LOW BACK PAIN AND OBESITY-RELATED FACTORS 
IN TWINS

Amabile Borges Dario, BAppSc (Physiotherapy), MSc

A Thesis submitted in fulfilment of the
requirements for the degree of

Doctor of Philosophy

Faculty of Health Sciences
The University of Sydney

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CANDIDATE’S STATEMENT

I, Amabile Borges Dario, hereby declare that this submission is my own work and that it contains no material previously published or written by another person except where acknowledged in the text. Nor does it contain material which has been accepted for the award of another degree.

I, Amabile Borges Dario, understand that if I am awarded a higher degree for my thesis entitled “Low back pain and obesity-related factors in twins” being lodged here with for examination, the thesis will be lodged in The University of Sydney library and be available immediately for use. I agree that the University Librarian (or in the case of a department, the Head of the Department) may supply a photocopy or microform of the thesis to an individual for research or study or to a library.

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Amabile Borges Dario

December 2016
SUPERVISOR’S STATEMENT

As primary supervisor of Amabile Borges Dario’s doctoral work, I certify that I consider her thesis “Low back pain and obesity-related factors in twins” to be suitable for examination.

Primary Supervisor:

Associate Professor Paulo Ferreira

Faculty of Health Sciences

The University of Sydney

December 2016
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PUBLICATIONS AND PRESENTATIONS

Parts of the material included in this thesis have been published, submitted for publication and/or presented in national and international congresses and symposiums in the following forms:

Publications in Peer-reviewed Journals


Submitted for Publications in Peer Reviewed Journal

Oral Presentations


**Dario A.** Ferreira M, Refshauge K, Rezende A, Noronha M, Ordoñana J, Ferreira P. Obesity does not increase the risk of chronic low back pain when genetics is considered. A prospective study of Spanish adult twins. *Physiotherapy Conference - Australian Physiotherapy Association.* Gold Coast, Australia, 2015.


*Poster Presentations*


Dario A, Moreti A, Almeida L, Simic M, Papas E, Ferreira M, Refshauge K, Ferreira P. Current telemedicine-based interventions are not effective in managing chronic low back
pain: systematic review with meta-analysis. XIV International Low Back Pain Forum.

**Media Coverage of Chapters Two and Three**


**Other manuscripts conducted during the PhD candidature**


Brígida G, **Dario A**, Zadro J, Sánchez Romera J, Ordoñana J, Ramos D, Ferreira P. Relationship between low back pain and asthma when genetics and early shared environment
factors are considered: Insights from two population-based twin studies. Submitted to *PLOS ONE* in 6th of October, 2016.

This thesis comprises six chapters where the first and last chapters are the introduction and conclusion, respectively. The other chapters are either published (Chapters Two, Three, and Four) or manuscripts submitted for publication (Chapter Five). Supplementary materials that are related to the work on this thesis and undertaken by the candidate have also been included. Ethics approval was obtained prior to commencement of the studies and, for the systematic review, the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO). Each chapter can be read independently and contains its own reference list, nevertheless contributes to the whole body of work.

**Chapter One** is an introduction to the thesis which provides an overview of the relevant literature on low back pain. The main topics evaluated include a review of the low back pain social and economic burden, risk factors for low back pain focusing on obesity, and causal paths between obesity and low back pain (e.g. genetic factors).

**Chapter Two** is a systematic review conducted to investigate the relationship between obesity-related measures (e.g. weight, body mass index) and low back pain and lumbar disc degeneration in twins, enabling the control for the effects of genetics and early environment. This study is presented as published in *The Spine Journal*.

**Chapter Three** is a cross-sectional study conducted to investigate the relationship between obesity, assessed through measures that consider the magnitude and distribution of body fat mass, and chronic low back pain. The co-twin design was used to allow the adjustment for
genetics and the early environment shared by twins. Ethics approval was obtained by the Murcia University Ethics Committee in Spain. This study is presented as published in *The European Spine Journal*. The studies presented in Chapters Two and Three have attracted media attention and a lay-friendly blog post is available at the BodyInmind.org website (Appendix A).

**Chapter Four** is a prospective twin cohort study conducted to investigate the role of obesity-related measures as a risk factor for chronic and activity limiting low back pain, as well as care seeking due to chronic low back pain. This manuscript is presented in the format required by *The Spine Journal* where it has been accepted for publication. Additionally, an analysis of the concordance rates in obesity-related measures according to low back pain status in Australian twins is presented as supplementary findings at the end of this chapter.

**Chapter Five** is an observational study, including both cross-sectional and longitudinal data, conducted to investigate the relationship between diabetes type 2 and back pain [including lower back pain, neck pain, and spinal pain (concurrent lower back and neck pain)]. A co-twin design was used to account for the influence of genetics and early shared environment. Ethics approval was obtained by the Murcia University Ethics Committee. This manuscript is presented in the format required by PLOS ONE where it is under review.

Lastly, **Chapter Six** consists of an overview of the main findings of the thesis, discusses the clinical implications, and proposes directions for future research.
ABSTRACT

Low back pain is a well-recognized worldwide health problem due to its high prevalence and substantial economic impact. Despite abundant research on risk factors for low back pain, the pathoanatomical cause in the majority of cases remains unknown and is commonly termed nonspecific low back pain. The lack of knowledge regarding risk factors for low back pain is likely to be a critical reason for the limited progress in identifying effective management and preventative strategies. Identifying factors associated with the onset of low back pain is crucial in the field, because of its direct implications for the design of effective evidence-based preventative approaches.

A large number of risk factors for low back pain have been proposed. One of the plausible modifiable risk factors, obesity, has been commonly investigated, given that it could be a potential target for preventative interventions. Despite a considerable number of published studies exploring the relationship between obesity and back pain, the nature of the relationship remains unclear. As both obesity and low back pain cluster in families with evidence suggesting moderate to high heritability (phenotypic variance attributable to genetic variance) of these traits, it is possible that the conflicting findings regarding a direct link between obesity and low back pain arise from limitations in previous studies such as the lack of adjustment for familial factors (e.g. genetics).

To overcome this gap in the literature and contribute to a better understanding of the effect of obesity on low back pain, this thesis reports a series of studies designed to evaluate whether obesity is a risk factor for low back pain in twins. The twin methodology is an excellent resource for studying the significance of genetics as identical twins [monozygotic (MZ)] and fraternal twins [dizygotic (DZ)] share approximately 100% and 50% of their genes, respectively.
The environment and gene-environment interaction are also taken into account because twin pairs tend to be exposed to a common environment until early adulthood. As a result, studying the relationship between obesity and low back pain in twins who are discordant for low back pain status, allows the control for genetic and early environmental influences on this relationship. Theoretically, this method (case-control co-twin design) permits a more robust examination of obesity as a risk for low back pain, rather than being merely an associated factor.

