, highlighting the importance of considering the presentation of an individual's LBP when deciding how it may impact his or her PA engagement.

Comparison with previous literature

Despite an abundance of research investigating the relationship between LBP and PA, different definitions of LBP and methods of assessing PA may be producing conflicting results between studies. This highlights the need to consider a definition of PA, which has broader implications for health promotion when investigating LBP. Many studies have failed to find an association between LBP and PA [16–18], whereas others show that individuals with LBP are more physically active than pain-free individuals [14,15]. Our study is the first to investigate the relationship between chronic LBP and meeting the PA guidelines, showing that individuals with recent LBP are less likely to meet the PA guidelines compared with those with no history of chronic LBP (OR=0.71, p=.034). This is consistent with research demonstrating that individuals with recent LBP are less likely to engage in regular PA [30], sporting activities [31], strength training [14], vigorous-intensity PA [32], or even more than 1 hour of PA per week [33]. Therefore, using the PA guidelines as a meaningful cutoff point for sufficient levels of PA has important implications for the promotion and maintenance of optimal health, and may help future studies obtain more consistent results.

Genetics and early shared environment

The results of our study highlight the importance of considering the influence, and potentially confounding effects, of genetics and early shared environment. Genetics and early shared environment have been shown to substantially contribute to the variance of LBP [19], and the engagement in PA [20], with twin studies supporting the importance of adjusting for these factors to better understand the relationship between LBP and PA [34]. Twins are considered representative of the non-twin population [35], with the sample of twins in our study being comparable with reference population surveys [21]. The results from our within-pair case-control analyses showed no association between chronic LBP (recent or persistent) and meeting the PA guidelines, even when the adjusted total sample analysis demonstrated a strong association for recent LBP (Fig. 3). This suggests that the relationship between LBP and meeting the PA guidelines may be confounded by genetic or shared environmental factors that influence both the presence of LBP and PA engagement. However, the findings from the within-pair case-control analysis may have simply been the result of a reduction in power (sample size), limiting our ability to find statistically significant results. Therefore, although genetics and early shared environment may be confounding the association between LBP and PA, higher powered twin studies are needed before definite conclusions are reached.

Strengths and limitations

The present study demonstrated considerable strengths in its design. First, using a sample of twins allowed us to adjust for the influence of genetics and early shared environment. Because these factors explain a significant amount of variance for the presence of chronic LBP [19], and the engagement in PA [20], failure to adjust for these factors may be considered a limitation of previous studies investigating the relationship between LBP and PA. Second, a comprehensive assessment of LBP allowed us to explore the association between PA and various phenotypes of chronic LBP, a common limitation of previous observational studies [10]. This limitation is particularly relevant for existing twin studies that have often analyzed simplistic definitions of LBP (eg doctor diagnosed, self-reported lifetime prevalence) because of the broad use of twin registries for research [34].

This study also has some limitations that need to be considered when interpreting the results. First, we included walking as a form of moderate-intensity PA, despite being unable to determine whether it was a brisk walk, which noticeably increased the participant's heart rate [36]. This may have overestimated the number of individuals meeting the PA guidelines. However, it is likely that walking is one of the most common forms of PA in the adult Spanish population, so excluding walking as a form of moderate-intensity PA activity may have resulted in a very small amount of individuals who met the PA guidelines through moderate-intensity PA (eg gentle swimming, social tennis, golf). Furthermore, including walking as a means to meeting the PA guidelines would only reduce the effect size of our results, because individuals with LBP may be more likely to engage in low-intensity PA compared with the pain-free population. Second, we were unable to investigate the relationship between pain-intensity and PA levels, an interesting area where more research is needed [37,38]. In addition, questions regarding LBP and PA status were self-reported and would inevitably result in a degree of recall bias. Third, the presence of different chronic LBP phenotypes was compared with individuals with no history of chronic LBP, defined as the presence of pain in the lower back lasting for 6 months or longer, including seasonal and recurrent episodes. Therefore, it is possible that some individuals with no history of chronic LBP had experienced LBP of shorter duration (<6 months), although this would only serve to underestimate the results we obtained. Finally, we acknowledge there are numerous variables that could influence

PA levels in individuals with LBP, such as the presence of sciatica [39], previous spinal surgery [40], and occupation [41]. However, because of the lack of available data, we were unable to control for these and many other factors. This is a common limitation in large observational studies as the burden of collecting an exhaustive list of variables from participants needs to be considered, and there are also many unknown factors likely to influence PA levels in individuals with LBP. Despite this, our within-pair case-control analysis allowed us to adjust for several variables and, importantly, for the influence of genetic factors, as well as numerous known and unknown factors shared within twin pairs.

Clinical implications

Because of the numerous health benefits associated with meeting the PA guidelines, these results have significant implications for PA promotion in people with chronic LBP. Individuals with recent chronic LBP are less likely to meet the PA guidelines compared with those who have never had chronic LBP, and would benefit from incorporating PA promotion into their treatment. Furthermore, PA levels appear to normalize following a recent episode of chronic LBP. This information may be used to reassure patients with chronic LBP who are concerned they will not return to their previous levels of PA. Our results appear to suggest genetic and early shared environmental factors are driving the association between LBP and PA, as these associations disappeared after adjusting for genetics and early shared environment. However, these results will need to be confirmed in a larger sample of twins before definite conclusions are reached.

Conclusion

Individuals with recent LBP are less likely to meet the PA guidelines when compared with those with no history of chronic LBP. However, a history of chronic LBP in individuals who are currently pain free does not influence meeting the PA guidelines. This highlights the importance of incorporating PA promotion in the treatment of individuals with a recent episode of chronic LBP. Whether genetics and early shared environment could affect the association between recent LBP and meeting the PA guidelines should be further tested in larger samples of twins discordant for LBP.

Acknowledgment

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CHAPTER THREE

Neighborhood walkability moderates the association between low back pain and physical activity: a co-twin control study

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Neighborhood walkability moderates the association between low back pain and physical activity: A co-twin control study

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ABSTRACT

The aim of this study was to investigate whether neighborhood walkability moderates the association between low back pain (LBP) and physical activity (PA), using a co-twin design to control for genetics and shared environmental factors. A cross-sectional analysis was performed on 10,228 twins from the Washington State Twin Registry with available data on LBP from recruitment surveys between 2009 and 2013. LBP within the past 3 months was our exposure variable. Our outcome variables were sufficient moderate or vigorous-intensity PA (MVPA, defined as at least 75 min of vigorous-intensity PA, or 150 min of moderate-intensity PA per week), and walking (≥150 min per week). Neighborhood walkability, estimated using the commercially available Walk Score®, was our moderator variable. After controlling for the influence of genetics and shared environment, individuals reporting LBP were significantly less likely to engage in sufficient MVPA if they lived in a neighborhood with high walkability (OR = 0.59, 95%CI: 0.36–0.96). There was no association between LBP and sufficient MVPA for individuals living in a neighborhood with low walkability (OR = 1.27, 95%CI: 0.93–1.72), demonstrating that walkability is a significant moderator of the association between LBP and PA (interaction $p = 0.013$). These findings were similar for the association between LBP and walking (high walkability OR = 0.42, 95%CI: 0.22–0.78; low walkability OR = 0.71, 95%CI: 0.46–1.12), although the interaction was not significant ($p = 0.700$). Neighborhood walkability moderates the association between LBP and PA. Our results highlight the importance of targeting interventions promoting PA towards individuals with LBP living in a neighborhood with good walkable access to amenities.

1. Introduction

Low back pain (LBP) is a global problem, resulting in disability (Murray et al., 2012) and an enormous financial burden across many countries (Gore et al., 2012; Wenig et al., 2009). Physical activity (PA) is commonly recommended for the management (van Middelkoop et al., 2010) and prevention of LBP (Steffens et al., 2016), with the important additional health benefits of increasing cardiorespiratory fitness and reducing the risk of non-communicable diseases (e.g. cardiovascular disease) (Global Recommendations on Physical Activity for Health, n.d.). Among commonly prescribed interventions for LBP, structured exercise programs appear to increase PA engagement in the short-term (Nassif et al., 2011; Hagen et al., 2010), but have failed to demonstrate long-term PA adoption (Kuukkanen et al., 2007; Sorensen et al., 2010; Bendix et al., 1998).

Despite numerous interventions employing a biopsychosocial approach, evidence appears to demonstrate limited benefits of these individual approaches on long-term adoption and maintenance of PA (Leonhardt et al., 2008). A shortcoming of these approaches may include a lack of consideration for the influence of external environmental factors (e.g. the physical or "built" environment). Furthermore, interventions for LBP on an individual level are costly, and may contribute to the substantial economic burden of LBP (Gore et al., 2012; Wenig et al., 2009). Therefore, a broader understanding of how environmental factors influence PA in people with LBP is warranted, and may aid the management of LBP at a population level.

Changes to the built environment to improve walkability is an approach that holds promise for increasing PA engagement at the population level, with individuals living in a neighborhood with high walkability more likely to engage in PA than individuals living in a neighborhood with low walkability (Global Advocacy for Physical Activity (GAPA) the Advocacy Council of the International Society for Physical Activity and Health (ISPAH), 2012; Van Holle et al., 2012). Walkability is used to quantify the extent the built environment

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surrounding the residence (neighborhood) promotes physical activity, most notably walking, for numerous purposes. Measures of neighborhood walkability incorporate information on environmental characteristics, for example the walkable distance to nearby amenities such as parks, shops, restaurants, fitness centres, etc. However, it is unclear how walkability impacts PA levels in people with LBP. Individuals experiencing LBP may be less likely to practice regular PA if they live in a neighborhood with low walkability. Conversely, they may be less likely to engage in PA despite living in an environment which promotes it. Therefore, to get a clearer understanding of the barriers to PA engagement in people with LBP, it is important to consider how walkability influences PA levels in this population.

Genetic and shared (familial) environmental factors have also been shown to substantially contribute to the variance of chronic and disabling LBP (Ferreira et al., 2012), PA engagement (de Vilhena Santos et al., 2012), and play a role in influencing residential selection (Duncan et al., 2012). It is possible that an individual's genetics (or family environment) could be a confounder between LBP and PA, and recent research investigating risk factors for LBP has utilized twins as a method of controlling for the effects of genetics and shared environment (Dario et al., 2015).

The aim of this study is to investigate whether walkability moderates the association between LBP and PA, using a cross-sectional co-twin design to control for the effects of genetics and shared environment.

2. Methods

2.1. Participants and data collection

The sample for this cross-sectional study was drawn from the Washington State Twin Registry (WSTR), a community-based registry of adult twins. Information regarding characteristics and data collection procedures can be found elsewhere (Afari et al., 2006). Participants completed a recruitment survey containing items on demographics (age, sex, race, education, marital status), health conditions (self-reported and physician diagnosed), and health-behaviours (PA, sleep quality, smoking, alcohol intake). There were 10,228 twins with data on LBP from the recruitment surveys between 2009 and 2013, forming the basis for this study. All recruitment and data collection procedures were approved by the local Institutional Review Board.

2.2. Zygosity ascertainment

Questions regarding childhood similarities between twins, for example, “As children were you and your twin as alike as 2 peas in a pod or of ordinary family resemblance?” were used to determine zygosity, with an agreement of 95–98% when compared to zygosity determined by biological markers (Eisen et al., 1989).

2.3. Exposure variable

Data on the presence of LBP within the last 3 months was collected in the recruitment survey and based on the following question: “In the past 3 months, have you had back pain that lasted for at least one day?”.

2.4. Moderator variable

Walkability served as our moderator variable and was assessed via Walk Score®, a publically available web-resource (www.walkscore.com) with good validity and reliability for estimating walkable access to nearby amenities (Carr et al., 2011). Walk Score® has been shown to significantly correlate with numerous objective (e.g. residential density, street connectivity) and subjective measures (e.g. perceived access to amenities) of the built environment (Carr et al., 2010). The Walk Score® algorithm calculates the walkable distance to 13 equally-weighted categories of amenities including: grocery stores, coffee shops, restaurants, bars, movie theatres, schools, parks, libraries, book stores, fitness centres, pharmacies, hardware stores, and clothing or music stores. Participant's residential addresses were entered into the Walk Score® website; values from each category were summed and normalized to yield a total Walk Score® from 0 to 100, where a higher score (higher walkability) represents shorter walkable distances to nearby amenities. We categorized Walk Score® into tertiles, and dichotomised it at the highest tertile.

2.5. Outcome variables

Data on moderate or vigorous-intensity PA (MVPA) and total walking time per week were collected in the recruitment survey and served as our outcome variables.

2.5.1. Assessment of PA

Data on MVPA was used to determine whether individuals met the World Health Organization PA guidelines for adults aged 18–64 (considered sufficiently active) (Global Recommendations on Physical Activity for Health, n.d.). The PA guidelines recommend a minimum of 75 min vigorous-intensity PA, 150 min moderate-intensity PA, or 150 min combined MVPA per week, accumulated in multiple bouts (Global Recommendations on Physical Activity for Health, n.d.). Questions regarding MVPA were adapted from a validated brief assessment tool (Smith et al., 2005). Moderate-intensity PA was assessed by the following question: “Over the past 4 weeks, how many days during a typical week did you exercise moderately for at least 30 minutes?”. Moderate-intensity PA was described as exercise causing only light sweating, or slight to moderate increases in breathing or heart rate, including brisk walking, bicycling for pleasure, golf, and dancing. Vigorous-intensity PA was assessed by a similar question: “Over the past 4 weeks, how many days during a typical week did you exercise vigorously for at least 20 minutes?”. Vigorous-intensity PA was described as exercise causing heavy sweating, or large increases in breathing or heart rate, including running, lap swimming, aerobics classes, and fast bicycling. Participants engaged in at least five days of moderate-intensity PA, or at least 4 days of vigorous-intensity PA, or engaged in a combination of moderate and vigorous-intensity PA of at least 150 min per week (e.g. three days of moderate-intensity PA and three days of vigorous-intensity PA would give a total of at least 150 min), were considered sufficiently active (dichotomised variable).

In a sub-sample of 104 twins who wore accelerometers and GPS devices over a two-week period in an ongoing funded study, subjective MVPA correlated significantly with objectively measured MVPA ($r = 0.46$, $p < 0.01$) (Duncan, G. Unpublished observations, 2016).

2.5.2. Assessment of walking

Total walking time per week was assessed by the following questions: i) “How many days during a typical week do you walk for recreation, exercise, to get from place to place, or for any other reasons in your neighborhood?”; and ii) “When you walk in your neighborhood, about how many minutes, on average, do you spend walking each time you walk?” For question ii) participants could select the following options: “<15”, “15”, “30”, “45”, “60”, “75”, “90 or more”. To calculate total walking time we considered “<15” as 7.5 min, “90 or more” as 90 min, and the rest of the values as outlined. Responses to questions i) and ii) were multiplied and then dichotomised as ≥150 min and <150 min of walking per week. This cut-off was based on meeting the PA guidelines since walking is commonly considered a form of moderate-intensity PA (Haskell et al., 2007).

2.6. Assessment of confounding variables

Data on age, sex, body mass index (BMI), smoking, educational attainment, sleep quality, depression, and leisure sitting time were

considered as possible confounding variables. BMI was calculated based on self-reported height and weight. Details on how the other confounding variables were assessed can be found in Appendix A.

2.7. Analysis

Descriptive analyses were conducted for all study variables. We performed multivariate logistic regression analyses to investigate the association between LBP and PA, and to quantify the extent walkability moderates this association (interaction analysis). Univariate logistic regression analyses were performed to identify confounders for inclusion into the multivariate models. The selection of confounding variables was based on data availability and previous studies examining risk factors for LBP (Shiri et al., 2010; Dario et al., 2016; Zadro et al., 2016; Pinheiro et al., 2015a; Kelly et al., 2011; Chen et al., 2009). If the *p*-value of the association between the confounder, and both the exposure and outcome were <0.2 in the univariate logistic regression, these variables were included in the multivariate models (Dario et al., 2016; Zadro et al., 2016; Pinheiro et al., 2015b). Age and sex were forced into the multivariate logistic regression models to facilitate comparison to the within-pair analysis, where identical [monozygotic (MZ)] twins are analysed in pairs, naturally resulting in the adjustment for age and sex. Each analysis was stratified by walkability with an interaction term ('PA' × 'walkability') used to quantify the significance of the moderation effect. Analyses were conducted using STATA statistical software (version 13.1) with odds ratios (OR) and 95% confidence intervals (CI) calculated from the regression models, and significance level set at 0.05.

2.7.1. Total sample analysis

We performed a total sample analysis on all complete and incomplete twin pairs, regardless of LBP status, to investigate whether walkability moderates the association between LBP and PA. Because twins are treated as individuals in this analysis, we used a robust sandwich estimator to account for the non-independence of twins. The variables that entered the adjusted total sample analysis were included in the within-pair analysis of MZ twins to facilitate the comparison of effect sizes.

2.7.1. Within-pair analysis

To control for the influence of genetics and shared environment we performed a within-pair analysis on all complete MZ twin pairs discordant for LBP status, i.e. one twin reported LBP (case) while the co-twin did not (control). Controlling for these factors is important because an individual's genetics (and family environment) may result in certain characteristics (e.g. the presence of LBP and low PA levels) that can influence any associations found between exposure and outcome among all twin pairs (i.e. total sample analysis whereby twins are treated as individuals). Twin pairs are usually exposed to a similar environment when growing up, especially for twins reared together as was the case in our study, and MZ twins share close to 100% of their segregating genes while DZ twins share no >50%. Therefore, the analysis of MZ twins allows us to control for genetics and shared environmental factors. In theory, when a significant relationship between two variables (LBP and PA) in the total sample analysis disappears in the within-pair analysis of MZ twins, it suggests genetics and shared environmental factors are confounding the previously observed relationship.

3. Results

3.1. Descriptive statistics

Of the 10,228 twins included in this study, there were 3975 males (38.9%), 5331 MZ twins (52.1%), and 9824 twins with data available on Walk Score® (96.1%). The mean age [standard deviation (SD)] of participants was 42.1 (18.4). Twins in the highest education category (*3: bachelor, graduate, or professional degree)* were less likely to report LBP (MZ twins: 37.2% vs. 43.2%; DZ twins: 35.1% vs. 42.8%), while twins in the lowest education category (*1: up to high school completion*) were more likely to report LBP (MZ twins: 24.8% vs. 22.5%; DZ twins: 27.8% vs. 23.0%). Further details regarding the characteristics of the total sample according to LBP status and zygosity are shown in Table 1. Levels of the various physical activity types by tertile of walkability and LBP status are shown in Table 2; differences in PA engagement between those with and without LBP were more pronounced in higher tertiles of Walk Score®.

3.1.1. Association between LBP and MVPA

Associations between LBP and MVPA (regardless of Walk Score®) are shown in Table 3 (row 'A'). Twins with LBP were significantly less likely to be sufficiently active in the unadjusted total sample analysis (OR = 0.82, 95%CI: 0.76–0.89, see row 1), although this failed to reach statistical significance in the total sample analysis adjusted for age, sex, BMI, smoking, education, depression, sleep quality, and leisure sitting time (OR = 0.93, 95%CI: 0.85–1.01, see row 2). The magnitude of the association further decreased and was not statistically significant when controlling for genetics and shared environment in the within-pair analysis of MZ twins (OR = 1.01, 95%CI: 0.81–1.25, see row 3).

3.1.2. Association between LBP and MVPA (moderated by Walk Score®)

Associations between LBP and MVPA for participants with their residential address in the highest tertile of Walk Score® are shown in Table 3 (row 'B'). In the unadjusted total sample analysis, twins with LBP were significantly less likely to be sufficiently active if their residential address was in the highest tertile of Walk Score® (OR = 0.78, 95%CI: 0.68–0.90, see row 1), although this was no longer statistically significant in the total sample analysis adjusted for age, sex, BMI, smoking, education, depression, sleep quality, and leisure sitting time (OR = 0.91, 95%CI: 0.78–1.05, see row 2). When controlling for genetics and shared environment in the within-pair analysis of MZ twins, the strength of this association increased and was statistically significant (OR = 0.55, 95%CI: 0.33–0.92, see row 3) (Table 3).

Associations between LBP and MVPA for participants with their residential address in the lower two tertiles of Walk Score® are shown in Table 3 (row 'C'). In the unadjusted total sample analysis, twins with LBP were significantly less likely to be sufficiently active if their residential address was in the lowest tertiles of Walk Score® (OR = 0.84, 95%CI: 0.76–0.93, see row 1), although this was no longer statistically significant in the total sample analysis adjusted for age, sex, BMI, smoking, education, depression, sleep quality, and leisure sitting time (OR = 0.94, 95%CI: 0.84–1.04, see row 2). There was no association between LBP and being sufficiently active in the within-pair analysis (OR = 1.23, 95%CI: 0.90–1.70, see row 3) (Table 3).

Walk Score® was a significant moderator of the association between LBP and being sufficiently active in the within-pair analysis of MZ twins ($p = 0.023$, final row in Table 3).

3.1.3. Association between LBP and walking

Associations between LBP and walking (regardless of Walk Score®) are shown in Table 4 (row 'A'). Twins with LBP were significantly less likely to walk 150 min or more per week in the unadjusted (OR = 0.84, 95%CI: 0.76–0.93, see row 1), and adjusted (age, sex, BMI, smoking, education, depression, and leisure sitting time) total sample analysis (OR = 0.89, 95%CI: 0.80–0.99, see row 2). The magnitude of this association was similar in the within-pair analysis (OR = 0.86, 95%CI: 0.66–1.14, see row 3) (Table 4).

3.1.4. Association between LBP and walking (moderated by Walk Score®)

Associations between LBP and walking for participants with their residential address in the highest tertile of Walk Score® are shown in Table 4 (row 'B'). In both the unadjusted and adjusted (age, sex, BMI, smoking, education, depression, and leisure sitting time) total sample analysis, twins with LBP were significantly less likely to walk 150 min

Table 1
Sample characteristics of twin participants stratified according to zygosity and low back pain status.

	MZ twins				DZ twins			
	LBP		No LBP		LBP		No LBP	
	Mean (SD) or n (%)	Total	Mean (SD) or n (%)	Total	Mean (SD) or n (%)	Total	Mean (SD) or n (%)	Total
Outcome variables								
Walking[a]	24.6 (17.0)	2194	24.8 (17.3)	2830	24.6 (17.3)	2060	25.8 (17.3)	2598
Vigorous PA[b]	42.7 (41.5)	2316	47.0 (41.6)	2971	41.1 (42.0)	2148	46.3 (43.4)	2705
Moderate PA[c]	82.0 (63.8)	2302	85.0 (63.4)	2955	81.0 (64.5)	2114	89.4 (66.1)	2690
MVPA[d]	123.3 (93.1)	2333	130.3 (91.7)	2998	120.1 (93.7)	2161	133.7 (95.7)	2736
Sufficiently active[e]	1047 (45.0%)	2328	1464 (49.0%)	2988	951 (44.1%)	2155	1371 (50.2%)	2730
Walking[f]	408 (18.7%)	2183	558 (19.8%)	2819	380 (18.6%)	2049	601 (23.2%)	2589
Moderator variable								
Walk score®	36.0 (27.2)	2245	36.4 (27.7)	2888	34.7 (27.3)	2063	36.8 (27.8)	2628
Confounding variables								
Age (years)	42.1 (17.2)	2333	40.4 (18.4)	2998	43.4 (18.3)	2161	43.0 (19.3)	2736
BMI	26.5 (5.9)	2308	25.3 (5.2)	2960	26.7 (5.8)	2141	25.6 (5.3)	2703
Males	788 (33.8%)	2333	1117 (37.3%)	2998	908 (42.0%)	2161	1162 (42.5%)	2736
Females	1545 (66.2%)	2333	1881 (62.7%)	2998	1253 (58.0%)	2161	1574 (57.5%)	2736
Current smoker	309 (13.4%)	2312	239 (8.1%)	2963	326 (15.3%)	2127	250 (9.3%)	2704
Education								
1: up to high school completion; 2: college or associates degree; 3: bachelor, graduate, or professional degree								
1	577 (24.8%)	2328	671 (22.5%)	2984	595 (27.8%)	2141	627 (23.0%)	2727
2	884 (38.0%)	2328	934 (31.3%)	2984	795 (37.1%)	2141	932 (34.2%)	2727
3	867 (37.2%)	2328	1379 (43.2%)	2984	751 (35.1%)	2141	1168 (42.8%)	2727
Sleep[g]	707 (30.4%)	2327	532 (17.8%)	2990	652 (30.2%)	2157	510 (18.7%)	2732
Depression[h]	830 (36.0%)	2303	716 (24.1%)	2977	781 (36.6%)	2135	675 (24.9%)	2714
Sedentary[i]	1224 (52.7%)	2321	1501 (50.2%)	2989	1192 (55.4%)	2150	1415 (52.0%)	2723

LBP: low back pain, MZ: monozygotic, DZ: dizygotic, SD: standard deviation, BMI: body mass index, PA: physical activity, MVPA: moderate or vigorous-intensity physical activity; n: number of individual twins.
[a] Minutes of walking each day.
[b] Minutes of vigorous-intensity physical activity per week.
[c] Minutes of moderate-intensity physical activity per week.
[d] Total moderate and vigorous-intensity physical activity per week.
[e] At least 75 min of vigorous PA or at least 150 min of moderate PA per week, including a combination of either which totals >150 min.
[f] Walking for >150 min per week.
[g] Difficulty falling or staying asleep.
[h] Bothered by symptoms of depression in the past 4 weeks.
[i] Sitting for 3 or more hours during leisure time each day.

or more per week if their residential address was in the highest tertile of Walk Score® (unadjusted OR = 0.79, 95%CI: 0.66–0.94; adjusted OR = 0.83, 95%CI: 0.70–1.00). When controlling for genetics and shared environment in the within-pair analysis the strength of this association increased (OR = 0.48, 95%CI: 0.25–0.92).

Associations between LBP and walking for participants with their residential address in the lower two tertiles of Walk Score® are shown in Table 4 (row 'C'). There was no association between LBP and walking in the total sample (see row 1 and 2), or within-pair analysis (see row 3) for twins with a residential address in the lowest tertiles of Walk Score® (Table 4).

Walk Score® did not significantly moderate the association between LBP and walking in the total sample (unadjusted: $p = 0.163$; adjusted: $p = 0.135$) or within-pair analysis ($p = 0.800$) (see final 3 rows of Table 4).

4. Discussion

Our results showed that individuals with LBP were significantly less likely to be sufficiently active, compared to those without LBP, if you considered those with a residential address in a neighborhood with a high Walk Score® (shorter walkable distance to nearby amenities). Thus, the findings of this study highlight the importance of considering neighborhood walkability (as a measure of the built environment) when investigating the relationship between LBP and PA. To our knowledge, this is the first study to investigate how the built environment

Table 2
Physical activity levels by tertile of Walk Score®.

	Tertile 1*			Tertile 2*			Tertile 3*		
	LBP	No LBP	Total	LBP	No LBP	Total	LBP	No LBP	Total
Walking[a]	25.0 (18.1)	25.1 (17.6)	25.0 (17.9)	25.0 (17.1)	25.0 (17.0)	25.0 (17.0)	24.4 (16.4)	25.7 (17.1)	25.1 (16.8)
Vigorous PA[b]	41.4 (42.8)	45.9 (42.9)	43.8 (42.9)	42.7 (41.2)	46.6 (42.2)	44.9 (41.8)	41.8 (40.8)	48.0 (42.2)	45.3 (41.7)
Moderate PA[c]	83.6 (65.5)	85.9 (65.5)	84.9 (65.5)	80.4 (63.0)	86.1 (63.8)	83.6 (63.5)	81.3 (63.5)	89.0 (64.6)	85.7 (64.2)
MVPA[d]	123.2 (95.0)	130.2 (94.2)	127.1 (94.6)	121.6 (92.1)	130.4 (92.2)	126.6 (92.2)	121.3 (92.2)	135.5 (94.4)	129.3 (93.7)

Data reported as means (standard deviations).
LBP: low back pain, PA: physical activity, MVPA: moderate or vigorous physical activity. *: each tertiles is ordered and contains a third of the total sample (1 = lowest 1/3 of Walk Score® values, 3 = highest 1/3 of Walk Score® values).
[a] Minutes of walking each day.
[b] Minutes of vigorous-intensity physical activity per week.
[c] Minutes of moderate-intensity physical activity per week.
[d] Total moderate and vigorous-intensity physical activity per week.

Table 3
Total sample and within-pair analysis for the association between LBP and sufficient moderate to vigorous physical activity, moderated by Walk Score®.

Sample			OR	95% CI	n
A. Total sample (regardless of Walk Score®)	Total sample analysis	Unadjusted	0.82	0.76–0.89	10,201
		Adjusted[a]	0.93	0.85–1.01	9796
	Within-pair analysis	MZ twins[a]	1.01	0.81–1.25	1780
B. Highest tertile (Walk Score®)	Total sample analysis	Unadjusted	0.78	0.68–0.90	3294
		Adjusted[a]	0.91	0.78–1.05	3170
	Within-pair analysis	MZ twins[a]	0.55	0.33–0.92	346
C. Lower two tertiles (Walk Score®)	Total sample analysis	Unadjusted	0.84	0.76–0.93	6505
		Adjusted[a]	0.94	0.84–1.04	6238
	Within-pair analysis	MZ twins[a]	1.23	0.90–1.70	840
Interaction	Total sample analysis	Unadjusted			$p = 0.390$
		Adjusted[a]			$p = 0.581$
	Within-pair analysis	MZ twins[a]			$p = 0.023$

LBP: low back pain; PA: physical activity; MVPA: moderate-vigorous physical activity, defined as at least 75 min of vigorous PA or at least 150 min of moderate PA per week, including a combination of either which totals >150 min; OR: odds ratio (reference: no low back pain within the past 3 months); CI: confidence interval; n: number of individual twins.
[a] Adjusted for age, gender, body mass index, smoking, education, depression, sleep quality, and leisure sitting time.

moderates the association between LBP and PA, and may serve as an important step towards future studies identifying external factors which could impact the effectiveness of interventions targeting long-term PA adoption. Our results highlight the importance of targeting interventions promoting PA towards individuals with LBP living in a neighborhood with good walkable access to amenities, since these individuals are less likely to practice regular PA despite living in an environment that promotes it. In addition, efforts to promote PA may be more effective in this population compared to individuals with LBP living in an environment that doesn't promote PA (low Walk Score®). This is because the presence of LBP didn't appear to influence PA levels for individuals living in a neighborhood with poor walkable access to amenities, and may highlight that the built environment is a larger barrier to PA engagement than having LBP. However, another interpretation of our results could be that individuals with LBP benefit less from living in a neighborhood with high walkability, highlighting the importance of considering other (individual and environmental-level) factors to support PA engagement, for example, education or social connectedness.

Socioeconomic factors may influence both an individual's residential address and the likelihood of experiencing LBP, and thus need to be considered when investigating how neighborhood walkability influences the relationship between LBP and PA. To explore this, we performed a logistic regression analysis and found a significant association between Walk Score® and higher educational attainment (a proxy for socioeconomic status) (Appendix B), suggesting that individuals with higher educational attainment are more likely to live in a neighborhood with good walkable access to amenities (high Walk Score®). In addition, Table 1 demonstrated that twins in the highest education category were less likely to report LBP, while twins in the lowest education category were more likely to report LBP. This may be explained by the exposure to heavy work-related PA in people with lower educational attainment, a hypothesis that has been highlighted in other studies investigating the relationship between educational attainment and LBP (Zadro et al., 2016). Therefore, given that educational attainment influences LBP, PA, and neighborhood walkability, it was an important factor to control for in our study.

4.1. Comparison to previous literature

Conflicting findings across studies of LBP and PA are preventing definite conclusions about this relationship from being reached. An early cross-sectional study (Wright et al., 1995) investigated LBP and PA levels in over 30,000 people in the UK and showed that individuals experiencing LBP within the past 12 months were more likely to be engaged in vigorous-intensity PA. In contrast, numerous studies have demonstrated that individuals with LBP are less likely to engage in sport (Cakmak et al., 2004), structured exercise (Eriksen et al., 1999; Kwon et al., 2006), or recreational PA (including walking) (Bjorck-van Dijken et al., 2008; Nilsen et al., 2011), while others have failed to find an association between LBP and PA (Cecchi et al., 2006; Croft et al., 1999; Schneider et al., 2005; Mortimer et al., 2001). Although variation in the methods used to assess LBP and PA may explain some of these

Table 4
Total sample and within-pair analysis for the association between LBP and walking (>150 min per week), moderated by Walk Score®.

Sample			OR	95% CI	n
A. Total sample (regardless of Walk Score®)	Total sample analysis	Unadjusted	0.84	0.76–0.93	9640
		Adjusted[a]	0.89	0.80–0.99	9290
	Within-pair analysis	MZ twins[a]	0.86	0.66–1.14	1606
B. Highest tertile (Walk Score®)	Total sample analysis	Unadjusted	0.79	0.66–0.94	3155
		Adjusted[a]	0.83	0.70–1.00	3048
	Within-pair analysis	MZ twins[a]	0.48	0.25–0.92	322
C. Lower two tertiles (Walk Score®)	Total sample analysis	Unadjusted	0.92	0.81–1.04	6103
		Adjusted[a]	0.97	0.84–1.10	5874
	Within-pair analysis	MZ twins[a]	0.72	0.45–1.14	744
Interaction	Total sample analysis	Unadjusted			$p = 0.163$
		Adjusted[a]			$p = 0.135$
	Within-pair analysis	MZ twins[a]			$p = 0.800$

LBP: low back pain; OR: odds ratio (reference: no low back pain within the past 3 months); CI: confidence interval; n: number of individual twins.
[a] Adjusted for age, gender, body mass index, smoking, education, depression, and leisure sitting time.

differences, there are additional factors that have not been investigated that may be influencing the relationship between LBP and PA, such as the built environment.

The results of our study showed that the inverse association between LBP and walking increased in magnitude when considering individuals living in an environment with a high Walk Score®, even after adjusting for genetics and shared environment. High levels of adjustment demonstrated in the within-pair analysis of MZ twins increase our suspicion of a direct association between LBP and walking for individuals living in an environment with a high Walk Score®, since confounding factors, including genetics, have been accounted for. In addition, the results of within-pair analysis of DZ twins were similar to the results from the total sample analysis (data not presented), further supporting that shared environmental factors are not confounding the main findings of our study. These findings were similar for the association between LBP and MVPA, and highlight that variation in the built environment is potentially impacting the findings of previous LBP-PA studies. For example, a study in which the majority of participants lived in a neighborhood with a low Walk Score® might fail to show a difference in PA levels between individuals with and without LBP, because PA levels may have been limited by the built environment. Furthermore, previous studies investigating interventions aimed at increasing long-term PA adoption in people with LBP have unknowingly neglected the influence of the built environment, a factor which could explain why these interventions have failed to demonstrate large effects, despite having good behavioral theoretical underpinning (Leonhardt et al., 2008; Meng et al., 2011). Future intervention studies may want to consider the influence of the built environment before conclusions regarding effectiveness are made.

4.2. Strengths and limitations

This study has numerous strengths including analysing data from a large sample of twins that not only allowed us to control for the influence of genetics and shared environment, but increased our confidence (power) in these findings, since small sample sizes are a common limitation of twin studies in the field (Dario et al., 2015). The importance of controlling for the potential confounding effects of genetics and shared environment is highlighted by the substantial influence these factors have on the variance of LBP (Ferreira et al., 2012), PA engagement (de Vilhena Santos et al., 2012), and residential selection (Duncan et al., 2012). Furthermore, previous studies investigating walkability measures have failed to adjust for genetics and shared environment, factors which could facilitate the self-selection bias of individuals who live in a neighborhood with high walkability (McCormack and Shiell, 2011).

This study also has a number of limitations. First, our assessment of LBP was self-reported and did not consider pain intensity or disability. Moreover, the term 'back pain' may encompass thoracic spine symptoms, potentially overestimating the prevalence of LBP in this sample. However, this is unlikely to significantly impact our results since the prevalence of isolated thoracic spine pain is low (Briggs et al., 2009) and individuals generally understand that 'back pain' refers to LBP (de Vet et al., 2002). Furthermore, because data on walkability was based on the residential address of participant's at survey completion it is important to acknowledge the possibility (although small) that a participant's experience of LBP within the past 3 months was captured at a previous residential address with different walkability. Second, self-reported data on PA will inevitably result in a degree of recall bias, with PA engagement potentially being overestimated. However, this is a common and somewhat unavoidable limitation in large observational studies, and would be somewhat nullified in the within-pair analysis. In addition, our walking variable captured walking for numerous purposes (recreation, exercise, transport, etc.) and did not allow us to differentiate walking of varying intensities. Third, by using cross-sectional data, we were not able to investigate the direction of the relationship between LBP and PA (the reverse causation problem). Finally, the measure of walkability used in this study (Walk Score®) only considers the walkable distance to nearby amenities from an individual's residential address, and does not take into account other commonly used community measures of how the built environment promotes PA (e.g. land-use mix, residential density, intersection density). However, Walk Score® has been shown to significantly correlate with these objective measures of the built environment (Carr et al., 2010) and is a validity and reliable tool for estimating walkable distance to nearby amenities (Carr et al., 2011).

5. Conclusion

Walkable distance to nearby amenities (Walk Score®) is a significant moderator of the association between LBP and being sufficiently active (even after adjusting for the influence of genetics and shared environment). Our results highlight the importance of targeting interventions promoting PA towards individuals with LBP living in a neighborhood with good walkable access to amenities. Future studies should consider the influence of these factors to gain a better understanding of the relationship between LBP and PA.

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Conflicts of interest

None.

Transparency document

The Transparency document associated with this article can be found, in online version.

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Supplementary material: Assessment of confounding variables.

Variable	Question	Response options
Smoking	"Do you currently smoke?"	i) Yes ii) No
Educational attainment	"What is the highest level of education you have completed?"	i) never attended school or only attended kindergarten ii) grade 1-8 iii) grade 9-11 iv) grade12/high school graduated v) some college vi) associates degree vii) technical or vocational degree viii) bachelor degree ix) graduate or professional degree
Sleep quality	"How often do you have difficulty falling asleep or staying asleep?"	i) never ii) sometimes iii) often iv) always
Depression	"In the past 4 weeks, how often have you been bothered by the following problems: feeling down, depressed, or hopeless?"	i) not at all ii) several days iii) more than half days iv) nearly every day
Leisure sitting time	"Over the past 4 weeks, how much time altogether did you spend on a typical day sitting and watching TV or videos or using a computer outside of work?"	i) 0 hours ii) 1-2 hours iii) 3-4 hours iv) 5 or more

Supplementary material: Association between educational attainment and Walk Score®.

	Educational attainment	OR*	95% CI
Total Sample (n=9,819)	Up to high school completion (reference)	0.00	-
	College or associates degree	1.18	0.98-1.42
	Bachelor, graduate, or professional degree	2.04	1.69-2.47

n: number of individual twins; OR: odds ratio; CI: confidence interval.

*: adjusted for age and gender.

CHAPTER FOUR

Does educational attainment increase the risk of low back pain when genetics is considered? A population-based study of Spanish twins

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Clinical Study

Does educational attainment increase the risk of low back pain when genetics are considered? A population-based study of Spanish twins

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Abstract

BACKGROUND CONTEXT: There is limited research investigating educational attainment as a risk factor for low back pain (LBP), with the influence of gender commonly being neglected. Furthermore, genetics and early shared environment explain a substantial proportion of LBP cases and need to be controlled for when investigating risk factors for LBP.

PURPOSE: To investigate whether educational attainment affects the prevalence and risk of LBP differently in men and women while controlling for the influence of genetics and early shared environment.

STUDY DESIGN: This is a cross-sectional and prospective twin case-control study.