The first study of this thesis, presented in Chapter Two, is a systematic review with meta-analysis that investigated the relationship between obesity-related measures (e.g. weight, body mass index) and low back pain, or lumbar disc degeneration, in twins. The use of twin studies allows the comparison of the estimates with and without adjustment for familial influences. A comprehensive search was conducted of five international databases, identifying 11 eligible twin studies that were included in this review. Due to the heterogeneity of the included studies, pooling the data for a meta-analysis was only possible for low back pain but not for disc degeneration. Findings from the unpaired analyses, when familial factors were not taken into account, suggested a consistent, but weak (odds ratios < 2) association between obesity and both low back pain and lumbar disc degeneration. Importantly, the magnitude of the estimates diminished, and did not remain significant, for the most well-adjusted models in which only MZ twins were included. These findings suggested that genetics and early environment shared by twins potentially confound the association between obesity and low back pain or lumbar disc degeneration.

Apart from the evidence of familial confounding, our systematic review revealed limitations in previous studies investigating the association between obesity and low back pain, such as the use of imprecise measures to define obesity (e.g. body mass index), and a lack of
longitudinal twin studies. To address these gaps in the literature, two studies were conducted, presented as Chapters Three and Four in this thesis. Using cross-sectional and longitudinal data from the Murcia Twin Registry, Spain, obesity measures that consider the magnitude and distribution of body fat mass were used to investigate the association between obesity and chronic low back pain in twins.

In both Chapters Three and Four, general obesity was assessed by both body mass index and percentage of fat mass (measured by bioimpedance), while abdominal obesity was evaluated through waist circumference and waist-hip ratios. All obesity measures were classified into four categories (quartiles) according to percentile distributions of the data (e.g. category one ≤ 25th lowest percentile). Chronic low back was the primary outcome. Sequential multivariate logistic regression models were used to investigate the association between obesity-related measures and chronic low back pain outcomes. In the first phase, also referred to as total sample analysis, twins were analysed independently (unpaired); and, therefore, the within-pair concordance for low back pain status was not taken into account. In the subsequent analytical steps, only complete twin pairs discordant for chronic low back pain (e.g. one twin reported low back pain whereas the co-twin did not) were included in the multivariate conditional logistic regression models, including all DZ and MZ pairs, followed by analysis of DZ pairs only, and then followed by analysis of MZ pairs only. Theoretically, the levels of adjustment for confounding factors such as genetics and early environment shared by twins increase throughout the analytical phases.

Our findings from the cross-sectional analysis (Chapter Three), which included 1128 female Spanish twins, revealed that lifetime prevalence of chronic low back pain was weakly associated [odds ratio (OR) < 2] with general obesity (body mass index = OR 1.13; 95% CI 1.02
to 1.26; percent body fat = OR 1.15, 95% CI 1.01 to 1.32) in the least adjusted models (total sample analyses). Nevertheless, after the full adjustment for genetics and early shared environmental factors in MZ twins dissimilar for low back pain status, the association did not persist. Consistent with the findings from the systematic review presented in Chapter Two, our results from the cross-sectional analysis indicated that obesity is unlikely to be directly, and independently, linked to chronic low back pain.

Similarly, the results from the longitudinal analysis presented in Chapter Four demonstrated no temporal effect of obesity on low back pain outcomes. For this longitudinal study, 1,098 twins who were free of chronic low back pain at baseline were included. After two to four years, no increase in the risk for the development chronic low back pain, activity-limiting low back pain, or care-seeking for low back pain due to obesity-related measures was observed.

A final exploration of the possible link between obesity and low back pain is presented as a supplementary analysis including intrapair correlations between obesity-related measures, according to low back pain status in 31 pairs of Australian MZ twins. The obesity-related measures investigated were the same as those investigated in Chapters Three and Four: body mass index, percent fat mass, waist circumference, and waist-hip ratio. For this analysis, low back pain was defined as pain in the lower back in the previous month. As suspected, due to the known moderate heritability of low back pain, the majority of twin pairs (24 pairs, 77.4%) were concordant for both having (12 pairs, 38.7%) and for not having (12 pairs, 38.7%) low back pain in the previous month. Only seven pairs (22.6%) reported being discordant for low back pain. Similarly, an excellent agreement for obesity-related measures was found within MZ twin pairs, with most intraclass correlation coefficients being greater than 0.8. Interestingly, the results of this analysis showed that the intrapair difference in obesity-related measures was not higher in
discordant twin pairs than in concordant pairs for low back pain status. Moreover, for the discordant pairs, the findings indicated that those twins with low back pain were not heavier than their co-twins. Consequently, these findings provide additional support for the lack of a direct link between obesity-related measures and LBP.

Obesity is a chronic metabolic condition associated with metabolically driven systemic inflammation, which is involved in the development of insulin resistance and type 2 diabetes. Systemic inflammation has been suggested as a possible trigger for the link between obesity, type 2 diabetes and chronic pain. For example, it has been shown that obese people with elevated inflammatory markers (e.g. C-reactive protein) are almost three times more likely to report low back pain than those with normal levels. Hence, the final study of this thesis (Chapter Five) aimed to investigate the relationship between chronic back pain and type 2 diabetes. Cross-sectional and longitudinal analyses were conducted to explore the bi-directional association between type 2 diabetes and chronic back pain [any or severe (≥ 9) low back pain, neck pain, or both]. Due to the well-recognised genetic influence on type 2 diabetes and back pain, the co-twin case-control design was used to adjust for familial confounders following the sequential analyses mentioned earlier. The sample investigated was from the Murcia Twin Registry, composed of 2,096 twins in the cross-sectional analysis and 1,098 twins in the longitudinal analysis. Type 2 diabetes was associated with the prevalence of chronic low back pain, neck pain, and both. The association was stronger for severe cases of back pain (i.e. severe chronic spinal pain: OR adjusted for age and sex = 3.33; 95% CI 1.47 to 7.53). No association was found in the cross-sectional case-control co-twin and the longitudinal analyses. Although our results suggest a positive association, based on the cross sectional total sample analysis, between type 2 diabetes
and chronic back pain, these conditions are unlikely to be directly linked, and instead, are likely to coexist due to common genetic or environmental factors in their pathogenesis.

In summary, the studies conducted as part of this thesis have provided an important contribution to a better understanding of suspected risk factors for low back pain such as obesity and type 2 diabetes. Based on the findings, a direct causal link between these risk factors and low back pain is questionable. Firstly, in the cross-sectional analyses, the magnitude of significant associations was mostly weak (OR < 2). When high levels of control for important confounding factors such as genetics was applied, these associations did not remain significant. In twin pairs discordant for low back pain status, no between-twin difference was observed in obesity-related measures. Lastly, obesity and type 2 diabetes do not seem to precede chronic low back pain as no temporal effect was observed. Consequently, our studies indicated that obesity and type 2 diabetes coexist with the presence of low back pain possibly due to common genetic or environmental influences on their pathogenesis. In light of the new evidence, novel study directions have been proposed in regards to innovative preventative and management approaches for low back pain.

**Keywords:** Low back pain, Risk Factors, Obesity, Body mass index, Twins
CHAPTER ONE

Introduction
INTRODUCTION

1.1 Definition and epidemiology of low back pain

Low back pain (LBP) is an extremely common health problem [1, 2]. It is usually defined as activity-limiting pain that occurs in the lower back, including any region from the lower gluteal folds to the lower margin of the twelfth ribs [3]. LBP is not a life-threatening condition. However, it represents one of the biggest challenges for the public health system because it is commonly associated with disability and substantial healthcare costs [2, 4]. Despite extensive research dedicated to understanding risk factors for LBP, the majority of LBP is still considered nonspecific in nature, due to the current lack of identified pathoanatomical causes of symptoms. The uncertainty regarding risk factors or identifiable causes of LBP may explain why current prevention and management strategies fail to yield substantial effects [3].

Approximately 40% of the global population experience at least one episode of LBP during their lifetime [5]. Pain recurrence is frequent, and roughly two-thirds of people with recent onset of chronic LBP (i.e. symptoms lasting longer than three months) will not recover within a year [6]. All age groups seem to be affected by LBP, and its prevalence does not substantially differ across the lifespan [7]. For example, the point prevalence of LBP in adults is approximately 11.9%, while in children and adolescents it is 12.0% [5, 8]. However, severe and persistent cases of LBP, which have a greater impact on disability and healthcare expenditure, are more common in older people. Regardless of age, LBP seems to be more prevalent among females than males [5].
1.2 The impact of low back pain on individuals and society

LBP is a major public health problem worldwide, owing largely to high healthcare utilisation and sick leave rates [2, 4, 5, 9-11]. In the last 20 years, LBP was the main contributor to the global disease burden in terms of years lived with disability (YLDs). Between 1990 and 2013, the YLDs due to LBP has increased by 57% [95% Confidence Interval (CI): 54 to 62%], and continues to rise [11]. LBP is also the fourth most burdensome disease, out of 315 health conditions, regarding disability-adjusted life years (DALYs). DALYs are another measure commonly used to quantify the overall disease burden, considering time lost due to ill-health, disability or premature mortality [12].

The economic burden attributed to LBP has been abundantly documented in the literature and is described in terms of direct, indirect, and/or total costs (i.e. including direct and indirect costs) [4, 13]. Direct costs refer to monetary exchange for healthcare services (e.g. medications, hospital services, imaging), while indirect costs refer to expenses resulting from LBP, such as work absences and productivity losses [13, 14]. Although differences in study methodologies have generated a wide range of cost outcomes related to the burden of LBP, the magnitude of the economic impact is evident nonetheless [13]. For example, the estimated total cost in Australia is AUS 9.17 billion per annum, while in the United Kingdom it is £12.33 billion [10, 15], and in the United States direct costs alone are estimated at $90.6 billion per year [16].

Despite the strong evidence that LBP is highly prevalent, disabling and costly, it seems that the burden of LBP remains largely unrecognised by policymakers due to little policy discussion of the options available to address LBP prevention [11, 17]. In recent years, in an attempt to mitigate the global burden of LBP, a shift in healthcare towards prevention of LBP
and related disability has been recommended to policymakers [11, 15, 17-19]. As a result, improving understanding of risk factors for LBP is now a recognised health priority [12, 17, 20].

1.3 Risk factors for low back pain

A risk factor is defined as a factor that plays a determinant role in the etiology of a health condition (e.g. LBP) [21]. Risk factors for LBP have become the subject of much research over recent decades, as identification of these factors could provide a rationale for establishing more effective preventative and management strategies. More than 100 potentially modifiable (e.g. obesity) and non-modifiable (e.g. age, sex) risk factors for LBP have been suggested, although the precise mechanisms responsible for the onset of LBP are still poorly understood [20, 22-30]. Risk factors that have been extensively investigated include those related to lifestyle (e.g. obesity, smoking), socioeconomic status (e.g. income), genetics, pathoanatomical changes (e.g. disc degeneration), psychological factors (e.g. depression), and the demands of an occupation (e.g. heavy physical work,) [20, 26, 27, 30-33]. In particular, focusing on potentially modifiable risk factors for LBP, such as obesity, is crucial for the development of evidence-based preventative strategies [34].

In this thesis, a series of studies has been conducted to explore whether obesity-related factors increase the risk of developing LBP. If obesity is confirmed as a determinant factor for LBP, preventative strategies targeting weight control could contribute to clinical outcome improvements on a public health level, resulting in substantial economic benefits. There are many successful examples in the literature of preventative approaches that have provided noteworthy benefits to public health by reducing the incidence of diseases (e.g. hypertension, cardiovascular diseases, and type 2 diabetes) [35-38]. For example, obesity is a risk factor for
chronic diseases such as type 2 diabetes and cardiovascular diseases [39]. Randomised clinical trials for type 2 diabetes have demonstrated that lifestyle-focused interventions, such as weight control, decreased body weight and plasma glucose, and have resulted in long-term protection against type 2 diabetes [40-42]. Consequently, the maintenance of healthy weight is relevant and recommended in current guidelines for the prevention of type 2 diabetes [43, 44]. Due to the inconclusive evidence concerning whether obesity is a true risk factor for LBP, the European Guideline for LBP prevention has stated that there is currently no evidence for or against recommending weight control as a preventative action to reduce LBP or its related disability [45].

1.4 Obesity and low back pain

Obesity is defined as an excessive fat accumulation that presents a risk to one’s health [46]. As the number of obese people has dramatically increased globally, obesity has become a major public health epidemic [47-49]. The most common method adopted worldwide to assess obesity is body mass index (BMI). BMI estimates obesity by dividing body weight (kilograms) by height (meters) squared. According to the World Health Organization, those with a BMI higher than 30.0 kg/m² are classified as obese [50]. Obesity has been associated with a wide range of disabling and/or life-threatening health conditions, such as type 2 diabetes, cardiovascular diseases, some cancers, and musculoskeletal pain [30, 51-55]. For several of these health conditions (e.g. type 2 diabetes, cancer), obesity is well established as a risk factor [54]. In contrast, the nature of the link between obesity and LBP remains unknown.

The causal relationship between obesity and LBP may be intuitive, on account of the cumulative increased mechanical demands on the spine [56]. To maintain a healthy spine,
mechanical load is necessary as it assists with the transportation of nutrients and applies a direct and indirect stimulus to the intervertebral discs [57]. Being overweight or obese could induce spine degeneration, due to prolonged, accumulated day-to-day hyper-physiological loading which could lead to osteoarthritis and chronic pain [56]. Nonetheless, the current evidence suggests that the simplistic hypothesis of mechanical overload on the spine may not be valid [56]. Other mechanisms explaining the obesity-LBP relationship warrant exploration, as obesity is a known risk factor for pain and osteoarthritis in non-weight-bearing joints (e.g. hand) [56]. Moreover, ethno-geographic factors strongly influence the relationship between obesity and LBP, as this relationship is not consistent across countries [58]. Currently, over 100 studies (including reviews) have been published, and the evidence of a direct link between obesity and LBP remains inconclusive [30, 59, 60].

The controversial epidemiologic evidence of the link between obesity and LBP can be attributed largely to the high number of studies with poor methodological quality. First, the data used to investigate the association between obesity and LBP have been derived mostly from cross-sectional studies [30]. Second, only a few prospective cohort studies have been published, and some of these studies may be affected by attrition bias [30]. Third, confounding factors potentially affecting the obesity-LBP relationship have often not been, or only partially, accounted for [30, 61]. Lastly, the most common anthropometric measure used to define obesity, BMI, has known limitations and can be inaccurate in quantifying obesity [62, 63].