PATIENT SAMPLE: Adult monozygotic (MZ) and dizygotic (DZ) twins from the Murcia Twin Registry, with available data on educational attainment, formed the base sample for this study. The prevalence analysis considered twins with available data on LBP in 2013 (n=1,580). The longitudinal analysis considered twins free of LBP at baseline (2009–2011), with available data on LBP at follow-up (2013) (n=1,077).

OUTCOME MEASURES: Data on the lifetime prevalence of activity limiting LBP (outcome) and educational attainment (risk factor) were self-reported.

METHODS: The prevalence analysis investigated the cross-sectional association between educational attainment and LBP, whereas the longitudinal analysis investigated whether educational attainment increased the risk of developing LBP. Both analyses were performed in the following sequence. First, a total sample analysis was performed on all twins (considering them as individuals), adjusting for confounding variables selected by the data. Second, to control for the influence of genetics and early shared environment, a within-pair case-control analysis (stratified by zygosity) was performed on complete twin pairs discordant for LBP (ie, one twin had LBP, whereas the co-twin did not). All analyses were stratified for gender where possible, with an interaction term determining whether gender was a significant moderator of the association between educational attainment and LBP.

RESULTS: Women with either general secondary or university education were less likely to experience (prevalence analysis) or to develop LBP (longitudinal analysis). Educational attainment did not affect the risk of LBP in men. When controlling for the effects of genetics and early shared environment, the relationship between educational status and LBP in women was no longer statistically significant.

FDA device/drug status: Not applicable.

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CONCLUSIONS: Educational attainment affects LBP differently in men and women, with higher levels of education only decreasing the risk of developing LBP in women. After adjusting for genetics and early shared environment, the relationship between educational attainment and LBP in women disappears. This suggests that genetics and early shared environment are confounding the relationship between educational attainment and LBP in women.

Keywords: Education; Gender; Genetics; Low back pain; Murcia Twin Registry; Twin study

Introduction

Low back pain (LBP) is a global problem, resulting in disability affecting people in many countries, regardless of income [1,2]. The most recent Global Burden of Disease Study has ranked LBP as the leading cause of global disability [3], with approximately 23% of individuals experiencing activity limiting LBP in the past month [4], and up to 15% of individuals estimated to experience a first-ever episode of LBP within the next year [5]. As a result of the high prevalence of LBP, the financial burden is enormous and has been estimated at AU$4.8 billion in Australia [6]. In addition, the financial burden is significant across other countries [7,8], with estimates for the whole of Europe being as high as €300 billion [8]. To effectively reduce the burden of LBP, it is necessary to identify risk factors for the condition so that effective prevention strategies can be properly designed.

Studies assessing risks for a first-time episode of LBP or LBP reoccurrence have failed to identify strong and consistent risk factors, with a previous history of LBP being the exception [9]. Although some commonly reported risk factors include poor general health, low levels of job satisfaction [10], and physically demanding work-related factors [9], there are still factors that are not well investigated, for example, educational attainment. There is an inverse relationship between educational attainment and the severity [11,12] and frequency [13] of LBP; however, only a few studies have investigated educational attainment as a risk factor for LBP. It appears that having a higher level of education reduces the risk of developing activity limiting LBP [14,15], although there are additional factors that need to be considered before definite conclusions can be made, including the influence of gender and genetics.

First, the impact gender has on the relationship between educational attainment and LBP has only been considered in a few observational studies. Some studies have reported that gender is important when considering the relationship between educational attainment and LBP [16,17], whereas others have not [11,12,15]. For example, Deyo and Tsui-Wu reported that increased educational attainment was associated with reduced functional limitations from LBP in men, but not in women [16], whereas increased educational attainment reduces the risk of disabling LBP irrespective of gender [15]. Before the design of effective intervention strategies, it is important to get a better understanding of the risk factors for LBP while considering differences between men and women. Gender-related differences exist in the experience of musculoskeletal pain [18,19], with women being more likely to report chronic pain [19] and LBP [20]. In addition, the outcome of interventions for LBP may be dependent on gender [21,22]. Therefore, to better understand whether educational attainment increases the risk of LBP, it is important to consider the influence of gender. Second, genetic factors have been shown to have a significant impact on educational attainment and LBP, accounting for between 34% and 67% of the variance in educational attainment [23], and up to 67% of variance in chronic and disabling LBP [24]. With genetics responsible for substantial variation in an individual's educational attainment and LBP, the confounding effects of genetics need to be considered if a direct relationship between these variables is to be elucidated. Co-twin control studies are being increasingly used to control for the effects of genetics and are producing interesting findings in the LBP field [25,26]. For example, a recent systematic review found that the strong association between obesity and LBP disappears after adjusting for genetic factors [25]. This finding supports the importance of considering genetic factors when investigating risk factors for LBP. Based on the results of previous twin studies, and given the strong influence genetics has over educational attainment and LBP, we hypothesize that the association between these variables may be confounded by genetic factors. The aim of the present study is to investigate how gender influences the relationship between educational attainment and the prevalence and risk of LBP by using a co-twin controlled design to adjust for the influence of genetics and early shared environment.

Methods

Participants and data collection

The sample for the present study was drawn from the Murcia Twin Registry (MTR). The MTR is a population-based registry of adult twins, born between 1940 and 1966, in the region of Murcia, southeast Spain. The Murcia Health Service identifies people who were born on the same day and share the same surname, and contacts them via mail and telephone to explain the purpose of the registry, request participation, and gather data. Participation in the MTR is voluntary, subject to informed consent, and not remunerated. Twins are included in the MTR if they meet the inclusion criteria: pairs with both members alive at the time of incorporation, residence in the region of Murcia, and absence of conditions or disability that may limit their voluntary participation. The global cooperation rate across data collection

EVIDENCE & METHODS

Context

Factors associated with the risk of developing chronic low back pain may be confounded by genetics and differences in developmental environment. Many recognized associations may be due to genetic or familial factors. The influence of education and socio-demographic factors on the etiology of chronic back pain are also debated. In this context, the current study reports the results of an analysis conducted using data from the Murcia Twin Registry.

Contribution

The study included more than 1,500 patients who had data available regarding the development of back pain. The authors report that the influence of education on back pain development is largely confounded by genetics and early shared environment in females. Education was not found to influence the development of back pain in males.

Implications

The authors' analysis adds to a growing body of literature that emphasizes the importance of genetics and environment in the development of back pain. The twin-twin design allows for the adjustment of a number of familial and genetic factors that may confound results in other study settings. The composition of this cohort, as well as unique socio-cultural characteristics may impair the generalizability of these results to other clinical contexts. However the data may have been originally collected, the design of this study and the associated limitations render the findings Level III evidence.

waves and subsamples is 72.5%. More detailed information about recruitment procedures and data collection is provided elsewhere [27]. Data were collected through a health-related questionnaire via face-to-face or phone interviews in three consecutive data waves, 2007, 2009–2011, and 2013. The health-related questionnaire included information on demographics, basic health history, and lifestyle factors. Data on educational attainment were collected at first contact and a comprehensive assessment of LBP was conducted in 2013 and formed the basis for the present study.

Prevalence analysis

Of the 2,120 adult twins with available data on educational attainment, 1,580 had data on LBP and were included in the prevalence analysis. The prevalence analysis investigated the cross-sectional association between educational attainment and LBP using data from the 2013 collection wave.

Longitudinal analysis

Participants were included in the longitudinal analysis if they answered "no" to the following question in the 2009–2011 data collection wave: "Have you ever suffered from chronic LBP?" with chronic LBP defined and explained to participants as the presence of pain in the lower back area that lasted for 6 months or longer, including seasonal or recurrent episodes. Of the 2,120 adult twins with available data on educational attainment, 1,077 did not report chronic LBP at baseline (2009–2011) and had data on LBP at follow-up (2013), and were included in the longitudinal analysis. Using baseline data in 2009–2011 and follow-up data in 2013, the longitudinal analysis investigated educational attainment as a risk factor for LBP (outcome).

Gender was the moderator variable for both prevalence and longitudinal analyses. If the relationship between educational attainment and LBP was different in men and women, gender was considered a moderator. Assessors were blinded to the risk factor (educational attainment) and outcome (LBP) of the present study. All registry and data collection procedures used in the MTR have been approved by the Committee of Research Ethics of the University of Murcia.

Zygosity ascertainment

Twin zygosity was ascertained by a 12-item questionnaire which included questions on whether twins were similar in eye color, hair color, face color, and face form. This zygosity-based questionnaire corresponds well with zygosity as determined by DNA testing with an agreement in nearly 96% of the cases [27].

Outcome—activity limiting LBP

Activity limiting LBP was assessed in the 2013 data collection wave and used as the outcome for the prevalence and longitudinal analyses. This was assessed by the following questions on the health-related questionnaire: "Have you ever suffered from chronic LBP?" Twins responding "yes" were prompted to answer a follow-up question: "Was this pain bad enough to limit your usual activities or change your daily routine for more than one day?" Those who answered "yes" to the second question were considered incident cases.

Risk factor—educational attainment

Educational attainment ranged from illiterate to university high-degree levels, following the guidelines of the Spanish National Statistics Institute [28]. Educational attainment was the risk factor in both prevalence and longitudinal analyses and was categorized as primary (from illiterate to completed primary studies), general secondary (general secondary or basic vocational education), superior secondary (superior secondary or superior vocational education), and university (completed a university degree). A description of the sample with data for each category of educational attainment in the prevalence and longitudinal analyses can be found in Tables 1 and 2, respectively.

Co-variables

Age, gender, smoking, body mass index, symptoms of depression or anxiety, and engagement in leisure and daily physical

Table 1
Prevalence analysis sample characteristics for twins with and without activity limiting LBP

	Activity limiting LBP absent		Activity limiting LBP present		Total	
	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n
Age (y)	56.9 (7.3)	1,142	56.3 (6.6)	438	56.7 (7.1)	1,580
Gender						
Man	45.3	517	45.2	198	45.3	715
Woman	54.7	625	54.8	240	54.7	865
MZ twins						
Man	13.8	158	14.6	64	14.1	222
Woman	22.2	253	17.1	75	20.8	328
DZ twins						
Man	15.6	178	17.4	76	16.1	254
Woman	19.2	219	19.0	83	19.1	302
Opposite gender	29.3	334	32.0	140	30.0	474
BMI	27.1 (4.2)	1,065	27.5 (4.6)	403	27.2 (4.3)	1,468
Smoking*	36.1	412	36.8	161	36.3	573
Depression or anxiety†	23.5	268	31.5	138	25.7	406
Daily physical activity‡	22.7	258	17.2	75	21.2	333
Leisure physical activity§	67.8	772	62.0	271	66.2	1,043
Educational attainment						
Primary	41.9	478	43.6	191	42.3	669
General secondary	34.3	392	34.3	150	34.3	542
Superior secondary	13.3	152	12.8	56	13.2	208
University	10.5	120	9.4	41	10.2	161

n, number of subjects; MZ, monozygotic; DZ, dizygotic; BMI, body mass index; LBP, low back pain; SD, standard deviation.
* Indicates current smokers.
† Indicates being moderately or extremely depressed or anxious.
‡ Indicates engagement in moderate or vigorous daily physical activity.
§ Indicates engagement in occasional or regular physical activity.

Table 2
Longitudinal analysis sample characteristics of twins with and without activity limiting LBP

	Activity limiting LBP absent		Activity limiting LBP present		Total	
	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n
Age (y)	53.9 (7.4)	909	52.6 (6.7)	168	53.7 (7.3)	1,077
Gender						
Man	51.0	464	62.5	105	52.8	569
Woman	49.0	445	37.5	63	47.2	508
MZ twins						
Man	15.8	144	18.5	31	16.3	175
Woman	19.4	176	7.7	13	17.6	189
DZ twins						
Man	17.2	156	26.8	45	18.7	201
Woman	15.7	143	14.9	25	15.6	168
Opposite gender	31.9	290	32.1	54	31.9	344
BMI	27.3 (4.1)	891	27.1 (4.2)	165	27.2 (4.1)	1,056
Smoking*	39.5	357	39.3	66	39.5	423
Depression or anxiety†	15.8	143	16.2	27	15.8	170
Daily physical activity‡	19.2	173	24.0	40	19.9	213
Leisure physical activity§	58.0	525	53.6	90	57.3	615
Educational attainment						
Primary	40.9	372	38.1	64	40.5	436
General secondary	34.3	312	36.9	62	34.7	374
Superior secondary	14.2	129	15.5	26	14.4	155
University	10.6	96	9.5	16	10.4	112

n, number of subjects; MZ, monozygotic; DZ, dizygotic; BMI, body mass index; LBP, low back pain; SD, standard deviation.
* Indicates current smokers.
† Indicates being moderately or extremely depressed or anxious.
‡ Indicates engagement in moderate or vigorous daily physical activity.
§ Indicates engagement in occasional or regular physical activity.

activities at follow-up were considered as possible confounding variables based on previous studies in the field [26,29] and data availability. Co-variables for the prevalence analysis were collected in 2013, whereas co-variables for the longitudinal analysis were collected in 2009–2011 (baseline). Data on smoking and physical activity were based on the Spanish National Health Survey Questionnaire (Ministry of Health) [30]. Smoking was dichotomized as ex-smoker or never smoked or current smoker. Symptoms of depression or anxiety were assessed through the EuroQol-5 with participants instructed to select one of the following options: (1) I am not anxious or depressed; (2) I am moderately anxious or depressed; or (3) I am extremely anxious or depressed. Responses were dichotomized as not depressed or anxious (1) and moderately or extremely depressed or anxious (2 and 3). Leisure physical activity was assessed by participants selecting one of the following options: (1) I don't practice exercise. My leisure time is mostly sedentary (reading, watching TV, etc.); (2) sport or physical activity occasionally (walking, gardening, light gym efforts, etc.); (3) regular physical activity several times a month (tennis, jogging, swimming, cycling, team sports, etc.); or (4) physical training several times a week. Responses were dichotomized as no physical activity or sedentary (1) or occasional or regular physical activity (2, 3, and 4). Daily physical activity was a categorical question where participants could select any of these options: (1) sitting most of the time; (2) standing, no big movements or effort; (3) walking, carrying light weights, and moving but no big effort; (4) tasks that require physical effort. Responses were dichotomized as absence of or low physical activity engagement (1 and 2) or moderate or vigorous physical activity engagement (3 and 4).

Analysis

Descriptive analyses were conducted for all study variables. The outcome variable was the presence of activity limiting LBP for the prevalence analysis, and risk of activity limiting LBP for the longitudinal analysis. The risk factor was categories of educational attainment, with "primary education" chosen as the reference due to its large representation of participants with data on educational attainment (42.3% and 40.5% in the prevalence and longitudinal analyses, respectively). All analyses were stratified for gender where possible, with an interaction term ("educational attainment"×"gender") quantifying the importance of gender as a moderator of the relationship between educational attainment and LBP. Analyses were conducted using STATA statistical software (StataCorp. 2013, *Stata Statistical Software: Release 13*, Version 13.1, StataCorp LP, College Station, TX, USA) with the significance level set at 0.05. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the regression models. A sample size calculation was performed for the total sample analysis (including when this analysis was stratified by gender) using an algorithm described by Demidenko [31]. Further details regarding the sample size calculation can be found in Supplementary Appendix S1.

Total sample analysis

First, a total sample analysis was conducted to investigate the association between educational attainment and LBP (prevalence analysis), and whether educational attainment increases the risk of LBP (longitudinal analysis). The total sample analysis included all complete and incomplete twin pairs analyzed as individuals. A univariate logistic regression was performed to explore possible co-variables that should be adjusted for in the multivariate models (described in the section "Co-variables"). Age and gender were forced into the multivariate logistic regression models to facilitate comparison to the within-pair case-control analysis, where twins are analyzed in pairs, naturally resulting in the adjustment for age (all case-control analyses) and gender (case-control analyses of same-gender twins). Furthermore, daily physical activity was forced into all multivariate models to control for the potential confounding of work-related physical activity. Additional variables were included in the multivariate logistic regression models if p-values in the univariate model (for both risk factor and outcome) reached a significance of <0.2 (Supplementary Appendix S2). To ensure that the measurements of standard error allowed for intra-group correlation when considering twin pairs, we used a robust sandwich estimator (*cluster* command in STATA).

Within-pair case-control analysis

To adjust for the influence of genetics and early shared environment on the relationship between educational attainment and LBP, a within-pair case-control analysis was performed on all complete monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for LBP in 2013; that is, one twin reported having suffered from activity limiting LBP (case), whereas the co-twin did not (control). Multivariate logistic regression models were used in a similar method to the total sample analysis (including the way confounding variables were identified), except that twins were analyzed as complete pairs rather than individuals. The following analytical steps were used in both prevalence and longitudinal analyses. First, we considered both DZ and MZ twin pairs in the within-pair case-control analysis. We then separated the analysis for DZ twins only followed by MZ twins only. DZ twins share on average 50% of their segregating genes, whereas MZ twins share approximately 100%, although it is usually assumed that both DZ and MZ twin pairs are exposed to the same early environment when growing up [32]. Hence, the analysis was performed in sequence to investigate changes in the relationship between educational attainment and LBP when controlling for 50% of genetics and early shared environment (DZ twins only) followed by 100% of genetics and early shared environment (MZ twins only). Theoretically, when an increased magnitude of the relationship between two variables (in this instance, educational attainment and LBP) is maintained through the analytical stages, a direct link between the two variables is more likely [33] (Fig. 1). However, a reduction in sample size in these analyses can generate some uncertainty around this interpretation.

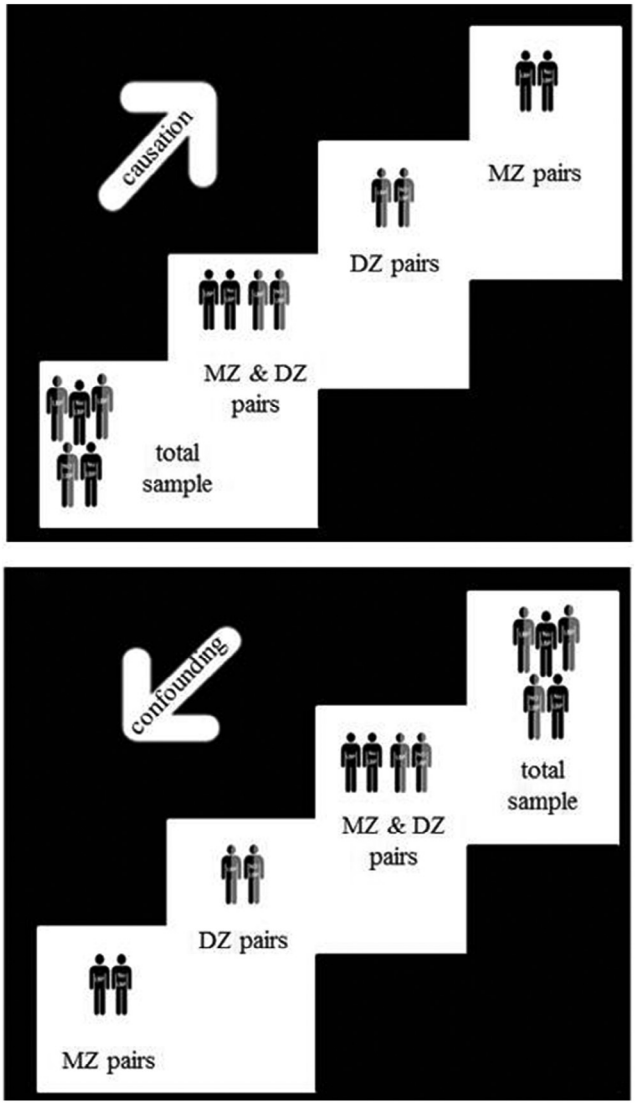

Fig. 1. Interpretation of the analytical sequences from the total sample analysis to the within-pair case-control analysis of MZ twins. When the magnitude of the relationship between two variables increases through the analytical stages, a direct link between the two variables is more likely (Top). When the magnitude of the relationship between two variables decreases through the analytical stages, it is likely that genetics and early shared environment are confounding this relationship (Bottom). DZ, dizygotic; MZ, monozygotic.

Results

Prevalence analysis: sample characteristics

Data on educational attainment was available from 2,120 adult twins in 2009–2011. Of these twins, 1,580 had data on activity limiting LBP in 2013 and were included in the prevalence analysis using the total sample, irrespective of concordance or discordance for LBP status (Fig. 2). The final sample for each analytical stage varied depending on data availability for all variables included in the models. The sample characteristics of twins with and without activity limiting LBP are described in Table 1. Sample characteristics for DZ and MZ twins discordant for LBP are described in Supplementary Appendix S3. The prevalence of activity limiting LBP in this sample was 27.7%. The mean age of all participants was 56.7 (standard deviation 7.1) years with 45.3% being men. Twins reporting activity limiting LBP were less likely to engage in moderate or vigorous daily physical activity (17.2% vs. 22.7%) and occasional or regular leisure physical activity (62.0% vs. 67.8%), and were more likely to report symptoms of depression or anxiety (31.5% vs. 23.5%). Twins reporting activity limiting LBP were more likely to have only attained primary education (43.6% vs. 41.9%) and were less likely to have completed a university degree (9.4% vs. 10.5%).

Prevalence total sample analysis

In the total sample analysis of the prevalence of activity limiting LBP, the variables age, gender (excluding when analyses were stratified by gender), daily and leisure physical activities, and symptoms of depression or anxiety were entered in the multivariate model. There was no significant association between educational attainment and LBP in the combined sample of men and women, although higher levels of education tended to decrease the likelihood of experiencing LBP (Table 3). There was a significant interaction between gender and educational attainment, with women having either general secondary (OR=0.7, 95% CI: 0.5–1.0, p=.040) or university education (OR=0.4, 95% CI: 0.2–0.7, p=.004) significantly less likely to experience activity limiting LBP (Table 4). There was no association between activity limiting LBP and superior secondary education in women, and no significant associations were observed for men (Table 4).

Prevalence within-pair case-control analysis

In the within-pair case-control analysis including both DZ and MZ twins (n=486), the variables gender and daily and leisure physical activities were entered in the multivariate model. In the analysis of DZ twins only (n=346), the variables gender and daily physical activity were entered in the multivariate model, whereas in the analysis of MZ twins only (n=142) the only variable that was entered in the multivariate model was daily physical activity. When controlling for genetics and early shared environment, there was no association between educational attainment and LBP (Table 3), even when analyses were stratified by gender for both DZ and MZ twins (Table 5) and DZ twins only (Table 6). Due to small numbers, it was not possible to stratify the within-pair case-control analyses for gender when analyzing MZ twins only.

Longitudinal analysis: sample characteristics

A total of 1,077 adult twins had data available on educational attainment, were free of LBP in the 2009–2011 data collection wave, and provided information about LBP in 2013 (Fig. 2). Therefore, these adult twins formed the sample for

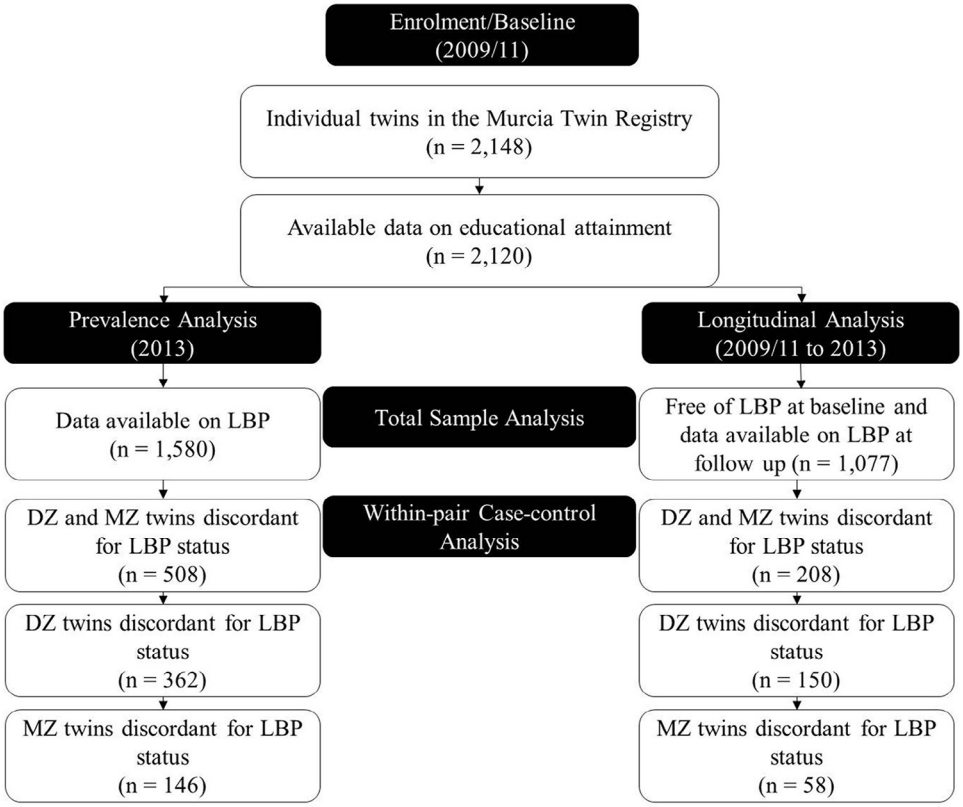

Fig. 2. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) study flowchart. LBP, low back pain; DZ, dizygotic; MZ, monozygotic.

the longitudinal analysis, irrespective of concordance or discordance for LBP status. The final sample for each analytical stage varied depending on data availability for all variables included in the models. The sample characteristics of twins with and without activity limiting LBP are described in Table 2. The sample characteristics of DZ and MZ twins discordant for LBP are described in Supplementary Appendix S4. The incidence of activity limiting LBP in this sample was 15.6%.

Table 3
Prevalence total sample analysis and within-pair case-control analysis of activity limiting low back pain (multivariate model)

	Educational attainment	OR	95% CI	p
Total sample (n=1,572)*	Primary (reference)	1.0	—	—
	General secondary	0.9	0.7–1.2	.348
	Superior secondary	0.8	0.6–1.2	.377
	University	0.8	0.5–1.2	.239
DZ and MZ (n=486)†	Primary (reference)	1.0	—	—
	General secondary	0.8	0.5–1.3	.389
	Superior secondary	1.3	0.5–3.0	.595
	University	1.3	0.5–3.6	.617
DZ (n=346)‡	Primary (reference)	1.0	—	—
	General secondary	0.8	0.4–1.4	.401
	Superior secondary	1.0	0.4–2.6	.972
	University	1.2	0.4–3.7	.745
MZ (n=142)§	Primary (reference)	1.0	—	—
	General secondary	0.8	0.3–1.9	.544
	Superior secondary	2.4	0.2–25.8	.467
	University	0.8	0.0–21.3	.896

n, number of individual twins; OR, odds ratio; CI, confidence interval; MZ, monozygotic; DZ, dizygotic.
* Adjusted for age, gender, daily physical activity, symptoms of depression or anxiety, and leisure physical activity.
† Adjusted for gender and daily and leisure physical activities.
‡ Adjusted for gender and daily physical activity.
§ Adjusted for daily physical activity.

Table 4
Total sample analysis of the prevalence of activity limiting low back pain, stratified by gender (multivariate model)

	Men (n=711)				Women (n=861)				Interaction
Educational attainment	OR	95% CI	p	n	OR	95% CI	p	n	p
Primary (reference)	1.0	—	—	271	1.0	—	—	393	—
General secondary	1.2	0.8–2.0	.335	234	0.7	0.5–1.0	.040	306	.003
Superior secondary	0.8	0.5–1.5	.555	121	0.9	0.5–1.6	.787	86	.653
University	1.5	0.9–2.8	.153	85	0.4	0.2–0.7	.004	76	<.001

n, number of individual twins; OR, odds ratio; CI, confidence interval.
Note: Analysis adjusted for age, daily and leisure physical activities, and symptoms of depression or anxiety.

Table 5
Within-pair case-control analysis of the prevalence of activity limiting low back pain, stratified by gender (multivariate model), in DZ and MZ twins

	Men (n=150)			Women (n=176)			Interaction
Educational attainment	OR	95% CI	p	OR	95% CI	p	p
Primary (reference)	1.0	—	—	1.0	—	—	—
General secondary	1.3	0.5–3.7	.585	0.8	0.4–1.8	.602	.650
Superior secondary	3.2	0.4–27.2	.281	1.7	0.4–7.8	.500	.978
University	4.7	0.4–51.2	.209	0.3	0.0–3.0	.304	.236

n, number of individual twins; OR, odds ratio; CI, confidence interval; DZ, dizygotic; MZ, monozygotic.
Note: Analysis adjusted for daily and leisure physical activities.

Table 6
Within-pair case-control analysis of the prevalence of activity limiting low back pain, stratified by gender (multivariate model), in DZ twins

	Men (n=82)			Women (n=104)			Interaction
Educational attainment	OR	95% CI	p	OR	95% CI	p	p
Primary (reference)	1.0	—	—	1.0	—	—	—
General secondary	0.9	0.2–3.2	.851	1.0	0.4–2.8	.970	.996
Superior secondary	2.0	0.1–30.9	.619	1.2	0.2–6.5	.861	.990
University	3.3	0.2–59.4	.417	0.2	0.0–2.6	.234	.265

n, number of individual twins; OR, odds ratio; CI, confidence interval; DZ, dizygotic; MZ, monozygotic.
Note: Analysis adjusted for daily physical activity.

The mean age of all participants was 53.7 (standard deviation 7.3) years and 52.8% were men. Twins who developed activity limiting LBP at follow-up were less likely to be engaged in occasional or regular leisure physical activity (53.6% vs. 58.0%) but were more likely to be engaged in moderate or vigorous daily physical activity at baseline (24.0% vs. 19.2%). Twins who developed activity limiting LBP at follow-up were less likely to have completed a university degree (9.4% vs. 10.5%).

Longitudinal total sample analysis

In the total sample analysis for the risk of developing activity limiting LBP, the variables age, gender (excluding when analyses were stratified by gender), and daily physical activity were entered in the multivariate model. Educational attainment did not significantly affect the risk of LBP in the combined sample of men and women, although higher levels of education tended to decrease the risk of LBP (Table 7). There was a significant interaction between gender and educational attainment, with women having general secondary education (OR=0.5, 95% CI: 0.2–0.9, p=.025) significantly less likely to develop LBP (Table 8). Women with university education also appear less likely to develop LBP (OR=0.3, 95% CI: 0.1–1.1, p=.066), although this finding was not statistically significant. Educational attainment did not affect the risk of LBP in men.

Longitudinal within-pair case-control analysis

In the within-pair case-control analysis for the risk of developing activity limiting LBP, the variables gender and daily physical activity were entered in the multivariate model when analyzing DZ and MZ twins (n=158) and DZ twins only (n=114). In the analysis of MZ twins only (n=44), the only variable that was entered in the model was daily physical activity. When controlling for genetics and early shared environment, educational attainment did not affect the risk of LBP, with the analysis failing to run when only considering MZ twins (Table 7). Due to small numbers, it was not possible to stratify the within-pair case-control analyses for gender.

Table 7
Longitudinal total sample analysis and within-pair case-control analysis of the risk of developing activity limiting low back pain (multivariate model)

	Educational attainment	OR	95% CI	p
Total sample (n=1,070)*	Primary (reference)	1.0	—	—
	General secondary	0.9	0.6–1.5	.795
	Superior secondary	0.9	0.5–1.7	.799
	University	0.8	0.4–1.5	.542
DZ and MZ (n=158)†	Primary (reference)	1.0	—	—
	General secondary	1.0	0.4–2.9	.993
	Superior secondary	1.3	0.3–6.1	.778
	University	2.1	0.3–13.0	.422
DZ (n=114)†	Primary (reference)	1.0	—	—
	General secondary	0.7	0.2–2.3	.599
	Superior secondary	0.8	0.1–4.2	.768
	University	2.4	0.3–19.5	.425
MZ (n=44)‡	Primary (reference)	1.0	—	—
	General secondary	—		
	Superior secondary	—		
	University	—		

n, number of individual twins; OR, odds ratio; CI, confidence interval; MZ, monozygotic, DZ, dizygotic.
* Adjusted for age, gender, and daily physical activity.
† Adjusted for gender and daily physical activity.
‡ Analysis failed to run due to sample size.

Table 8
Longitudinal total sample analysis of the risk of developing activity limiting low back pain, stratified by gender (multivariate model)

	Men (n=563)				Women (n=507)				Interaction
Educational attainment	OR	95% CI	p	n	OR	95% CI	p	n	p
Primary (reference)	1.0	—	—	219	1.0	—	—	216	—
General secondary	1.5	0.8–2.7	.184	189	0.5	0.2–0.9	.025	182	.001
Superior secondary	0.8	0.4–1.8	.637	96	1.2	0.5–2.8	.635	57	.727
University	1.4	0.6–3.1	.387	59	0.3	0.1–1.1	.066	52	.014

n, number of individual twins; OR, odds ratio; CI, confidence interval.
Note: Analysis adjusted for age and daily physical activity.

Discussion

The results of the present study show that women with either general secondary or university education are less likely to experience or develop activity limiting LBP compared with women with primary education. However, after controlling for genetics and early shared environment, this relationship disappears, highlighting the potential confounding effect these factors may have on the relationship between educational attainment and LBP. Furthermore, educational attainment did not influence the risk of LBP for men, suggesting that gender is an important moderator of the relationship between educational attainment and LBP.

Effect of gender on the relationship between educational attainment and LBP

The results of our study support the relationship between educational attainment and LBP, which is influenced by gender, although conflicting evidence from existing cross-sectional studies, as well as a lack of longitudinal studies, makes it difficult to conclude whether educational attainment influences the risk of LBP to a greater extent in men or women. Previous cross-sectional studies have demonstrated a clear association between educational attainment and LBP [11,13], but have failed to find a difference between men and women [11,12,17]. However, a more detailed assessment of LBP used in some of these studies [11,12] may have elicited different responses between men and women, because women are more likely to report LBP [20]. Furthermore, Deyo and Tsui-Wu found a significant inverse association between high educational attainment and activity limiting LBP in men but not in women [16], although women in this study were analyzed as subgroups, reducing the sample size and potentially explaining why the association was not significant in women. Longitudinal studies investigating the relationship between educational attainment and LBP, especially those that consider the influence of gender, are scarce. Low educational attainment appears to predict worse outcomes for LBP disability [34,35], whereas high educational attainment reduces the risk of developing activity limiting LBP [14]. However, these studies did not stratify their results for gender. After stratifying for gender, our results showed that women with either general secondary or university education have a significantly reduced risk of developing activity limiting LBP (OR=0.5

and 0.3, respectively), although this was only statistically significant for general secondary education. No significant effect was observed for men, suggesting gender is influencing educational attainment as a risk factor for LBP in this sample. In contrast, a longitudinal study by Hagen et al. reported that each year of additional education reduced the risk of developing activity limiting LBP in a similar way for men and women [15]. However, using educational attainment as a continuous variable rather than as a categorical variable might not reflect changes in work-related factors that are associated with people in different educational categories. Therefore, our study is one of the very few longitudinal studies investigating educational attainment as a risk factor for LBP and highlights the importance of taking gender into account when deciding whether an individual's education will impact the risk of LBP.

The differences between men and women in the relationship between educational attainment and LBP might be explained by sample specific issues, such as work-related factors. Exposure to prolonged postures and lifting heavy loads have been shown to account for the relationship between low educational attainment and LBP [36]. However, we adjusted all analyses for "daily physical activity" as a proxy for work-related physical activity, suggesting other work-related factors that impact men and women differently might explain our results. Men appear to be impacted to a greater extent by physical work-related factors compared with women [15], which might be explained by more men being exposed to physically demanding occupations. Nonetheless, women in rural areas may be more likely to be subject to physically demanding tasks than those in urban areas, thereby increasing their likelihood of LBP. In contrast, women are usually more affected by non-physical work-related factors, such as job insecurity [37] or high emotional demands [38], which have been shown to increase the risk of developing LBP and having time off work because of LBP [39]. These factors are not a unique feature of physically demanding occupations and can be present for any occupation, regardless of educational attainment. Another hypothesis that deserves attention is the potential for women to be experiencing external factors that impact their occupational load (eg, additional domestic duties, being pregnant, or going through menopause). It is suggested these factors impact the frequency [40] and severity of LBP [41,42]. Therefore, work-related factors may have different effects on men and women, impacting the relationship between educational attainment and LBP.

Women with general secondary or university education were less likely to experience or develop LBP compared with women with primary education. However, this relationship was not found for women with superior secondary education. Although it is likely that a small sample of women with superior secondary education in both prevalence and longitudinal total sample analyses (5.4% and 5.3%, respectively) is the reason for this finding, the influence of work-related factors cannot be ignored. Women who completed high school or received advanced vocational training may be more likely to find themselves in occupations that involve long periods of sedentary behavior (eg, administrative jobs), or occupations that have low job security and high emotional demands. It is suggested that these factors have a greater influence on LBP in women [37,38,43] and may explain why superior secondary education failed to reduce the risk of developing LBP in our sample.

Although a sample of twins was used for the present study, the twins were considered representative of the population from which they were drawn [27], and also the non-twin population [44]. Twins have a similar mortality rate when compared with the general population [45] and demonstrate comparable prevalence for numerous diseases, including diabetes mellitus [46], asthma [47], and thyroid disease [48]. In addition, the lifetime prevalence of activity limiting LBP in this sample of twins appears to be similar to global estimates (27.7% and 23%, respectively) [49]. Therefore, we consider the sample used for the present study as representative of the general population, making the results generalizable.

Effects of genetics on the relationship between educational attainment and LBP

Identifying risk factors for LBP is integral to the design of prevention strategies. Controlling for genetics and early shared environment allow us to see if a direct relationship exists between educational attainment and LBP, and represent a considerable strength of the co-twin control design. Similar to the total sample analyses, there was no association between educational attainment and LBP in within-pair case-control analyses including men and women together. However, when the prevalence within-pair case-control analysis was stratified for gender, the strong association between educational attainment and LBP for women (observed in the total sample analysis) was no longer statistically significant. This suggests that the relationship between these variables is likely to be confounded by genetics or early shared environment (Fig. 1). The absence of a direct relationship between educational attainment and LBP, found after adjusting for these factors, may explain why existing education-based prevention strategies for LBP are ineffective in isolation [50,51]. However, the possibility that a reduced sample size in the within-pair case-control analyses resulted in a lack of statistically significant findings cannot be ruled out.

Strength and limitations of the present study

Our study employed high levels of control, ensuring the relationship between educational attainment and LBP was not confounded by other variables. A co-twin control design allowed us to adjust for the potential confounding effects of genetics and early shared environment. With genetics accounting for up to 67% of the variance in LBP [24] and educational attainment [23], not controlling for this is a potential limitation of previous studies. We adjusted for other potential confounding variables by exploring the relationship between individual covariables and activity limiting LBP. Furthermore, we controlled our analyses for "daily physical activity" as a proxy for

work-related physical activity because there is a well-established association between educational attainment and work-related factors [36] that was also found in our sample (Supplementary Appendix S5). The measures of LBP and educational attainment used in the present study have been used widely, suggesting our results would be generalizable to an international audience. Although data on LBP were self-reported and will inevitably result in a degree of recall bias, the questions used in the present study were based on standardized definitions, facilitating the comparison of our results to other observational studies [2,52]. The classification of educational attainment used in the present study was based on guidelines from the Spanish National Statistics Institute [28]. These guidelines are based on the International Standard Classification of Education (ISCED) and have been developed to facilitate international comparison [53]. For example, the ISCED is comparable to the Australian Standard Classification of Education [54]. There is currently no consensus regarding the best way to categorize educational attainment when investigating the risk of common health conditions, although studies investigating the relationship between educational attainment and LBP have commonly used cutoff points based on schooling and university milestones [11,12,14,16,17]. Therefore, to facilitate the comparison between our study and the existing literature, we categorized the original classification of education in a similar way. Finally, our study was sufficiently powered in the prevalence and longitudinal total sample analyses, including when these analyses were stratified by gender (Supplementary Appendix S1).