1.4.1 Factors influencing the obesity- low back pain relationship

A significant obstacle in ascertaining whether obesity is a risk factor for LBP is, undoubtedly, the need for considering potential confounders that may be implicated in obesity,
LBP, or both. Evidence suggests that the obesity-LBP relationship is affected by a large number of factors, including age, sex, body fat distribution, low-grade systemic inflammation, physical activity, emotional disorder, smoking, education, environmental, cultural, and genetic factors [2, 64-67]. For example, one study showed that obesity, indicated by higher BMI and larger waist circumferences, was associated with chronic LBP in males and females. However, these associations did not remain significant after adjusting for age, smoking, and educational levels in males. In contrast, in the adjusted analysis for females, the magnitude of the association increased between obesity measures and chronic LBP [68]. Levels of physical activity have also been shown to influence the association between obesity and LBP [65]. Obese sedentary individuals are at a greater risk of suffering LBP compared to those who are obese but physically active. There is also evidence of a biopsychosocial interaction between emotional disorders, obesity, and LBP, as the association between LBP and obesity-related measures is stronger in individuals with symptoms of depression and anxiety [64].

It is likely that the complex relationship between obesity and LBP also involves genetic and familial factors [33, 69-72]. It has been shown that the association between obesity measures and LBP does not remain significant after controlling for genetic and environmental factors shared by twins [69, 70]. Several studies have consistently reported a substantial genetic contribution to both LBP and obesity, as well as to other variables that could affect obesity, LBP, or both (e.g. physical activity, depression, eating disorders) [32, 33, 71, 73-77]. For example, eating disorders aggregate in families (heritability of 57%; 95% CI 30 to 77%) [78]. Illness behaviour, including how people communicate symptoms and cope with pain, may also be passed on by family members [79]. Moreover, demographic and lifestyle factors shared by family members, such as the intake of complex carbohydrates and alcohol, educational
achievements, and exercise habits may all influence the development of health conditions such as obesity and LBP [80]. Thus, genetic and environmental factors shared by families may be important contributors in the aetiology and maintenance of LBP, obesity, or both. However, genetic and familial factors have rarely been adjusted for as potential confounders when investigating the obesity-LBP relationship [32, 33, 81, 82].

Environmentally determined differences (e.g. variation in socioeconomic status, diet) and the genetic background of populations also appear to influence the obesity-LBP relationship. Evidence from a study that used cross-sectional data from nine countries found that the association between obesity and LBP varies substantially across countries [58]. Whilst in some countries the association is strong [e.g. Russia: Odds ratio (OR) 2.76; 95% CI 1.83 to 4.17], in other countries, the association is weak (Poland: OR 1.47; 95% CI 1.10 to 1.96) or absent (e.g. China: OR 1.08; 95% CI 0.87 to 1.34) [58]. This difference may be attributed to not only environmental (e.g. geographic location, cultural influences) or genetic differences, but also to gene-environmental interactions [83]. Growing evidence suggests that genetic susceptibility to chronic health conditions may be, at least, partially dependent upon environmental influences [82, 84]. A simple example is the rapid increase in obesity prevalence in recent decades being the result of environmental and cultural influences rather than genetic factors [85]. Environmental exposures such as diet and physical activity, which are often driven by family habits, can induce persistent alterations in genes - a phenomenon known as epigenetics [80, 86-89]. Epigenetic processes, such as DNA methylation, appear to play an important role in the development of chronic health conditions [90-93]. Thus, it is likely that genes act differently in the presence of certain environmental factors, thereby influencing the obesity-LBP relationship.
To gain a clearer understanding as to whether obesity is a strong risk factor for LBP, it is plausible to use a study design that allows for the control of genetic and shared environmental factors. The twin design is a unique and powerful alternative for the study of risk factors for complex health conditions such as LBP [94]. Using twins in research has an additional important advantage over traditional methods because genetic and early shared environmental factors are accounted for as potential factors that influence the association between obesity and LBP. Consequently, the twin design allows for more precise estimates of risks for LBP, which are currently lacking. This thesis enriches the LBP field by exploring the relationship between obesity-related risk factors for chronic LBP in adult twins, accounting for the effect of genetic and environmental influences.

1.4.1.1 The twin design

Genetic and environmental mechanisms underlying the development of obesity and LBP are supported by overwhelming evidence [71, 77, 82, 95, 96]. Importantly, gene-environment interactions are also likely to be a source of variation for these complex phenotypes [58, 83]. Twin studies, in particular when a within-pair twin case-control design is employed, represent a unique method to overcome the nature-nurture dilemma when investigating the obesity-LBP relationship. Studying twin pairs discordant for a health condition (e.g. one twin reports LBP, whereas the co-twin do not) is regarded as an experimental opportunity, as it allows the most efficient match for both genetic and environmental influences as well as gene-environmental interactions in early life [97, 98]. The twin method is based on the fact that identical twins [monozygotic (MZ)] and fraternal twins [dizygotic (DZ)] share approximately 100% and 50% of their genes, respectively. Analysing twin pairs also parses environmental influences on a trait or
disease, as twins tend to be exposed to a common environment until early adulthood (e.g. diet, education, and parents socio-economic status) [98, 99]. Theoretically, greater control for potential confounders in twin pair analyses, allows for more precise estimates of the magnitude of association between obesity-related risk factors and LBP and, in turn, provides an opportunity to understand whether obesity is a true risk factor for LBP.

This thesis focusses on twin studies, particularly the use of the within-pair twin case-control design. First, **Chapter Two** presents a systematic review with meta-analysis aimed at critically evaluating the literature on obesity-related measures (e.g. weight, BMI) as risk factors for LBP, or lumbar disc degeneration, in twins. For the first time, the comparison of the estimates for the obesity-LBP association was performed when genetics and familial influences are, or are not, adjusted for. In **Chapters Three, Four, and Five**, obesity-related risk factors (including general obesity, abdominal obesity, and type 2 diabetes) for LBP are investigated using a within-pair twin case-control design. The twin studies presented in this thesis are primarily made up of cross-sectional and longitudinal data from the Murcia Twin Registry in Spain.

**1.4.2 Limitations in the assessment of obesity**

In addition to the lack of adjustment for important confounders, a major limitation in many studies investigating obesity as a risk factor for LBP is the use of BMI as the sole measure to classify obesity [30]. BMI, an index based on height and weight, is a crude measure that estimates body fatness [50]. While BMI is very commonly used in clinical settings and research contexts worldwide, several reports have cautioned against its use because of serious methodological flaws [63, 100, 101].
One of the deficiencies of using BMI as a measure of obesity is its crude estimation of fat mass without distinguishing adipose tissue from other body components such as muscle and bone [63, 100-102]. As genetic backgrounds (i.e. genotypic base of a population) influence body composition, a given BMI value does not necessarily correspond to the same degree of adiposity in different ethnic populations [103]. Furthermore, although body composition changes across the lifespan, BMI does not take age into consideration [62]. As a result, the standard BMI cut-off values may not be valid to identify obesity across different ages and ethnicities [101, 103]. For these reasons, BMI has poor sensitivity and specificity in classifying obesity [62]. For example, 41% of men and 32% of women were misclassified as obese when BMI was used, compared to the ‘gold standard’ method of assessing body fat percentages, dual-energy x-ray absorptiometry [104]. Another factor rendering impression to the results of previous studies is that self-reported data (height and weight) are frequently used to calculate BMI [62]. Self-reported values tend to result in underestimation of weight and overestimation of height [105]. These limitations of BMI as a measure of obesity may lead to misclassification of fatness, potentially over- or under-estimating the prevalence of obesity [62, 63, 102-104]. Therefore, the use of BMI as a sole measure to define obesity may introduce bias to studies that have investigated the effects of obesity on LBP and may, in turn, provide imprecise estimates of the link between obesity and LBP.

Another limitation when using BMI to assess obesity is that the distribution of fat mass in the body is not taken into account. Several studies in adults have suggested that greater abdominal adiposity (greater fat mass around the waist) presents a higher health risk than overall adiposity [106-109]. Due to the large variation in body fat distribution within a narrow range of BMI, abdominal obesity can differ substantially across populations [103]. Preliminary evidence
suggests that body fat distribution influences the association between obesity and LBP [68, 110, 111]. Rather than the amount of body fat, abdominal obesity appears to have a stronger association with LBP [66, 110]. Consequently, additional anthropometric measures that consider not only the total amount, but also the distribution, of body fat should be used to reach valid conclusions on the effects of obesity on LBP [102].

To overcome the limitations in the previous research, the studies presented in this thesis (Chapters Three and Four) explored the association between obesity-related measures and LBP in twins using measures that consider the magnitude of fatness as well as body fat distribution. To investigate general obesity, in addition to BMI, the percentage of fat mass was investigated. Percentage of fat mass was measured by bioelectrical impedance which is a valid, non-invasive method [112]. This method uses a small electric current that passes through the body to calculate the impedance of both extracellular and intracellular fluids to estimate the amount of fat and lean mass separately [113]. Other measures of fatness related to abdominal obesity (excess intra-abdominal fat), like waist circumference and waist-to-hip ratio, were also investigated in this thesis. Waist circumference has been proposed as one of the most appropriate measures to estimate risk to health, as it predicts the risk for several health conditions (e.g. cardiovascular diseases, diabetes) [106]. Furthermore, waist-to-hip ratio has also been used as an obesity-risk estimator, as it has a highly significant association with a number of health conditions (e.g., cardiovascular disease) [109, 114]. To further investigate if obesity measures are strong determinates for LBP, a Supplementary Analysis is presented in Chapter Four comparing the concordance of these four obesity measures (BMI, percentage of fat mass, waist circumference, and waist-to-hip ratio) in identical twins dissimilar for LBP status.
1.4.3 Obesity, type 2 diabetes, and low-grade systemic inflammation

Obesity, in particular abdominal obesity, is associated with metabolically driven systemic inflammation which is involved in the pathogenesis of obesity-related insulin resistance and type 2 diabetes [115]. A number of studies have suggested that systemic inflammation possibly explains the link between obesity, type 2 diabetes, and chronic pain [115-117]. It has been shown that obese people with elevated systemic inflammation (e.g. C-reactive protein) are almost three times more likely to report LBP than those with normal levels [118]. Furthermore, people with type 2 diabetes, who have well-recognised low-grade systemic inflammation, are twice as likely to report LBP [119]. Importantly, it has been suggested that having both diabetes and LBP result in a greater impact on people’s health and the complexity of healthcare required [120, 121]. Therefore, the final study of this thesis (Chapter Five) explored the relationship between another obesity-related health risk factor, “type 2 diabetes”, and chronic back pain (including LBP, neck pain, or both) in twins. As previously mentioned, the within-pair twin case-control design accounts for the possible influence of familial factors in these relationships [71, 122, 123]. The presence of genetic component underlying the variation (heritability) of these conditions is well established [heritability of LBP (52%; 95% CI 33 to 72%), neck pain (48%; 95% CI 29 to 67%), and type 2 diabetes (72%; 95% CI 61 to 78%)] [71, 122].

1.5 Aims of this thesis

The aims of this thesis were to:
1. Systematically review the literature on twin studies to investigate the strength of the relationship between obesity-related measures and LBP, or lumbar disc degeneration; and to determine whether genetics and the early environment influence these associations.

2. Investigate the strength of the association between obesity and chronic LBP when obesity is assessed in terms of the total amount as well as the distribution of body fat; and accounting for genetic and early shared environmental factors.

3. Examine whether obesity-related measures increase the risk of developing chronic LBP using longitudinal data accounting for genetic and early shared environmental factors.

4. Investigate whether the intra-pair differences in obesity-related measures are higher in twin pairs discordant for LBP than in pairs concordant for LBP.

5. Explore the potential bi-directional relationship between type 2 diabetes and chronic back pain (including chronic LBP, chronic neck pain, or both) in twins.
1.6 References


34. Brady S, et al., Predictors of back pain in middle aged women: Data from the australian longitudinal study on women's health. Arthritis Care Research (Hoboken), 2016.


The relationship between obesity, low back pain, and lumbar disc degeneration when genetics and the environment are considered:

A systematic review of twin studies

Reprinted from: The Spine Journal, volume 15, Dario, A.B., et al., The relationship between obesity, low back pain, and lumbar disc degeneration when genetics and the environment are considered: a systematic review of twin studies, page numbers 1106-1117, 2015, with permission from Elsevier.
The co-authors of the paper “The relationship between obesity, low back pain, and lumbar disc degeneration when genetics and the environment are considered: a systematic review of twin studies” confirm that Amabile Borges Dario has made the following contributions:

- Conception and design of the research
- Extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript and critical appraisal of content

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the above authorship attribution statement is correct.

...........................................................................................................

Associate Professor Paulo Henrique Ferreira
The University of Sydney
December 2016
The relationship between obesity, low back pain, and lumbar disc degeneration when genetics and the environment are considered: a systematic review of twin studies

Amabile B. Dario, MSc\textsuperscript{a,\ast}, Manuela L. Ferreira, PhD\textsuperscript{b}, Kathryn M. Refshauge, PhD\textsuperscript{a}, Thais S. Lima, MSc\textsuperscript{c}, Juan R. Ordo\~{n}ana, PhD\textsuperscript{d,e}, Paulo H. Ferreira, PhD\textsuperscript{a}

\textsuperscript{a}Discipline of Physiotherapy, Faculty of Health Sciences, The University of Sydney, PO Box 170, 75 East Street Lidcombe, Sydney, NSW, Australia 2141
\textsuperscript{b}The George Institute for Global Health and Institute of Bone and Joint Research, Kolling Institute, Sydney Medical School, The University of Sydney, Level 13, 321 Kent Street, Sydney, NSW, Australia 2141
\textsuperscript{c}Biomechanics and Motor Control Research Group, Science and Technology Faculty-Universidade Estadual Paulista, Presidente Prudente, Sao Paulo, Brazil 19060-900
\textsuperscript{d}Murcia Twin Registry, Department of Human Anatomy and Psychobiology, University of Murcia, Spain 30100
\textsuperscript{e}IMIB-Arrixaca, Department of Human Anatomy and Psychobiology, Murcia, Spain 30100

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Abstract

BACKGROUND CONTEXT: The relationships between obesity and low back pain (LBP) and lumbar disc degeneration (LDD) remain unclear. It is possible that familial factors, including genetics and early environment, affect these relationships.