There are a few limitations that should be taken into account when interpreting the results. First, we were unable to stratify the longitudinal within-pair case-control analyses for gender due to an insufficient sample size. This may have yielded interesting results due to the number of statistically significant results we observed when separating the total sample analyses by gender, and because heritability for LBP has been reportedly higher in women [55]. In addition, we do not know whether the confounding effects of genetics and early shared environment demonstrated in the prevalence analyses are demonstrated in the longitudinal analyses, a question to be investigated in future studies using a larger sample of twins. Based on our sample size calculations for the total sample analysis, the possibility that our within-pair case-control analysis was underpowered cannot be ignored. However, due to high levels of control demonstrated when analyzing twins as matched pairs, it is expected that the required sample size would be less than that in the analysis of the non-twin population [56,57]. Second, due to the inclusion of twins never having suffered from chronic LBP, there is a possibility that twins with LBP lasting less than 6 months were included in our longitudinal analysis. This limitation may have impacted our results because a previous history of LBP is a strong risk factor for future LBP [9].

Clinical implications

At first sight, our results appear to deny the presence of a significant relationship between educational attainment and LBP. In fact, none of the analyses including the whole sample reached significant levels of association, suggesting that no preventive or intervention strategy taking into account educational attainment can be generalized to the entire population. However, our results show that educational attainment may affect LBP differently in men and women. Compared with women with primary education, women with either general secondary or university education were less likely to experience or develop LBP. This relationship was not found in men. Because women with increased education were significantly less likely to experience or develop LBP, there may be a benefit of targeting intervention and prevention strategies toward education of back care and early management of LBP in women with low education levels.

Our results highlight the importance of using twins for future research into LBP. The relationship between educational attainment and LBP in women disappeared when we controlled for genetics and early shared environment. However, the possibility that this association disappeared due to a reduction in sample size cannot be ruled out. Therefore, genetics and early shared environment may play a role in the relationship between educational attainment and LBP, although this hypothesis needs to be confirmed in future twin studies if we are to better understand those at greater risk of LBP.

Conclusions

Educational attainment affects the prevalence and risk of LBP differently in men and women. Women with either general secondary or university education have a significantly reduced risk of developing activity limiting LBP. After adjusting for genetics and early shared environment, the association between educational attainment and LBP in women disappears, although future studies using greater sample sizes are needed to confirm these results.

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Supplementary material

Supplementary material related to this article can be found at http://dx.doi.org/10.1016/j.spinee.2016.10.021.

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Supplementary material: Sample size estimation

A sample size calculation was performed for the total sample analysis (including when this analysis was stratified by gender) using an algorithm described in "Demidenko E. (2007). Sample size determination for logistic regression revisited. *Statistics in Medicine* 26:3385-3397" [1]. Our calculations were based on the ability to detect a difference in OR between those with primary education and university education of 0.3 (Table 17). This value was an estimate from existing observational studies which found a similar effect size when investigating the association between educational attainment and LBP [2-5], and was used for the stratified analyses given the lack of research investigating whether gender influences this relationship. We required 179 participants in the prevalence analysis and 344 participants in the longitudinal analysis to provide us with 80% power and alpha set at 0.05. Our calculations were based on a 27.7% prevalence of chronic LBP and 43.6% prevalence of primary education in affected cases (prevalence analysis), and a 15.6% incidence of chronic LBP and 38.1% prevalence of primary education in incident cases (longitudinal analysis). For the analyses stratified by gender, we required 166 females in the prevalence analysis (given a 27.7% prevalence of chronic LBP and 53.3% prevalence of primary education in affected cases) and 383 females in the longitudinal analysis (given a 12.4% incidence of chronic LBP and 52.4% prevalence of primary education in incident cases). We required 220 males in the prevalence analysis (given a 27.7% prevalence of chronic LBP and 31.8% prevalence of primary education in affected cases) and 344 males in the longitudinal analysis (given an 18.5% incidence of chronic LBP and 29.5% prevalence of primary education in incident cases). Our total sample analysis stratified by gender included 861 females and 711 males in the prevalence analysis, and 507 females and 563 males in the longitudinal analysis, thus was adequately powered. Based on these figures it would appear our

within-pair case-control analyses were underpowered. We acknowledge this possibility and have highlighted this throughout the manuscript. However, due to high levels of control demonstrated when analysing twins as matched pairs, it is expected the required sample size would be less than an analysis of the non-twin population [6,7].

Table 9. Sample size calculation for the total sample analyses.

	Prevalence analysis*		**Longitudinal analysis***	
Males and females	Prevalence of LBP	27.7%	Incidence of LBP	15.6%
	Prevalence of primary education in affected cases	43.6%	Prevalence of primary education in incident cases	38.1%
	Required	**179**	**Required**	**344**
	Analysed	**1572**	**Analysed**	**1070**
Males	Prevalence of LBP	27.7%	Incidence of LBP	18.5%
	Prevalence of primary education in affected cases	31.8%	Prevalence of primary education in incident cases	29.5%
	Required	**220**	**Required**	**344**
	Analysed	**711**	**Analysed**	**563**
Females	Prevalence of LBP	27.7%	Incidence of LBP	12.4%
	Prevalence of primary education in affected cases	53.3%	Prevalence of primary education in incident cases	52.4%
	Required	**166**	**Required**	**383**
	Analysed	**861**	**Analysed**	**507**

LBP: low back pain.
*calculations were based on the ability to detect a difference in odds ratio between those with primary education and university education of 0.3, with 80% power and alpha set at 0.05.

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Supplementary material: Identification of confounding variables.

Table 10. Univariate analyses to identify confounding variables for inclusion in the multivariate models (prevalence analysis)*

Total sample analysis

	Activity limiting LBP				**Educational attainment**				
Co-variables	**OR**	**95%CI**	**p**	**n**	**B**	**95%CI**	**p**	**n**	**Decision**
BMI	1.02	0.99-1.05	0.228	1468	-0.04	-0.05--0.03	**<0.001**	1468	N
Smoking	1.03	0.82-1.30	0.790	1578	0.10	-0.00-0.21	0.061	1578	N
Leisure PA	0.78	0.62-0.98	**0.032**	1576	0.19	0.09-0.29	**<0.001**	1576	Y
Depression/ anxiety	1.50	1.17-1.92	**0.001**	1580	-0.22	-0.33--0.11	**<0.001**	1580	Y

Within-pair case-control analysis (DZ & MZ twins)

Co-variables	**OR**	**95%CI**	**p**	**n**	**B**	**95%CI**	**p**	**n**	**Decision**
BMI	1.00	0.95-1.06	0.916	430	-0.03	-0.05--0.01	**0.005**	464	N
Smoking	0.69	0.44-1.07	**0.098**	490	0.01	-0.17-0.19	0.888	499	N
Leisure PA	0.67	0.45-0.99	**0.047**	488	0.21	0.03-0.39	**0.023**	498	Y
Depression/ anxiety	1.12	0.74-1.68	0.600	490	-0.27	-0.45--0.09	**0.004**	499	N

Within-pair case-control analysis (DZ & MZ twins)

Co-variables	**OR**	**95%CI**	**p**	**n**	**B**	**95%CI**	**p**	**n**	**Decision**
BMI	1.00	0.95-1.06	0.953	310	-0.03	-0.06--0.01	**0.008**	332	N
Smoking	0.63	0.38-1.03	**0.065**	348	0.03	-0.19-0.25	0.772	355	N
Leisure PA	0.75	0.47-1.20	0.234	348	0.22	0.01-0.43	**0.040**	355	N
Depression/ anxiety	1.12	0.70-1.79	0.633	348	-0.32	-0.53--0.10	**0.004**	355	N

Within-pair case-control analysis (DZ & MZ twins)

Co-variables	OR	95%CI	p	n	B	95%CI	p	n	Decision
BMI	1.01	0.88-1.16	0.892	120	-0.02	-0.06-0.02	0.337	132	N
Smoking	1.0	0.38-2.66	1.000	142	-0.04	-0.37-0.28	0.789	144	N
Leisure PA	0.50	0.23-1.07	**0.074**	140	0.19	-0.15-0.53	0.259	143	N
Depression/ anxiety	1.10	0.47-2.59	0.827	142	-0.11	-0.45-0.24	0.531	144	N

n: number of individual twins; OR: odds ratio; CI: confidence interval; B: beta coefficient; MZ: monozygotic, DZ: dizygotic. LBP: low back pain; BMI: body mass index; PA: physical activity; Y: included in the multivariate model; N: not included in the multivariate model.
*: if the univariate association between the co-variable, and both activity limiting LBP and educational attainment reached a significance of $p<0.2$, the co-variable was included in the multivariate model.

Table 11. Univariate analyses to identify confounding variables for inclusion in the multivariate models (longitudinal analysis)*

Total sample analysis

	Activity limiting LBP				**Educational attainment**				
Co-variables	**OR**	**95%CI**	**p**	**n**	**B**	**95%CI**	**p**	**n**	**Decision**
BMI	0.99	0.95-1.03	0.610	1056	-0.05	-0.06--0.03	**<0.001**	1056	N
Smoking	0.99	0.72-1.37	0.958	1072	0.16	0.04-0.29	**0.012**	1072	N
Leisure PA	0.84	0.60-1.16	0.281	1073	0.25	0.13-0.37	**<0.001**	1073	N
Depression/ anxiety	1.03	0.66-1.61	0.900	1073	-0.16	-0.32--0.01	**0.043**	1073	N

Within-pair case-control analysis (DZ & MZ twins)

Co-variables	**OR**	**95%CI**	**p**	**n**	**B**	**95%CI**	**p**	**n**	**Decision**
BMI	0.95	0.86-1.04	0.255	154	-0.05	-0.08--0.02	**0.001**	289	N
Smoking	0.92	0.40-2.08	0.835	160	0.06	-0.19-0.31	0.648	293	N
Leisure PA	0.67	0.32-1.39	0.277	160	0.33	0.10-0.57	**0.005**	293	N
Depression/ anxiety	1.56	0.67-3.59	0.301	158	-0.10	-0.40-0.20	0.501	292	N

Within-pair case-control analysis (DZ & MZ twins)

Co-variables	**OR**	**95%CI**	**p**	**n**	**B**	**95%CI**	**p**	**n**	**Decision**
BMI	0.94	0.85-1.04	0.207	112	-0.06	-0.09--0.03	**<0.001**	207	N
Smoking	1.00	0.42-2.40	1.000	116	-0.02	-0.30-0.26	0.885	210	N
Leisure PA	0.79	0.36-1.73	0.549	116	0.43	0.19-0.67	**0.001**	210	N
Depression/ anxiety	1.63	0.67-3.92	0.280	114	-0.06	-0.39-0.27	0.720	209	N

Within-pair case-control analysis (MZ twins)

No adjustment since analysis failed to run due to low number

n: number of individual twins; OR: odds ratio; CI: confidence interval; B: beta coefficient; MZ: monozygotic, DZ: dizygotic. LBP: low back pain; BMI: body mass index; PA: physical activity; Y: included in the multivariate model; N: not included in the multivariate model.
*: if the univariate association between the co-variable, and both activity limiting LBP and educational attainment reached a significance of $p<0.2$, the co-variable was included in the multivariate model.

Supplementary material: Sample characteristics for discordant twin pairs in the prevalence analysis.

Table 12. Prevalence analysis sample characteristics for DZ twins discordant for activity limiting low back pain (LBP).

	Activity Limiting LBP absent		**Activity Limiting LBP present**		**Total**	
	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n
Age (years)	56.7 (6.6)	176	56.8 (6.7)	179	56.8 (6.7)	355
Gender (male)	56.9%	95	43.1%	72	47.0%	167
Gender (female)	43.1%	81	56.9%	107	53.0%	188
BMI	27.6 (4.0)	165	27.5 (4.5)	167	27.6 (4.2)	332
Smoking ¥	44.9%	79	36.3%	65	40.6%	144
Depression/anxiety♓	29.6%	52	32.4%	58	31.0%	110
Daily Physical activity£	24.6%	43	13.4%	24	18.9%	67
Leisure Physical activity€	70.5%	124	63.7%	114	67.0%	238
Educational Attainment						
Primary	39.2%	69	45.3%	81	42.3%	150
General Secondary	37.5%	66	30.2%	54	33.8%	120
Superior Secondary	13.6%	24	14.0%	25	13.8%	49
University	9.7%	17	10.6%	19	10.1%	36

n: number of subjects, MZ: monozygotic, DZ: dizygotic, BMI: body mass index.
¥: indicates current smokers; ♓: indicates being moderately/extremely depressed or anxious; £: indicates the engagement in moderate/vigorous daily physical activity; €: indicates the engagement in occasional/regular physical activity.

Table 13. Prevalence analysis sample characteristics for MZ twins discordant for activity limiting low back pain (LBP).

	Activity Limiting LBP absent		**Activity Limiting LBP present**		**Total**	
	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n
Age (years)	54.8 (6.8)	72	54.9 (6.8)	72	54.8 (6.8)	144
Gender (male)	51.4%	37	48.6%	35	50.0%	72
Gender (female)	51.4%	37	48.6%	35	50.0%	72
BMI	27.3 (3.7)	67	27.4 (4.3)	65	27.3 (4.0)	132
Smoking ¥	45.8%	33	44.4%	32	45.1%	65
Depression/anxiety♓	22.2%	16	23.6%	17	22.9%	33
Daily Physical activity£	20.8%	15	22.2%	16	21.5%	31
Leisure Physical activity€	67.6%	48	54.2%	39	60.8%	87
Educational Attainment						
Primary	31.9%	23	36.1%	26	34.0%	49
General Secondary	45.8%	33	40.3%	29	43.1%	62
Superior Secondary	9.7%	7	15.3%	11	12.5%	18
University	12.5%	9	8.3%	6	10.4%	15

n: number of subjects, MZ: monozygotic, DZ: dizygotic, BMI: body mass index.
¥: indicates current smokers; ♓: indicates being moderately/extremely depressed or anxious; £: indicates the engagement in moderate/vigorous daily physical activity; €: indicates the engagement in occasional/regular physical activity.

Supplementary material: Sample characteristics for discordant twin pairs in the longitudinal analysis.

Table 14. Longitudinal analysis sample characteristics for DZ twins discordant for activity limiting low back pain (LBP).

	Activity Limiting LBP absent		**Activity Limiting LBP present**		**Total**	
	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n
Age (years)	53.5 (6.4)	137	52.9 (6.9)	73	53.3 (6.6)	210
Gender (male)	66.7%	82	33.3%	41	58.6%	123
Gender (female)	63.2%	55	36.8%	32	41.4%	87
BMI	27.4 (4.1)	135	27.1 (4.0)	72	27.3 (4.0)	207
Smoking ¥	40.9%	56	37.0%	27	39.5%	83
Depression/anxiety♓	19.7%	27	20.8%	15	20.1%	42
Daily Physical activity£	19.7%	27	26.4%	19	22.0%	46
Leisure Physical activity€	61.3%	84	53.4%	39	58.6%	123
Educational Attainment						
Primary	34.3%	47	42.5%	31	37.1%	78
General Secondary	41.6%	57	31.5%	23	38.1%	80
Superior Secondary	14.6%	20	15.1%	11	14.8%	31
University	9.5%	13	11.0%	8	10.0%	21

n: number of subjects, MZ: monozygotic, DZ: dizygotic, BMI: body mass index.
¥: indicates current smokers; ♓: indicates being moderately/extremely depressed or anxious; £: indicates the engagement in moderate/vigorous daily physical activity; €: indicates the engagement in occasional/regular physical activity.

Table 15. Longitudinal analysis sample characteristics for MZ twins discordant for activity limiting low back pain (LBP).

	Activity Limiting LBP absent		**Activity Limiting LBP present**		**Total**	
	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n
Age (years)	51.6 (6.9)	55	51.6 (7.2)	28	51.6 (7.0)	83
Gender (male)	63.3%	31	36.7%	18	59.0%	49
Gender (female)	70.6%	24	29.4%	10	41.0%	34
BMI	27.2 (3.4)	55	26.6 (3.8)	27	27.0 (3.5)	82
Smoking ¥	47.3%	26	53.6%	15	49.4%	41
Depression/anxiety♓	14.6%	8	7.1%	2	12.1%	10
Daily Physical activity£	18.2%	10	10.7%	3	15.7%	13
Leisure Physical activity€	63.6%	35	46.4%	13	57.8%	48
Educational Attainment						
Primary	30.9%	17	32.1%	9	31.3%	26
General Secondary	45.5%	25	39.3%	11	43.4%	36
Superior Secondary	9.1%	5	14.3%	4	10.8%	9
University	14.6%	8	14.3%	4	14.5%	12

n: number of subjects, MZ: monozygotic, DZ: dizygotic, BMI: body mass index.
¥: indicates current smokers; ♓: indicates being moderately/extremely depressed or anxious; £: indicates the engagement in moderate/vigorous daily physical activity; €: indicates the engagement in occasional/regular physical activity.

Supplementary material: Association between educational attainment and work-related physical activity.

Table 16. Univariate association between educational attainment and moderate/vigorous daily physical activity for the total sample of twins (2013)

	Educational Attainment	**OR**	**95% CI**	**p**
Total Sample	Primary (reference)	1.0	-	-
(n = 1574)	General Secondary	0.8	0.6 – 1.1	0.117
	Superior Secondary	0.7	0.4 – 1.0	0.038
	University	0.2	0.1 – 0.4	<0.001

n: number of individual twins; OR: odds ratio; CI: confidence interval.

Table 17. Univariate association between educational attainment and moderate/vigorous daily physical activity for the total sample of twins (2009)

	Educational Attainment	**OR**	**95% CI**	**p**
Total Sample	Primary (reference)	1.0	-	-
(n = 1571)	General Secondary	1.0	0.8 – 1.4	0.827
	Superior Secondary	0.6	0.4 – 0.9	0.015
	University	0.3	0.1 – 0.5	<0.001

n: number of individual twins; OR: odds ratio; CI: confidence interval.

CHAPTER FIVE

Does familial aggregation of chronic low back pain impact on recovery? A population-based twin study

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EPIDEMIOLOGY

Does Familial Aggregation of Chronic Low Back Pain Affect Recovery?

A Population-Based Twin Study

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Study Design. Longitudinal twin-cohort study.

Objective. To investigate the effect familial aggregation of chronic low back pain (LBP) has on the recovery from chronic LBP.

Summary of Background Data. LBP is a worldwide problem, with pain and disability often becoming chronic. Genetics and familial behaviors could significantly affect the recovery from chronic LBP but have not been extensively investigated.

Methods. A total of 624 Spanish twins from the Murcia Twin Registry reported experiencing chronic LBP within the past 2 years during the 2009/11 data collection wave and were followed up in 2013. Familial aggregation of chronic LBP was determined by the co-twin experiencing chronic LBP within the past 2 years at baseline. Twins reporting LBP ''within the past 4 weeks'' at follow-up were considered to have not recovered.

Results. There were 455 twins with available data on LBP at follow-up and available data on LBP from their co-twin at baseline. Twins with an affected co-twin at baseline were significantly more likely to have not recovered from chronic LBP at follow-up (odds ratio [OR] = 1.6, 95% confidence interval [CI]: 1.0–2.4, $P = 0.046$). This relationship was stronger for monozygotic twins (OR = 2.5, 95% CI: 1.3–4.8, $P = 0.006$) (n = 172) but disappeared when considering only dizygotic twins (OR = 1.1, 95% CI: 0.6–2.0, $P = 0.668$) (n = 283). Sibling-relative recurrence risk (λ_s) was 1.2 for the total sample, 1.5 for monozygotic twins, and 1.1 for dizygotic twins.

Conclusion. Having a sibling with chronic LBP at baseline increased the likelihood of LBP at follow-up by 20%, with this likelihood increasing to 50% if the sibling was an identical twin. These results are novel and highlight the important influence genetics have on people's recovery from chronic LBP. Information regarding the presence of chronic LBP within a family is easy to obtain and has the potential to inform clinicians on which patients are less likely to recover when treatment implementation is not considered.

Key words: chronic low back pain, dizygotic twins, familial aggregation, monozygotic twins, Murcia Twin Registry, prospective, recovery, relative recurrence risk, siblings, twin study.

Level of Evidence: 3

Spine 2017;42:1295–1301

Disability resulting from low back pain (LBP) is a worldwide problem.[1] Although most people improve within the first 6 weeks after an episode of LBP, many fail to completely recover, with pain and disability becoming chronic.[2] Numerous factors have been investigated in the recovery from chronic LBP[3] with only a few demonstrating a consistent negative effect, including a previous history of LBP[2,4] and longer symptom duration.[5] The effect of familial factors on the recovery from chronic LBP has, however, not been analyzed.

Genetics have been shown to account for up to 67% of chronic LBP cases,[6] with the family environment accounting for up to 41% of chronic LBP cases in children.[7] Therefore, among familial factors that could influence the recovery from chronic LBP, familial aggregation of chronic LBP is likely to be relevant. Familial aggregation of chronic LBP is associated with the presence of chronic LBP in adults,[8] whereas having family members suffering from chronic LBP increases the likelihood of developing chronic LBP[9] and displaying high fear avoidance beliefs about LBP.[10] Despite this, familial aggregation of chronic LBP is yet to be investigated in the recovery from chronic LBP.

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The manuscript submitted does not contain information about medical device(s)/drug(s).

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Understanding how familial aggregation of chronic LBP affects the recovery from chronic LBP will help clinicians identify those at risk of poor outcomes and potentially inform the direction of treatment. This will help extend the understanding of factors affecting recovery from chronic LBP beyond the individual and toward family. Hence, the aim of the present study is to investigate the effect familial aggregation of chronic LBP has on recovery from chronic LBP, while gaining insights into the influence of genetics and the environment.

MATERIALS AND METHODS

Participants and Data Collection

The sample for this longitudinal study was drawn from the Murcia Twin Registry (MTR), a population-based registry of adult twins born between 1940 and 1966 in the region of Murcia, Spain. Detailed information about sample recruitment practices and characteristics of the MTR can be found elsewhere.[11] Data were collected through a health-related questionnaire *via* face-to-face or phone interviews in three consecutive data waves: 2007, 2009/11, and 2013. The second data collection wave (2009/11) was performed in consecutive years for female-female pairs, male-male pairs, and opposite sex pairs in 2009, 2010, and 2011, respectively. The health-related questionnaire included information on demographics, basic health history, and lifestyle factors. Data from the 2009/11 and 2013 collection waves formed the basis of the analyses. We decided not to use data from the 2007 collection wave as limited data on LBP were collected from a smaller number of female-female pairs. Assessors were blinded to the predictor and outcomes of the present study. All registry and data collection procedures used in the MTR have been approved by the Committee of Research Ethics of the University of Murcia.

There were 2148 twins between 43 and 71 years old who provided information regarding LBP status at baseline by responding to the following question: "Have you ever suffered from chronic LBP?" Chronic LBP was considered as the presence of LBP lasting for 6 months or longer, including seasonal or recurrent episodes, and was clearly outlined to participants by a researcher involved in data collection. Those who answered "yes" were asked a follow-up question: "Have you experienced chronic LBP in the last 2 years?" There were 624 twins who answered "yes" to both questions and were included in this longitudinal analysis (Figure 1).

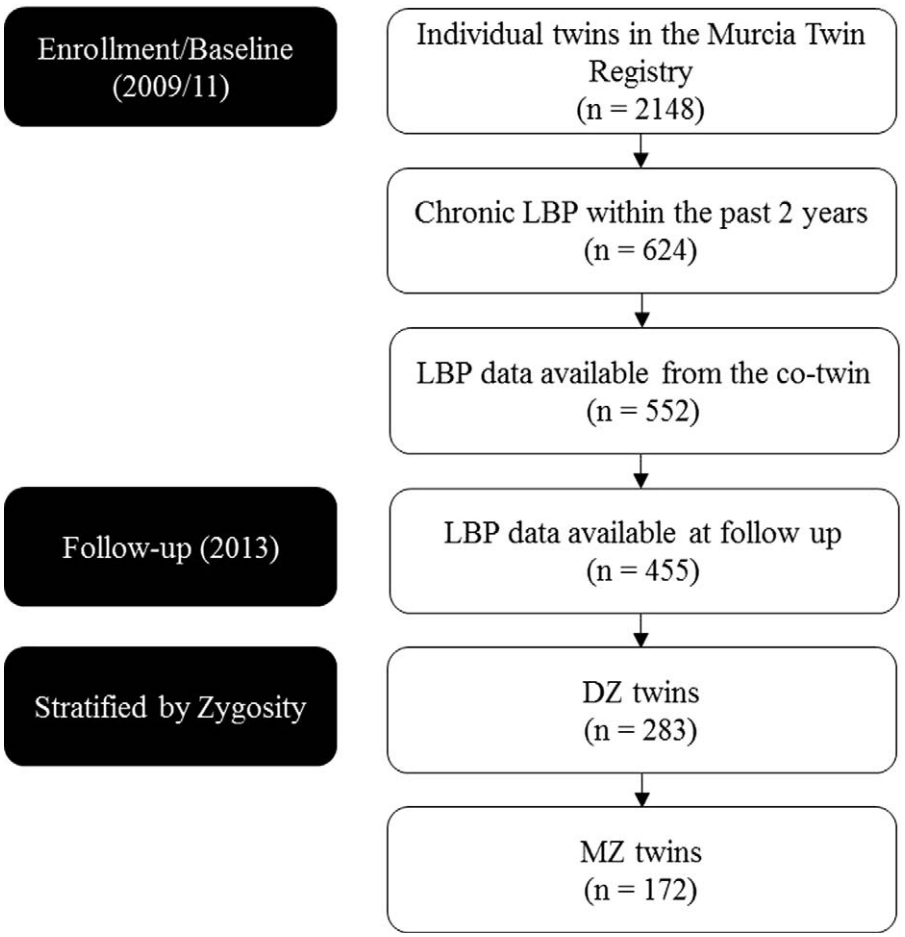

Figure 1. STROBE flow diagram. DZ indicates dizygotic; LBP, low back pain; MZ, monozygotic.

Zygosity Ascertainment

Zygosity was ascertained by a 12-item questionnaire focusing on the degree of similarity and mistaken identity between twins. This questionnaire correlates with zygosity determined by DNA in approximately 96% of the cases.[11]

Assessment of Recovery From Chronic Low Back Pain

Questions regarding LBP status at follow-up were adapted from standardized definitions developed to facilitate comparison across epidemiological studies.[12] Participants who had experienced chronic LBP in the last 2 years were asked the following question at follow-up: "When was the last time you experienced LBP?" Participants who selected "within the past 4 weeks" were considered to have not recovered from chronic LBP. This definition is based on the best available evidence, suggesting being pain-free for the duration of a month is sufficient to infer recovery.[13]

Assessment of Familial Aggregation of Chronic Low Back Pain

Familial aggregation of chronic LBP (predictor variable) was determined by the co-twin suffering from chronic LBP within the past 2 years at baseline.

Assessment of Covariables

We selected potential confounders based on previous literature and data availability including: age, sex, body mass index, smoking, sedentary behavior, symptoms of depression/anxiety, and sleep quality. Data on body mass index were either self-reported (67.4%) or objectively measured (32.6%). Data on smoking and sedentary behavior were based on the Spanish National Health Survey Questionnaire.[14] Smoking was dichotomized as ex-smoker/never smoked or current smoker. Sedentary behavior was determined by participants' engagement in leisure and daily physical activities. Leisure physical activity was assessed by participants selecting one of the following options: (i) I do not practice exercise. My leisure time is mostly sedentary (reading, watching, TV, movies, *etc.*); (ii) sport or physical activity occasionally (walking, gardening, soft gym, light efforts, *etc.*); (iii) regular physical activity several times a month (tennis, jogging, swimming, cycling, team sports, *etc.*); (iv) physical training several times a week. Responses were dichotomized as no physical activity/sedentary (i) or occasional/regular physical activity (ii, iii, and iv). Daily physical activity was assessed by participants selecting one of the following options: (i) sitting most of the time; (ii) standing. No big movements or effort; (iii) walking, carrying light weights, moving but no big effort; (iv) tasks that require physical effort. Responses were dichotomized as no/low physical activity engagement (i and ii) or moderate/vigorous physical activity engagement (iii and iv). Participants who had engaged in no leisure physical activity and no/low daily physical activity were considered sedentary. Symptoms of depression/anxiety were assessed by participants selecting one of the following options based on the depression/anxiety domain of the EuroQol-5 dimension: (i) I am not anxious or depressed; (ii) I am moderately anxious or depressed; (iii) I am extremely anxious or depressed. Responses were dichotomized as not depressed or anxious (i) or moderately/extremely depressed or anxious (ii and iii). Sleep quality was assessed by participants' score on the Spanish version of the Pittsburgh Sleep Quality Index. Responses were dichotomized as poor sleep quality (score >5) or good sleep quality (score ≤ 5).[15]

Analysis

First, we conducted analyses to identify whether familial aggregation of chronic LBP affected the recovery from LBP. Univariate logistic regressions were performed to identify possible confounders that should enter the multivariate logistic regression models. Covariables were included in multivariate models if the *P* values from the univariate relationship between the covariables, and both the predictor and outcome were <0.2. Because baseline data were collected between 2009/11 we adjusted all analyses for follow-up length. Twin pairs were considered as clusters to account for their nonindependence. To gain insights into the role of genetics as a familial predictor of recovery, we stratified analyses by zygosity. Dizygotic (DZ) twins share on average 50% of their segregating genes, whereas monozygotic (MZ) twins share approximately 100% of their segregating genes.[16] Therefore, if the association is similar between analyses regardless of zygosity, this is likely to suggest genetics are less influential as a familial predictor of recovery. If the magnitude of the association is, however, higher for MZ twins, this is likely to suggest genetics play an important role as a familial predictor of recovery. Analyses were conducted using STATA statistical software (version 13.1) with the significance level set at.05. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the regression models.

Second, we calculated the sibling recurrence relative risk (λ_s). For our study, λ_s represents the risk of nonrecovery from chronic LBP in the presence of an affected sibling (chronic LBP at baseline), compare to the risk of nonrecovery in the total sample (population prevalence). This is a commonly reported measure of familial aggregation, and has been adapted to reduce the bias when considering conditions with a high prevalence (*e.g.*, LBP).[17] We calculated λ_s using the formula

$$\lambda_s = \frac{\mathrm{OR}}{1 - \mathrm{Prev} + \mathrm{OR}(\mathrm{Prev})}$$

where "OR" is the odds of nonrecovery from chronic LBP given a co-twin with chronic LBP at baseline, and "Prev" is the prevalence of nonrecovery at follow-up in the total sample.

RESULTS

Sample Characteristics

There were 552 twins that experienced chronic LBP within the past 2 years at baseline and had available data from their

co-twin. Of these 552 twins, 455 had data on LBP at follow-up and were included in the following analyses. A total of 183 twins (MZ = 83, DZ = 100) had an affected co-twin and 272 twins (MZ = 89, DZ = 183) did not (Table 1). The prevalence of nonrecovery was 44.2% in the total sample, 44.5% in DZ twins, and 43.6% in MZ twins. The mean age (standard deviation) of participants was 53.5 (7.0) years old, with 330 women (72.5%) and 172 MZ twins (37.8%). Twins with an affected co-twin were more likely to have poor sleep quality (64.5% *vs* 55.5%).

Familial Aggregation of Chronic Low Back Pain and Recovery

In our adjusted analyses, participants with a co-twin reporting chronic LBP at baseline were significantly less likely to recover from LBP at follow-up (OR = 1.6, 95% CI: 1.0–2.4, $P = 0.046$, n = 455; Table 2), with familial aggregation of chronic LBP significantly affecting MZ twins (OR = 2.5, 95% CI: 1.3–4.8, $P = 0.006$, n = 172) but not DZ twins (OR = 1.1, 95% CI: 0.6–2.0, $P = 0.668$, n = 283; Figure 2). The total sample analysis was adjusted for sex and sleep quality. When the analyses were stratified by zygosity, no covariables entered the multivariate models.

Sibling Recurrence Risk Ratio (λ_s)

Using the OR from our multivariate logistic regression models, and the prevalence of nonrecovery, we calculated λ_s. Having a twin (sibling) with chronic LBP at baseline appears to increase the risk of nonrecovery at follow-up ($\lambda_s = 1.2$), with a higher risk in MZ twins ($\lambda_s = 1.5$) compared to DZ twins ($\lambda_s = 1.1$) (Table 2).

DISCUSSION

Familial aggregation of chronic LBP increases the risk of not recovering from chronic LBP, with genetics appearing to play a role in this relationship. These results have implications for extending the understanding of factors affecting the recovery from chronic LBP beyond the individual and toward familial factors. Further research in this area has the potential to assist clinicians identify those at risk of nonrecovery.

Familial Aggregation of Chronic Low Back Pain and Recovery

A sample of twins was utilized in the present study to gain insight into the role of genetics in the recovery from chronic LBP. Our results showed that having a co-twin with chronic LBP at baseline significantly predicted nonrecovery at follow-up (OR = 1.6, 95% CI: 1.0–2.4, $P = 0.046$). When this analysis was, however, stratified by zygosity, the magnitude of the relationship increased for MZ twins (OR = 2.5, 95% CI: 1.3–4.8, $P = 0.006$) and decreased for DZ twins (OR = 1.1, 95% CI: 0.6–2.0, $P = 0.668$). Because MZ twins share approximately 100% of their segregating genes, whereas DZ twins only share approximately 50%,[16] the increase in magnitude when considering only MZ twins is

TABLE 1. Sample Characteristics of Participants With Low Back Pain at Baseline and Data on Low Back Pain at Follow-up

	Co-twin With LBP at Baseline				Co-twin Without LBP at Baseline			
Variables	MZ Mean (SD) or %	n	DZ Mean (SD) or %	n	MZ Mean (SD) or %	n	DZ Mean (SD) or %	n
Confounding variables (baseline)								
Age (yr)	51.9 (6.1)	83	53.9 (7.1)	100	51.3 (6.5)	89	55.0 (7.2)	183
Males	14.5%	12	26.0%	26	32.6%	29	31.7%	58
Females	85.5%	71	74.0%	74	67.4%	60	68.3%	125
BMI	27.3 (5.4)	80	27.6 (4.7)	99	27.6 (4.9)	88	28.0 (5.4)	177
Smoking*	47.0%	39	44.4%	44	49.4%	44	37.2%	68
Sedentary†	48.2%	40	42.4%	42	40.5%	36	42.3%	77
Depression‡	37.0%	30	33.0%	33	21.4%	19	37.2%	68
Sleep quality§	63.9%	53	65.0%	65	51.7%	46	57.4%	105
Outcome variable (follow-up)								
LBP within the past 4 weeks	55.4%	46	45.0%	45	32.6%	29	44.3%	81

*Indicates current smokers.

†Indicates the engagement in no/low daily physical activity and no leisure physical activity.

‡Indicates being moderately/very depressed or anxious.

§Indicating the presence of sleep disturbance (>5 on the PSQITOT scale).

BMI indicates body mass index; DZ, dizygotic; LBP, low back pain; MZ, monozygotic; n, number of subjects.

TABLE 2. The Effect of Familial Aggregation of Chronic Low Back Pain on Recovery and the Sibling Recurrence Relative Risk (λ_s)

	OR	95% CI	*P*	λ_s
Total sample—unadjusted (n = 455)	1.5	1.0–2.2	0.064	1.2
Total sample (n = 455)*	1.6	1.0–2.4	0.046*	1.2
DZ (n = 283)	1.1	0.6–2.0	0.668	1.1
MZ (n = 172)	2.5	1.3–4.8	0.006*	1.5

*Adjusted for sex and sleep quality. All analyses were adjusted for follow-up length unless reported as unadjusted.
CI indicates confidence interval; DZ, dizygotic; MZ, monozygotic; OR, odds ratio.

likely reflecting the role of genetics in the recovery from chronic LBP. Furthermore, the results from our sibling recurrence relative risk analysis demonstrated the risk of non-recovery increases 1.2 times in the presence of a sibling who has suffered from chronic LBP. This risk was higher in MZ twins ($\lambda_s = 1.5$), but lower in DZ twins ($\lambda_s = 1.1$), consistent with an influence of genetics factors in the recovery from chronic LBP.

Our study did not intend to explain why familial aggregation of chronic LBP affects recovery, and although genetics appear to be playing a role, additional hypotheses deserve attention. Our results appear to be consistent with existing research highlighting the negative impact having family members suffering from chronic LBP have on the prevalence,[8] and risk[9] of chronic LBP. Therefore, one possible explanation is that negative beliefs about chronic LBP, shown to be associated with greater pain and disability,[18] may have been shared among twin pairs concordant for chronic LBP, negatively affecting recovery.[19] Twin pairs share numerous environmental factors throughout their childhood,[16] with a strong twin bond potentially influencing each other's beliefs. Furthermore, it has been suggested that MZ twins share a stronger bond compared with DZ twins.[20] The possibility of this bond increasing the influence of each other's beliefs and potentially explaining why familial aggregation of chronic LBP had a greater effect on MZ twins cannot be ruled out. Finally, having an adult sibling with LBP appears to have a larger effect on LBP outcomes than having parents or children with LBP.[21] Therefore, shared beliefs between adult siblings in our study might explain the strong effect familial aggregation of chronic LBP has on recovery.

Strengths and Limitations

Our study has numerous strengths. First, we employed strict criteria for the adjustment of confounding variables. Although it is not always necessary to adjust for confounders in prognostic cohort studies, adjusting for strong known confounders allows us to make these results more generalizable.[22] Secondly, we were able to use subjective data from co-twins to inform on the familial aggregation of chronic LBP. We believe this is more accurate than participants reporting on behalf of their family members, which has previously been employed in studies investigating familial aggregation of LBP.[8,9,23] Thirdly, stratifying the analyses by zygosity, while performing a sibling recurrence relative risk analysis, provided insights on the contribution of genetics, which previous studies in the field have been unable to achieve. Finally, the sample of twins used in the present study are representative of the general population from

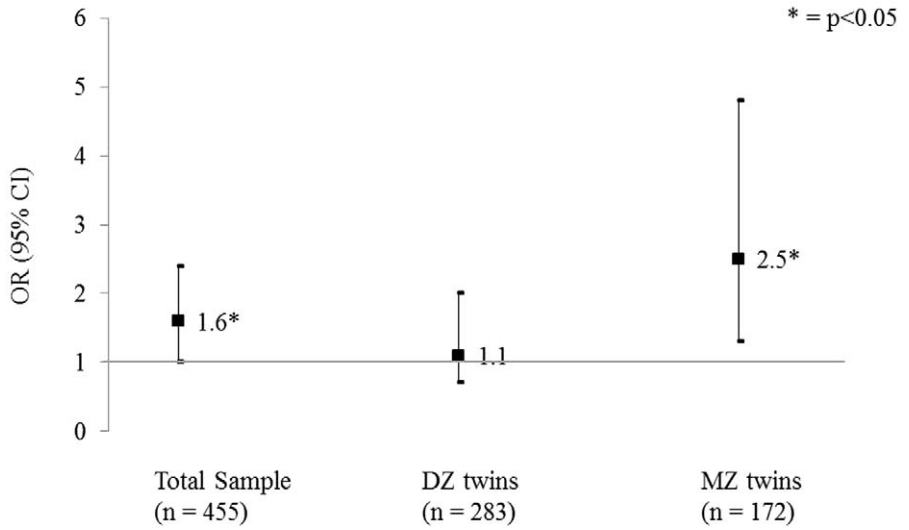

Figure 2. The effect of familial aggregation of chronic LBP on recovery. CI indicates confidence interval; DZ, dizygotic; LBP, low back pain; MZ, monozygotic; OR, odds ratio.

which they were drawn and can be considered representative of the nontwin population for the prevalence of numerous diseases, including LBP.[24] Our study, however, pre- sented a few limitations which need to be considered. First, our assessment of chronic LBP at baseline was based on the following question: ''Have you experienced chronic LBP in the last 2 years?'' As a result, participants at baseline did not necessarily experience chronic LBP at study entry. Second, our outcome variable for the recovery from chronic LBP gives us an indication of whether the participant experienced LBP within the past 4 weeks, but does not give us information on LBP disability or pain intensity. Because these data were not collected from participants specifically for this episode of LBP, we were unable to investigate whether familial aggregation of chronic LBP affects disability or pain intensity at follow-up. In addition, baseline data on care seeking and treatment would have been valuable to determine whether the effect familial aggregation of chronic LBP has on recovery is moderated by ongoing treatment. Third, we did not have adequate data on LBP from the 2007 collection wave, and did not have data on LBP between assessment points. This information would have been valuable for analyzing the recurrence or persistence of LBP symptoms over time. Finally, our definition of familial aggregation of chronic LBP only considered data from the co-twin, without considering characteristics of the whole family. This would, however, likely underestimate the true effect of familial aggregation, because both twins with, or without a co-twin with chronic LBP may have had other family members with chronic LBP.