PURPOSE: To investigate the relationship between obesity-related measures (e.g., weight, body mass index [BMI]) and LBP and LDD using twin studies, where the effect of genetics and early environment can be controlled.

STUDY DESIGN: A systematic review with meta-analysis.

METHODS: MEDLINE, CINAHL, Scopus, Web of Science, and EMBASE databases were searched from the earliest records to August 2014. All cross-sectional and longitudinal observational twin studies identified by the search strategy were considered for inclusion. Two investigators independently assessed the eligibility, conducted the quality assessment, and extracted the data. Meta-analyses (fixed or random effects, as appropriate) were used to pool studies' estimates of association.

RESULTS: In total, 11 articles met the inclusion criteria. Five studies were included in the LBP analysis and seven in the LDD analysis. For the LBP analysis, pooling of the five studies showed that the risk of having LBP for individuals with the highest levels of BMI or weight was almost twice that of people with a lower BMI (odds ratio [OR] 1.8; 95% confidence interval [CI] 1.6–2.0; \(I^2=0\%\)). A dose-response relationship was also identified. When genetics and the effects of a shared early environment were adjusted for using a within-pair twin case-control analysis, pooling of three studies showed a reduced but statistically positive association between obesity and prevalence of LBP (OR 1.5; 95% CI 1.1–2.1; \(I^2=0\%\)). However, the association was further diminished and not significant (OR 1.4; 95% CI 0.8–2.3; \(I^2=0\%\)) when pooling included two studies on monozygotic twin pairs only. Seven studies met the inclusion criteria for LDD. When familial factors were not controlled for, body weight was positively associated with LDD in all five cross-sectional studies. Only two cross-sectional studies investigated the relationship between obesity-related measures and LDD accounting for familial factors, and the results were conflicting. One longitudinal study in LBP and three longitudinal studies in LDD found no increase in risk in obese individuals, whether or not familial factors were controlled for.

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Conflict of interest: The authors declare that they have no competing interests.

* Corresponding author. Faculty of Health Sciences, University of Sydney, PO Box 170, Lidcombe 1825, Australia. Tel.: (61) 293-519-562; fax: (61) 293-519-601.

E-mail address: adar3900@sydney.edu.au (A.B. Dario)
CONCLUSIONS: Findings from this review suggest that genetics and early environment are possible mechanisms underlying the relationship between obesity and LBP; however, a direct causal link between these conditions appears to be weak. Further longitudinal studies using the twin design are needed to better understand the complex mechanisms underlying the associations between obesity, LBP, and LDD. © 2015 Elsevier Inc. All rights reserved.

Keywords: Obesity; Body mass index; Body weight; Low back pain; Lumbar disc degeneration; Genetics; Twins

Introduction

Low back pain (LBP) is a major health problem globally [1], being the largest contributor to the number of years that people live with disability [2]. Although decades of research have been dedicated to identifying the etiology of LBP, the factors that trigger an episode of LBP remain unclear [3], limiting the possibility of designing effective preventative strategies. A variety of factors have inconsistently been found to be associated with LBP, and the increased risk has been small. One of these factors, obesity, is a potential target for prevention strategies, and therefore, it has been the focus of several studies in the field [4,5].

Obesity is recognized as a major public health problem, and its prevalence is increasing rapidly in westernized countries [6,7]. Obese individuals are at higher risk of developing a wide spectrum of chronic diseases such as diabetes, cardiovascular disease, cancer, and musculoskeletal disorders, such as spinal problems [8]. Body weight, an important factor related to spinal loading, has been associated with several signs of lumbar disc degeneration (LDD), including disc space narrowing [9] and decreased signal intensity of the lumbar intervertebral discs [10]. Despite controversy [11–13], LDD has been proposed as one of the main risk factors of LBP [10,14].

Previous studies have suggested that familial factors (ie, early environmental and genetic influences) play an important role on obesity, LBP, and LDD. According to twin studies, the estimated contribution from heritability to total body fat ranges between 70% and 80% [15], for LBP between 30% and 46% [16], and for LDD the contribution ranges between 47% and 60% [14], suggesting a major genetic component in these conditions. However, most studies that investigated the relationship between obesity, LBP, and LDD did not account for genetic or early environmental factors, which might explain their conflicting findings.

Twin studies represent a unique and powerful design for investigating risk factors for health conditions as they allow controlling for various confounders, including genetic factors, consequently providing more precise estimates of risk. To our knowledge, there has been no published systematic review specifically investigating the relationship between obesity, LBP, and LDD in twin studies. Therefore, this systematic review aimed to investigate whether there is an association between obesity and LBP and obesity and LDD, and whether this association is influenced by genetics and early environment.

Methods

A review protocol was registered in the “International prospective register of systematic reviews” under the registration number CRD42014005747. We used the Meta-analysis of Observational Studies in Epidemiology guidelines to lead each section of this systematic review [17].

Search strategy

MEDLINE, CINAHL, Scopus, Web of Science, and EMBASE databases were searched using a combination of key words related to obesity, LBP, and LDD. The search was conducted from the earliest records to August 2014 to identify cross-sectional and longitudinal observational twin studies that investigated the obesity-LBP and obesity-LDD relationships. Additionally, citation tracking was conducted of the reference list of included studies and relevant publications in the field. If additional clarification or data were required, authors were contacted by email.

Selection of studies

All articles identified by the search strategy were independently screened by two investigators (ABD and TL), with a third independent investigator (PHF) resolving any disagreement. The assessment involved three stages: screening of titles, abstracts, and full text. The number of studies identified was recorded for all screening stages.

Inclusion and exclusion criteria

We included cross-sectional and longitudinal observational studies that investigated the relationship between obesity and LBP and obesity and LDD using twins, where the genetic and early shared environment components were or were not adjusted for (case-control studies and studies that recruited twin samples, respectively). Twins needed to account for at least 90% of the total sample, with no restriction on age, gender, or zygosity. No restriction was applied on the year of publication or language. Studies were excluded if they investigated specific spinal pathologies (fracture, cancer, and systemic diseases) or pregnancy-related LBP.

Exposure factors

The exposure factors were obesity or a measure of obesity such as body mass index (BMI), percent fat mass, or weight.
Outcomes

The outcomes of interest were present occurrence (prevalence) of LBP or LDD in cross-sectional studies and future occurrence (incidence) of LBP and LDD in longitudinal studies. All definitions for LBP were accepted, as these varied considerably among studies. For LDD, studies were included if the outcome was a pathoanatomical finding based on imaging, such as disc space narrowing or changes in disc signal.

Data extraction

Data were extracted from all included studies regarding participants, sampling methods, response rates, length of follow-up, and information on exposure factors (obesity-related measures) and potential confounders (eg, gender, age). A standardized form developed for this systematic review was used to extract data. When studies performed longitudinal and cross-sectional analyses, data from both analyses were extracted. When studies reported more than one cross-sectional analysis, estimates were extracted from the analysis with the largest sample size. We extracted estimators such as odds ratios (ORs) and measurements of variability for the associations between obesity and both LBP and LDD. To investigate if genetics and early shared environment factors affected these associations, data from studies reporting results from the total sample and from case-control analyses were extracted separately. In the total sample analysis, no adjustment for genetics or early shared environment factors was performed and twins were analyzed as individuals rather than pairs, irrespective of discordance for LBP within twin pairs. The case-control analysis included only complete twin pairs who were discordant for LBP status, that is, one twin reported LBP, whereas the other did not.