Clinical Implications

Obtaining information from patients regarding family history of chronic LBP has the potential to inform which patients are less likely to recover, and help clinicians make more accurate prognosis. More importantly, an understanding of the mechanisms behind familial aggregation of chronic LBP and nonrecovery (such as the relative contribution of genetics and environmental factors to LBP) may have the potential to inform the direction of treatment. For example, if negative beliefs about LBP have been passed on by family members with chronic LBP and are significantly affecting recovery, providing the appropriate reassurance and education could be extremely valuable. In addition, the plausibly important role of genetics on the prognosis of chronic LBP should lead to attempts to identify genetic variants for these phenotypes. Therefore, further studies on quantitative and molecular genetics (*e.g.*, genome-wide association studies) should investigate the pathways between familial aggregation of chronic LBP and nonrecovery to build on these results.

CONCLUSION

Familial aggregation of chronic LBP significantly predicted nonrecovery, with genetics playing a role in this relationship. Although previous research has considered familial factors associated with LBP, the present study is the first to investigate how familial aggregation affects recovery. Future research should further explore familial aggregation in the recovery from LBP, and investigate the mechanisms behind familial predictors of nonrecovery.

➢ Key Points

- ❑ Familial aggregation of chronic LBP increases the risk of not recovering from chronic LBP.
- ❑ Genetics appear to play a role in the recovery from chronic LBP, with familial aggregation of chronic LBP having a larger effect on nonrecovery in identical twins than in fraternal twins.
- ❑ The presence of chronic LBP within a family has the potential to inform clinicians on which patients are less likely to recover and may guide future management strategies.

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CHAPTER SIX

The Beneficial Effects of Physical Activity: Is It Down to Your Genes? A Systematic Review and Meta-Analysis of Twin and Family Studies

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SYSTEMATIC REVIEW Open Access

The Beneficial Effects of Physical Activity: Is It Down to Your Genes? A Systematic Review and Meta-Analysis of Twin and Family Studies

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Abstract

Background: There is evidence for considerable heterogeneity in the responsiveness to regular physical activity (PA) which might reflect the influence of genetic factors. The aim of this systematic review was to assess whether the response to a PA intervention for measures of body composition and cardiorespiratory fitness is (i) correlated within twin pairs and/or families and (ii) more correlated in monozygotic twins (MZ) compared to dizygotic twins (DZ), which would be consistent with genetic effects.

Methods: We performed electronic database searches, combining key words relating to "physical activity" and "genetics", in MEDLINE, CINAHL, EMBASE, SPORTS Discuss, AMED, PsycINFO, WEB OF SCIENCE, and SCOPUS from the earliest records to March 2016.
Twin and family studies were included if they assessed body composition and/or cardiorespiratory fitness following a PA intervention, and provided a heritability estimate, maximal heritability estimate, or within MZ twin pair correlation (r_{MZ}).
Data on heritability (twin studies), maximal heritability (family studies), and the r_{MZ} were extracted from included studies, although heritability estimates were not reported as small sample sizes made them uninformative.

Results: After screening 224 full texts, nine twin and five family studies were included in this review. The pooled r_{MZ} in response to PA was significant for body mass index ($r_{MZ} = 0.69$, $n = 58$), fat mass ($r_{MZ} = 0.58$, $n = 48$), body fat percentage ($r_{MZ} = 0.55$, $n = 72$), waist circumference ($r_{MZ} = 0.50$, $n = 27$), and VO_2max ($r_{MZ} = 0.39$, $n = 48$), where "n" represents the total number of twin pairs from all studies. Maximal heritability estimates ranged from 0–21% for measures of body composition, and 22–57% for cardiorespiratory fitness.
Twin studies differed in sample age, baseline values, and PA intervention, although the exclusion of any one study did not affect the results.

Conclusions: Shared familial factors, including genetics, are likely to be a significant contributor to the response of body composition and cardiorespiratory fitness following PA.
Genetic factors may explain individual variation in the response to PA.

Trial Registrations: PROSPERO Registration No CRD42015020056.

Keywords: Genetics, Heritability, Familial aggregation, Physical activity, Body composition, Cardiorespiratory fitness

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Key points

- Shared familial factors, including genetics, are likely to play a stronger role in the response of body composition when compared to cardiorespiratory fitness.
- The response of body mass index, fat mass, and body fat percentage to PA appear to be more dependent on shared familial factors than measures such as waist-to-hip ratio.
- These results have implications for the management of conditions which advocate increased levels of PA, since shared familial factors, including genetics, might serve as an explanation for why some people respond more effectively than others in specific measures of PA.

Background

Engagement in regular physical activity (PA) is one of the most important aspects for maintaining optimal health and is recommended for reducing the risk of numerous diseases (including cardiovascular disease) in people of all ages [1–4]. In addition, PA is used as a non-pharmacological treatment option for coronary heart disease [5], osteoporosis [6], rheumatoid arthritis [7], anxiety disorders [8], and a variety of musculoskeletal conditions, including low back pain [9]. Although the benefits of PA are numerous, their positive effects on cardiorespiratory fitness [e.g., maximal oxygen uptake (VO_2max)] and measures of body composition [e.g., body mass index (BMI)] [10] deserve special attention, due to their subsequent influence on cardiovascular disease and mortality rates. Cardiorespiratory fitness is a strong and independent risk factor for cardiovascular disease and all-cause mortality [11], with up to 7% of deaths being attributed to low cardiorespiratory fitness [12]. Similarly, high values of body composition measures, such as BMI and waist circumference, are significantly associated with greater all-cause [13] and CVD-related mortality [14].

Although the benefits of PA are clear and substantial, research has demonstrated that genetic factors have a strong influence on PA engagement [15], with the heritability of time-spent in moderate-to-vigorous intensity PA estimated at 47% [16]. In addition, not everyone engaged in PA will benefit to the same extent, with strong evidence for considerable heterogeneity in the responsiveness to regular PA [17–19]. This variation might also reflect the influence of genetic factors.

Twin and family studies are commonly used to investigate the extent to which shared familial factors, including genetics, contribute to the variation of a phenotype. Monozygotic (MZ) twins share 100% of their segregating genes, while dizygotic (DZ) twins share 50% on average. If genes influence a phenotype, we would expect to see a greater correlation for MZ twins than for DZ twins, and if genes are the only influence on a phenotype the ratio should be 2:1, with a heritability estimate of 100%. Smaller differences between the correlations would indicate that shared environmental effects are involved, with the shared environment referring to the exposure to similar environmental (non-genetic) factors within twin pairs (e.g., nutrition, physical activity, childhood experiences, parental beliefs and values, socioeconomic status, etc.). Family studies can estimate maximal heritability using correlations between parent-offspring pairs and siblings (sometimes adjusted for correlation between spouses) [19]. However, unlike heritability estimates from twin studies, these studies are unable to tease apart the contribution from genetic and shared environmental factors. This is because different proportions of genetic sharing are required to separate genetic and shared environmental sources of variation, and in nuclear families parent-offspring pairs and sibling-pairs share equal proportions of their genes (50%). Although we can estimate spouse correlations, we cannot tell whether this correlation is due to shared genes (assortative mating) or shared environmental factors.

The role of both genetic and environmental factors shared within families in the response to a PA intervention has been investigated in a number of studies. MZ twin pairs who completed a standardized PA intervention demonstrated great variation in the amount of weight lost between twin pairs, but only a small amount of variation within twin pairs [20]. In addition, individual differences in the response of VO_2max following an exercise program were 2.5 times more variable between families than within families [19]. These results suggest that factors shared within families, including genes, play a role in the response to a PA intervention, although their exact contribution, across measures of body composition and cardiorespiratory fitness, are not well understood. A better understanding of the contribution genetics and shared environmental effects make to people's response to PA may help health practitioners understand the possible reasons behind individual variation in response to a PA targeted intervention, and why some patients demonstrate a more favorable response.

The aim of this systematic review is to obtain quantitative estimates of twin correlations (both MZ and DZ), heritability (from twin studies), and maximal heritability (from family studies), for measures of body composition and cardiorespiratory fitness in response to a PA intervention.

Methods

Search Strategy

We conducted a systematic review and meta-analysis in accordance with the "Preferred reporting items for

systematic reviews and meta-analyses" (PRISMA) statement [21]. The protocol for this systematic review has been registered on PROSPERO (Registration No: CRD42015020056). We performed electronic database searches in MEDLINE, CINAHL, EMBASE, SPORTS Discuss, AMED, PsycINFO, WEB OF SCIENCE, and SCOPUS from the earliest records to May 2015. The search was then updated in March 2016. We used a comprehensive key word search strategy (Additional file 1) combining key words relating to PA (e.g., "physical activi*" OR "exercise" OR "resistance training" etc.) and genetics (e.g., "genetic*" OR "herita*" OR "family resemblance" etc.). The search strategy remained sensitive to capture all outcomes related to body composition and cardiorespiratory fitness. To identify additional studies we performed a hand search of the reference lists from included papers.

Study Selection

Two reviewers (TA and JZ) independently performed the selection of studies and consensus was used to resolve any disagreement. Studies were included if they investigated clinically relevant outcome measures of body composition or cardiorespiratory fitness following a PA or exercise intervention (referred to hereafter as PA interventions) amongst twin pairs and/or family members. Studies investigating a PA intervention in combination with other interventions (e.g., diet) were included. We included randomised controlled trials and case series provided they reported a within MZ twin pair correlation (r_{MZ}), heritability estimate (from a twin study), or maximal heritability estimate (from a family study). Heritability estimates and the r_{MZ} for the response of an intervention (based on change scores) are commonly reported in studies where twin pairs are considered as clusters, with the treatment effect as a fixed variable [22]. To investigate the intra-pair resemblance in the response to PA it is essential that twin pairs participate in an identical intervention. This is similar to the methodology employed in family studies to obtain a maximal heritability estimate (where the variance explained by genetic and shared environmental factors cannot be teased apart). Therefore, we decided not to use methodological quality as part of the inclusion/exclusion criteria as it is not practical to consider items commonly assessed in systematic reviews of randomized controlled trials (such as allocation concealment, blinding, and intention-to-treat) [23] when considering this study design. It is unlikely results from twin and family studies investigating heritability are subject to publication bias, since the contribution of genetics and shared environment is relevant regardless of whether the estimates are small or large. However, we acknowledge the possibility that individual studies may only report results for traits that demonstrate a high heritability. To minimize the risk of reporting bias, we contacted authors when there was data available on body composition and cardiorespiratory fitness but within twin pair correlations were not reported. Observational studies or studies only assessing the heritability of PA engagement, without a PA intervention, were excluded. There was no restriction on the age or gender of participants, nor the type of PA intervention investigated. We included published conference abstracts and dissertations provided they met the inclusion criteria.

Data Extraction

Two reviewers (DS and JZ) independently performed the extraction of data. A standardized data extraction form was used to collect data on participants' characteristics (age, gender, and zygosity), sample size, prescribed PA intervention (frequency, intensity, duration, and type), co-prescription of other interventions (e.g., diet), outcomes assessed, loss to follow up, and study type.

Data Analysis

Data on correlation (r), equality of variances (F), heritability (h^2), and maximal heritability were extracted from included studies. In family studies, "heritability" estimates were derived from the familial correlation model and termed "maximal heritability", since the model is unable to partition the variance explained by genetic and non-genetic sources shared within families [24]. In twin studies, heritability estimates were calculated from the following formula: $h^2 = 2(r_{MZ}-r_{DZ})$, where r_{DZ} is the within DZ twin pair correlation. When h^2 was greater than 1 we used r_{MZ} as the heritability estimate, since it is not possible for genetics to contribute more than 100% to the variance of a phenotype. In addition, if there were no data available for DZ twins, we used r_{MZ} as an estimate of the upper bound of heritability (including variance from genetic and shared environmental factors). In cases where the F-ratio was reported but the r_{MZ} was not, we used the following formula to calculate r_{MZ} as described by Haggard: $r = (F-1)/(F+1)$ [25]. Authors were contacted when required data were not published. When raw data were obtained from twin studies, we attempted to fit variance components models to change scores in order to estimate the r_{MZ} and r_{DZ} simultaneously and formally compare models in which these two parameters were forced to be equal with models in which they were allowed to differ. However, for many phenotypes the models could not be fitted or failed to converge due to small sample sizes (no results shown from these models). Instead, for all phenotypes, and separately for MZ and DZ twin pairs, we performed a one-way (twin pair identifier) analysis of variance with change score as the outcome (calculated from the pre

and post-intervention raw data). Specifying change score as a repeated measure within a twin pair in the models enabled calculation of the within twin pair correlation. When possible and applicable, we adjusted the analyses for age, gender, and baseline values [22]. If studies were considered homogenous in terms of outcomes and PA interventions, we performed a meta-analysis using Comprehensive Meta-Analysis Version 3.0. Additionally, if there were enough studies investigating PA interventions of varying durations, the co-prescription of other interventions (e.g., diet), or analyzing data from males and females separately, we sub-grouped our meta-analyses accordingly. If pooling data on heritability/maximal heritability was not possible (from either twin or family studies), we attempted to pool data on the r_{MZ}. Data on correlation and sample size from each study with greater than or equal to four twin pairs (the minimum number of observations allowed to be entered into the software) was used to provide a pooled estimate of the r_{MZ}, 95% confidence interval (CI), and p-value. Heterogeneity between studies was assessed using the I^2 statistic. An I^2 value <25% indicates low heterogeneity between studies. We used fixed-effects where I^2 was <50% and random-effects when I^2 was ≥50% (moderate heterogeneity). We did not display pooled estimates where the I^2 value indicated high heterogeneity (≥75%) [26].

Results

Description of Studies

The comprehensive key word search yielded 27,830 results, with one additional study retrieved from hand searching the reference lists of included studies. After removing duplicates and screening titles and abstracts there were 224 full texts which were screened. A total of 14 studies (nine twin and five family studies) were included in this systematic review, with eight twin studies forming the basis for our meta-analyses (Fig. 1). The nine twin studies included data from a total of 83 complete MZ twin pairs, and 15 complete DZ twin pairs, with no twin pairs used in more than one study (as confirmed by authors named in multiple included studies). The five family studies were based off the same sample of 199 families (which did not include any twin pairs). Although there were numerous twin and family studies similar in design and outcomes, we were unable to pool heritability estimates for any outcomes for two main reasons. First, there were an insufficient number of family studies deriving results from independent samples. Second, although we were able to obtain heritability estimates from three twin studies, these estimates were uninformative since the 95% CI covered the whole range (0,1) (apart from Danis and colleagues who estimated heritability without utilizing DZ twins in its design [27]), and differences between the r_{MZ} and r_{DZ} were not statistically significant (Table 1).Instead, we were

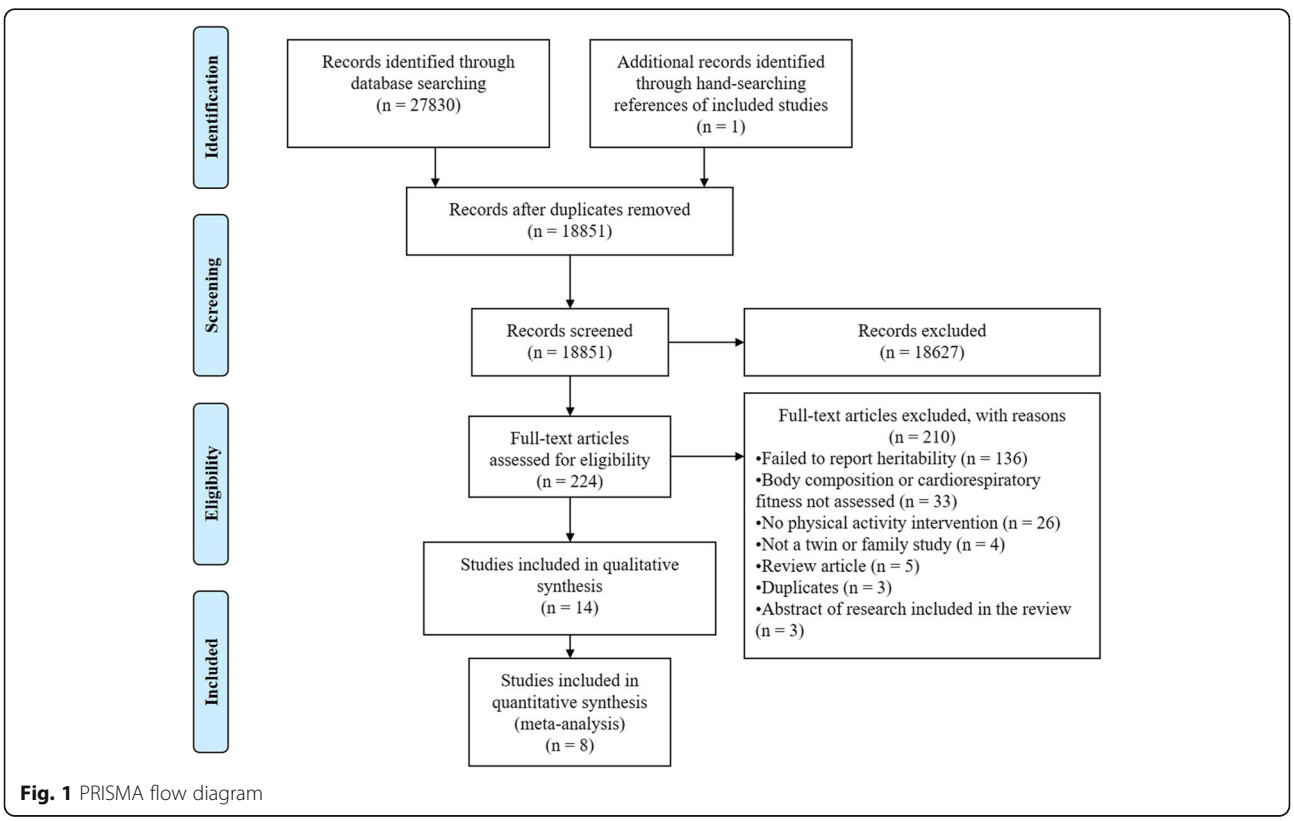

Fig. 1 PRISMA flow diagram

Table 1 Within MZ and DZ twin pair correlations for the response of body composition and cardiorespiratory fitness following a physical activity intervention in twin studies

Author (year)	Sample	Age [mean (SD)]	Baseline status [mean (SD)]	Within MZ correlation (95% CI)	Within DZ correlation (95% CI)	Between MZ and DZ correlation significance[d]
Body fat percentage (%)						
Hopkins ND (2012)[a]	6 MZ (1 male and 5 female) and 6 DZ (2 male and 4 female) twin pairs	MZ: 13.5 (0.8) DZ: 13.4 (0.8)	MZ: 27.1 (6.9) DZ: 26.0 (11.3)	0.63 (−0.37 to 0.95)	0.31 (−0.67 to 0.90)	$p = 0.606$
Afman G (1988)[b]	18 MZ (2 males and 16 females) and 9 DZ (3 males and 6 females) twin pairs	MZ: 19.0 (1.4) DZ: 19.4 (1.8)	MZ: 21.3 (9.0) DZ: 19.9 (7.2)	0.61 (0.20 to 0.84)	0.50 (−0.25 to 0.87)	$p = 0.742$
Danis A (2003)	9 MZ male twin pairs	11–14[c]	E: 17.8 (4.1) C: 16.8 (2.8)	*	*	$h^2 = 69\%$**
BMI						
Hopkins ND (2012)[a]	6 MZ (1 male and 5 female) and 6 DZ (2 male and 4 female) twin pairs	MZ: 13.5 (0.8) DZ: 13.4 (0.8)	MZ: 21.5 (3.5) DZ: 21.9 (3.5)	0.81 (0.00 to 0.98)	0.57 (−0.45 to 0.94)	$p = 0.557$
Afman G (1988)[b]	16 MZ (3 males and 13 females) and 6 DZ (2 males and 4 females) twin pairs	MZ:18.6 (1.1) DZ: 19.3 (1.3)	MZ: 21.9 (1.9) DZ: 22.6 (3.7)	0.42 (−0.10 to 0.76)	0.00 (−0.81 to 0.81)	$p = 0.485$
Weight (kg)						
Hopkins ND (2012)[a]	6 MZ (1 male and 5 female) and 6 DZ (2 male and 4 female) twin pairs	MZ: 13.5 (0.8) DZ: 13.4 (0.8)	MZ: 59.0 (11.5) DZ: 58.9 (12.6)	0.89 (0.28 to 0.99)	0.00 (−0.81 to 0.81)	$p = 0.091$
Afman G (1988)[b]	19 MZ (3 males and 16 females) and 9 DZ (3 males and 6 females) twin pairs	MZ: 18.7 (1.0) DZ: 19.4 (1.8)	MZ: 60.4 (10.6) DZ: 67.1 (13.4)	0.53 (0.10 to 0.79)	0.13 (−0.58 to 0.73)	$p = 0.337$
Fat free mass						
Hopkins ND (2012)[a]	6 MZ (1 male and 5 female) and 6 DZ (2 male and 4 female) twin pairs	MZ: 13.5 (0.8) DZ: 13.4 (0.8)	MZ: 69.9 (6.8)% DZ: 69.9 (6.8)%	0.52 (−0.50 to 0.94)	0.34 (−0.65 to 0.90)	$p = 0.785$
Afman G (1988)[b]	19 MZ (3 males and 16 females) and 9 DZ (3 males and 6 females) twin pairs	MZ: 18.9 (1.4) DZ: 19.4 (1.8)	MZ: 48.2 (8.1) kg DZ: 53.2 (13.2) kg	0.40 (−0.07 to 0.72)	0.18 (−0.55 to 0.75)	$p = 1.000$
Relative VO_2 max ($mL.kg^{-1}min^{-1}$)						
Hopkins ND (2012)[a]	6 MZ (1 male and 5 female) and 6 DZ (2 male and 4 female) twin pairs	MZ: 13.5 (0.8) DZ: 13.4 (0.8)	MZ: 44.4 (8.1) DZ: 45.7 (8.1)	0.43 (−0.59 to 0.92)	0.21 (−0.73 to 0.87)	$p = 0.763$
Afman G (1988)[b]	19 MZ (3 males and 16 females) and 9 DZ (3 males and 6 females) twin pairs	MZ: 18.9 (1.4) DZ: 19.4 (1.8)	MZ: 33.3 (7.3) DZ: 37.1 (8.0)	0.44 (0.00 to 0.74)	0.00 (−0.66 to 0.66)	$p = 0.324$
Danis A (2003)	9 MZ male twin pairs	11–14[c]	E: 52.1 (3.6) C: 54.0 (3.9)	*	*	$h^2 = 44\%$**
Absolute VO_2 max ($L.min^{-1}$)						
Afman G (1988)[b]	20 MZ (3 males and 16 females) and 9 DZ (3 males and 6 females) twin pairs	MZ: 18.9 (1.4) DZ: 19.4 (1.8)	MZ: 2.0 (0.6) DZ: 2.5 (0.9)	0.44 (0.00 to 0.74)	0.00 (−0.66 to 0.66)	$p = 0.320$
Danis A (2003)	9 MZ male twin pairs	11–14[c]	E: 2.1 (0.4) C: 2.1 (0.4)	*	*	$h^2 = 54\%$**

MZ monozygotic, *DZ* dizygotic, *E* experimental group, *C* control group, *SD* standard deviation, *CI* confidence interval, h^2 heritability, VO_2 *max* maximal oxygen uptake, *BMI* body mass index

*No reported correlation due to a different method used to estimate heritability

**Unable to calculate the standard error and thus present the 95% CI

[a]Within twin pair correlations (95% CI) extracted from the publication

[b]Within twin pair correlations (95% CI) calculated from raw data

[c]Did not report a mean age (SD)

[d]Unable to calculate the within MZ and DZ twin pair correlations for Danis A (2003) due to methodology, so the h^2 is presented instead

able to pool the r_{MZ} for selected outcomes, giving us quantitative estimates of the upper bound of heritability. Included studies that reported more than one outcome measure were used in multiple meta-analyses.

The characteristics of the included twin and family studies, including sample size, age, baseline PA status, and PA intervention are described in Tables 2 and 3. The mean age [standard deviation (SD)] of participants ranged from 13 (1) to 39 (2) in twin studies, and 17 to 65 years in family studies. At study entry, participants were mostly sedentary or engaged in light PA but not highly physically trained. Only two twin studies [20, 28] analysed data from twin pairs living apart at the time of enrolment [mean age (SD) 30 (8) and 39 (2), respectively], while another reported that more than 50% of the twin pairs were living together at this time [mean age (SD) 19 (2)] [29]. Every study recruited healthy individuals from the community, except Hainer and colleagues

Table 2 Characteristics of twin studies

Twin studies					
Author (year)	Sample*	Age [mean (SD)]	Baseline physical activity status	Physical activity intervention	Diet intervention
Poehlam A (1987)	6 MZ male twin pairs	19 (1.3)	Sedentary	F: 22 consecutive days I: 56% VO2 max T: 116 min per day T: Cycle ergometer	Energy balance deficit of ~4.2 MJ/day
Koenigstorfer J (2011)	6 MZ females twin pairs	30 (8)	Sedentary	F: 3 times per week (aerobic) and 2 times per week (strength) for 8 weeks I: 68% (±8%) heart rate maximum (aerobic) and 70% of 12 repetition maximum (12RM) T: 45 min each T: Cycle ergometer and strength training (crunches, butterfly crunches, leg press, leg curl, and latissimus pull down)	Individual counseling for a low fat (25%), hypocaloric diet (5.0–5.8 MJ/day) in accordance with their usual eating patterns and preferences
Hopkins ND (2012)	6 MZ (1 male and 5 female) and 6 DZ (2 male and 4 female) twin pairs	MZ: 13.5 (0.8) DZ: 13.4 (0.8)	Light and moderate physical activity	F: 3 times per week for 8 weeks I: 65–85% heart rate maximum T: 45 min T: gym-based aerobic exercise	None
Bouchard C (1994)	7 MZ male twin pairs[a]	21.0 (2.7)	Sedentary	F: Twice per day every 9 of 10 days for 93 days I: 50–55%VO_2 max T: 60 min T: Cycle ergometer	Energy balance deficit of ~4.2 MJ/day
Hainer V (2000)	14 MZ female twin pairs	39 (1.7)	Sedentary	F: Daily for 28 days I: 60%VO2 max T: 20 min T: cycle ergometer aerobic exercises Additional exercise: 4 km walk and 30 min of aerobic exercise	Hypocaloric diet of 1.6 MJ/day
Hamel P (1986)	6 MZ twin pairs (3 male and 3 female)	21.2 (3.7)	Not reported	F: 3–5 times per week for 15 weeks I: 60–85% heart rate reserve T: 30–45 min T: Cycle ergometer	None
Prud'Homme D (1984)	10 MZ twin pairs (4 male and 6 female)	20.0 (2.9)	None highly trained but some participated in recreational activities	F: 4–5 times per week for 20 weeks I: 60–85% heart rate reserve T: 40–45 min T: Cycle ergometer	None
Afman G (1988)	19 MZ (3 male and 16 female) and 9 DZ (3 male and 6 female) twin pairs[b]	MZ: 18.9 (1.4) DZ: 19.4 (1.8)	Not reported	F: 4 times per week for 11 weeks I: 70–85 heart rate maximum T: 15–45 min T: cycle ergometer and treadmill running	None
Danis A (2003)	9 MZ male twin pairs	11–14**	Not participating in sporting activities	F: 3 times per week for 6 months I: 75–97% VO2 max T: 60–90 min T: treadmill running	None

MZ monozygotic, *DZ* dizygotic, *MJ* mega joules, *SD* standard deviation, *FITT* frequency, intensity, time, type

*Twin pairs were generally living together at the time of enrollment, except those in Koenigstorfer J [20] and Hainer V (2000) [28]. Afman G [29] reported that more than 50% of the twin pairs were living together at the time of enrollment

**Did not report a mean age (SD)

[a]11 MZ twin pairs were initially enrolled but only seven MZ twin pairs completed the exercise protocol (the definition of 'completing the exercise protocol' was not outlined)

[b]34 twin pairs (MZ and DZ) were initially enrolled but only 28 twin pairs (MZ and DZ) completed the protocol (defined as attending 75% or more of the exercise sessions, and having fewer than eight sessions where one twin participated and the co-twin did not)

[28] who recruited twin pairs admitted to an obesity unit for a 40-day PA and diet program. The frequency of the PA interventions ranged from three times a week to daily, with the duration ranging from 15 min to 2 h. The exercise intensity ranged from 50 to 97% VO_2max, with numerous modes of PA being utilized, including a cycle ergometer, resistance training, walking or running, over a period of 22 days up to 6 months. Two twin studies [29, 30] reported drop outs based on participants failing to complete the training protocol (Table 2), while the

Table 3 Characteristics of family studies

Family Studies (all studies were based on the sample from "The HERITAGE Family Study")					
Author (year)	Sample[a]	Age	Baseline physical activity status	Physical activity intervention	Diet intervention
Rice T (1999)	98 Caucasian families (440 individuals)	Parents were less than 65 years old, while offspring ranged from 17–40 years old	Sedentary	F: 3 times per week for 20 weeks I: 55–75% VO_2 max T: 30–50 min T: Cycle ergometer	None.
Bouchard C (1999)	98 Caucasian families (481 individuals)				
Perusse L (2000)	99 Caucasian families (483 individuals)				
Perusse L (2001)	99 Caucasian families (483 individuals)				
Gaskill SE (2001)	100 Caucasian families (339 individuals) and 99 African-American families (172 individuals)				

FITT frequency, intensity, time, type, *VO_2 max* maximal oxygen uptake
[a]Participants needed to complete 60 exercise sessions within 21 weeks to satisfy the protocol and be included in the study

included family studies only analyzed data from participants who completed 60 exercise sessions in 21 weeks [31] (Table 3).

Due to significant between-study variation for the intervention frequency and duration, we were unable to stratify meta-analyses in this way. Instead, we examined the correlations for each outcome to investigate if studies with more frequent bouts of PA, or longer intervention durations reported higher r_{MZ}, but, we were unable to identify any trends. We were able to stratify our meta-analyses by the co-prescription of a diet intervention, and by gender.

Outcomes of Body Composition

There were 11 studies (nine twin studies [20, 27–30, 32–35] and two family studies [24, 36]) which investigated body composition measures and their response following a PA intervention. Pooling of eight twin studies results (excluding Danis and colleagues [27] due to different methodology) suggest there is a significant r_{MZ} across the majority of body composition measures (Table 4). The pooled r_{MZ} was highest for BMI ($r_{MZ} = 0.69$, 95% CI: 0.49–0.82, $n = 58$) and the ratio of fat mass to fat free mass ($r_{MZ} = 0.69$, 95% CI: 0.42–0.85, $n = 36$) (Fig. 2), where "n" represents the total number of twin pairs from all studies. There were significant pooled r_{MZ} for fat mass ($r_{MZ} = 0.58$, 95% CI: 0.13–0.83, $n = 48$), fat free mass ($r_{MZ} = 0.57$, 95% CI: 0.35–0.73, $n = 73$) (Fig. 3), body fat percentage ($r_{MZ} = 0.55$, 95% CI: 0.32–0.72, $n = 72$), waist circumference ($r_{MZ} = 0.50$, 95% CI: 0.09–0.77, $n = 27$) and hip circumference ($r_{MZ} = 0.51$, 95% CI: 0.11–0.77, $n = 27$) (Fig. 4). However, the pooled r_{MZ} was lower and not statistically significantly different from 0 for waist-to-hip ratio ($r_{MZ} = 0.29$, 95% CI: −0.16–0.64, $n = 27$) (Fig. 5).

When we pooled data from twin studies that included a combined PA and diet intervention (four studies [20, 28, 30, 33], there was a trend for the r_{MZ} to be higher across all measures of body composition compared to twin studies that only involved a PA intervention (four studies [29, 32, 34, 35]) (Table 4). The r_{MZ} for BMI was higher when results were pooled for studies including a combined PA and diet intervention ($r_{MZ} = 0.79$, 95% CI: 0.54–0.91, $n = 27$), compared to studies only involving a PA intervention ($r_{MZ} = 0.58$, 95% CI: 0.23–0.79, $n = 31$) (Fig. 6), although confidence intervals were wide. Meta-analyses for each outcome were stratified by gender. The r_{MZ} was variable between males and females, depending on the outcome assessed (Table 5), with wide confidence intervals observed for both males and females. The pooled r_{MZ} for the response of fat mass following PA was higher and statistically significant in females ($r_{MZ} = 0.85$, 95% CI: 0.63–0.94, $n = 25$) compared to males ($r_{MZ} = 0.40$, 95% CI: −0.26–0.81, $n = 17$) (Fig. 7). However, the pooled r_{MZ} for fat free mass was higher in males ($r_{MZ} = 0.80$, 95% CI: 0.39–0.95, $n = 17$) compared to females ($r_{MZ} = 0.52$, 95% CI: 0.19–0.75, $n = 38$) (Fig. 8), both being statistically significantly different from 0 but not from each other.

We were able to extract heritability, and maximal heritability estimates for measures of body composition from three twin studies [27, 29, 32] (with raw data used to generate heritability estimates from one [29]), and two family studies, respectively [24, 36]. However, we did not report the heritability estimates from two twin studies [29, 32], as there were no statistically significant differences between the r_{MZ} and r_{DZ}, making the estimates uninformative (Table 1). Danis and colleagues [27] used different methodology to calculate heritability and we reported the estimates in Table 1. Maximal heritability estimates ranged from 0–21% in family studies, with higher estimates for trunk and extremity skin folds compared to measures of fat mass and waist circumference (Table 6).

Outcomes of Cardiorespiratory Fitness

There were nine studies (six twin studies [27, 29, 30, 32, 34, 35] and three family studies [19, 37, 38]) which investigated cardiorespiratory fitness measures and their response following a PA intervention. Pooling of five twin studies results (excluding Danis and colleagues

Table 4 Pooled within monozygotic (MZ) twin pair correlations (95% confidence intervals)

Outcome	All studies	Studies including a combined physical activity and diet intervention	Studies only including a physical activity intervention
Body fat percentage (%)	0.55 (0.32–0.72)*** (*n* = 72) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Hopkins N et al. (2012) Bouchard C et al. (1994) Hainer V et al. (2000) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.61 (0.28–0.82)** (*n* = 33) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)	0.49 (0.16–0.73)** (*n* = 39) Hopkins N et al. (2012) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)
BMI	0.69 (0.49–0.82)*** (*n* = 58) Koenigstorfer J et al. (2011) Hopkins N et al. (2012) Bouchard C et al. (1994) Hainer V et al. (2000) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.79 (0.54–0.91)*** (*n* = 27) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)	0.58 (0.23–0.79)** (*n* = 31) Hopkins N et al. (2012) Prud'Homme D et al. (1984) Afman G et al. (1988)
Fat free mass (kg)	0.57 (0.35–0.73)*** (*n* = 73) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Hopkins N et al. (2012) Bouchard C et al. (1994) Hainer V et al. (2000) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.71 (0.43–0.87)*** (*n* = 33) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)	0.43 (0.09–0.68)* (*n* = 40) Hopkins N et al. (2012) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)
Fat mass (kg)	0.58 (0.13–0.83)* (*n* = 48) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000) Hamel P et al. (1986) Prud'Homme D et al. (1984)	0.68 (0.16–0.90)* (*n* = 33) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)	0.27 (−0.36–0.73) (*n* = 15) Hamel P et al. (1986) Prud'Homme D et al. (1984)
Fat mass to fat free mass ratio	0.69 (0.42–0.85)*** (*n* = 36) Bouchard C et al. (1994) Hainer V et al. (2000) Hamel P et al. (1986) Prud'Homme D et al. (1984)	0.82 (0.58–0.93)*** (*n* = 21) Bouchard C et al. (1994) Hainer V et al. (2000)	0.30 (−0.33–0.75) (*n* = 15) Hamel P et al. (1986) Prud'Homme D et al. (1984)
Waist circumference (cm)	0.50 (0.09–0.77)* (*n* = 27) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)		–
Hip circumference (cm)	0.51 (0.11–0.77)* (*n* = 27) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)		–
Waist to hip ratio	0.29 (−0.16–0.64) (*n* = 27) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)		–
Sum of skin folds (cm)	0.67 (0.37–0.85)*** (*n* = 30) Bouchard C et al. (1994) Hainer V et al. (2000) Prud'Homme D et al. (1984)	0.73 (0.39–0.89)*** (*n* = 21) Bouchard C et al. (1994) Hainer V et al. (2000)	0.49 (−0.26–0.87) (*n* = 9) Prud'Homme D et al. (1984)
Trunk fat	0.52 (0.12–0.78)* (*n* = 27)	0.56 (0.13–0.82)* (*n* = 21)	0.30 (−0.68–0.89) (*n* = 6)

Table 4 Pooled within monozygotic (MZ) twin pair correlations (95% confidence intervals) *(Continued)*

	Hopkins N et al. (2012) Bouchard C et al. (1994) Hainer V et al. (2000)	Bouchard C et al. (1994) Hainer V et al. (2000)	Hopkins N et al. (2012)
Extremity skin fold (cm)	0.54 (−0.39–0.92) (*n* = 21) Bouchard C et al. (1994) Hainer V et al. (2000)		–
Trunk to extremity ratio	0.48 (−0.30–0.88) (*n* = 21) Bouchard C et al. (1994) Hainer V et al. (2000)		–
Weight (kg)	0.67 (0.48–0.79)*** (*n* = 73) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Hopkins N et al. (2012) Bouchard C et al. (1994) Hainer V et al. (2000) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.73 (0.47–0.88)*** (*n* = 33) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)	0.61 (0.32–0.79)*** (*n* = 40) Hopkins N et al. (2012) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)
Absolute VO_2 max ($L.min^{-1}$)	0.38 (0.04–0.64)* (*n* = 42) Bouchard C et al. (1994) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.52 (−0.38–0.92) (*n* = 7) Bouchard C et al. (1994)	0.36 (−0.01–0.64) (*n* = 35) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)
Relative VO_2 max ($mL.min^{-1}.kg^{-1}$)	0.39 (0.07–0.64)* (*n* = 48) Hopkins N et al. (2012) Bouchard C et al. (1994) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.48 (−0.43–0.91) (*n* = 7) Bouchard C et al. (1994)	0.38 (0.04–0.64)* (*n* = 41) Hopkins N et al. (2012) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)

n number of twin pairs, *VO_2 max* maximal oxygen uptake, *BMI* body mass index
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

[27] due to different methodology) suggests there are significant pooled r_{MZ} for absolute VO_2max ($L.min^{-1}$) ($r_{MZ} = 0.38$, 95% CI: 0.04–0.64, $n = 42$) and relative VO_2max ($mL.min^{-1}.kg^{-1}$) ($r_{MZ} = 0.39$, 95% CI: 0.07–0.64, $n = 48$) (Table 4).

There was one twin study which investigated the response of cardiorespiratory fitness following a combined PA and diet intervention [30] and four twin studies which investigated the response of cardiorespiratory fitness following an isolated PA intervention [29, 32, 34, 35].

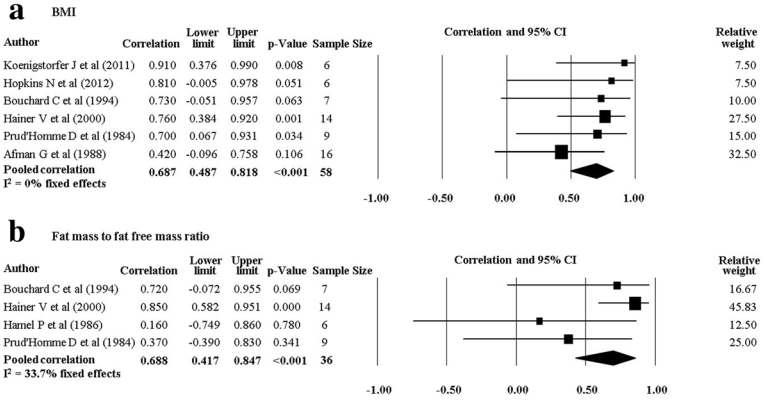

Fig. 2 Pooled within monozygotic (MZ) twin pair correlations for BMI and the ratio of fat mass to fat free mass in response to physical activity. CI: confidence interval; sample size; number of twin pairs

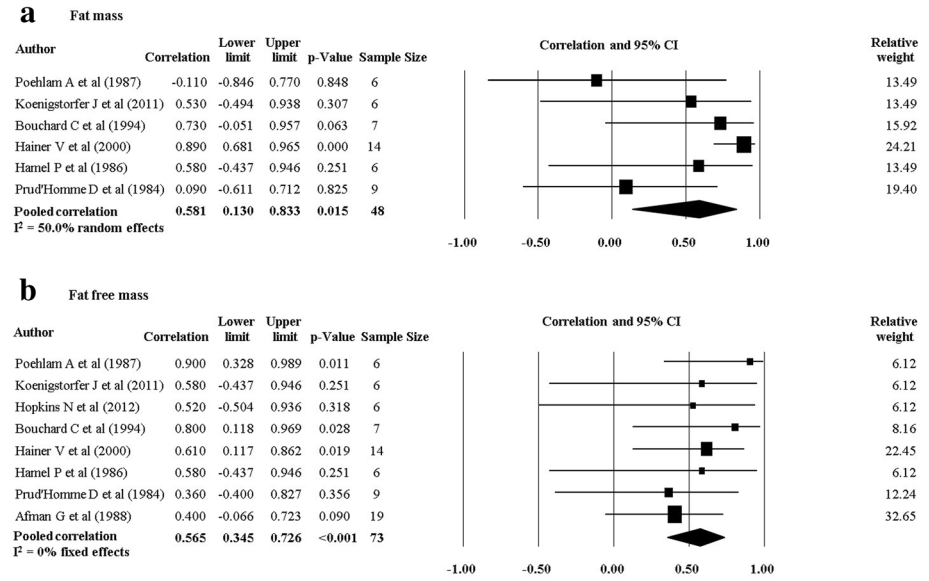

Fig. 3 Pooled within monozygotic (MZ) twin pair correlations for fat mass and fat free mass in response to physical activity. CI: confidence interval; sample size; number of twin pairs

The r_{MZ} for absolute and relative VO_2max in the study ($n = 7$) which combined PA with diet ($r_{MZ} = 0.52$, 95% CI: −0.38–0.92, and $r_{MZ} = 0.48$, 95% CI: −0.43–0.91, respectively) was higher than the pooled r_{MZ} from the studies which only investigated a PA intervention ($r_{MZ} = 0.36$, 95% CI: −0.01–0.64, $n = 35$, and $r_{MZ} = 0.38$, 95% CI: 0.04–0.64, $n = 41$, respectively) (Fig. 9) although the confidence intervals overlapped, and the r_{MZ} from the individual study was not statistically significantly different from 0 (with 95% CIs generated from the meta-analysis software). Meta-analyses for absolute and relative VO_2max were stratified by gender, with the pooled r_{MZ} being higher in females (Table 5). The pooled r_{MZ} for the response of absolute VO_2max following PA was 0.74 in females ($n = 21$) and 0.49 in males ($n = 11$), although neither were statistically significantly different from 0 (Fig. 10).

Heritability estimates for the response of VO_2max from two twin studies [29, 32] were not reported, as there were no statistically significant differences between the r_{MZ} and r_{DZ} (Table 1). Danis and colleagues [27] used different methodology to calculate heritability and we reported the estimates in Table 1 .Maximal heritability estimates from the three included family studies [19, 37, 38] were variable, ranging from 22–57% depending on race and when VO_2max was measured (e.g., ventilatory threshold, pre-determined power levels, etc.) (Table 6).

Discussion

Our results demonstrate consistent evidence that shared familial factors (whether genetic or environmental) play a role in the response of body composition and cardiorespiratory fitness following PA, despite varying on the outcome being assessed, particularly when results were stratified by gender. The pooled r_{MZ} were generally >0.5, and the bulk of most CIs also exceeded 0.5. Shared familial factors appear to play a larger role in the response of body composition when compared to cardiorespiratory fitness, and may have more influence on the response for most outcomes when considering a combined PA and diet intervention.

Heritability Estimates and the Within MZ Twin Pair Correlation

Only a few studies included DZ twins ($n = 2$) [29, 32], so we pooled the r_{MZ} to provide an estimate of the upper bound of heritability. Traditionally, twin and family studies investigating the heritability of a phenotype (e.g., PA engagement [15, 16], BMI [39], and chronic pain [40]) have done so using a cross-sectional design, with twin studies dividing the variance of a phenotype into components or proportions due to additive genetic factors (heritability), shared environmental factors, and unique environmental factors. Our pooled estimates represent the upper bound of heritability, including variance from additive genetic and shared environmental factors. However, our study investigated how shared familial factors influence the response to PA, with the r_{MZ} derived from the change in outcome status following an intervention. Since interventions were implemented over a specified timeframe, with training parameters controlled, it has been suggested that unique and shared environmental factors

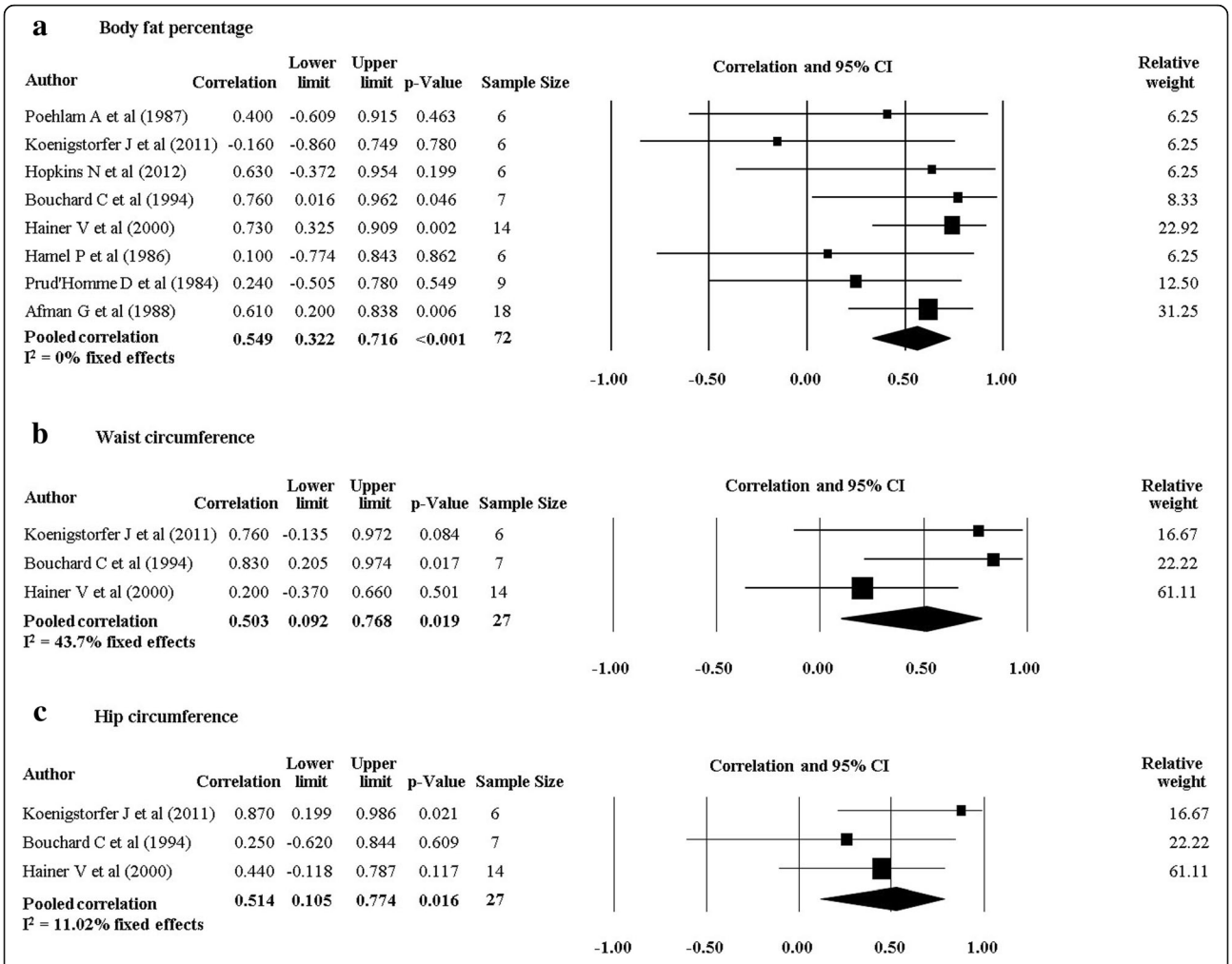

Fig. 4 Pooled within monozygotic (MZ) twin pair correlations for body fat percentage, waist circumference and hip circumference in response to physical activity. CI: confidence interval; sample size; number of twin pairs

would make minor contributions to the variance of the response to PA [22], resulting in a r_{MZ} that would give a close estimate of heritability. However, family studies included in this review found significant correlations between spouses for the response of body composition [38] and cardiorespiratory fitness [19, 24] following a PA intervention. Although some suggest this indicates a greater influence of shared environmental factors [19], this correlation may equally be due to shared genes (assortative mating), so without making strong assumptions as to which is occurring in spouses, this is unlikely to indicate a greater influence of shared environmental factors.

Shared Familial Influence on Changes of Body Composition

Factors shared within MZ twin pairs appear to play a strong role in the response of BMI (pooled $r_{MZ} = 0.69$) following a PA intervention (Fig. 2), although they

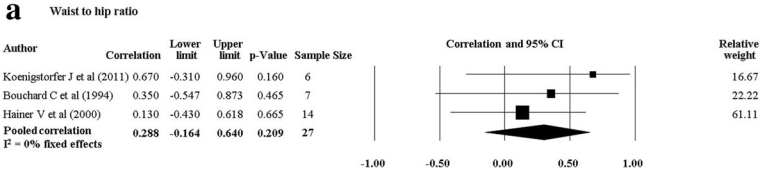

Fig. 5 Pooled within monozygotic (MZ) twin pair correlations for waist-to-hip ratio in response to physical activity. CI: confidence interval; sample size; number of twin pairs

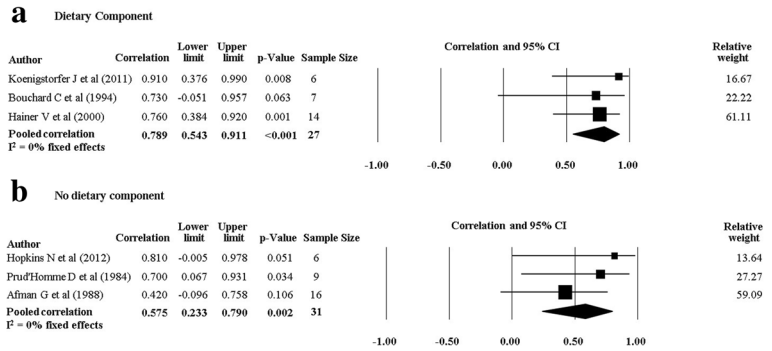

Fig. 6 Pooled within monozygotic (MZ) twin pair correlations for BMI in response to physical activity combined with diet, and physical activity without a dietary component. CI: confidence interval; sample size; number of twin pairs

appear to be less influential in the response of other outcomes (e.g., waist-to-hip ratio) (Fig. 5). Although we were unable to pool heritability estimates, our pooled r_{MZ} for the response of BMI following PA appears to be within the range of previous studies reporting the cross-sectional heritability of BMI (ranging from 47–90% in twins studies [39]). However, other cross-sectional studies have reported heritability estimates for waist circumference (66%) and body fat percentage (68%) [41] that appear to be slightly higher than our r_{MZ} in response to exercise (pooled r_{MZ} = 0.50 and 0.55, respectively), especially considering our results represent the upper bound of heritability. Therefore, by comparing our results to those of previous investigations, it appears the genetic influences on an individual's body composition (cross-sectional association) might be different, and perhaps higher, than the way their body composition responds to PA.

Previous cross-sectional twin studies have reported gender differences for the heritability of body composition, although they appear to vary depending on the outcome of interest. A twin study by Schousboe and colleagues [42] reported that males have higher heritability estimates compared to females for body fat percentage (63 and 59%, respectively), sum of skin folds (65 and 61%, respectively), waist circumference (61 and 48%, respectively) and waist-to-hip ratio (22 and 10%, respectively). However, other studies have reported higher heritability estimates in females across a variety of body composition measures [43, 44]. The variability between genders for the heritability of body composition has been supported in various twin studies, regardless of the sample size, methods of analyses or ethnicity [43, 45–47]. Our results extend the understanding that gender influences the role shared familial factors, including genes, play in the variation of body composition (cross-sectional association), and suggests gender influences how shared familial factors influence the response of body composition measures following PA. In particular, shared familial factors appear to have a greater influence on changes in fat mass for females engaged in PA (Fig. 7) and fat free mass for males engaged in PA (Fig. 8). Therefore, to better understand how both genetics and shared environmental factors impact an individual's response to PA, it may be important to take into consideration the gender of the individual, and the outcome of interest.

Shared Familial Influence on Changes in Cardiorespiratory Fitness

The heritability of VO_2max assessed in cross-sectional studies ranges from 40–71% in twin studies [41, 48] and has been reported at 50% (maximal heritability) in the HERITAGE Family Study [49]. Our pooled r_{MZ} were 0.38 and 0.39 for absolute and relative VO_2max, respectively, and appear to be smaller than heritability estimates for an individual's pre-training VO_2max, although the CIs for our results include the cross-sectional estimates. This suggests genetics may be more influential in determining an individual's cardiorespiratory fitness, compared to their fitness response following PA, although the biological explanation for this is unclear.

The point estimates of the r_{MZ} for the response of cardiorespiratory fitness following PA appear slightly greater in females (Fig. 10), although the CIs for both the male and female correlations cover almost all the possible range of values due to small sample sizes in the original studies. Similarly, existing studies investigating the heritability of cardiorespiratory fitness have been limited in their ability to analyze the effect of gender due to small sample sizes [41], and single gender cohorts [48]. Therefore, our results should be viewed as preliminary with this area deserving attention in future studies.

Strengths and Limitations

Our study demonstrated considerable strengths in its design. First, previous studies have predominantly focussed on investigating the heritability of PA engagement (cross-sectional association) [15], without considering

Table 5 Pooled within monozygotic (MZ) twin pair correlations (95% confidence intervals)

Outcome	All studies	Females	Males
Body fat percentage (%)	0.55 (0.32–0.72)*** (*n* = 72) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Hopkins N et al. (2012) Bouchard C et al. (1994) Hainer V et al. (2000) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.63 (0.36–0.80)*** (*n* = 41) Koenigstorfer J et al. (2011) Hainer V et al. (2000) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.58 (−0.04–0.87) (*n* = 17) Poehlam A et al. (1987) Bouchard C et al. (1994) Prud'Homme D et al. (1984)
BMI	0.69 (0.49–0.82)*** (*n* = 58) Koenigstorfer J et al. (2011) Hopkins N et al. (2012) Bouchard C et al. (1994) Hainer V et al. (2000) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.63 (0.36–0.80)*** (*n* = 41) Koenigstorfer J et al. (2011) Hainer V et al. (2000) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.63 (−0.13–0.93) (*n* = 11) Bouchard C et al. (1994) Prud'Homme D et al. (1984)
Fat free mass (kg)	0.57 (0.35–0.73)*** (*n* = 73) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Hopkins N et al. (2012) Bouchard C et al. (1994) Hainer V et al. (2000) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.52 (0.19–0.75)** (*n* = 38) Koenigstorfer J et al. (2011) Hainer V et al. (2000) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.80 (0.39–0.95)** (*n* = 17) Poehlam A et al. (1987) Bouchard C et al. (1994) Prud'Homme D et al. (1984)
Fat mass (kg)	0.58 (0.13–0.83)* (*n* = 48) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000) Hamel P et al. (1986) Prud'Homme D et al. (1984)	0.85 (0.63–0.94)*** (*n* = 25) Koenigstorfer J et al. (2011) Hainer V et al. (2000) Prud'Homme D et al. (1984)	0.40 (−0.26–0.81) (*n* = 17) Poehlam A et al. (1987) Bouchard C et al. (1994) Prud'Homme D et al. (1984)
Fat mass to fat free mass ratio	0.69 (0.42–0.85)*** (*n* = 36) Bouchard C et al. (1994) Hainer V et al. (2000) Hamel P et al. (1986) Prud'Homme D et al. (1984)	0.85 (0.61–0.95)*** (*n* = 19) Hainer V et al. (2000) Prud'Homme D et al. (1984)	0.62 (−0.15–0.92) (*n* = 11) Bouchard C et al. (1994) Prud'Homme D et al. (1984)
Waist circumference (cm)	0.50 (0.09–0.77)* (*n* = 27) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)	0.36 (−0.15–0.72) (*n* = 20) Koenigstorfer J et al. (2011) Hainer V et al. (2000)	0.83 (0.21–0.97)* (*n* = 7) Bouchard C et al. (1994)
Hip circumference (cm)	0.51 (0.11–0.77)* (*n* = 27) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)	0.58 (0.13–0.83)* (*n* = 20) Koenigstorfer J et al. (2011) Hainer V et al. (2000)	0.25 (−0.62–0.84) (*n* = 7) Bouchard C et al. (1994)
Waist to hip ratio	0.29 (−0.16–0.64) (*n* = 27) Koenigstorfer J et al. (2011) Bouchard C et al. (1994) Hainer V et al. (2000)	0.27 (−0.24–0.66) (*n* = 20) Koenigstorfer J et al. (2011) Hainer V et al. (2000)	0.35 (−0.55–0.87) (*n* = 7) Bouchard C et al. (1994)
Sum of skin folds (cm)	0.67 (0.37–0.85)*** (*n* = 30) Bouchard C et al. (1994) Hainer V et al. (2000) Prud'Homme D et al. (1984)	0.78 (0.46–0.92)*** (*n* = 19) Hainer V et al. (2000) Prud'Homme D et al. (1984)	0.51 (−0.30–0.89) (*n* = 11) Bouchard C et al. (1994) Prud'Homme D et al. (1984)

Table 5 Pooled within monozygotic (MZ) twin pair correlations (95% confidence intervals) *(Continued)*

Trunk fat	0.52 (0.12–0.78)* (*n* = 27) Hopkins N et al. (2012) Bouchard C et al. (1994) Hainer V et al. (2000)	0.67 (0.22–0.89)** (*n* = 14) Hainer V et al. (2000)	0.15 (−0.68–0.81) (*n* = 7) Bouchard C et al. (1994)
Extremity skin fold (cm)	0.54 (−0.39–0.92) (*n* = 21) Bouchard C et al. (1994) Hainer V et al. (2000)	0.78 (0.43–0.93)** (*n* = 14) Hainer V et al. (2000)	0.00 (−0.75–0.75) (*n* = 7) Bouchard C et al. (1994)
Trunk to extremity ratio	0.48 (−0.30–0.88) (*n* = 21) Bouchard C et al. (1994) Hainer V et al. (2000)	0.70 (0.27–0.90)** (*n* = 14) Hainer V et al. (2000)	0.00 (−0.75–0.75) (*n* = 7) Bouchard C et al. (1994)
Weight (kg)	0.67 (0.48–0.79)*** (*n* = 73) Poehlam A et al. (1987) Koenigstorfer J et al. (2011) Hopkins N et al. (2012) Bouchard C et al. (1994) Hainer V et al. (2000) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.70 (0.46–0.84)*** (*n* = 41) Koenigstorfer J et al. (2011) Hainer V et al. (2000) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.45 (−0.20–0.83) (*n* = 17) Poehlam A et al. (1987) Bouchard C et al. (1994) Prud'Homme D et al. (1984)
Absolute VO_2 max ($L.min^{-1}$)	0.38 (0.04–0.64)* (*n* = 42) Bouchard C et al. (1994) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.74 (−0.18–0.97) (*n* = 21) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.49 (−0.33–0.89) (*n* = 11) Bouchard C et al. (1994) Prud'Homme D et al. (1984)
Relative VO_2 max ($mL.min^{-1}.kg^{-1}$)	0.39 (0.07–0.64)* (*n* = 48) Hopkins N et al. (2012) Bouchard C et al. (1994) Hamel P et al. (1986) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.51 (0.06–0.79)* (*n* = 21) Prud'Homme D et al. (1984) Afman G et al. (1988)	0.40 (−0.43–0.86) (*n* = 11) Bouchard C et al. (1994) Prud'Homme D et al. (1984)

n number of twin pairs, *VO_2 max* maximal oxygen uptake, *BMI* body mass index
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

how genetics and shared environmental factors impact an individual's response to PA. From a health-care perspective, it may be more important to investigate how genetics and environmental factors influence the response to PA. It is likely the response to PA would be more dependent on unique environmental factors, such as training parameters (frequency, intensity, duration, type), adherence, therapeutic alliance, and many more. However, neither training frequency nor duration appeared to influence the r_{MZ} for either body composition

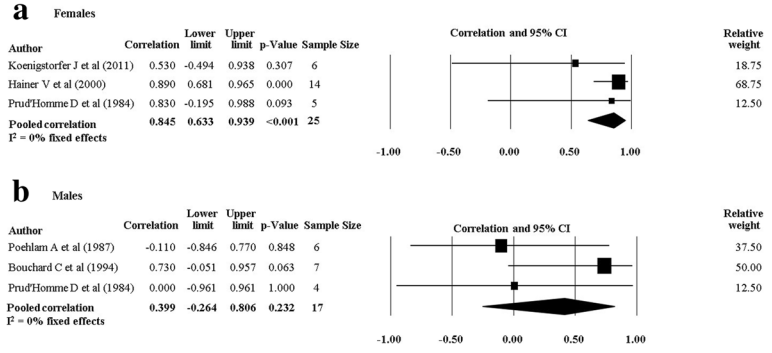

Fig. 7 Pooled within monozygotic (MZ) twin pair correlations for fat mass in response to physical activity for females and males. CI: confidence interval; sample size; number of twin pairs

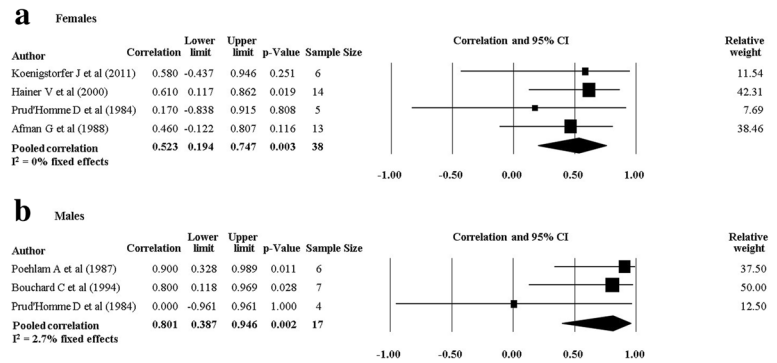

Fig. 8 Pooled within monozygotic (MZ) twin pair correlations for fat free mass in response to physical activity for females and males. CI: confidence interval; sample size; number of twin pairs

or cardiorespiratory fitness, which may suggest the role genetics plays in response to PA is independent of these parameters. Quantifying the influence of genetics and environmental factors on the response to PA may serve to explain why certain individuals do not respond as well to a structured PA program across a variety of outcomes, with implications for how we can modify the training environment to achieve a positive response. Second, twin studies which have investigated how genetics influence the response to PA have been limited in their ability to draw firm conclusions due to small sample sizes. Small sample sizes of the included studies explain cases where our pooled CIs were wide, even though we were able to pool results for up to 83 MZ twin pairs, improving the precision around these estimates. To obtain 95% CIs of sufficiently small width to be informative (e.g., a total width of 0.1), in studies that include only MZ twins, approximately 400 twin pairs are required if the correlation is moderately high (0.7), and greater than 1000 twin pairs if the correlation is 0.4. For studies including both MZ and DZ twins, 150 twin pairs of each zygosity would be required to detect a significant difference ($p = 0.05$) between $r_{MZ} = 0.7$ and $r_{DZ} = 0.5$, with 80% power. If both correlations are lower (e.g., $r_{MZ} = 0.5$ and $r_{DZ} = 0.3$), 275 twins pairs of each zygosity would be required. Many of the studies which reported heritability or maximal heritability also failed to report confidence intervals for their estimates, or provide sufficient information to enable these to be estimated accurately (Tables 1 and 6). Although point estimates are available, there is clearly a substantial information difference between a heritability of 47% with a 95% CI of 44–50% and the same heritability with a 95% CI of 10–85%, and we expect that studies included in this review are more like to the second situation, limiting the utility of the reported estimates. Third, raw data were used to re-analyse previously reported correlations in four twin studies [29, 30, 34, 35] and adjust for age, gender (if applicable), and baseline values. This provided a more precise estimate for quantifying the role genetics plays in the response to PA.

Table 6 Maximal heritability estimates from family studies (includes variance explained by genetic and non-genetic sources shared within families)

Outcome	Author (year)	Maximal heritability (95% CI)
Fat mass (kg)	Rice T (1999)	0%[a]
Trunk skin folds (cm)	Perusse L (2000)	21% (14 to 28%)
Extremity skin folds (cm)	Perusse L (2000)	15% (5 to 25%)
Subcutaneous fat (sum of eight skin folds) (cm)	Perusse L (2000)	15% (8 to 22%)
Trunk to extremity skin fold ratio (adjusted for subcutaneous fat)	Perusse L (2000)	14% (10 to 18%)
Waist circumference (cm) (adjusted for BMI)	Perusse L (2000)	0%[a]
Absolute VO_2 max ($L.min^{-1}$)	Bouchard C (1999)	47%[a]
Absolute VO_2 max at ventilatory threshold ($L.min^{-1}$)	Gaskill SE (2001)	Caucasian: 22% (−2 to 46%) African-American: 51 (27% to 75%)
Relative VO_2 max ($mL.min^{-1}.kg^{-1}$)	Perusse L (2001)	50 W: 57%[a]
		60% VO_2 max: 23%[a]
		80% VO_2 max: 44%[a]

CI confidence interval, *VO_2 max* maximal oxygen uptake, *W* watts, *BMI* body mass index
[a]Unable to calculate the standard error and thus present the 95% CI

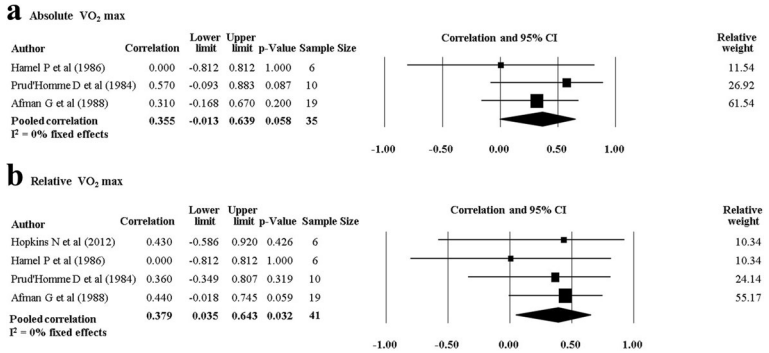

Fig. 9 Pooled within monozygotic (MZ) twin pair correlations for absolute and relative maximal oxygen uptake (VO_2 max) in response to physical activity without a dietary component. CI: confidence interval; sample size; number of twin pairs

Our study has a few limitations which need to be considered when interpreting the results. First, samples from included twin studies differed in their age, baseline values, PA interventions, and diet interventions. Furthermore, one study recruited twin pairs admitted to an obesity unit for a 40-day physical activity and diet program [28], a sample not representative of the general population. However, we conducted a number of sensitivity analyses and the exclusion of any single study did not significantly affect the results for any of the outcomes (Additional file 2). In addition, we performed separate meta-analyses for studies which included a diet intervention, to better understand how the difference between interventions impacted our results. Second, two twin studies [29, 30] reported drop outs on the basis of twin pairs failing to complete the training protocol (Table 2), while the family studies only analyzed data from participants who completed the training protocol (Table 3). We acknowledge that this may limit the generalizability of the results, as participants who completed the training protocol are likely to be more motivated to engage in PA than the general population. Third, although using a classical twin design to estimate heritability is a widely reported method to investigate how genetics contributes to the variation of a phenotype, it does have some limitations, and together with the fact that individual twin studies had small sample sizes, is the reason we did not focus our results on these estimates. The use of self-reported zygosity measures, based on the difficulty of being told apart by parents, is often criticized. MZ twins who differ in their height and weight can be mistakenly classified as DZ twins when using self-reported measures, resulting in an underestimation of heritability [50]. However, only one study included in this review assessed zygosity using only a self-reported questionnaire [32], with another failing to describe how zygosity was assessed [20]. The remaining twin studies ($n = 7$) verified questionnaire-based zygosity through DNA mapping. In addition, not considering the genotype-environment interaction is a limitation of the classical twin design, since genetic factors can influence an individual's choice/exposure to the environment. However, studies included in this review utilized a controlled training environment, reducing the likelihood that an individual's genetics would impact their environment for the experimental period. Furthermore, the use of heritability as a measure, although widely reported, has some limitations; it is dependent on the modeling of the mean, on the amount of variance and measurement error (which may be larger in studies of changes in outcomes compared with cross-sectional studies of

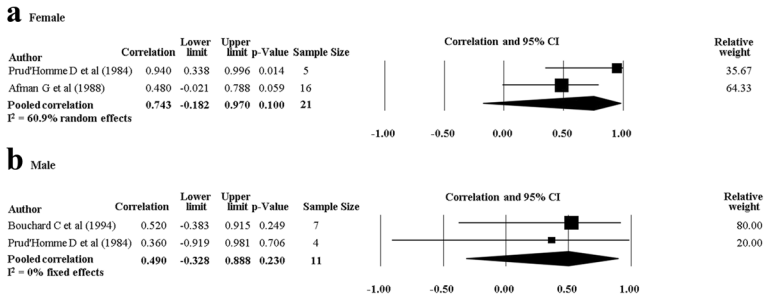

Fig. 10 Pooled within monozygotic (MZ) twin pair correlations for absolute maximal oxygen uptake (VO_2 max) in response to physical activity for females and males. CI: confidence interval; sample size; number of twin pairs

outcomes [51]) and on the total variation within a population, which may differ between populations and between the same population measured at different times [52]. Finally, when estimated from classic twin studies, this estimate depends on the assumption that environments are shared to the same extent by MZ and DZ pairs—an assumption that is rarely considered or tested in practice [53].

Clinical Implications

The results of this current investigation are consistent with a substantial influence of genes on the response of body composition and cardiorespiratory fitness following PA. These results have implications for conditions which utilize PA as a management strategy, for example, diabetes, and low back pain. If an individual's response to a PA intervention is partially dictated by genetic factors this could potentially explain why some individuals fail to respond to increased PA. This has implications for changing the modifiable training environment to achieve a desired effect (e.g., increased intensity, frequency, or duration), or excluding people who demonstrate a poor response to reduce treatment costs and consumer disappointment. Furthermore, if genetic factors are involved in the poor response to PA as an intervention, this has implications for the selection of alternative management strategies, or a modification to the outcome investigated, since individuals who show a low training response to one parameter (e.g., VO_2max) might in fact respond positively to another (e.g., BMI).

Research linking genetic markers to a specific phenotype (quantitative trait locus analysis) have aided the mechanistic understanding of how genetics influence the response of body composition and cardiorespiratory fitness following PA, although more genetic research needs to be done. A family study investigated over 300,000 single-nucleotide polymorphisms (SNPs) and identified 21 SNPs which accounted for 49% of the variance in the response of VO_2max following a PA intervention, with one SNP (rs6552828) accounting for ~6% of the variance [54]. The variance explained by these 21 SNPs is similar to the maximal heritability of VO_2max response from the family study included in this review (47%), although this study observed significant spouse correlations which some consider consistent with shared environmental effects, thereby reducing the variance explained by genetics [19]. Similarly, nine SNPs were found to explain 20% of the variance of submaximal heart rate in response to PA, with one SNP (rs2253206) accounting for ~5% of the variance [55]. Earlier studies have identified candidate genes that are strongly linked to or associated with the response of BMI, fat mass, fat-free mass, and body fat percentage following a PA intervention [56]. For example, the insulin-like growth factor-1 (IGF-1) gene marker was strongly linked to response of fat-free mass following PA [57], with linkage also present for a polymorphism in the S100A gene [56] (predominantly found in slow-twitch skeletal and cardiac muscle fibers [58]). Research identifying genetic markers is promising and may aid the prediction of how an individual's body composition and cardiorespiratory fitness will respond following PA, although it is essential these results are replicated in larger samples, and through a variety of genetic analyses before definite conclusions are reached [59, 60]. Furthermore, research investigating practical and cost-effective methods to identify those who will respond positively to a PA intervention would be of significant interest from a public health and clinical perspective. For example, information regarding how family members have previously responded to PA may help to predict how an individual will respond to a similar intervention, potentially reducing the need for costly genetic testing.

Conclusions

Shared familial factors, including genetics, are likely to be significant contributors to the response of several markers of body composition and cardiorespiratory fitness following PA. Shared familial factors may play a stronger role in the response of body composition when compared to cardiorespiratory fitness, and may be more influential in dictating the response for measures of BMI, fat mass, and body fat percentage, compared to waist-to-hip ratio. The influence shared familial factors have on the response to PA may be different in males and females, with such factors having a greater influence on changes in fat mass for females, and fat-free mass for males. In addition, shared familial factors appear to be more influential in dictating the response of body composition and cardiorespiratory fitness when PA is combined with diet.

These results have implications for the management of conditions which advocate increased levels of PA, since genetic factors might serve as an explanation for why some people respond more effectively than others in specific measures of PA. To further quantify the role genetics and environmental factors play in the response to PA future research should focus on adequately powered studies including both MZ and DZ twins, and the replication of existing genome-wide association studies to identify important genetic markers for the response to PA.

Additional files

Additional file 1: Search strategy. (DOCX 18 kb)

Additional file 2: Sensitivity analysis excluding one study at a time. (JPG 363 kb)

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Authors' Contributions
All authors critically revised the manuscript for important intellectual content and approved the final manuscript. Please find below a detailed description of the role of each author. JRZ contributed to the conception and design, acquisition, and assembly of data, analysis and interpretation of data, drafting and revision of the manuscript and final approval of the version to be published. DHS contributed to the conception and design, interpretation of data and results, drafting and revision of the manuscript, and final approval of the version to be published. TBA contributed to the conception and design, acquisition and assembly of data, drafting and revision of the manuscript, and final approval of the version to be published. KS contributed to the conception and design, acquisition and assembly of data, revision of the manuscript, and final approval of the version to be published. AB contributed to the conception and design, interpretation of data, drafting and revision of the manuscript, and final approval of the version to be published. PHF contributed to the conception and design, analysis and interpretation of data, drafting and revision of the manuscript, and final approval of the version to be published. All authors read and approved the final manuscript.

Competing Interests
Zadro JR, Shirley D, Andrade TB, Scurrah KJ, Bauman A, and Ferreira PH declare that they have no competing interests.

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Supplementary material: Search Strategy.

MEDLINE

	Searches
Physical Activity	1. "physical activit*".mp 2. exp Motor Activity/ 3. "plyometric exercise".mp 4. exp Exercise Therapy/ 5. exp Physical Endurance/ 6. exp Exercise/ 7. exp "Physical Education and Training"/ 8. "physical fitness".mp 9. "endurance training".mp 10. "aerobic exercise".mp 11. exp Physical Exertion/ 12. "resistance training".mp 13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
Twin and Family studies	14. "twin*".mp 15. exp Twins, Monozygotic/ 16. exp Twins, Dizygotic/ 17. exp Diseases in Twins/ 18. exp Genetics/ 19. exp Genetic Linkage/ 20. "twin stud*".mp 21. "herita*".mp 22. "identical twin*".mp 23. "family resemblance".mp 24. exp Family Characteristics/ 25. exp Family Relations/ 26. exp Phenotype/ 27. exp Genotype/ 28. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
	29. 13 and 28 30. Limit 29 to humans

CINHAL

	Searches
Physical Activity	1. MH "Physical Endurance+" 2. “physical activit*” 3. MH "Physical Education and Training+" 4. “physical fitness” 5. MH "Education, Physical Education" 6. MH "Exercise+" 7. “exercise” 8. “motor activity” 9. MH "Therapeutic Exercise+" 10. “endurance training” 11. "resistance training" 12. MH "Aerobic Exercises+" 13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
Twin and Family studies	14. "Twin*" 15. “twin stud*” 16. MH "Multiple Offspring+" 17. "monozygotic twin*" 18. “dizygotic twin*” 19. MH "Genetics+" 20. “herita*” 21. MH "Genetic Diseases, X-Linked+" 22. MH "Hereditary Diseases+" 23. MH "Family Characteristics+" 24. MH "Family Relations+" 25. "family resemblance" 26. ”phenotype” 27. ”genotype” 28. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
	29. 13 and 28

EMBASE

	Searches
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Twin and Family studies	12. Heritage:de,ab,ti 13. 'monozygotic twins' 14. 'dizygotic twins' 15. ‘identical twins’ 16. 'genetic linkage' 17. 'family resemblance' 18. 'family relation' 19. 'family characteristics' 20. herita* 21. 'twin study' 22. Twin* 23. 'genetic variability' 24. 'genetic variation' 25. Genetics:de,ab,ti 26. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
	27. 11 and 26 28. Limit 27 to humans

Sports Discuss

	Searches
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Twin and Family studies	14. "twin*" 15. "monozygotic twin*" 16. "dizygotic twin*" 17. "diseases in twins" 18. "genetic*" 19. "genetic linkage" 20. "twin stud*" 21. "herita*" 22. "family characteristics" 23. "family resemblance" 24. "family relations" 25. “identical twin*” 26. “genotype” 27. “phenotype” 28. 14 or 15 or16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
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AMED

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Twin and Family studies	12. "twin*".mp 13. "monozygotic twin*".mp 14. "dizygotic twin*".mp 15. "genetic*".mp 16. "twin stud*".mp 17. "herita*".mp 18. "identical twin*".mp 19. exp Family Characteristics/ 20. exp Family Relations/ 21. "genotype".mp 22. "phenotype".mp 23. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
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	26. 11 and 25 27. Limit 26 to humans

Scopus

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	32. 11 and 22 33. 32 and not 31 34. Exclude: “animals” and “animal”

Web of Science

	Searches
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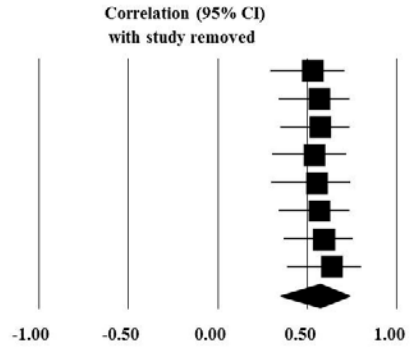
Twins and Family studies	13. TS=("twin*") 14. TS=("monozygotic twin*") 15. TS=("dizygotic twin*") 16. TS=("diseases in twins") 17. TS=("genetics") 18. TS=("genetic linkage") 19. TS=("twin stud*") 20. TS=("herita*") 21. TS=("family characteristics") 22. TS=("family resemblance") 23. TS=("family relations") 24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
Study Type	25. 12 and 24 26. TS=(animals) NOT TS=(humans) 27. 25 not 26

Supplementary material: Sensitivity analysis excluding one study at a time.