This approach enabled control of various confounders, including genetic factors and twins’ early shared environmental factors. It was assumed that the case-control design allowed clear identification of a relationship between an outcome (eg, LDD) and an exposure factor (eg, BMI) because it controls for genetic factors and early shared environment. Theoretically, when the magnitude of the association between two variables (eg, LDD and BMI) increases from the total sample analysis (no adjustment for genetic factors or early shared environment) to a monozygotic (MZ) case-control analysis (adjustment for early shared environment and approximately 100% of genetic factors), the relationship between the two variables is more direct and possibly more consistent with a direct causal path [18].

Methodologic quality

The quality of included studies was assessed using a standardized checklist based on the recommendations for publishing a systematic review [19,20] and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology Statement) guidelines [21]. The checklist comprised eight criteria: representative sample, defined sample, blinding of assessors to the predictor, blinding of assessors to the outcome, follow-up rate greater than 85%, defined method of assessment, reporting on outcome data, and statistical adjustment for potential confounders. Two members (ABD and TL) of the research team conducted the critical appraisal independently. Results were compared and disagreements were resolved by the third independent investigator (PHF).

Meta-analysis

Extracted estimates of risk and confidence intervals (CIs) were synthesized in a meta-analysis, when the data reported were sufficiently homogenous. Where studies provided results for more than one description of LBP, we chose the definition that involved longer and more disabling symptoms (eg, chronic instead of acute LBP). When predictors were presented in incremental categories, we selected the category with higher levels of exposure for the meta-analysis. Dose-response relationship was calculated when studies provided estimated risks for different levels of exposure (eg, overweight and obesity). For those studies with different degrees of control for confounders, we used the model that adjusted for the greatest number of variables. We used the lowest available anthropometric level for weight or the normal category for BMI as the reference category. Data were pooled using Comprehensive Meta-Analysis software, version 2.2.064 (Biostat, Englewood, USA, 2008). Study heterogeneity was analyzed using visual inspection of graphs and the I² statistic. True homogeneity was considered to be I²=0, low heterogeneity lower than 30%, moderate 30% to 49%, substantial 50% to 74%, and considerable heterogeneity greater than 75% [22]. In case of heterogeneity equal to or higher than substantial, a random effects model was used to calculate the pooled OR estimates and their variances.

Results

Included studies

The systematic search identified 822 publications, 769 were removed after screening for duplicates and ineligible titles and abstracts (Fig. 1). Fifty-three studies were identified as potentially eligible and, after full-text screening, 11 publications met our inclusion criteria and were included in the review [4,5,14,23–30]. One study reported data for LBP and LDD [26]. The included studies were published between 1999 and 2011. The total number of participants from studies assessing LBP and LDD was 45,784 and 4,205, respectively. Included studies recruited twins from registries in the United States [5], Finland [14,23–25,27], Australia [28], United Kingdom [26,28,30], and Denmark [4,29]. Comprehensive descriptions are provided in

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Table 1 for studies investigating the relationship between obesity and LBP symptoms and in Table 2 for obesity and LDD [31].

Methodologic quality

A summary of the methodologic quality of included studies is shown in Table 3. All five (100%) studies investigating LBP had a representative and well-defined sample, well-defined method of assessment of predictors and outcomes, and reported outcome data and conducted adjustment for potentially confounding factors. One study did not include blinded assessors for predictors and outcomes [26], and the only included longitudinal study had a follow-up rate below 85% [29]. For LDD, six (86%) studies had a representative sample and all seven (100%) defined the sample and the method of assessment of predictors and outcomes. Assessors were blinded for predictors in six (86%) and for outcomes in five (71%) studies. Four (57%) of the studies reported outcome data and adjusted the analysis for potentially confounding factors. Two of the three longitudinal studies for LDD had a follow-up rate below 85%.

Assessment and definition of obesity-related measures

The most common measure of obesity in the included studies was BMI [4,5,26,28,29]. The second most common measure was body weight [14,24–27,30], followed by percentage of body fat [24] and intrinsic disc loading (estimated by body weight divided by the axial spinal disc area) [23]. The definition and cutoff points used in each study are provided in Table 1 and Table 2 (LBP and LDD studies, respectively).

Assessment and definition of LBP and LDD

Low back pain was assessed by questionnaires with a body chart in all [4,26,29,30] except one study [5]. Low back pain was defined as pain, stiffness, and discomfort in the lumbar area accompanied [26,30] or not [4,5,29] by disability. Duration of pain and disability ranged from...
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study population</th>
<th>Obesity measure</th>
<th>Low back pain measure</th>
<th>Results: total sample</th>
<th>Results: case-control or genetic analysis</th>
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<tr>
<td>Leboeuf-Yde et al. [4], 1999</td>
<td>Cross-sectional</td>
<td>Danish twins aged 12 to 41 y n=28,424 (3,751 complete MZ pairs)</td>
<td>BMI (underweight, &lt;20 kg; normal weight, 20–24 kg; overweight, 25–29 kg; heavily overweight, &gt;29 kg)</td>
<td>Yes/no: questionnaire with body chart. LBP previous y lasting 1–7; 8–30; and &gt;30 d.</td>
<td>Overweight positively associated with LBP. Higher ORs for LBP &gt;30 d were found when compared with LBP 1–7 d in overweight and heavily overweight. In heavily overweight twins, the OR rose from 0.8 in LBP 1–7 d to 1.7 in LBP &gt;30 d. Dose response found for LBP &gt;30 d: 0.7 underweight; 1.6 overweight; and 1.7 heavily overweight.</td>
<td>The significant association between BMI and LBP was not found in MZ twin pairs of dissimilar body weight: overweight OR 1.1 (95% CI 0.8–1.5); heavily overweight OR 1.1 (95% CI 0.5–2.0).</td>
</tr>
<tr>
<td>MacGregor et al. [30], 2004</td>
<td>Cross-sectional</td>
<td>English twins aged 45 to 72 y n=1,064 (181 MZ and 351 DZ pairs)</td>
<td>Weight</td>
<td>Yes/no: questionnaire with body chart. Persistent LBP: pain with a total duration of &gt;30 d associated with disability.</td>
<td>Heavier twins have 2.36 times (95% CI 1.47–3.76) greater chance of having LBP than lighter twins (p&lt;.01). Dose response found with ORs increasing according to the increase in quartiles of weight (1&lt; quartile OR 1; 2&lt; quartile OR 1.94, 95% CI 1.22–3.09; 3&lt; quartile OR 2.25, 95% CI 1.42–3.56; 4&lt; quartile OR 2.36, 95% CI 1.47–3.76).</td>
<td>Weight-LBP association is explained mostly by shared genetic factors rather than shared familial environmental factors.</td>
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<tr>
<td>Hestbaek et al. [29], 2006</td>
<td>Cross-sectional and longitudinal (8-y follow-up)</td>
<td>Danish twins aged 12 to 22 y n=9,569 (413 MZ pairs discordant for LBP at the baseline)</td>
<td>BMI (underweight &lt;17 kg; normal weight 17–23.9 kg; overweight 24–28.9 kg; obesity &gt;29 kg/BMI dichotomized &gt;24 kg overweight)</td>
<td>Yes/no: questionnaire with body chart. LBP (at all): at least 1 d during the previous y. Persistent LBP: at least 30 d during the previous y.</td>
<td>Cross-sectional: Overweight positively associated with persistent LBP (OR 1.38; 95% CI 1.06–1.79). Dose response not found: overweight OR 1.41 (95%CI 0.82–2.43); Obese OR 1.01 (95% CI 0.41–2.49). Sex: overweight associated with LBP only for girls (OR 1.7; 95% CI not reported).</td>
<td>Cross-sectional: Overweight not associated with present LBP (at all) (OR 1.75; 95% CI 0.82–3.90)</td>
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<td>Cross-sectional: Overweight positively associated with persistent LBP (OR 1.38; 95% CI 1.06–1.79). Dose response not found: overweight OR 1.41 (95% CI 0.82–2.43); Obese OR 1.01 (95% CI 0.41–2.49). Sex: overweight associated with LBP only for girls (OR 1.7; 95% CI not reported).</td>
<td>Longitudinal: Overweight not associated with future LBP (at all) (OR 0.89; 95% CI 0.30–2.60)</td>
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1110
1 day in the previous year [26] to a lifetime total of 3 months [5]. Magnetic resonance imaging was used in all studies to identify LDD through qualitative assessment [14,24,26,28] or a combination of qualitative and quantitative assessments [23,25,27]. The phenotype of LDD was characterized by decreased disc height [14,23–28] or disc signal intensity [14,24–28], disc bulging [14,23,25–28], osteophytes [14,26,28], disc irregularity [14,23], disc herniation [14], or a combination of different parameters [26,28].