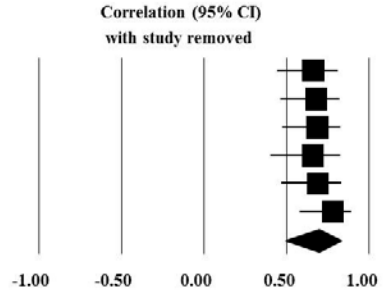
Panel A: Fat free mass

Author	Correlation	Lower limit	Upper limit	p-Value
Poehlam A et al (1987)	0.527	0.288	0.704	<0.001
Koenigstorfer J et al (2011)	0.564	0.336	0.729	<0.001
Hopkins N et al (2012)	0.568	0.341	0.732	<0.001
Bouchard C et al (1994)	0.536	0.298	0.712	<0.001
Hainer V et al (2001)	0.551	0.293	0.734	<0.001
Hamel P et al (1986)	0.564	0.336	0.729	<0.001
Prud'Homme D et al (1984)	0.589	0.361	0.751	<0.001
Afman G et al (1988)	0.632	0.383	0.795	<0.001
Pooled correlation including all studies	**0.565**	**0.345**	**0.726**	**<0.001**
I^2 = 0% fixed effects				



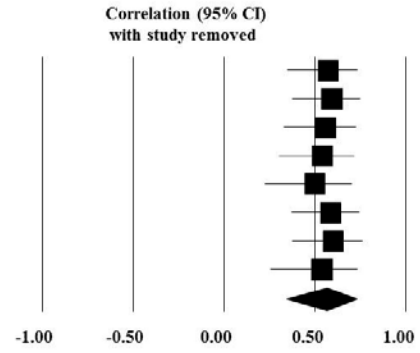
Panel B: BMI

Author	Correlation	Lower limit	Upper limit	p-Value
Koenigstorfer J et al (2011)	0.656	0.433	0.803	<0.001
Hopkins N et al (2012)	0.674	0.459	0.815	<0.001
Bouchard C et al (1994)	0.681	0.466	0.821	<0.001
Hainer V et al (2001)	0.654	0.396	0.817	<0.001
Prud'Homme D et al (1984)	0.684	0.463	0.825	<0.001
Afman G et al (1988)	0.774	0.574	0.887	<0.001
Pooled correlation including all studies	**0.687**	**0.487**	**0.818**	**<0.001**
I^2 = 0% fixed effects				



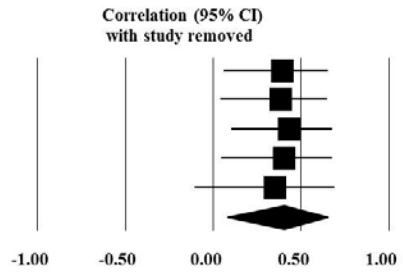
Panel C: Body fat percentage

Author	Correlation	Lower limit	Upper limit	p-Value
Poehlam A et al (1987)	0.565	0.335	0.732	<0.001
Koenigstorfer J et al (2011)	0.584	0.360	0.745	<0.001
Hopkins N et al (2012)	0.551	0.316	0.722	<0.001
Bouchard C et al (1994)	0.532	0.290	0.711	<0.001
Hainer V et al (2001)	0.491	0.212	0.696	0.001
Hamel P et al (1986)	0.580	0.354	0.742	<0.001
Prud'Homme D et al (1984)	0.593	0.362	0.755	<0.001
Afman G et al (1988)	0.530	0.244	0.731	0.001
Pooled correlation including all studies	**0.556**	**0.331**	**0.721**	<0.001
I^2 = 0% fixed effects				



Panel D: Relative VO_2 max

Author	Correlation	Lower limit	Upper limit	p-Value
Hopkins N et al (2012)	0.388	0.052	0.645	0.025
Bouchard C et al (1994)	0.379	0.035	0.643	0.032
Hamel P et al (1986)	0.426	0.097	0.671	0.013
Prud'Homme D et al (1984)	0.400	0.040	0.669	0.031
Afman G et al (1988)	0.345	-0.115	0.683	0.138
Pooled correlation including all studies	**0.392**	**0.073**	**0.638**	**0.017**
I^2 = 0% fixed effects				



CHAPTER SEVEN

Video-game based exercises for older people with chronic low back pain: a protocol for a feasibility randomised controlled trial (the GAMEBACK trial)

Chapter Seven has been published as:

Zadro JR, Shirley D, Simic M, Mousavi SJ, Ceprnja D, Maka K, Ferreira PH. Video-game based exercises for older people with chronic low back pain: a protocol for a feasibility randomised controlled trial (the GAMEBACK trial). *Physiotherapy*. 2016;103(2):146-53.

ELSEVIER

Physiotherapy

Physiotherapy 103 (2017) 146–153

Protocol Paper

Video-game based exercises for older people with chronic low back pain: a protocol for a feasibility randomised controlled trial (the GAMEBACK trial)

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Abstract

Objectives To investigate the feasibility of implementing a video-game exercise programme for older people with chronic low back pain (LBP).
Design Single-centred single-blinded randomised controlled trial (RCT).
Setting Physiotherapy outpatient department in a public hospital in Western Sydney, Australia.
Participants We will recruit 60 participants over 55 years old with chronic LBP from the waiting list.
Interventions Participants will be randomised to receive video-game exercise ($n = 30$) or to remain on the waiting list ($n = 30$) for 8 weeks, with follow up at 3 and 6 months. Participants engaging in video-game exercises will be unsupervised and will complete video-game exercise for 60 minutes, 3 times per week. Participants allocated to remain on the waiting list will be encouraged to maintain their usual levels of physical activity.
Main outcome measure The primary outcomes for this feasibility study will be study processes (recruitment and response rates, adherence to and experience with the intervention, and incidence of adverse events) relevant to the future design of a large RCT. Estimates of treatment efficacy (point estimates and 95% confidence intervals) on pain self-efficacy, care seeking, physical activity, fear of movement/re-injury, pain, physical function, disability, falls-efficacy, strength, and walking speed, will be our secondary outcome measures.
Results Recruitment for this trial began in November 2015.
Conclusion This study describes the rationale and processes of a feasibility study investigating a video-game exercise programme for older people with chronic LBP. Results from the feasibility study will inform on the design and sample required for a large multicentre RCT.
Trial registration Australian New Zealand Clinical Trials Registry: ACTRN12615000703505.

Keywords: Exercise therapy; Low back pain; Video-game technology; Wii

Introduction

Low back pain (LBP) is a global problem [1] and the highest contributor to disability in Australia [2]. In 2012, the financial burden of LBP was estimated to be AU$4.8 billion, with direct healthcare expenditure for LBP being the greatest amongst all musculoskeletal conditions [3]. People who suffer from LBP have lower levels of physical activity [4], and lower cardiorespiratory fitness when compared to the healthy population [5]. These factors might explain why LBP can have a significant impact on physical performance [6], particularly in older people [7]. Older people with LBP have reduced self-efficacy and mobility when compared to older people without LBP [8]. However, despite the large personal impact of LBP in older people, they are commonly

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0031-9406/

excluded from randomised controlled trials (RCT) evaluating management of LBP [9].

Exercise therapy as a self-management strategy has the potential to improve outcomes in older people with chronic LBP. Exercise therapy plays an important role in the management of chronic LBP [10], however, current evidence only demonstrates low-to-moderate improvements for function and disability [11]. One proposed reason is that pain self-efficacy significantly influences treatment outcomes in people with chronic pain [12], and is the strongest mediator between pain and disability in people with LBP [13]. Since people with high levels of disability are eight times more likely to seek care for their LBP [14], we need to consider pain self-efficacy if we are to reduce direct healthcare expenditure [15] and waiting times for treatment of LBP. In addition, poor adherence to exercise programmes [10] suggests an increased need for supervision [16]. However, this can be problematic for older people with disability, who prefer a home-based exercise programme that does not require transport [17]. Therefore, these issues call for a new exercise management approach for older people with chronic LBP, involving home-based exercise therapy, aimed at improving pain self-efficacy and reducing the need to travel to clinics for treatment.

Video-game technologies are among novel interventions demonstrating clinical effectiveness for musculoskeletal rehabilitation [18] and present a unique opportunity for the self-management of chronic LBP in older people. Video-game exercises have been shown to improve balance [19] and falls-efficacy [20], with emerging evidence supporting video-game based interventions in people with chronic LBP. Middle-aged women with chronic LBP demonstrated significant improvements in pain, disability and fear avoidance following a four week video-game exercise intervention [21], while industrial workers with chronic LBP participating in video-game exercises significantly improved their health-related quality of life [22]. Adherence to video-game exercises is high [23], which is likely due to improvements in patients' motivation levels to complete the video-game exercises [23]. Therefore, home-based video-game exercises for older people with chronic LBP could be particularly useful at improving pain self-efficacy and reducing the need to travel to clinics for treatment.

The aim of this pilot RCT is to investigate the feasibility of implementing a video-game exercise programme for older people with chronic low back pain (LBP). The primary aim of this study is to investigate the following trial processes: recruitment and response rates, adherence to and experience with the video-game exercise programme, and the incidence of adverse events. The secondary aim will be to evaluate the immediate, medium (3 months) and long term (6 months) clinical effects of an 8 week video-game exercise programme on pain self-efficacy, care seeking behaviours, physical activity levels, fear avoidance beliefs, pain, physical function, disability, falls-efficacy, strength, and walking speed. Findings from this study will inform on the design and sample size required for a large multicentre RCT.

Methods

Design

A single-centre single-blinded feasibility RCT will be conducted with participants allocated to one of two treatment groups: a home-based video-game exercise group or a control group that will remain on the waiting list of a public hospital musculoskeletal outpatient department in Sydney, Australia (Supplementary Fig. 1). This trial has been designed according to the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) statement [24] and will be reported according to the CONsolidated Standards OF Reporting Trials (CONSORT) statement [25]. This protocol has been registered at the Australian New Zealand Clinical Trials Registry (ACTRN12615000703505) and approved by the Human Research Ethics Committee from the Western Sydney Local Health District (Local HREC reference (4266) AU RED HREC/15/WMEAD/143). Modifications to the trial protocol will be communicated to the HREC from the Western Sydney Local Health District.

Data protection, storage and dissemination

The information collected from participants will be stored securely and coded to be non-identifiable to staff involved in the trial except the principal investigator. Data will be entered into a secure server and all trial investigators will have access to the final dataset. Information collected for, used in, or generated by this project will be disseminated to the public via journal publication or conference presentations. No information about individual participants will be reported in the publications and dissemination of research results.

Sample size estimation

A formal sample size calculation was not performed for this feasibility study as one of the study aims is to provide sample size estimation for a large RCT. Instead we decided on recruiting 30 participants per group, recommended as a rule of thumb for feasibility studies [26].

Participants

Sixty participants aged over 55 years and experiencing chronic LBP will be recruited and allocated to either a video-game exercise group ($n = 30$) or control group ($n = 30$). The inclusion/exclusion criteria for this study are outlined in Table 1.

Recruitment method and screening procedures

Participants on the waiting list of the musculoskeletal outpatient department of 'X', who meet the inclusion criteria, will be contacted via mail and telephone. Recruitment flyers throughout the hospital will serve as an additional form

Table 1
Inclusion and exclusion criteria.

Inclusion	Exclusion
>55 years old	Diagnosis of serious pathology in the spine (such as fracture, metastatic disease, spinal stenosis, cauda equina syndrome)
Non-specific mechanical LBP for at least 3 months	Evidence of nerve root compromise
Usual pain intensity 3/10 or greater on the NRS	Any medical condition or disability that will prevent participation in the exercise programme, including:
Sufficient English ability to understand exercise instructions	• Cardiovascular risk factors: assessed using the PAR-Q, a screening tool recommended for all adults willing to initiate an exercise programme[a]
Able to mobilise independently without the use of walking aids	• Cognitive limitations: Mini Mental State Examination <25/30, a reliable and valid test of cognitive function[b]
Have access to a HDMI compatible television at home	• High risk of falls: Falls Risk Assessment Tool score >15, a reliable measure of falls risk in older adults[c]
	Physiotherapy treatment for their LBP in the last 6 months
Need for clearance from their general practitioner before participating in this trial:	
Participants who experience dizziness or altered consciousness, use prescribed medications or have uncontrolled diabetes	

LBP: low back pain; NRS: Numerical Rating Scale; HDMI: High-Definition Multimedia Interface; PAR-Q: Physical Activity Readiness-Questionnaire.

[a] Thompson PD, Arena R, Riebe D, Pescatello LS. ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription, ninth edition. Curr Sports Med Rep. 2013;12:215–7.

[b] Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.

[c] Stapleton C, Hough P, Oldmeadow L, Bull K, Hill K, Greenwood K. Four-item fall risk screening tool for subacute and residential aged care: The first step in fall prevention. Australas J Ageing. 2009;28:139–43.

of recruitment, with participants who view themselves as potentially eligible being prompted to contact an associate investigator. Participants will indicate their understanding and consent for involvement in this trial by signing the 'Participant Information and Consent Form' (Appendix 1). Consenting participants will be screened for eligibility at the hospital by a physiotherapist who will collect baseline data from eligible participants, remaining blinded to group allocation.

Randomisation

Following the baseline assessment, participants will be randomised to either the video-game exercise or control group, via a 1:1 ratio. Randomisation will be conducted using a computer-generated number system and operated by a blinded investigator. Block randomisation will be conducted to ensure balance in sample size across groups over time. Ten blocks of size six will be used. Allocation will involve contacting an 'off-site' investigator who will have access to the allocation schedule.

Intervention

Participants in the video-game exercise group will participate in a home-based exercise programme over 8 weeks using Nintendo Wii U console technology and the Wii-Fit-U software. Participants allocated to receive video-game exercises will be visited at home by an associate investigator who will set up the video-game equipment and teach them how to use it. Since the Wii-Fit-U software is commercially available, participants will have access to all the games on the software. To reduce the likelihood of participants engaging in inappropriate exercises and to standardise the intervention, they will be provided with a document which outlines a range of appropriate exercises preselected by the principal investigator. If the participant needs assistance or experiences an increase in their LBP >2/10 during a functional task (squats, lunges, single leg stance, etc.), activities on the Wii-Fit-U software which involve these movements will be excluded from the programme. The participant will have the flexibility to choose from the remaining exercises. A detailed description of the functional assessment is documented in Appendix 2.

Exercises will be included under the following categories: 'yoga', 'muscle', 'aerobic', and 'balance.' Participants will be asked to engage in the video-game exercises for 60 minutes, 3 times per week, and with at least one day of rest between exercise sessions. Participants will be encouraged to breakdown the 60 minutes exercise session as follows: 5 minutes 'yoga', 25 minutes 'muscle', 10 minutes 'aerobic' and 20 minutes 'balance.' This breakdown is based on evidence supporting strength and coordination exercises for the management of chronic LBP [27]. Participants will be asked to maintain exercise intensity at 12–13 on the Borg rating scale ('somewhat hard') during 'muscle' and 'aerobic' activities. This scale has been shown to correlate with measures of heart rate during exercise using the Wii-Fit-U [28]. Descriptions of exercises included in each category are described in Table 2.

The associate investigator will schedule fortnightly phone calls with the participant to monitor for any adverse events and provide an opportunity for the participant to progress their exercises if appropriate. The participant will also be given an information booklet containing information on how to safely progress their exercises.

Participants in the control group will remain on the waiting list and be asked to continue their current levels of physical activity. They will be offered the intervention for 8 weeks after the 6 month follow up data has been collected.

Table 2
Descriptions of exercises available on the Wii-Fit-U software included for this trial.

Wii-Fit-U exercise label	Exercise description	Time/dosage per activity
Yoga – *5 minutes*		
Deep Breathing	Deep breathing while evenly distributing weight through both feet	~40 seconds
Chair	Deep breathing while maintaining a squat	~45 seconds
Warrior	Deep breathing while maintaining a small lunge	~45 seconds/side
Palm Tree	Double leg heel raise while extending both arms backwards	~45 seconds
Tree	Single leg stance while elevating both arms	~45 seconds/side
Standing Knee	Single leg stance while holding the opposite knee	~30 seconds/side
Bridge	Extending both hips in crook lying	~30 seconds
Crocodile Twist	Lumbar rotations in supine	~55 seconds/side
Cobra	Lumbar extension in prone	~45 seconds
Strength – *25 minutes*		
Arm & Leg Lift	Extending an arm and the opposite leg in 4-point kneeling	10 repetitions/side
Rowing Squat	Squatting while performing a rowing motion	15 repetitions
Lunge	Lunging with one foot on the balance board	10 repetitions/side
Single Leg Twist	Single leg stance while lifting and lowering the opposite leg forwards	10 repetitions/side
Sideways Leg Lift	Single leg stance while lifting and lowering the opposite leg sideways	10 repetitions/side
Single Leg Extension	Single leg stance while moving the opposite leg backwards	6 repetitions/side
Single Leg Reach	Single leg stance while reaching towards the floor	6 repetitions/side
Torso and Waist Twist	Twisting from side to side while feet remain in the same position	3 repetitions/side
Aerobic – *10 minutes*		
Step Basic; Step Plus	Step ups on the balance board in time with visual cues	2.5 to 4.5 minutes
Jogging; Cycling; Orienteering	Marching on the balance board while using the Wii controller to complete a virtual task	>2 minutes
Hula Hoop; Super Hula Hoop	Shifting body weight in a circular motion	70 to 90 seconds
Driving Range	Performing the motion of a golf swing	20 swings
Balance – *20 minutes* (all movements are performed to complete a virtual challenge)		
Heading	Shifting body weight side to side	1 minute
Table Tilt	Shifting body weight side to side	30 seconds to 3 minutes
Ski Slalom	Shifting body weight side to side	30 seconds
Balance Bubble	Shifting body weight side to side	10 to 30 seconds
Tilt City	Shifting body weight side to side	[a]
Snowball Fight	Shifting body weight side to side	[a]
Ski Jump	Squatting, with a fast extension phase	1 minute
Trampoline Target	Squatting, with a fast extension phase	20 seconds to 2 minutes
Perfect 10	Moving hips forwards, backwards and sideways	45 seconds to 1 minute
Hose down	Lunging with one foot on the balance board	2 minutes
Dessert Course	Marching on the balance board	2.5 minutes
Obstacle Course	A combination of squatting and marching	1 to 4 minutes
Ultimate Obstacle Course	A combination of squatting and marching	1.5 to 3 minutes

[a] Time varies depending on the performance of the task.

Feasibility

Data on the following outcomes will be collected to inform on the study processes and if necessary, make modifications to the study design in preparation for a large multicentre RCT.

Recruitment and response rates

Data on recruitment rates (number of participants/week) and the most successful recruitment medium (mail, telephone, or flyer) will be collected throughout the trial. The response rate for the 3 and 6 month mail-out survey will be calculated.

Assessment and data collection procedures

Time to complete the eligibility screening procedures (Table 1) and baseline questionnaires will be measured to investigate the burden for participants and investigators collecting data, while informing on the approximate number of outcome measures feasible for a large RCT.

Adherence

Adherence to the exercise programme will be assessed through the use of an exercise diary. Participants will track the duration and frequency of their exercise sessions in the diary.

Experience with the intervention

Participants' experience with the video-game intervention will be assessed immediately post intervention through a questionnaire developed for this trial. This 14-item questionnaire will allow participants to rate their experience with the intervention on a NRS. Participants will rate their level

of satisfaction with the exercises and use of technology, informing on the facilitators and barriers to the video-game intervention. The questionnaire will be given to the participant, along with a reply paid envelope, when the associate investigator collects the Nintendo Wii U equipment immediately following the 8 week intervention. The participant will complete the questionnaire and post it to 'X'.

Cost-effectiveness

Prior to enrolment in the study, participants are informed that they will maintain their position on the waiting list but will be unable to receive outpatient physiotherapy during the trial (except in the case of drop-outs). Therefore, costs to the healthcare system from general practitioner visits and medication use will be derived from the Medical Benefits Scheme standard fees and the Pharmaceutical Benefits Scheme cost for medications. Self-reported costs include the utlilisation of private non-medical health care services, miscellaneous expenses (e.g. lumbar support, gym or pool attendance, etc.) and absence from work (calculated as the number of days absent from work multiplied by the average wage; although we suspect our inclusion criteria will predominately capture people retired from work). Effectiveness will be measured by reported changes in pain self-efficacy, our most important clinical outcome. The between-group differences in cost will be divided by the between-group differences in effect, creating an incremental cost-effectiveness ratio.

Adverse events

Adverse events are defined as any undesirable outcome related to the intervention, such as falls, injury, discomfort and increased LBP symptoms. Participants will be encouraged to report any adverse events to the associate investigator during the fortnightly telephone call. These adverse events and their possible connection with the use of the Wii-Fit-U will be monitored and documented. Participants will be encouraged to seek appropriate medical advice in the event of a serious adverse event.

Clinical outcome measures

Clinical outcome measures will be collected from participants at baseline, 8 weeks, 3 months and 6 months. Baseline and 8 week outcome measures will be collected at the musculoskeletal outpatient department of 'X'. Participants will be requested to complete the follow up assessments even if they stop using the Wii-Fit-U software during the trial. The 3 and 6 month assessments consist of self-reported questionnaires and will be mailed to participants home addresses (along with a reply paid envelope), where they will complete it and mail it back to the hospital. Participants will be contacted prior to the mail-out of the 3 and 6 month questionnaires to increase the response rate.

Demographic/descriptor variables

Data on age, gender, body mass index (BMI), marital status, ethnicity, alcohol consumption, smoking history, educational attainment, employment status, comorbidities and family characteristics will be collected at baseline. Data on family characteristics will consider the presence and type of LBP, as well as the level of physical activity engagement, of the participant's immediate family members (parents, children and siblings).

Pain self-efficacy

Pain self-efficacy will be assessed using the Pain Self-Efficacy Questionnaire (PSEQ) which has been shown to have good reliability ($r = 0.79$) and validity in patients with chronic pain [29]. The PSEQ assesses how confidently participants can do a variety of daily activities despite their pain [29]. Participants are instructed to score their confidence for completing an activity on a scale from 0 to 6; where 0 = 'not confident at all' and 6 = 'completely confident.' Data on pain self-efficacy will be collected at baseline, 8 weeks, 3 months and 6 months, however, the data collected at 3 and 6 months will be considered the most important clinical outcome measure.

Care seeking

Care seeking will be assessed by a 3-item questionnaire developed for this trial. This questionnaire will collect information on current care seeking (e.g. GP visits, private physiotherapy, private chiropractic, etc.), future care seeking, and medication use (e.g. type and dosage). Care seeking will be evaluated at baseline, 8 weeks, 3 months and 6 months.

Physical activity

Physical activity levels will be assessed by the Rapid Assessment of Physical Activity (RAPA) questionnaire which has been validated for use among older adults and demonstrates good discrimination between active and inactive older adults [30]. The RAPA assesses the self-reported amount and intensity of physical activity and is divided into an 'aerobic' and 'strength and flexibility' section. Physical activity levels will be collected at baseline, 8 weeks, 3 months and 6 months.

The following clinical outcomes will only be collected at baseline and 8 weeks to reduce to burden on participants for the 3 and 6 month follow up survey and improve the response rate.

Fear of movement/re-injury

Fear of movement/re-injury will be assessed using the 11-item Tampa Scale of Kinesiophobia (TSK). Participants indicate their level of agreement with each statement on a 4-point scale, where 1 indicates 'strongly disagree' and 4 indicates 'strongly agree.' Higher scores reflect greater fear of movement/re-injury. The TSK is a valid, reliable and

responsive tool for assessing pain related fear in people with chronic LBP [31].

Physical function

Physical function will be assessed using the Patient Specific Functional Scale (PSFS). The PSFS instructs the participant to nominate three activities they currently have trouble with because of their LBP. Each activity is scored on an 11-point scale from 0 (unable to perform the activity) to 10 (able to perform the activity at pre-injury level) [32]. The PSFS has demonstrated good reliability, validity and responsiveness to detect change in people with LBP over time [32].

Pain

Pain will be assessed using the NRS [33], an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable). The NRS assesses the usual intensity of pain experienced in the last week.

Disability

Disability will be assessed using the Roland Morris Disability Questionnaire (RMDQ), a 24-item questionnaire containing statements describing activities which might be impacted by the participants' LBP. For each statement, the participant will answer 'yes' or 'no,' forming a total score out of 24. The RMDQ is a valid, reliable and sensitive tool in detecting change in patients with LBP over time [34].

Falls-efficacy

Falls-efficacy will be assessed using the Falls Efficacy Scale-International (FES-I), a 16-item questionnaire assessing how concerned participants are about the possibility of falling during activities of daily living (cleaning, clothing, cooking, shopping, etc.). The participant will score each activity on a 4-point scale, where 1 indicates not being concerned at all and 4 indicates feeling very concerned, forming a total score out of 64. The FES-I has been shown to have good test retest reliability and internal reliability in older adults [35].

Strength

Strength will be indirectly assessed by the Timed Up and Down Stairs Test (TUDS). The TUDS will be performed on a set of 9 stairs, each step being 14.5 cm high and 26 cm deep. Participants will stand 27 cm from the first step and be instructed to safely go up, turn around and come down the stairs as fast as they can without running. The test will be repeated three times to yield an average time. The TUDS has been shown to be a clinically relevant measure of leg muscle power and mobility performance in older adults [36].

Walking speed

Maximal and preferred walking speed will be assessed using the 10 m Walk Test. Participants will be asked to walk unassisted for 10 m, with the middle 6 m being timed to reduce the effects of acceleration and deceleration. The tests for maximal and preferred walking speed will be repeated three times to yield an average maximal and preferred walking speed. Walking speed has shown good prognostic value in identifying lower extremity limitations in well-functioning older people [37].

Data analysis

The primary focus of the analysis will be on process outcomes, including the calculation of recruitment and response rates, adherence to the video-game intervention and experience with the intervention. Estimates of treatment efficacy (means and 95% Confidence Intervals (CI)) will be calculated using mixed-models to accommodate for the repeated measures over time while adjusting for baseline outcomes. Emphasis will be placed on effect sizes and 95%CI, rather than hypothesis testing. The investigator analysing the data will be blinded to the group identification code. To ensure all analyses are performed by intention-to-treat we will attempt to follow up all participants, regardless of whether they withdraw from their allocation. When data is missing 'completely at random' (e.g. administrative error) analyses will only include complete cases. When it is plausible that missing data has originated from non-random causes, we will perform sensitivity analyses to investigate whether different assumptions on the mechanism of missing data impact the results [38].

Participant withdrawal from study and/or from follow-up

If a participant decides to withdraw from the study, the principal investigator will be notified by the associate investigator, and will contact the participant. If the participant is happy to give a reason for their withdrawal from the study, this will be documented. The principal investigator will determine whether the participant wishes to be included in the follow up assessments or withdraw completely.

Discussion

This manuscript describes the rationale and processes of a pilot study investigating the feasibility of implementing a video-game exercise programme for older people with chronic LBP. Although exercise therapy is the most recommended intervention for the management of chronic LBP, motivation to engage in an unsupervised exercise programme for people with musculoskeletal conditions can often be a problem [10]. This is particularly problematic for older people with chronic LBP who are more likely to have impaired physical performance [6] and prefer a home-based exercise programme that does not require transport [17]. Video-game exercises present a unique opportunity to increase older people's motivation to engage in an exercise programme [16] and potentially manage their chronic LBP. Results from the feasibility study will inform on the design and sample size required for a large multicentre RCT, which will aim to investigate the

long term effects of an innovative self-management strategy, utilising video-game technology, on older people's capacity to self-manage their chronic LBP. If video-game exercises are found to be effective at improving self-management in older people with chronic LBP this could reduce care-seeking for LBP in this population, resulting in reduced waiting times for treatment in public hospitals, and decreased health-care expenditure for chronic LBP.

Acknowledgments

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Ethical approval: This protocol has been granted ethics approval by the Human Research Ethics Committee from the Western Sydney Local Health District (Local HREC reference (4266) AU RED HREC/15/WMEAD/143).

Conflict of interest: None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.physio.2016.05.004.

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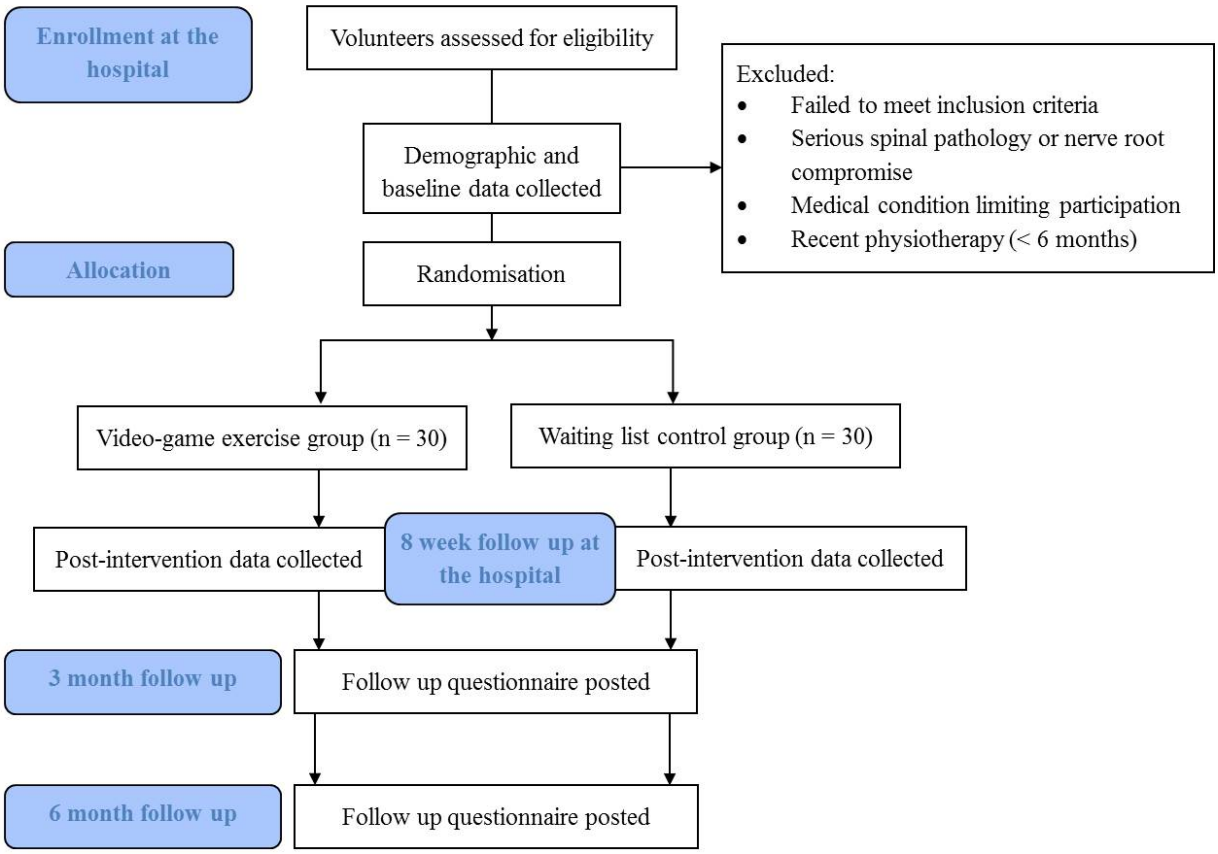
Supplementary material: CONSORT flowchart for the GAMEBACK Trial.



Supplementary material: Participant information sheet/consent form.

THE UNIVERSITY OF SYDNEY

Health
Western Sydney
Local Health District

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Westmead Public Hospital

Title	Video-game based exercises for older people with chronic low back pain: A pilot randomised controlled trial
Short Title	The GAMEBACK Trial
Protocol Number	1
Coordinating Principal Investigator/ Principal Investigator	Ms Katherine Maka
Associate Investigator(s)	Mr Joshua Zadro, Dr Paulo Ferreira, Dr Debra Shirley, Dr Milena Simic, Dr Seyed Javad Mousavi, Mrs Dragana Ceprnja
Location	Physiotherapy Outpatient Department (WPH)

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have chronic low back pain and this project is testing a new treatment for the management of chronic low back pain. The new treatment utilises video-game technology as a form of home exercise.
This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The aim of this study is to investigate how well people with low back pain can manage their symptoms following a video-game exercise program. We are specifically interested in people who are currently awaiting treatment for their back at the Physiotherapy Department of Westmead Hospital.

Low back pain is the leading cause of disability in Australia and is more disabling in older people. Exercise programs are frequently used to treat low back pain and are known to offer moderate improvements for pain and function. However, usually exercise programs require supervision and the need for patients to travel to treatment sites, which can be problematic for older people with disability. Additionally, limited availability of health resources and an increasing number of people with chronic diseases means patients are often on long waiting lists for treatment. Video-game exercises for low back pain could be particularly useful in older people because they can be implemented at home and therefore reduce the need to travel to treatment sites. This has the potential to reduce the number of people waiting for treatment in public hospitals and reduce management costs of chronic low back pain. Video-game exercises are starting to be used to treat a variety of conditions and have been shown to increase motivation for completing a home-based exercise program. Therefore, this study will determine whether video-game exercises done in the home are effective in the management of low back pain.

The results of this research will be used by the study investigator Joshua Zadro to obtain a Doctor of Philosophy (PhD). This research has been initiated by the principal study physiotherapist, Ms Katherine Maka. This research has been funded by the University of Sydney and additional funding may be sourced from the Physiotherapy Research Foundation if our funding application is successful. This research is being conducted by the University of Sydney at the Faculty of Health Sciences.

3 What does participation in this research involve?

All assessment procedures will be conducted after you have; read all of this information carefully, asked any questions about anything that you don’t understand or want to know more about and you have signed the consent form.

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments and put people into groups which receive different treatments. The results are compared to see if one is better. To try to make sure the groups are the same, each

participant is put into a group by chance (randomised). The groups we are comparing include a 'video-game exercise' group and a 'remain on the waiting list' group.

On the following page is a table outlining the activities involved if you decide to participate in this study:

Stage	Activity	Estimated time to complete
Week 1: Hospital Visit If eligible:	Lower back assessment & screening for eligibility	30-45 minutes
	Baseline questionnaire	15-20 minutes
Weeks 1-8: you will be allocated to one of the groups	**Video-game exercise group:** - Remain on the waiting list - 3 x 60 min unsupervised exercise sessions - Fill out weekly exercise diary	~3 hours/week for 8 weeks
	Control group: - Remain on the waiting list - Maintain usual activities	No time commitment
Week 9 : Hospital Visit	Follow up questionnaires	10-15 minutes
3 Months	Complete questionnaires posted to you and return by mail	5-10 minutes
6 Months	Complete questionnaires posted to you and return by mail	5-10 minutes

You will be eligible to participate in this study if:

i) you are over 55 years old;
ii) you have experienced low back pain for at least the last 3 months;
iii) you have pain in your lower back which is greater than 3/10;
iv) you have sufficient English ability;
v) you can walk without anyone's assistance or the assistance of any aids (e.g. walking stick, walking frame, etc.);
vi) your scheduled physiotherapy treatment at Westmead Hospital doesn't fall within the next 8 weeks;
vii) you have a HDMI compatible television at home (this is a requirement to use the video-game equipment).
viii) You have not received physiotherapy treatment for your low back pain in the last 6 months

You will be excluded from this study if:

i) you have been diagnosed with a serious pathology in the spine (such as fracture, metastatic disease, spinal stenosis, cauda equina syndrome). If you unsure about this statement, please ask the study researcher;
ii) you have any medical condition or disability that will prevent you from participating in an exercise program;
iii) if the physiotherapist determines that participating in this study wouldn't be beneficial for you.

Here are some reasons the physiotherapist might decide that participating in this study would not be beneficial for you:

i) you demonstrate a high degree of fear of movement due to your low back pain;
ii) you are at risk of cardiovascular (heart) complications;
iii) you are at high risk of falls

If eligible we will then ask you to complete a number of written questionnaires about your general characteristics (e.g. age, height, weight, education status, etc.) and characteristics related to your low back pain. You will also be required to complete a short physical test (a walk speed and stair climb test).

You will then be randomised to either complete the video-game exercise program over 8 weeks or to remain on the waiting. Regardless of which group you are allocated to you will remain on the waiting list for the next 6 months. Since the average waiting time for treatment at the Physiotherapy Department of Westmead Hospital is 12 months, we suspect your waiting time for treatment will not be impacted if you decide to participate in this trial. Both groups will maintain their position on the waiting list throughout the trial. Randomisation will be computer-generated so you have a one in two chance of being allocated to the video-game exercise group.

If you are allocated to remain on the waiting list you will have to the option to receive the video-game exercise program for 8 weeks after the 6 month follow-up period unless it interferes with scheduled physiotherapy outpatient treatment and you would prefer to only be seen by a physiotherapist.

If you are allocated to the video-game exercise group another physiotherapist will arrange a time to visit you at home to set up the Nintendo Wii Console, help you create a profile on the Wii Fit program ('Mii'),conduct a functional assessment to determine which exercises will be safe for you to participate in (the physiotherapist will give you a document outlining which exercises are appropriate for you) and go through your first exercise session with you. The home visit may take up to 2 hours. It is suggested you use the Wii Fit program for 60 minutes on 3 separate occasions per week, with at least one day of rest between sessions. You will be able to tailor your exercise sessions by selecting which exercises you would like to participate in. You will arrange fortnightly phone calls with the physiotherapist to discuss what exercises you have been using and the potential to progress to other exercises if appropriate. This phone call will also be a chance for you to discuss any issues you are having with the equipment. The physiotherapist will guide your choice in exercises but overall it is up to you. You will be given an exercise diary to log the number of times you used the Wii Fit program during the week and how long each session went for.

After 8 weeks, if you were allocated to the video-game exercise group the physiotherapist who conducted the initial home visit will organise a time to collect the Nintendo equipment from you. At this time you will be given a short survey to fill out regarding your experiences with the video- game exercises. You will be required to bring this survey to the hospital for your follow up assessment. Regardless of what group you were allocated to, you will return to the hospital after 8 weeks for your follow up assessment. This assessment will involve completing a short questionnaire and a physical test. This will take approximately 15 minutes.

At 3 months and 6 months we will mail out a short questionnaire on characteristics related to your back pain to assess how the exercise program has impacted you in the medium and long term.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study physiotherapists or participants jumping to conclusions.

There are no additional costs associated with participating in this research project, nor will you be paid. All video-game equipment required as part of the research project will be provided to you on loan, free of charge, and collected from you following the 8 week program period.

There will be no reimbursement for any travel related costs for participating in this study.

4 What do I have to do?

You will be required to complete three 60 minute sessions per week, with at least one day between sessions to rest. You will arrange a time for the physiotherapist to call you, once a fortnight, to progress exercises if appropriate. You will be given an exercise diary to log the number of times you used the Wii Fit program during the week and how long each session went for.

5 Other relevant information about the research project

The study is being conducted at the Physiotherapy Department of Westmead Hospital, in collaboration with Dr Paulo Ferreira and his team of researchers from the Discipline of Physiotherapy, the University of Sydney.

We aim to recruit sixty participants for this study, thirty to participate in the video-game exercise program and thirty to remain on the waiting list.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with The University of Sydney or Westmead Public Hospital.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; these include continuing to remain on the waiting list until you receive outpatient physiotherapy treatment. Your study coordinator will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research. However, possible benefits for those allocated to the video-game exercise program may include: an improvement in your ability to manage your lower back symptoms, a reduction in pain, disability, use of health care services or falls risk, an improvement in function, quality of life or physical activity levels. Findings from this study will determine whether home-based video-game exercises are effective in the management of low back pain. If video-game exercises are found to be effective, waiting lists for treatment in public hospitals and management costs of chronic low back pain could be reduced since video-game exercises potentially require less supervision than a traditional exercise program.

9 What are the possible risks and disadvantages of taking part?

There may be side effects or adverse events that the researchers do not expect or do not know about and that may be serious. Tell your study physiotherapist immediately about any new or unusual symptoms that you get, or if something serious occurs. If you require emergency assistance, or you experience chest pain or excessive shortness of breath, call 000.

There will be no risks or disadvantages if you are allocated to remain on the waiting list since you will have the option to receive the video-game intervention after 6 months. If you are allocated to the video game exercise program there may be some exercises which will challenge your strength, fitness, balance and coordination. You may feel soreness in your muscles one or even two days after participating in an exercise session, however, this is completely normal and somewhat expected. The risk for an injury or a fall is inherent to any exercise program. However, a physiotherapist will minimise the risk of this occurring by identifying which exercises you can safely choose to participate in.

10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study physiotherapist will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study physiotherapist will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form. Also, on receiving new information, your study physiotherapist might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

11 Can I have other treatments during this research project?

Whilst you are participating in this research project, you will be encouraged not to undergo any other physiotherapy treatments. As this is an 8 week trial, we will make it clear if you are within 8 weeks of receiving outpatient physiotherapy treatment. If the waiting list suddenly becomes shorter during the trial and you wish to receive outpatient physiotherapy treatment, it is your choice to do so.

12 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team so they can take you off the phone call or email list, and also collect the Nintendo Wii equipment from your home if you were allocated to the video-game exercise group. If you do withdraw your consent during the research project, the study physiotherapist and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the physiotherapist up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

13 Could this research project be stopped unexpectedly?

No.

14 What happens when the research project ends?

Upon completion of the trial, if you were allocated to remain on the waiting list you will be given the option to receive the video-game exercise program or wait for your outpatient physiotherapy consult.

If you participated in the video-game exercise program a research investigator will organise a time to collect the Nintendo equipment.

Your results will be communicated to you at the end of the exercise program. The research assistant in charge of collecting assessment data will be responsible for communicating these results to you.

The results of the research are intended for Journal publication, conference presentations and hospital in-service with allied health professionals. You may request a copy of the results.

Part 2 How is the research project being conducted?

15 What will happen to information about me?

By signing the consent form you consent to the study physiotherapist and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential.

All questionnaires will be stored in a locked filing cabinet in the office of the senior physiotherapist in the Physiotherapy Department at Westmead Hospital. All collected data will be de-identified before leaving Western Sydney Local Health District. Data transported to the University of Sydney will be kept in a locked filing cabinet, accessible only by the researchers associated with the project.

Data will be coded and stored on computer files on the University of Sydney Secure Server. Only the principal researchers will have access to the code. It is necessary to store this data as re-identifiable, because in accordance with Australian and NSW privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information. The data will be kept for a minimum of 7 years after which time the data may be disposed of in a secure manner. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Data on your general characteristics and characteristics related to your back pain will be presented in the tables or results section without referring to your individual data.

16 Complaints and compensation

If you suffer any serious injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital. If your symptoms get worse as a result of this research project, let the study team know at the scheduled fortnightly follow up time and they will discuss appropriate options with you.

17 Who is organising and funding the research?

This research project is being conducted by a team of researchers at Discipline of Physiotherapy, University of Sydney and Westmead Hospital, led by Dr Paulo Ferreira. The University of Sydney has supplied us with Nintendo® Wii equipment to conduct this trial.

Nintendo® may benefit financially from this research project if, for example, the project assists Nintendo® to sell more Nintendo Wii® consoles for the management of chronic low back pain.

You will not benefit financially from your involvement in this research project. In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to Nintendo®, the study physiotherapists or their institutions, there will be no financial benefit to you or your family from these discoveries.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

18 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the Western Sydney Local Health District.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

19 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the following people:

Clinical contact person

Name	Mr Joshua Zadro
Position	Associate Investigator
Telephone	0449906121
Email	jzad3326@uni.sydney.edu.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Position	Westmead Hospital Patient Representative
Telephone	9845 7014

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Western Sydney Local Health District HREC
HREC Executive Officer	Mrs Kellie Hansen
Telephone	9845 8183
Email	wslhd-researchoffice@health.nsw.gov.au

Local HREC Office contact (Single Site -Research Governance Officer)

Name	Mrs Margaret Piper
Position	Research Governance Officer
Telephone	9845 9634
Email	wslhd-rgo@health.nsw.gov.au

Consent Form - *Adult providing own consent*

Title	Video-game based exercises for older people with chronic low back pain: A pilot randomised controlled trial.
Short Title	The GAMEBACK Trial
Protocol Number	1
Coordinating Principal Investigator/	Ms Katherine Maka
Associate Investigator(s)	Mr Joshua Zadro, Dr Paulo Ferreira Dr Debra Shirley, Dr Milena Simic, Dr Seyed Javad Mousavi, Mrs Dragana Ceprnja
Location	Physiotherapy Outpatient Department (WPH)

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand. I understand the purposes, procedures and risks of the research described in the project. I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to The University of Sydney concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential. I have had an opportunity to ask questions and I am satisfied with the answers I have received. I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care. I understand that I will be given a signed copy of this document to keep.

Name of Participant (please _____

Signature _____ Date _____

Declaration by Study Physiotherapist/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Physiotherapist/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	Video-game based exercises for older people with chronic low back pain: A pilot randomised controlled trial
Short Title	The GAMEBACK Trial
Protocol Number	1
Coordinating Principal Investigator/	Ms Katherine Maka
Associate Investigator(s)	Mr Joshua Zadro, Dr Paulo Ferreira, Dr Debra Shirley, Dr Milena Simic, Dr Seyed Javad Mousavi, Mrs Dragana Ceprnja
Location	Physiotherapy Outpatient Department (WPH)

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with The University of Sydney.

Name of Participant (please _____

Signature _____ Date _____

Description of withdrawal circumstances ***(to be completed by the study physiotherapist)***

Declaration by Study Physiotherapist/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Physiotherapist/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.
Note: All parties signing the consent section must date their own signature.

Supplementary material: Participant Wii-Fit-U screening tool.

This document describes the range of movements involved in certain exercises on the Wii-Fit-U, and will help determine which exercises are appropriate for each participant.

Tick the box next to each movement if the participant is able to perform the movement safely. If the participant needs assistance, or experiences an increase in their low back pain > 2/10 on the Numeric Pain Rating Scale (NRS), remove the indicated Wii-Fit-U exercises from their program.

Squat ☐

- If box isn't ticked remove: *Chair, Rowing Squat, Ski Jump, Trampoline Target, Obstacle Course and Ultimate Obstacle Course*

Unsupported double leg heel raise ☐

- If box isn't ticked remove: *Palm Tree*

Single leg stance ☐

- If box isn't ticked remove: *Tree, Standing Knee, Single Leg Extension, Single Leg Twist, Sideways Leg Lift and Single Leg Reach.*

Single leg reach towards the floor (drinking bird) ☐

- If box isn't ticked remove: *Single Leg Reach*

Lunge ☐

- If box isn't ticked remove: *Lunge*

Marching on the spot ☐

- If box isn't ticked remove: *Jogging, Free Jogging, Cycling, Dessert Course, Scuba Search, Obstacle Course and Ultimate Obstacle Course*

Stepping up and down off the balance board ☐

- If box isn't ticked remove: *Step Basic, Step Plus, Free Step and Hose Down*

Side stepping ☐

- If box isn't ticked remove: *Step Basic, Step Plus, Free Step*

Moving hips forward, back, and side to side ☐

- If box isn't ticked remove: *Perfect 10*

Bridge: double leg hip extension in crook lying ☐

- If box isn't ticked remove: *Bridge*

4 point kneel ☐

- If box isn't ticked remove: *Arm and Leg Lift*

Prone lumbar extension ☐

- If box isn't ticked remove: *Cobra*

CHAPTER EIGHT

Video-game based exercises for older people with chronic low back pain: a pilot randomised controlled trial (GAMEBACK)

Chapter Eight has been submitted for publication as:

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Video-game based exercises for older people with chronic low back pain: A pilot randomised controlled trial (GAMEBACK).

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Abstract

Background: Video-game technology can increase adherence to home-exercise and is a promising self-management strategy for older people with chronic low back pain (LBP).

Objectives: To investigate the feasibility and efficacy of an 8 week home-based video-game exercise program for older people with chronic LBP.

Design: Randomised controlled trial (RCT).

Setting: Community and outpatient rehabilitation waiting list.

Patients: Sixty participants over 55 years of age with chronic LBP were randomised to receive Wii-Fit-U exercises (n=30) or instructed to continue their usual activities (n=30) for 8 weeks.

Intervention: Wii-Fit-U flexibility, strengthening and aerobic exercises at home for 60 minutes, three times per week, with fortnightly follow-up calls from a physiotherapist.

Measurements: Recruitment and response rates, adherence, experience with the intervention, incidence of adverse events, pain self-efficacy, care seeking, physical activity, pain, function, disability, fear of movement/re-injury, and falls-efficacy.

Results: We screened 117 participants and included 60 (51.3%). The mean age (standard deviation) was 67.8 (6.0) years old, and 93.3% of participants were recruited from the community (recruitment rate =11.2 participants/month). Follow-up data was available from 57 participants at 6 months (95.0%). Average adherence to the total recommended exercise time was 70.8% and no adverse events were reported. Participants completing Wii-Fit-U exercises had significantly higher pain self-efficacy at 6 months, were more likely to engage in flexibility exercises at 6 months, and demonstrated significantly greater improvements in pain and function at 8 weeks compared to the control group. There were no significant between-group differences

for the remaining outcomes.

Limitations: Participants and the therapist delivering the intervention were not blinded.

Conclusion: Wii-Fit-U exercises are feasible and can improve pain self-efficacy, pain, and function in older people with chronic LBP.

Keywords: Home exercise, Low back pain, Video-game, Nintendo Wii, Older people.

Introduction

Low back pain (LBP) is the most disabling and costly musculoskeletal condition worldwide[1-3], with the majority of this burden accounted for by older people who develop chronic symptoms[4]. Chronic LBP becomes more severe[5] and disabling with age[6], and can have a significant impact on physical functioning[7]. Despite this, older people with chronic LBP are commonly excluded from randomised controlled trials (RCT) evaluating treatment options[8], and given the global population of people over 60 years old is expected to triple by 2050[9], more research on this population should be a priority.

Structured exercise programs are recommended for the management of chronic LBP[10], although adherence to unsupervised home-exercise is poor[10-13]. Despite this, older people with poor physical functioning prefer home-based exercises as travelling to treatment facilities can be difficult and supervised exercise can be costly[14]. Poor adherence to home-exercise is likely explained by a lack of motivation to perform exercises without supervision, but could also be the result of low levels of pain self-efficacy[15]. Pain self-efficacy is the ability to continue daily activities despite pain[16] and has been shown to significantly influence treatment outcomes in people with chronic pain[13]. Pain self-efficacy also accounts for how pain leads to disability[17]. Therefore, given that disability is associated with greater health-care utilisation[18], improving pain self-efficacy should be a priority if older people with chronic LBP are to effectively self-manage their condition and reduce their health-care utilisation[19].

Video-game exercise programs are being increasingly used for musculoskeletal rehabilitation[20], and can improve balance[21] and falls-efficacy[22] in older people with poor physical function. In addition, video-game exercises can improve pain, disability, fear avoidance, and quality of life in

adults with chronic LBP[23,24], but have not been investigated as a self-management strategy for older people with chronic LBP. Video-game exercises are interactive and may increase patients' adherence to home-exercise[25,26], mostly because of video and audio instructions, and feedback on performance[27,28]. With this in mind, video-game exercises could be a unique solution to increase older people's motivation to self-manage their chronic LBP through home-exercise and improve their pain self-efficacy. In addition, using video-game exercises as a self-management strategy could have important implications for reducing health-care costs for chronic LBP in the long-term.

The aim of this pilot RCT was to investigate the feasibility of an 8-week unsupervised home-based video-game exercise program for older people with chronic LBP by evaluating the recruitment and response rates, adherence to and experience with the intervention, and the incidence of adverse events. The secondary aim was to investigate the immediate, short (3 months), and long term (6 months) clinical effects of an 8-week video-game exercise program on pain self-efficacy, care seeking, physical activity, pain, function, disability, fear of movement/re-injury, and falls-efficacy.

Methods

Design

We conducted a single-blinded feasibility RCT in people over 55 years of age with chronic LBP and compared an unsupervised home-based video-game exercise program to a control group instructed to maintain their usual activities (including care-seeking behaviours). This trial is reported in accordance with the CONsolidated Standards OF Reporting Trials (CONSORT)

statement[29] and the intervention has been documented according to the Template for Intervention Description and Replication (TIDieR) checklist[30]. The study protocol was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000703505) and has been published[31]. All recruitment and data collection procedures were approved by the Human Research Ethics Committee from the Western Sydney Local Health District [Local HREC reference: (4266) AU RED HREC/15/WMEAD/143] and participants gave informed written consent.

Participants

Sixty participants over 55 years with chronic LBP were randomly allocated to a video-game exercise (n=30) or control group (n=30). Given that the findings from this study will inform on the sample size required for a large RCT we based our sample size on a rule of thumb for feasibility studies[32]. The inclusion/exclusion criteria we specified in our protocol can be found in Table 1. However, to increase the recruitment rate we didn't exclude participants who received physiotherapy for their LBP in the past 6 months.

Recruitment method and screening procedures

Participants were recruited from: i) the local community via advertisements in an online seniors' newsletter; and ii) the waiting list of the Outpatient Physiotherapy Department at Westmead Hospital, Sydney, Australia. People over 55 years on the waiting list with a referral for chronic LBP treatment were contacted via mail or presented with information about the study during routine telephone communication from their physiotherapist. Those interested in the trial contacted a research investigator who clarified the inclusion/exclusion criteria over the phone,

sent them detailed information about the trial, and screened consenting and potentially eligible participants. Eligible participants were guided through the baseline assessment by a qualified physiotherapist who remained blind to group allocation. From November 2015 to August 2016 only four participants from the waiting list were interested and eligible for the trial, so we modified our recruitment strategy to include participants from the general community to increase the recruitment rate.

Randomisation

Following the baseline assessment, the assessing physiotherapist contacted a blinded "off-site" investigator who used a computer-generated number system to determine group allocation. Participants were randomised (1:1) to either the video-game exercise or control group, with randomisation performed in ten blocks of six to ensure balance in sample size across groups over time.

Intervention

Participants in the video-game exercise group engaged in an unsupervised home-based exercise program for 8 weeks using a Nintendo Wii-U console with Wii-Fit-U software. These participants were visited at home by a physiotherapist with three years clinical experience who set up the video-game equipment and guided them through their first session. The Wii-Fit-U exercises are commercially available and it was not possible to alter which exercises were displayed to participants. Therefore, participants were given a booklet which outlined a range of flexibility, body weight resistance, and aerobic exercises pre-selected by the research team to standardize the intervention. Prior to instructing the participant how to perform Wii-Fit-U

exercises, the physiotherapist assessed their ability to perform several movements included in the program. If the participant appeared unsafe while performing any of these movements or reported at least a 2/10 increase in their pain that failed to subside when the movement stopped, Wii-Fit-U exercises that involved these movements were removed from the exercise list. Further details regarding the included Wii-Fit-U exercises and the movements assessed during the initial visit can be found in our protocol[31].Wii-Fit-U exercises included video and audio instructions, gave participants feedback on their performance during and after exercises, and scored their performance. For example, visual representation of the pressure participants were applying through their foot while performing 'lunges' encouraged them to perform the movement with more hip and knee flexion (and subsequently more pressure on the balance board). Once the participant felt confident performing Wii-Fit-U exercises independently the physiotherapist outlined the exercise protocol they were to follow over the next 8 weeks.

Participants were asked to perform Wii-Fit-U exercises for 60 minutes, 3 times per week[31]. They were instructed to have at least one day of rest between exercise sessions and to use their symptoms in the 24 hours post-exercise to guide whether they should increase or decrease the duration and intensity of subsequent sessions. A physiotherapist contacted participants fortnightly to encourage them to progress their exercises, if appropriate, while also monitoring for any adverse events or equipment issues. Exercise progression was centred on increasing the repetitions of an exercise or selecting more challenging exercises to maintain a perceived exertion of 13 on the Borg rating scale. This was outlined to participants during the initial session. On the other hand, participants were encouraged to modify exercises they found too difficult by reducing the repetitions, range of movement, balance requirements, or the duration of

the exercise sessions to maintain a similar perceived exertion.

Feasibility outcomes

Adherence. Participants tracked the duration and frequency of their exercise sessions in a paper exercise diary. Despite reporting issues associated with paper exercise diaries[33] they are simple and likely appropriate for an older population[34]. Adherence was based on the extent the participants exercise behaviours corresponded to our recommendations[15]: i) total minutes, expressed as a percentage of the total recommended exercise time (60 minutes x 3 x 8 weeks = 1,440 minutes); ii) number of weeks adherent to the protocol (≥180 minutes/week), expressed as a percentage of 8 weeks; iii) total number of sessions ≥60 minutes; and iv) total number of sessions, irrespective of duration. Both iii) and iv) were expressed as a percentage of the total number of recommended sessions (n=24).

Experience with the intervention. Participants in the video-game exercise group completed a 12-item questionnaire that allowed them to rate the following aspects of the intervention: i) usability; ii) exercise variation; iii) ease of exercise progression; iv) the extent symptoms interfered with the program; and v) overall experience (Appendix A).

Clinical outcomes

All baseline data was collected in-person at The University of Sydney (participants from the community) or at the Outpatient Physiotherapy Department of Westmead Hospital (participants on the waiting list). All remaining follow-up surveys (8 weeks, 3 and 6 months) were either sent to participants' email address via Research Electronic Data Capture (REDCap) or posted to their

residential address. Participants who did not adhere to the intervention were encouraged to complete all follow-up assessments. All study data were collected and managed using REDCap electronic data capture tools hosted at The University of Sydney[35].

Pain self-efficacy was assessed using the 10-item Pain Self-Efficacy Questionnaire (PSEQ), a valid and reliable tool for detecting changes in people with chronic pain over time[16]. Care Seeking was assessed using a 3-item questionnaire developed for this trial which asked participants to indicate whether they were: i) currently receiving treatment (e.g. GP visits, private physiotherapy, etc.); ii) planning to start treatment in the coming months; or iii) currently taking medication for their LBP. Engagement in physical activity was assessed by the RAPA questionnaire, a valid tool for discriminating between active and inactive older adults[36]. Participants selected the time and intensity of physical activity that best described how much aerobic physical activity they usually do over the course of a week (e.g. "I do 30 minutes or more per day of moderate physical activities 5 or more days per week"). Participants also indicated whether they performed any 'strength' or 'flexibility' exercises at least once per week. The American College of Sports Medicine (ACSM) recommends that all adults perform a weekly minimum of 150 minutes moderate-intensity or 60 minutes vigorous-intensity physical activity[37]. In light of these recommendations, we formed three categories of physical activity engagement that has also been used in a previous study[38]: i) sedentary or only light physical activity (items 1-3); ii) moderate or vigorous-intensity physical activity less than recommended by the ACSM (items 4-5); and iii) physical activity that met the ACSM recommendations (items 6-7). Data on pain self-efficacy, care-seeking, and engagement in physical activity levels were collected at baseline, 8 weeks, 3 months, and 6 months.

The remaining outcomes were only collected at baseline and 8 weeks[31]. Usual pain intensity over the last week was assessed using the 11-point NRS[39]. Function was assessed using the Patient Specific Functional Scale (PSFS), a valid, reliable, and responsive tool for detecting changes in function over time in people with LBP[40]. Disability was measured using the 24-item Roland Morris Disability Questionnaire (RMDQ) which has demonstrated good validity, reliability and sensitivity for detecting changes in disability over time in people with LBP[41]. Fear of movement/re-injury was assessed using the 17-item Tampa Scale of Kinesiophobia (TSK) which has demonstrated good validity, reliability and responsiveness for evaluating changes in pain-related fear in people suffering chronic LBP[42]. Falls-efficacy was measured using the 16-item Falls-Efficacy Scale-International (FES-I) questionnaire which assesses participants' concerns about the possibility of falling during a number of daily activities (e.g. walking upstairs)[43].

Data Analysis

We reported data on feasibility outcomes using descriptive statistics [means, standard deviations (SD), %]. We investigated the clinical effects of home-based video-game exercises using linear regression for continuous outcome variables (e.g. pain, function) and logistic regression for dichotomous outcome variables (e.g. care seeking). Estimates were adjusted for baseline covariates and any variable that was significantly different between groups at baseline. STATA statistical software (version 13.1) was used to conduct all analyses (StataCorp LP. 2013, College Station, TX, USA). Coefficients (β) and 95% confidence intervals (CI) were calculated from regression models, with significance level set at 0.05. We attempted to follow up all participants regardless of whether they withdrew from their allocation.

Results

One hundred and seventeen individuals with chronic LBP interested in participating in this trial were screened for eligibility between November 2015 and February 2017 (Fig 1). Sixty people (51%) were eligible to participate and were randomised to the video-game exercise (n=30) or control group (n=30), with 56 participants (93.3%) recruited from the community and four participants (6.7%) recruited from the waiting list. The recruitment rates for the total sample, participants on the waiting list, and participants from the community were 4.3, 0.4 and 11.2 participants per month, respectively. The mean age (SD) of participants was 67.8 (6.0) years old, and there were 31 females (51.7%). At baseline, participants allocated to receive Wii-Fit-U exercises had higher levels of function (PSFS) [5.3 (1.4) vs. 4.3 (2.1), p=0.04]. There were no significant between-group differences for the remaining baseline characteristics (Table 2).

Of the 30 participants allocated to receive Wii-Fit-U exercises, four participants were not able to start the program due to personal commitments. The remaining participants commenced the program (n=26). All participants in the intervention group and 28 participants in the control group (93.3%) completed the post-intervention follow-up questionnaire. Follow-up data was available from 56 (93.3%) and 57 (95.0%) participants at 3 and 6 months respectively (Fig 1), as one participant responded to the questionnaire at 6 months, but not at 3 months. During the fortnightly calls, it was relatively common for participants to report some temporary soreness during or after performing Wii-Fit-U exercises. However, no participant reported any soreness that limited their participation in the program or any other adverse events related to Wii-Fit-U exercises (e.g. fall, injury, etc.).

Adherence

The average adherence to the total recommended exercise time was 70.8%, with scores ranging from 7.6% to 144.4%. The average number of sessions irrespective of duration was 20.4 (out of 24, 85.1%), while the average number of sessions ≥60 minutes was only 10.1 (42.0%). The average number of weeks participants were adherent to the protocol was 2.6 (out of 8, 32.7%). Furthermore, the average number of minutes and average number of sessions each week tended to decrease throughout the 8 week program (Table 3).

Experience with the intervention

Overall, participants reported high usability (average scores ranged from 7.9-8.7/10), sufficient exercise variety (8.2/10) and challenge (7.4/10), and a positive overall experience using the program (7.3/10). Participants felt confident to progress their exercises throughout the program with (7.6/10) or without (6.8/10) the physiotherapist's guidance, rarely had symptoms that stopped them from using the program (3.3/10), but occasionally experienced symptoms following an exercise session (5.7/10). On average, participants indicated that a 50.8% improvement in their LBP would make participating in the 8 week program worthwhile (Appendix B).

Clinical outcomes

There were no between-group differences for PSEQ scores immediately post-intervention (β=1.20, 95% CI: -3.23 to 5.64, p=0.59). However, participants completing Wii-Fit-U exercises had significantly higher PSEQ scores at 6 months (β=5.17, 95% CI: 0.52 to 9.82, p=0.03) and

tended to have higher PSEQ scores at 3 months compared to the control group (β=4.33, 95% CI: -0.24 to 8.80, p=0.06) (Table 4). Participants completing Wii-Fit-U exercises also demonstrated significantly greater improvements in pain (β=-1.07, 95% CI: -2.11 to -0.03, p=0.04) and function (β=1.21, 95% CI: 0.10 to 2.33, p=0.03), and tended to reduce their fear of movement/re-injury more than the control group immediately post-intervention (β=-2.97, 95% CI: -6.14 to 0.21, p=0.07). There were no significant between-group differences for disability (β=-0.85, 95% CI: -2.58 to 0.89, p=0.33) and falls-efficacy (β=-1.08, 95% CI: -3.08 to 0.92, p=0.28) immediately post-intervention, or in any care seeking or physical activity behaviours at 8 weeks and 3 months (Table 5). However, participants completing Wii-Fit-U exercises were significantly more likely to engage in flexibility exercises at least once per week at 6 months (OR=4.36, 95% CI: 1.06 to 17.93, p=0.04), and tended to be less likely to be on medication at 6 months compared to the control group (OR=0.24, 95% CI: 0.06 to 1.04, p=0.06) (Table 5).

Discussion

This trial demonstrated a high recruitment rate in community-dwelling older people, follow-up data was available from 57 participants at 6 months (95.0%), and there were no reported adverse events. Adherence to the intervention was high when considering the total time and total number of sessions performed. However, as the average number of participants completing sessions ≥60 minutes or doing a weekly total of 180 minutes was low, it suggests the exercise protocol might need to be revised for future trials in this population. Nevertheless, these features highlight the feasibility of Wii-Fit-U exercises for older people with chronic LBP. Participants completing Wii-Fit-U exercises also reported significantly better pain self-efficacy at 6 months, and significantly greater improvements in pain and function immediately post-intervention compared

to the control group. In addition, participants completing Wii-Fit-U exercises were more likely to be engaged in flexibility exercises at 6 months, tended to be less likely to be taking medication at 6 months, and tended to have less fear of movement/re-injury immediately post-intervention compared to the control group. Given the feasibility and preliminary efficacy of Wii-Fit-U exercises for older people with chronic LBP, a large RCT is needed to build on these results.

Our study showed that adherence to Wii-Fit-U exercises in older people with chronic LBP is high, particularly when compared to studies where people with chronic LBP are instructed to exercise without supervision[11,12,15,44-46]. For example, the adherence to an unsupervised exercise program at local health clubs in people with chronic LBP by completing the number of recommended sessions was only 33%[46]. This figure is similar across a number of other studies[12,44,45] and is considerably less than the corresponding value found in our study (85.1%). High adherence to Wii-Fit-U exercises in our study could be due to a number of factors. First, adherence was likely facilitated during the fortnightly follow-up calls where participants were encouraged to progress their exercises. Second, Wii-Fit-U exercises provide video and audio instructions, and feedback on performance, factors that promote adherence to home exercise in people with chronic LBP[27,28]. Video-game technology also increases motivation to perform home exercises[25], and there is preliminary evidence supporting the use of supervised Wii-Fit-U exercises for adults with chronic LBP[23,24]. However, given the lack of studies investigating unsupervised Wii-Fit-U exercises for chronic LBP, additional studies investigating how Wii-Fit-U exercises influence the adherence to home-exercise in older people with chronic LBP are needed to build on the findings of this study.

Our study showed a high recruitment rate in community-dwelling older people (11.2 participants per month), but a very low recruitment rate from the waiting list (0.4 participants per month). This is despite reassuring people they would not lose their position on the waiting list. We hypothesise these recruitment rate differences are due to the sample's desire to self-manage their condition through home-exercise, which is likely a reflection of their pain self-efficacy. Participants in our trial had high baseline pain self-efficacy, with 56 participants recruited from the community and four from the waiting list. With this in mind, high levels of pain-self efficacy might be a trait of participants willing to engage in home-based Wii-Fit-U exercises and might not be common in patients on a waiting list for treatment. In addition, older people managing their chronic LBP in the community might be more willing to engage in Wii-Fit-U exercises than patients on the waiting list. High baseline pain self-efficacy might also explain why there were no between-group differences in pain self-efficacy immediately post-intervention, despite significantly higher pain self-efficacy in the intervention group at 6 months. Previous studies have demonstrated post-intervention improvements in pain self-efficacy for people with chronic LBP when the sample had low baseline pain self-efficacy[47-52], therefore, high baseline pain self-efficacy likely reduces the scope for improvement. Nevertheless, the adjusted between-group difference in pain self-efficacy scores at 6 months was 5.2, which is just below the minimal important change (MIC) for people with chronic LBP (5.5)[53]. Therefore, a home-based video-game exercise program may be even more beneficial for older people with chronic LBP and lower levels of pain self-efficacy, and strategies to recruit these individuals should be considered in future trials.

Given the enormous global cost of chronic LBP[3,54], increasing an individual's capacity to self-

manage their pain, while reducing the need for therapist supervision, should be a priority. Numerous studies have investigated self-management approaches involving pain education and exercise[55], showing moderate effect sizes for pain and disability[55]. However, most of these interventions involve extensive interactions with a therapist[55,56]. Despite this, the few studies that investigated self-management strategies for chronic LBP with minimal supervision showed promising results[57-59]. For example, a moderated email discussion group, combined with pain education and exercise advice was more beneficial than usual care for reducing pain and disability[58]. On the other hand, there has only been one study investigating a self-management approach for older people with chronic LBP, and this involved extensive therapist supervision. This study compared six weekly education seminars on the benefits of exercise, relaxation, and goal setting, to a waiting list control group, but found no between-group differences in pain and self-management attitudes[60]. A possible explanation for these findings could be poor adherence to the seminars, with only 16% of participants attending every session. However, the possibility that promoting self-management in older people with chronic LBP is more complex, cannot be ruled out. This is highlighted by the findings of our trial, where pain and function significantly improved following Wii-Fit-U exercises, but improvements in pain-self-efficacy and medication usage were only greater than the control group at 6 months. Despite high adherence, improvements in other outcomes may be more dependent on therapist supervision and may not be adequately addressed during an unsupervised exercise program. In addition, the lack of research on web-based or video-game self-management strategies in older people with chronic LBP may reflect concerns with the familiarity and access to modern technology, but should nonetheless be a consideration for future research.

Strengths and limitations

This study has numerous strengths. First, we ensured transparency by registering and publishing our study protocol[31]. Second, Wii-Fit-U exercises are commercially available and of relative low cost, making it suitable for use at home and direct implementation to the community if shown to be effective in a large trial. In contrast, video-game interventions developed specifically for research are rarely manufactured on a large scale, resulting in issues related to cost and accessibility[61-64]. Third, consistency of the intervention was enhanced by only one physiotherapist setting up the exercise program. Finally, we had a high response rate to the questionnaires posted to participants at 3-months (93.3%) and 6-months (95.0%), which was likely due to participants in the control group being offered Wii-Fit-U exercises following the completion of the trial.

This study has limitations. First, we were unable to blind the participants and physiotherapist administering the intervention. However, since Wii-Fit-U exercises were performed without supervision this is unlikely to have a large impact on internal validity. Second, participants used a paper exercise diary to track adherence, which may result in a degree of inaccuracy[33]. However, unlike other studies in the field, we expressed adherence in numerous ways to get an overall picture of how compliant the participants were to our recommendations[34]. Third, it was not possible to extract exercise selection data from the software so there was no way to ensure participants stuck to our recommendations, despite being reminded during fortnightly follow-up calls. In addition, we did not ask participants to write down which exercises they performed each session as this could have decreased motivation to use the program. However, since no single

type of exercise is superior for people with chronic LBP[65-67], this information is unlikely to influence the design of future trials.

Conclusion

This study provides preliminary evidence that an unsupervised home-based video-game exercise program is feasible and can improve pain self-efficacy, pain, and function in older people with chronic LBP. On the other hand, strategies to improve care-seeking behaviours, physical activity, disability, fear of movement/re-injury, and falls-efficacy in this population need to be considered in future trials. If the efficacy of video-game exercises is supported in a large trial, this will have immediate implications for the self-management of LBP and is likely to reduce the management costs of chronic LBP.

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Conflict of Interest

None declared.

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Table 1. Inclusion and exclusion criteria.

Inclusion	Exclusion
> 55 years old Non-specific mechanical LBP for at least 3 months Usual pain intensity 3/10 or greater on the NRS Sufficient English ability to understand exercise instructions Able to mobilise independently without the use of walking aids Have access to a HDMI compatible television at home	Diagnosis of serious pathology in the spine (such as fracture, metastatic disease, spinal stenosis, cauda equina syndrome) Evidence of nerve root compromise Any medical condition or disability that will prevent participation in the exercise program, including: • Cardiovascular risk factors: assessed using the PAR-Q, a screening tool recommended for all adults willing to initiate an exercise program[a] • Cognitive limitations: Mini Mental State Examination <25/30, a reliable and valid test of cognitive function[b] • High risk of falls: Falls Risk Assessment Tool score >15, a reliable measure of falls risk in older adults[c] Physiotherapy treatment for their LBP in the last 6 months
Need for clearance from their general practitioner before participating in this trial: Participants who experience dizziness or altered consciousness, use prescribed medications or have uncontrolled diabetes	

LBP: low back pain; NRS: Numerical Rating Scale; HDMI: High-Definition Multimedia Interface; PAR-Q: Physical Activity Readiness-Questionnaire.

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[b]Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.

[c]Stapleton C, Hough P, Oldmeadow L, Bull K, Hill K, Greenwood K. Four-item fall risk screening tool for subacute and residential aged care: The first step in fall prevention. Australas J Ageing. 2009;28:139-43.

Table 2. Baseline demographic and outcome characteristics of included participants				
	Total sample (n=60)	Video-game exercise group (n=30)	Control group (n=30)	
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Between-group difference (p)
Demographic variables				
Males	29 (48.3%)	12 (20%)	17 (28.3%)	0.20
Females	31 (51.7%)	18 (30%)	13 (21.7%)	0.20
Age	68.3 (5.7)	68.8 (5.5)	67.8 (6.0)	0.47
BMI	27.2 (3.9)	26.9 (4.1)	27.4 (3.6)	0.56
Married	48 (80.0%)	26 (43.3%)	22 (36.7%)	0.40
Alcohol consumption[a]	29 (48.3%)	14 (23.3%)	15 (25.0%)	0.64
Current smoker	2 (3.3%)	1 (1.7%)	1 (1.7%)	1.00
Educational attainment[b]	53 (88.3%)	26 (43.3%)	27 (45.0%)	0.26
Employed	13 (21.7%)	6 (10.0%)	7 (11.7%)	0.35
Number of comorbidities	1.2 (1.4)	1.1 (1.3)	1.1 (1.3)	0.64
Outcome variables				
PSEQ	49.5 (8.3)	50.7 (8.2)	48.2 (8.3)	0.23
Care seeking				
Current[c]	27 (45.0%)	16 (26.7%)	11 (18.3%)	0.19
Future[d]	12 (20.0%)	6 (10.0%)	6 (10.0%)	1.00
Medication[e]	27 (45.0%)	16 (26.7%)	11 (18.3%)	0.19
Physical activity				
Strength exercises[f]	24 (40.0%)	12 (20.0%)	12 (20.0%)	1.00
Flexibility exercises[g]	44 (73.3%)	24 (40.0%)	20 (33.3%)	0.24
Sedentary or light PA[h]	14 (23.3%)	8 (13.3%)	6 (10.0%)	0.54
PA less than recommended[i]	21 (35.0%)	10 (16.7%)	11 (18.3%)	0.79
PA more than recommended[j]	25 (41.7%)	12 (20%)	13 (21.7%)	0.79
NRS (0-10)	5.0 (1.7)	5.2 (1.6)	4.8 (1.7)	0.42
PSFS (0-10)	4.8 (1.8)	5.3 (1.4)	4.3 (2.1)	**0.04**
RMDQ (0-24)	6.8 (5.0)	6.3 (4.8)	7.4 (5.2)	0.39
TSK (17-68)	34.2 (5.9)	33.6 (6.1)	34.7 (5.8)	0.48
FEQ-I (16-64)	22.2 (6.2)	21.5 (6.1)	22.9 (6.2)	0.37

SD: Standard Deviation; n: number of participants; BMI: Body Mass Index; PA: Physical Activity; PSEQ: Pain Self-Efficacy Questionnaire; TSK: Tampa Scale of Kinesiophobia; NRS: Numeric Rating Scale; PSFS: Patient Specific Functional Scale; Roland Morris Disability Questionnaire; FEQ-I: Falls Efficacy Questionnaire-International.

[a]: a few times a week or more; [b]: indicates those who have at least completed high school; [c]: currently receiving treatment for their low back pain; [d]: planning to start treatment for their low back pain in the coming months; [e]: currently taking medication for their low back pain; [f]: engagement in exercises to increase strength at least once per week; [g]: engagement in exercises to improve flexibility at least once per week; [h]: engagement in no physical activity or only light

physical activity each week; [i]: engagement in moderate or vigorous-intensity physical activity each week that is less than recommended by the American College of Sports Medicine (ACSM); [j]: engagement in physical activity that meets the ACSM recommendations.

Table 3. Adherence to Wii-Fit-U exercises

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Total
Average minutes (%)	169.3 (94.1)	146.4 (81.3)	131.7 (73.2)	126.8 (70.5)	126.7 (70.4)	124.2 (69.0)	107.3 (59.6)	93.7 (52.0)	1019.1 (70.8)
Average number of adherent sessions (%)	1.42 (47.4)	1.54 (51.3)	1.35 (44.9)	1.27 (42.3)	1.35 (44.9)	1.19 (39.7)	1.15 (38.5)	0.81 (26.9)	10.08 (42.0)
Average number of sessions (%)	3.46 (115.4)	2.92 (97.4)	2.77 (92.3)	2.46 (82.1)	2.42 (80.8)	2.38 (79.5)	2.08 (69.2)	1.92 (64.1)	20.42 (85.1)

Table 4. Effect of a video-game exercise program on pain self-efficacy, pain, function, disability, fear of movement/re-injury and falls efficacy

	Video-game exercise group[+]	Control group[++]	Unadjusted between-group difference			Adjusted between-group difference		
	Mean (SD)	Mean (SD)	β	95% CI	p	β*	95% CI	p
PSEQ								
Baseline	50.7 (8.2)	48.2 (8.3)						
8 weeks	47.8 (10.3)	44.6 (9.6)	3.20	-2.04 to 8.43	0.23	1.20	-3.23 to 5.64	0.59
3 months	49.2 (8.8)	43.1 (12.1)	6.06	0.43 to 11.69	**0.04**	4.33	-0.24 to 8.80	0.06
6 months	48.8 (10.5)	41.7 (11.2)	7.11	1.34 to 12.89	**0.02**	5.17	0.52 to 9.82	**0.03**
NRS								
Baseline	5.2 (1.6)	4.8 (1.7)						
8 weeks	3.8 (2.4)	4.4 (2.3)	-0.66	-1.90 to 0.58	0.29	-1.07	-2.11 to -0.03	**0.04**
PSFS								
Baseline	5.3 (1.4)	4.3 (2.1)						
8 weeks	6.5 (2.1)	4.8 (2.5)	1.69	0.50 to 2.88	**0.01**	1.21	0.10 to 2.33	**0.03**
RMDQ								
Baseline	6.3 (4.8)	7.4 (5.2)						
8 weeks	4.9 (4.5)	6.4 (4.4)	-1.49	-3.85 to 0.86	0.21	-0.85	-2.58 to 0.89	0.33
TSK								
Baseline	33.6 (6.1)	34.7 (5.8)						
8 weeks	32.3 (7.1)	35.9 (5.8)	-3.52	-6.97 to -0.08	0.05	-2.97	-6.14 to 0.21	0.07
FEQ-I								
Baseline	21.5 (6.1)	22.9 (6.2)						
8 weeks	21.1 (5.8)	23.4 (7.0)	-2.30	-5.65 to 1.06	0.18	-1.08	-3.08 to 0.92	0.28

SD: Standard Deviation; n: number of participants; CI: confidence interval; PSEQ: Pain Self-Efficacy Questionnaire; TSK: Tampa Scale of Kinesiophobia; NRS: Numeric Rating Scale; PSFS: Patient Specific Functional Scale; Roland Morris Disability Questionnaire; FEQ-I: Falls Efficacy Questionnaire-International.

[+]: there were 30, 30, 29, and 29 participants with follow-up data at baseline, 8 weeks, 3 months, and 6 months respectively;

[++]: there were 30, 28, 27, and 28 participants with follow-up data at baseline, 8 weeks, 3 months, and 6 months respectively.

*: adjusted for baseline values and function (baseline Patient Specific Functional Scale).

Table 5. Effect of a video-game exercise program on care seeking and physical activity behaviours

	Video-game exercise group[+]	Control group[++]	Unadjusted between-group difference			Adjusted between-group difference*		
	N (%)	N (%)	OR	95% CI	p	OR	95% CI	p
Care seeking								
Current treatment								
Baseline	16 (53.3%)	11 (36.7%)						
8 weeks	13 (43.3%)	15 (53.6%)	0.66	0.24 to 1.87	0.44	0.50	0.14 to 1.75	0.28
3 months	9 (31.0%)	8 (29.6%)	1.07	0.34 to 3.34	0.91	1.40	0.38 to 5.13	0.61
6 months	7 (24.1%)	9 (32.1%)	0.67	0.21 to 2.15	0.50	0.50	0.13 to 1.91	0.31
Planning to start treatment in coming months								
Baseline	6 (20.0%)	6 (20.0%)						
8 weeks	8 (26.7%)	7 (25.0%)	1.09	0.34 to 3.54	0.89	1.16	0.33 to 4.13	0.82
3 months	5 (17.2%)	7 (25.9%)	0.60	0.16 to 2.17	0.43	0.65	0.16 to 2.58	0.54
6 months	3 (10.3%)	4 (14.3%)	0.69	0.14 to 3.42	0.65	1.06	0.17 to 6.48	0.95
Currently taking medication								
Baseline	16 (53.3%)	11 (36.7%)						
8 weeks	16 (53.3%)	13 (45.4%)	1.32	0.47 to 3.70	0.60	1.28	0.34 to 4.78	0.71
3 months	11 (37.9%)	9 (33.3%)	1.22	0.41 to 3.66	0.72	0.76	0.18 to 3.20	0.71
6 months	10 (34.5%)	14 (50.0%)	0.53	0.18 to 1.53	0.24	0.24	0.06 to 1.04	0.06
Physical activity								
Strength exercises at least once per week								
Baseline	12 (40.0%)	12 (40.0%)						
8 weeks	15 (50.0%)	12 (42.9%)	1.33	0.47 to 3.76	0.59	1.58	0.45 to 5.55	0.48
3 months	14 (48.3%)	10 (37.0%)	1.59	0.55 to 4.62	0.40	2.33	0.51 to 10.53	0.27
6 months	10 (34.5%)	12 (42.9%)	0.70	0.24 to 2.05	0.52	0.68	0.18 to 2.53	0.57
Flexibility exercises at least once per week								
Baseline	24 (80.0%)	20 (66.7%)						
8 weeks	24 (80.0%)	18 (64.3%)	2.22	0.68 to 7.25	0.19	1.97	0.41 to 9.58	0.40
3 months	24 (82.8%)	20 (74.1%)	1.68	0.46 to 6.12	0.43	1.45	0.33 to 6.43	0.62
6 months	25 (86.2%)	16 (57.1%)	4.69	1.29 to 17.10	**0.02**	4.36	1.06 to 17.93	**0.04**
Sedentary or only light physical activity each week								
Baseline	8 (26.7%)	6 (20.0%)						
8 weeks	5 (16.7%)	4 (14.3%)	1.20	0.29 to 5.01	0.80	1.24	0.22 to 7.04	0.81
3 months	4 (13.8%)	5 (18.5%)	0.70	0.17 to 2.96	0.63	0.67	0.12 to 3.60	0.64
6 months	4 (13.8%)	4 (14.3%)	0.96	0.22 to 4.28	0.96	1.07	0.17 to 6.63	0.95
Moderate or vigorous-intensity physical activity less than the ACSM recommendations								
Baseline	10 (33.3%)	11 (36.7%)						
8 weeks	9 (30.0%)	10 (35.7%)	0.77	0.26 to 2.31	0.64	1.00	0.27 to 3.63	1.00
3 months	8 (27.6%)	5 (18.5%)	1.68	0.47 to 5.95	0.42	1.58	0.42 to 5.86	0.50
6 months	6 (20.7%)	9 (32.1%)	0.55	0.17 to 1.83	0.33	0.85	0.22 to 3.32	0.81
Physical activity that meets the ACSM recommendations								
Baseline	12 (40.0%)	13 (43.3%)						

8 weeks	16 (53.3%)	14 (50.0%)	1.14	0.41 to 3.20	0.80	1.02	0.28 to 3.72	0.98
3 months	17 (58.6%)	17 (63.0%)	0.83	0.28 to 2.44	0.74	1.04	0.28 to 3.83	0.95
6 months	19 (65.5%)	15 (53.6%)	1.65	0.57 to 4.79	0.36	1.33	0.36 to 4.89	0.67

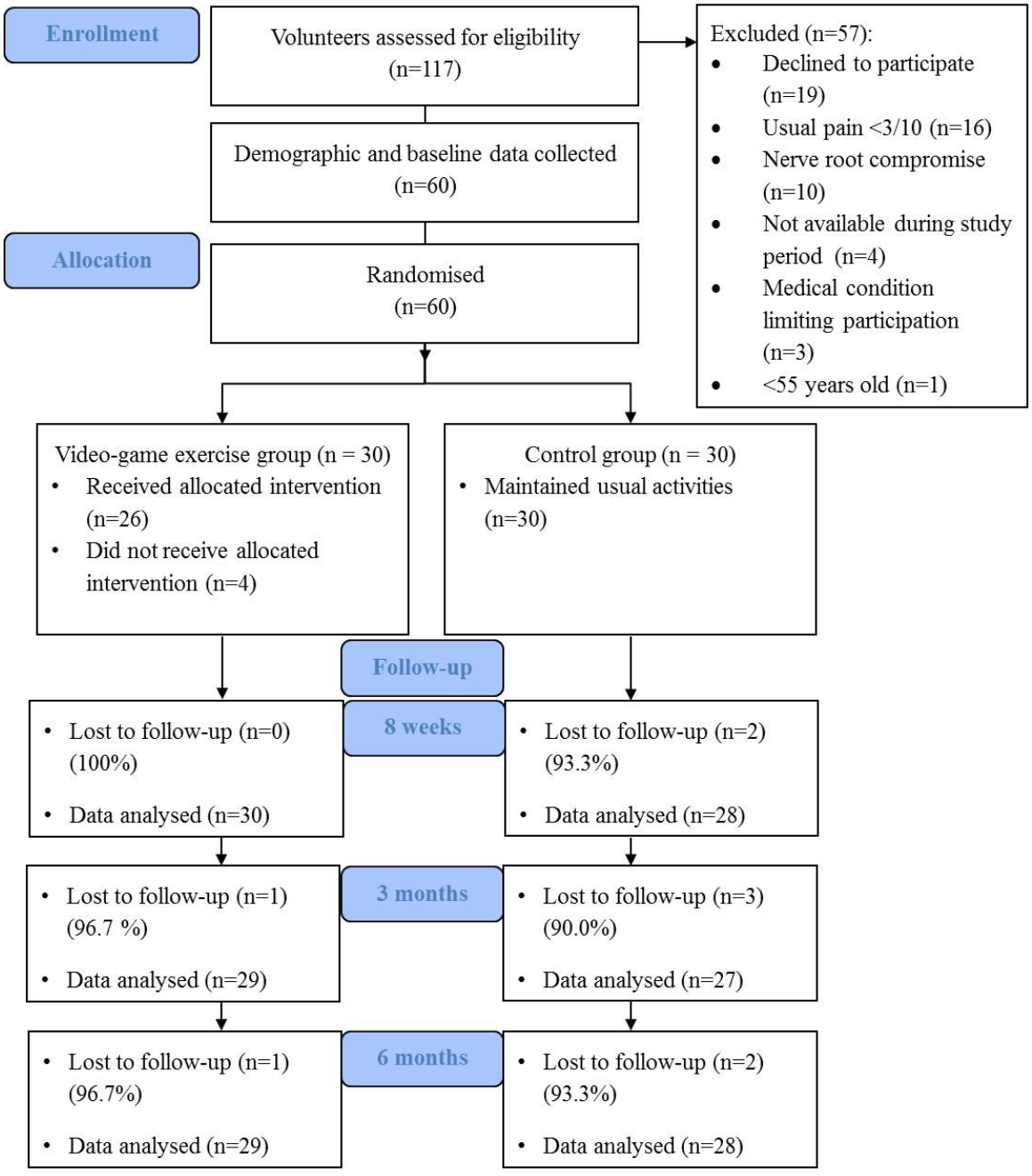
N: number of participants; OR: Odds Ratio; CI: Confidence Interval; ACSM: American College of Sports Medicine

$^{+}$: there were 30, 30, 29, and 29 participants with follow-up data at baseline, 8 weeks, 3 months, and 6 months respectively; $^{++}$: there were 30, 28, 27, and 28 participants with follow-up data at baseline, 8 weeks, 3 months, and 6 months respectively.

*: adjusted for baseline values and function (baseline Patient Specific Functional Scale).

Figure legend

Fig 1. CONSORT flowchart



Appendix A. Experience with the intervention questionnaire

i) How do you rate your overall experience using the Wii Fit U program?

0 1 2 3 4 5 6 7 8 9 10
Bad experience Great experience

ii) How easy was the Nintendo Wii console and Wii Fit U program to use once everything was set up?

0 1 2 3 4 5 6 7 8 9 10
Extremely difficult Extremely easy

iii) How often did you have trouble navigating your way to the exercises?

0 1 2 3 4 5 6 7 8 9 10
Every time Never

iv) When you had trouble navigating your way to the exercises, how helpful were the written instructions the research physiotherapist gave you?

0 1 2 3 4 5 6 7 8 9 10
Not at all helpful Extremely helpful

v) When you had trouble navigating your way to the exercises, how helpful was following the prompts on the Wii Fit U program?

0 1 2 3 4 5 6 7 8 9 10
Not at all helpful Extremely helpful

vi) From the exercises you could choose from, please rate the amount of variety you felt there was.

0 1 2 3 4 5 6 7 8 9 10
No variety, got repetitive very quickly Lots of variety

vii) Please rate how challenging you thought the exercise activities were overall.

0 1 2 3 4 5 6 7 8 9 10
Not challenging at all Extremely challenging

viii) How confident did you feel to progress to harder exercises when prompted by the research physiotherapist?

0 1 2 3 4 5 6 7 8 9 10
Not at all confident Extremely confident

ix) How confident would you have felt to progress to harder exercises if you weren't prompted by the research physiotherapist?

0 1 2 3 4 5 6 7 8 9 10
Not at all confident Extremely confident

x) How often did you feel sore after using the Wii Fit U program?

0 1 2 3 4 5 6 7 8 9 10
Never Every time

xi) How often did your low back pain stop you from using the Wii Fit U program?

0 1 2 3 4 5 6 7 8 9 10
Never Extremely often

xii) Overall, how much of an improvement (%) in your low back pain would make participating in this video-game program worthwhile?

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No improvement Full recovery

Appendix B. Experience with the intervention results*

Overall impression		**Usability**			
How do you rate your overall experience using the Wii Fit U program?	*Overall, how much of an improvement (%) in your low back pain would make participating in this video-game program worthwhile?*	*How easy was the Nintendo Wii console and Wii Fit U program to use once everything was set up?*	*How often did you have trouble navigating your way to the exercises?*	*When you had trouble navigating your way to the exercises, how helpful were the written instructions the research physiotherapist gave you?*	*When you had trouble navigating your way to the exercises, how helpful was following the prompts on the Wii Fit U program?*
Bad experience (0); Great experience (10)	No improvement (0%); Full recovery (100%)	Extremely difficult (0); Extremely easy (10)	Every time (0); Never (10)	Not at all helpful (0); Extremely helpful (10)	Not at all helpful (0); Extremely helpful (10)
7.3	50.8%	8.6	8.3	8.7	7.9

Exercise variety and challenge		**Exercise progression**		**Symptoms**	
From the exercises you could choose from, please rate the amount of variety you felt there was.	*Please rate how challenging you thought the exercise activities were overall.*	*How confident did you feel to progress to harder exercises when prompted by the research physiotherapist?*	*How confident would you have felt to progress to harder exercises if you weren't prompted by the research physiotherapist?*	*How often did you feel sore after using the Wii Fit U program?*	*How often did your low back pain stop you from using the Wii Fit U program?*
No variety, got repetitive very quickly (0); Lots of variety (10)	Not challenging at all (0); Extremely challenging (10)	Not at all confident (0); Extremely confident (10)	Not at all confident (0); Extremely confident (10)	Never (0); Every time (10)	Never (0); Extremely often (10)
8.2	7.4	7.6	6.8	5.7	3.3

*responses from the 26 participants that completed the video-game exercise program were averaged.

CHAPTER NINE

Conclusion

9.1. Overview of findings

The broad aims of this thesis were to investigate the role of shared familial factors in the development of LBP, and in the recovery and management of chronic LBP; and to investigate a novel home-based exercise program for older people with chronic LBP. More specifically this thesis investigated : i) the relationship between chronic low back pain (LBP) and physical activity, LBP and the built environment , and chronic LBP and educational attainment, while using a co-twin design to control for the confounding effects of shared familial factors (Chapters Two, Three and Four); ii) the role of shared familial factors in the recovery from chronic LBP (Chapter Five); iii) the role of shared familial factors in the response to increased physical activity in healthy adults (Chapter Six); and iv) the feasibility and clinical effects of a home-based video-game exercise program for older people with chronic LBP through a pilot randomized controlled trial (Chapters Seven and Eight).

9.1.1. Risk factors and factors associated with low back pain and chronic low back pain

A better understanding of risk factors and factors associated with LBP and chronic LBP will help guide the development of future intervention and prevention strategies and was the main focus of Chapters Two, Three and Four. Chapter Two presented the results of a cross-sectional study investigating whether individuals with chronic LBP are meeting the World Health Organisation physical activity guidelines. Our results showed that individuals with a history of chronic LBP who experienced pain in the past 4 weeks were less likely to meet the physical activity guidelines compared to those with no history of chronic LBP. Furthermore, individuals who hadn't experienced a pain free month in the last 6 months, and individuals with a history of chronic LBP but without LBP in the past 4 weeks, had a similar likelihood of meeting the physical activity guidelines compared to those with no history of chronic LBP. These findings have important implications for the prescription of physical activity for

individuals with chronic LBP. However, the association between recent LBP and physical activity in people with a history of chronic LBP disappeared after controlling for the influence of genetics and shared environmental factors, highlighting that shared familial factors are driving this relationship. To put it another way, the observed relationship between recent chronic LBP and physical activity might be explained by the presence of genetic or shared environmental factors common to the development of both traits, and should be considered in future studies investigating the relationship between chronic LBP and physical activity.

Chapter Three presented the results of a cross-sectional study that aimed to confirm the findings of Chapter Two in a larger sample of twins, while investigating whether the built environment moderated the relationship between LBP and physical activity. Our results showed that individuals with LBP were less likely to meet the physical activity guidelines, or walk more than 150 minutes per week, compared to those free of LBP if they lived in an environment with a short walkable distance to nearby amenities (high walkability). Unlike the results presented in Chapters Two, the magnitude of these findings strengthened when we adjusted for the influence of genetics and shared environmental factors. This indicates the presence of a direct relationship between LBP and physical activity for individuals living in an environment with high walkability, or that this relationship exists independent of shared familial factors. Furthermore, physical activity levels did not differ between individuals with or without LBP living in an environment with low walkability, which may suggest the built environment is a larger barrier to physical activity engagement than LBP.

Chapter Four built on the methodology used in Chapters Two and Three and applied it to a longitudinal study design investigating educational attainment as a risk factor for chronic

LBP. The results showed that females with low educational attainment had an increased risk of chronic LBP, while females with high educational attainment had a decreased the risk of chronic LBP. However, similar to the findings in Chapter Two, genetics and shared environmental factors are likely confounders of the relationship between educational attainment and chronic LBP in females, since these associations disappeared when controlling for genetics and shared environmental factors. We found no association between educational attainment and the risk of chronic LBP in males. Taken together, these findings highlight the importance of considering the role of gender and shared familial factors in the relationship between educational attainment and chronic LBP.

Chapters Two, Three and Four investigated the role of shared familial factors in the development of LBP and found that genetics and shared environmental factors appear to be confounding the relationship between recent chronic LBP and physical activity, and chronic LBP and educational attainment in females. However, the strong relationship observed between LBP and physical activity for individuals living in an environment with high walkability is independent of shared familial factors. These findings were novel and prompted us to consider whether shared familial factors play a role in the recovery from chronic LBP, and in the response to a physical activity intervention.

9.1.2. Shared familial factors and the recovery from chronic low back pain

Chapter Five presented the results of a longitudinal study investigating the influence of familial aggregation of chronic LBP on the recovery from chronic LBP. People who had a sibling with chronic LBP had a 20% increased likelihood of non-recovery from chronic LBP, with this likelihood increasing to 50% if the sibling was an identical twin. These findings are novel and suggest genetics influence the recovery from chronic LBP more so than shared

environmental factors. In other words, the presence of certain candidate genes or single-nucleotide polymorphisms may influence the likelihood of recovering from chronic LBP. Research aimed at identifying these genetic markers will help build on these findings. With this in mind, we were also interested in investigating the role of shared familial factors in the response to a commonly prescribed intervention for chronic LBP, physical activity.

9.1.3. Shared familial factors and the response to physical activity

Chapter Six presented the findings from a systematic review investigating the role of shared familial factors in the response of body composition and cardiorespiratory fitness following a physical activity intervention. At the time of this review, no study had investigated how shared familial factors influence the response to a physical activity intervention in people with LBP so we performed this review on healthy adults to provide background for future studies. Our review showed that genetics and shared environmental factors significantly influence the response of body composition and cardiorespiratory fitness following a physical activity intervention. Furthermore, genetics and shared environmental factors appear to influence the response of body composition to a greater extent compared to cardiorespiratory fitness. Chapters Five and Six have laid the foundations for future research exploring the role of shared familial factors in the recovery from chronic LBP, and in the response to a physical activity intervention.

9.1.4. Home-based video-game exercises for older people with chronic low back pain

Chapters Seven and Eight explored the feasibility and clinical effects of a novel home-based video-game exercise program for older people with chronic LBP, addressing the final aim of this thesis. Physical activity is vital for promoting health and well-being[1], and for preventing chronic disease in older people[2, 3]. Physical activity interventions are also recommended for

the management of chronic LBP in older people[4, 5] but strategies to facilitate self-management in this population are largely missing from the literature. Chapter Seven outlined the protocol for a randomised controlled trial investigating a home-based video-game exercise program for older people with chronic LBP. Chapter Eight outlined the results. The recruitment rate was high amongst older people suffering from chronic LBP in the community (11 participants per month), but was low in older people waiting for physiotherapy treatment in a public hospital (0.4 participants per month). On average, participants had high baseline levels of pain self-efficacy, suggesting good pain self-efficacy is a trait of individuals willing to participate in an unsupervised home-based video-game exercise program. With this in mind, the difference in recruitment rates between older people in the community compared to those on the waiting list could be reflecting different levels of pain self-efficacy in these populations. Adherence to the intervention was high when considering the total time engaged in video-game exercises (71%) and the total number of sessions performed (85%), and no adverse events were reported. Finally, we had a high response rate to the surveys at 3 months (93%) and 6 months (95%), which was likely due to participants in the control group being offered the video-game exercise program following the completion of the trial. These findings support the feasibility of conducting a large multi-centre randomised controlled trial. In terms of clinical effects, participants engaged in video-game exercises reported significantly higher pain self-efficacy in the long-term (6 months), and demonstrated significantly greater improvements in pain and function immediately post-intervention compared to the control group. The control group was instructed to maintain their usual activities and care-seeking behaviors. Improvements in pain self-efficacy also favored the video-game exercise group in the medium term (3 months) despite not being statistically significant. However, high baseline levels of pain self-efficacy in both groups are likely to explain why there was no between-group difference in pain self-efficacy scores

immediately post-intervention (8 weeks). Participants completing video-game exercises were significantly more likely to regularly engage in flexibility exercises in the long-term, tended to be less likely to take pain medication in the long-term, and tended to have less fear of movement immediately post-intervention compared to the control group. On the other hand, there were no between-group differences for the remaining physical activity and care-seeking variables, nor disability or falls-efficacy at any time point. Given the feasibility and positive preliminary effects of video-game exercises for improving pain self-efficacy, pain and function in older people with chronic LBP, an adequately powered randomised controlled trial is needed to build on these results.

9.2. Clinical implications

The results presented in this thesis have important implications for clinical practice and may guide the selection of intervention and prevention strategies for people with chronic LBP. First, we conducted three studies (Chapters Two, Three, and Four) to address the lack of knowledge regarding risk factors and factors associated with LBP (particularly chronic LBP). Primarily, we were interested in investigating the relationship between LBP, physical activity, the built environment, and educational attainment. Individuals with a history of chronic LBP and pain in the past 4 weeks (recent chronic LBP) are less likely to meet the physical activity guidelines compared to those with no history of chronic LBP, while individuals with a history of chronic LBP who are currently pain free are just as likely to meet the physical activity guidelines compared to those with no history of chronic LBP. The importance of physical activity for individuals with chronic LBP is clear. Physical activity interventions are recommended in most evidence-based guidelines for the management of chronic LBP[6-8], and can reduce the risk of recurrent episodes[9, 10]. Based on our findings and the well-established benefits of physical activity for people with chronic LBP, clinicians could incorporate specific strategies to encourage individuals with a recent episode of chronic LBP to gradually increase their physical activity. Specific strategies to encourage increased physical activity may include: i) education regarding the benefits of physical activity; ii) practical ways to increase physical activity (e.g. active transportation, sports participation); iii) information on nearby facilities that could promote increased physical activity (e.g. parks, gyms, cycle paths); and iv) guidance on how to gradually increase physical activity in the presence of symptoms.

Understanding how the built environment influences the relationship between physical activity and LBP could also help clinicians tailor strategies to facilitate increased physical

activity. Individuals with LBP are less likely to meet the physical activity guidelines, or walk more than 150 minutes per week, compared to those free of LBP if they live in an environment with a short walkable distance to nearby amenities (high walkability). These findings have implications for targeting physical activity interventions towards individuals with LBP living in an environment with high walkability, or for considering other individual and social-level factors to support increased physical activity engagement, such as education or social connectedness. Although individuals with LBP who live in an environment with a short walkable distance to nearby amenities are less active than people without LBP, they are in a perfect position to respond to interventions targeting increased physical activity because of their environment. These individuals should be given education regarding the benefits of increased physical activity for their LBP and overall health and well-being, as well as information on nearby amenities that can promote physical activity (e.g. walking paths, cycling paths, parks and gyms). Furthermore, clinicians could utilise a behaviour counselling and cognitive behavioural therapy approach to identify and address barriers to increased physical activity in this population (e.g. beliefs that physical activity is detrimental for the spine).

To gain a broader understanding of risk factors for chronic LBP this thesis investigated the relationship between educational attainment and the development of chronic LBP. Females with low educational attainment are at increased risk of developing chronic LBP, while females with high educational attainment are at decreased risk of developing chronic LBP. These findings highlight a population at risk of developing chronic LBP that could benefit from an effective prevention strategy to reduce this risk. Unfortunately, research on interventions for reducing the risk of chronic LBP are largely missing from the literature, with graded activity and pain education emerging as promising strategies[11, 12]. With this in

mind, clinicians may wish to implement a prevention strategy involving graded activity and pain education in a population of females with low educational attainment, as these individuals are at increased risk of developing chronic LBP. Overall, the findings presented in Chapters Two, Three and Four highlighted populations at risk of chronic LBP or reduced physical activity, and prompted us to investigate the role of shared familial factors in the recovery from chronic LBP and in the response to a commonly prescribed intervention for chronic LBP, physical activity (Chapters Five and Six).

The familial aggregation of chronic LBP significantly impacts on the recovery from chronic LBP, highlighting the strong prognostic role of shared familial factors (particularly genetics). From a clinical perspective, identifying the presence of chronic LBP in family members (particularly siblings) has the potential to inform clinicians on which patients are less likely to recover. A better understanding of factors influencing the recovery from chronic LBP may have implications for targeting specific interventions towards individuals who present with poor prognostic factors. If negative beliefs and experiences regarding LBP are shared among family members, and are negatively impacting the recovery from chronic LBP, intervening on these beliefs has the potential to improve outcomes for these individuals. Cognitive behavioral therapy is commonly recommended for people with chronic LBP and often involves addressing unhelpful beliefs and attitudes towards pain[13, 14]. People reporting a family history of chronic LBP may respond positively to a cognitive behavioral therapy approach that addresses unhelpful shared familial beliefs regarding pain, and involving family members in this intervention may further reinforce positive beliefs and attitudes in the family environment. Therefore, clinicians could consider the presence of chronic LBP within a family as an indicator of poor recovery and use this information to guide treatment.

Shared familial factors (including genetics) also significantly influence the response of body composition and cardiorespiratory fitness following a physical activity intervention in healthy adults. Therefore, shared familial factors are likely to be a significant contributor to the large individual variation seen in the response to increased physical activity. Shared familial factors may explain why some individuals fail to respond to increased physical activity, while others demonstrate a more favorable response. These findings have implications for changing modifiable training parameters (intensity, frequency, duration) to achieve the desired response, or for selecting an alternative management strategy in individuals who demonstrate an ongoing poor response to physical activity despite these changes. Understanding the role of shared familial factors in an individual's response to increased physical activity could also be important for individuals with chronic conditions where physical activity is strongly recommended (such as chronic LBP). This information could guide a clinician's choice of intervention and has the potential to improve treatment effectiveness, reduce treatment costs, and avoid patient disappointment.

Lastly, this thesis investigated a novel self-management strategy for older people with chronic LBP and provided strong evidence supporting the feasibility and preliminary clinical effects of a home-based video-game exercise program in this population (Chapters Seven and Eight). The feasibility of this novel self-management strategy was highlighted by a high recruitment rate of community-dwelling older people with chronic LBP, a high response rate, high adherence to the intervention, and no reported adverse events. Furthermore, older people with chronic LBP performing a home-based video-game exercise program reported significant long-term improvements in pain self-efficacy, and significant reductions in pain and increases in function following the intervention compared to a control group instructed to maintain their usual activities and care-seeking behaviours. Considering the enormous

benefits of physical activity engagement for older people[2, 15], the positive clinical effects of home-based video-game exercises, and the high adherence to the intervention; clinicians should recommend home-based video-game exercises as a self-management strategy for older people with chronic LBP. If home-based video-game exercises are implemented to community-dwelling older people with chronic LBP on a large scale, this could significantly reduce health-care expenditure for LBP in the long-term.

9.3 Future directions

This thesis showcased novel and innovative approaches to better understand how shared familial factors influence risk factors and factors associated with chronic LBP, the recovery from chronic LBP, and the response to increased physical activity. Further, this thesis investigated the feasibility and clinical effects of a novel physical activity intervention targeting improvements in pain self-efficacy for older people with chronic LBP. The methods and findings presented in this thesis will guide future research that aims to better understand why current intervention and prevention strategies are failing to reduce the enormous personal and financial burden associated with LBP.

The relationship between recent chronic LBP and physical activity disappeared after controlling for genetics and shared environmental factors, suggesting that shared familial factors are confounding this relationship. This brings into question whether shared familial factors could also be confounding the association between LBP and physical activity reported in existing studies and warrants further investigation. In the within-pair analyses which controlled for shared familial factors, there was a substantial sample size reduction. This could explain why the relationship between recent chronic LBP and physical activity was no longer statistically significant. To overcome the limitation pertaining to a small sample size, we investigated the association between LBP and physical activity in a larger sample of twins, while also using this data to determine whether the built environment influenced the association between LBP and physical activity.

The association between LBP and physical activity is moderated by the built environment, with individuals suffering from LBP and living in an environment with high walkability less likely to engage in sufficient physical activity compared to people without LBP. These

findings highlight the importance of considering external environmental factors when trying to promote increased physical activity in people with LBP, since the built environment could be a barrier or facilitator to physical activity engagement. Existing studies investigating education or behaviour counselling approaches for increasing physical activity in people with LBP have only demonstrated short-term physical activity behaviour change[16, 17]. However, information regarding the built environment is missing from these trials and may explain why some individuals fail to increase their physical activity in the long-term[18-21]. Future research investigating physical activity interventions for LBP should consider the influence of the built environment when discussing the efficacy of an intervention, or barriers and facilitators to long-term physical activity behaviour change. In addition, shared familial factors need to be considered in future studies investigating the relationship between LBP, physical activity, and the built environment, since the association between LBP and physical activity for individuals living in an environment with high walkability increased in magnitude after controlling for genetics and shared environmental factors. This suggests the presence of a direct relationship between LBP and physical activity for individuals living in an environment with high walkability, independent of shared familial factors.

The methodology used in Chapters Two and Three was applied to a longitudinal study investigating whether educational attainment increased the risk of developing chronic LBP. Educational attainment significantly influenced the risk of developing chronic LBP in females, but did not affect the risk of developing chronic LBP in males. Research must therefore explore why gender moderates the relationship between educational attainment and the risk of developing chronic LBP, since a better understanding of the interaction between educational attainment and gender has the potential to guide the design of future prevention strategies for chronic LBP. On the other hand, genetics and shared environmental factors

appear to be confounding the relationship between educational attainment and chronic LBP in females, which was concluded on the basis that these findings were no longer statistically significant in the within-pair analyses (despite negligible changes in effect sizes). A reduction in the sample size when considering twin pairs discordant for chronic LBP in the within-pair analyses might explain the non-significant findings and highlights the need for larger twin samples – particularly when analysing longitudinal data. Nevertheless, our findings showcase the promise of twin studies for investigating the relationship between educational attainment and chronic LBP.

To further twin research worldwide and overcome limitations pertaining to small sample sizes, an International Network of Twin Registries (INTR) has been established[22]. The INTR aims to foster international multi-centre collaborations and expand the resources of existing twin registries around the world. To achieve this, the INTR will support data harmonization between existing twin registries, and create a web-based search engine to help researchers identify registries that have appropriate data sources and research expertise to complete a given project. This will no doubt strengthen the design of future twin studies and allow researchers to get a clearer understanding of how shared familial factors influence various conditions, such as LBP. Chapters Two, Three and Four of this thesis investigated risk factors and factors associated with LBP (particularly chronic LBP) while utilising a co-twin control design to adjust for the confounding effects of genetics and shared environmental factors. The primary benefit of a co-twin design compared to non-twin population-based studies is the ability to adjust for higher levels of confounding and obtain more precise estimates of association. However, there still remain other sources of confounding that cannot be controlled for when investigating identical twins discordant for a trait. One potentially important source of confounding that cannot be controlled for when using a co-twin design

are epigenetic differences between identical twins[23]. Epigenetics is the study of how altered gene expression, rather than changes in gene sequence, influence the presence of certain diseases or traits. Altered gene expression commonly results from environmental exposures throughout life and is more pronounced in identical twins who are older, have spent less time together or who have different medical histories[23]. Therefore, although identical twins share the same gene sequence, epigenetic differences may contribute to the discordance of a disease or trait and act as residual confounding. This is a limitation of the discordant co-twin design that we must acknowledge. Future studies investigating epigenetic differences in identical twins will help identify changes in gene expression that could confound the results of studies aimed at understanding the etiology of a condition, such as LBP. This information could be incorporated into the design of future observational studies and allow researchers to obtain higher levels of adjustment for confounding and more precise estimates of association. Nevertheless, the findings presented in Chapters Two, Three and Four have highlighted the importance of considering shared familial factors when investigating risk factors and factors associated with LBP (particularly chronic LBP), and should be used to guide the design of future studies on these topics.

The role shared familial factors play in the recovery from chronic LBP and in response to increase physical activity have important implications for future research. Having a sibling with chronic LBP significantly increased the risk of not recovering from chronic LBP, particularly if this sibling was an identical twin. This highlights the strong role of genetics in the recovery from chronic LBP and the need to consider the influence of shared familial factors (particularly genetics) in future prognostic studies of chronic LBP. Furthermore, a recent study demonstrated that two single-nucleotide polymorphisms which are known to influence the development of persistent LBP, also influence the 5-year recovery from

persistent LBP[24]. This provides additional evidence supporting the strong role of genetics in the recovery from persistent or chronic LBP. To build on these findings, future research should continue to use quantitative genetic testing (e.g. genome-wide association or epigenetic studies) to identify genetic polymorphisms predicting the recovery from chronic LBP. This will further our understanding of the mechanisms between the familial aggregation of chronic LBP and non-recovery and will have significant implications for the design of future intervention strategies for individuals presenting with familial/genetic factors negatively impacting recovery.

Shared familial factors (including genetics) also influenced the response of body composition and cardiorespiratory fitness following a physical activity intervention in healthy adults. To build on these findings, future twin and family studies should investigate the role of shared familial factors in the response to a physical activity intervention for individuals with chronic conditions, such as LBP. If shared familial factors strongly influence the response to a physical activity intervention in people with chronic LBP, this would have significant implications for changing the parameters of a physical activity intervention to achieve a desired response (e.g. exercise modality, intensity, frequency), or for selecting a different management strategy for non-responders. From a quantitative genetic perspective, future research should focus on genome-wide association studies with large sample sizes to identify candidate genes or single-nucleotide polymorphisms that can aid the prediction of how an individual will respond to increased physical activity. However, until quantitative genetic testing becomes affordable for clinicians, research should endeavor to identify practical and cost-effective methods that can predict an individual's response to increased physical activity (e.g. previous responses or responses from family members). These findings have laid the foundation for future research to explore the role of shared familial factors in response to a

physical activity intervention for people with chronic LBP, and to identify clinical tests that can identify individuals likely to demonstrate a poor or favorable response.

In regards to the final aim of this thesis, our pilot randomised controlled trial demonstrated the positive preliminary effects of home-based video-game exercises for older people with chronic LBP, while also highlighting the feasibility of this novel self-management strategy. These findings have implications for the design and sample size required for a large multi-centre randomised controlled trial where the effectiveness of this intervention can be established. Pain self-efficacy was the primary outcome for this pilot study, as we anticipated a home-based video-game exercise program would be more effective at improving older people's ability to self-manage their chronic LBP compared to a control group instructed to maintain their usual activities. Despite this, there was only a significant between-group difference in pain self-efficacy at 6 months, which was the result of a decline in the control group's pain self-efficacy from baseline. This finding is likely explained by the high levels of pain self-efficacy reported in both groups at baseline, since older people willing to participate in an unsupervised home-based video-game exercise program already appear to have the capacity to continue with their daily activities despite pain. These findings may also reflect the need to recruit individuals with lower levels of pain self-efficacy in future trials. Nevertheless, home-based video-game exercises significantly reduced pain and increased function in older people with chronic LBP. This potentially highlights more appropriate primary outcome measures for a large multi-centre randomized controlled trial, particularly since the nature of the intervention lends itself to recruiting participants with high pain self-efficacy.

9.4 Concluding remarks

Overall, this thesis has highlighted a number of populations at risk of poor outcomes from chronic LBP and that would benefit from targeted intervention or prevention strategies. Chapter Two demonstrated that individuals with a recent episode of chronic LBP are less likely to be sufficiently active compared to people with no history of chronic LBP, and would benefit from a physical activity intervention to prevent recurrent episodes and promote increased physical activity for overall health and well-being. However, given the influence the built environment has on physical activity levels in people with LBP, both individual and environmental factors supporting physical activity engagement need to be taken into consideration. People suffering from LBP are less likely to be physically active compared to people without LBP when considering individuals living in an environment which promotes physical activity (i.e. good walkable access to amenities - high walkability). With this in mind, clinicians should consider other individual and social-level factors (such as education and social connectedness) to promote increased physical activity in people with LBP living in an environment with high walkability. Furthermore, females with low educational attainment are at increased risk of developing chronic LBP. Therefore, effective prevention strategies involving education, in addition to established evidence-based interventions such as physical activity[25], should be targeted toward this population.

This thesis demonstrated that the familial aggregation of chronic LBP is a strong predictor of non-recovery from chronic LBP, particularly in identical twins. This highlights the important role our genes play in the recovery from chronic LBP, but also the need to address shared environmental factors that could potentially reduce the likelihood of recovery in these populations (such as negative beliefs about pain). Finally, this thesis supported the feasibility and preliminary effectiveness of home-based video-game exercises for improving pain self-

efficacy, pain, and function in older people with chronic LBP. However, Chapter Six highlighted the strong role of shared familial factors in the response of body composition and cardiorespiratory fitness following a physical activity intervention in healthy adults. Therefore, the possibility that outcomes following a physical activity intervention for people with chronic LBP are influenced by shared familial factors cannot be ruled out, and needs to be investigated in future studies.

9.5 References

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APPENDICES

APPENDIX 1

Media coverage of Chapter Two publication

ONLINE NEWS ARTICLE

Twin study investigates recent low back pain and meeting physical activity guidelines

Healio Orthopedics Today - 11/05/2017

https://www.healio.com/orthopedics/spine/news/online/%7Ba37c0670-6d75-4a69-bb07-d174e0b1e7a6%7D/twin-study-investigates-recent-low-back-pain-and-meeting-physical-activity-guidelines.

ONLINE NEWS ARTICLE

Physical Activity Important In Low Back Pain

Broussard Clinic: Chiropractic, Acupuncture, Trigenics, Short Term Neck and Back Care - 15/06/2017

http://cajunchiro.net/2017/06/15/physical-activity-important-in-low-back-pain/.

APPENDIX 2

Media coverage of Chapter Four publication

ONLINE NEWS ARTICLE

Study highlights link between educational attainment, LBP and gender

Healio Spine Surgery Today - 28/11/2016

http://www.healio.com/spine-surgery/pain-management/news/online/%7B8c82467e-d8ab-4afe-8c45-f832db6bd15a%7D/study-highlights-link-between-educational-attainment-lbp-and-gender.

APPENDIX 3

Media coverage of Chapter Six publication

ONLINE NEWS ARTICLE

Exercise, genetics and the fat gene: New studies are showing why some people may respond differently to exercise

The Irish Times – 23/05/2017

http://www.irishtimes.com/life-and-style/health-family/fitness/exercise-genetics-and-the-fat-gene-1.3083671.

ONLINE NEWS ARTICLE

There's Diet and Exercise and There's Genetics

Genome Web - 23/05/2017

https://www.genomeweb.com/scan/theres-diet-and-exercise-and-theres-genetics.

ONLINE NEWS ARTICLE

Unzipping genes for the good of humanity: Genes Determine Our Weight Loss Ability

Front Line Genomics - 24/05/2017

http://www.frontlinegenomics.com/news/12145/genes-determine-weight-loss-ability/.