Association between obesity-related measures and LBP symptoms

Results of studies reporting total sample analyses

Five studies investigated the relationship between obesity-related measures (ie, BMI and body weight) and LBP using total samples of twins with no adjustment for familial factors [4,5,26,29,30]. All studies reported sufficient and similar data to be pooled in a meta-analysis. Pooling of the data (Fig. 2) revealed that twins classified in the highest level of BMI or weight had 1.8 times increased odds of having LBP (OR 1.8; 95% CI 1.6–2.0; p < 0.001; I² = 0%) compared with those with normal or lighter body weight. Pooling of longitudinal data was not possible as only one study was identified. This study, conducted in Denmark, followed participants for 8 years, finding no effect of BMI on LBP incidence (OR 1.0; 95% CI 0.9–1.4) [29].

Obesity-LBP dose-response relationship

A possible dose-response relationship between obesity-related measures (weight or BMI) and LBP was investigated in four studies [4,5,29,30]. Pooling of the four studies (Fig. 2) revealed that the prevalence of LBP in obese twins (OR 1.8; 95% CI 1.6–2.0; p = .001; I² = 0%) was higher than the prevalence of LBP in overweight twins (OR 1.5; 95% CI 1.3–1.7; p = .001; I² = 55%). In addition, one study found that twins who were underweight had a lower prevalence of LBP than those with normal values of BMI (OR 0.7; 95% CI not reported) [4].

Results of studies reporting analyses that accounted for genetic and early environmental factors

A total of four studies investigated the effect of genetic factors and early shared environment on the LBP-obesity relationship [4,5,29,30]. Three [4,29] studies conducted a within-pair case-control analysis, where twin pairs dissimilar for body weight (one twin classified as normal weight and the other as overweight or obese) were analyzed. Pooling of these twin studies showed a statistically significant positive association between obesity/overweight and prevalence of LBP (OR 1.5; 95% CI 1.1–2.1; p = .02; I² = 0%). However, when pooling included case-control studies with MZ twins only [4,29], the association was no longer statistically significant (OR 1.4; 95% CI 0.8–2.3; p = .26; I² = 0%). The only longitudinal study that used a within-pair case-control design did not identify a significant
Table 2
Characteristics of the included studies for lumbar disc degeneration

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study population</th>
<th>Obesity measure</th>
<th>Lumbar disc degeneration measure*</th>
<th>Results: total sample</th>
<th>Results: case-control or genetic analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Videman et al. [14], 2006</td>
<td>Longitudinal (5-y follow-up)</td>
<td>Finish twins aged 35 to 69 y at baseline</td>
<td>Weight</td>
<td>Disc height</td>
<td>Body weight not associated with the progression of LDD over 5 y.</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=140 (70 MZ twin pairs)</td>
<td></td>
<td>Disc bulging</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex: 100% male</td>
<td></td>
<td>Disc herniation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Osteophytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Battie et al. [25], 2008</td>
<td>Cross-sectional</td>
<td>Finish twins aged 35 to 70 y n=600 (152 MZ and 148 DZ twin pairs)</td>
<td>Weight</td>
<td>Disc height</td>
<td>Body weight associated with signs of LDD, at least at one spinal level.</td>
<td>NA</td>
</tr>
<tr>
<td>Videman et al. [23], 2008a</td>
<td>Longitudinal (5-y follow-up)</td>
<td>Finish twins aged 35 to 69 y at baseline</td>
<td>Weight; BMI</td>
<td>Disc height</td>
<td>Body weight not associated with the progression of LDD over 5 y.</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=134 (67 MZ twin pairs)</td>
<td></td>
<td>Disc bulging</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex: 100% male</td>
<td></td>
<td>Disc signal intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Videman et al. [27], 2008b</td>
<td>Cross-sectional</td>
<td>Finish twins aged 35 to 70 y at baseline</td>
<td>Intrinsic disc loading parameter (body weight/axial disc area)</td>
<td>Disc height</td>
<td>The variance explained by the intrinsic disc loading in the L1–L4 discs was 3% in disc height narrowing, 8% in anterior bulging, 5% in posterior bulging, and 7% in the adjusted disc signal.</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=519 (234 MZ and 285 DZ twin pairs)</td>
<td></td>
<td>Disc bulging</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex: 100% male</td>
<td></td>
<td>Disc signal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Disc irregularity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Videman et al. [24], 2010</td>
<td>Cross-sectional</td>
<td>Finish male twins aged 36 to 69 y n=88 (44 MZ pairs with 8 kg or more weight discordant)</td>
<td>Weight; BMI; body fat variation</td>
<td>Disc signal intensity</td>
<td>NA</td>
<td>Heavier MZ twins had 5.4% (p=.005) higher disc signal variation in L1–L4 compared with the lighter co-twin. Greater body mass appears to delay L1–L4 disc desiccation slightly. Body weight not associated with the disc height.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex: 100% male</td>
<td></td>
<td>Disc height</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Disc bulging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Livshits et al. [26], 2011</td>
<td>Cross-sectional</td>
<td>English twins aged 18 to 84 y n=2,256 (371 and 698 MZ and DZ pairs)</td>
<td>Weight; BMI</td>
<td>Disc signal intensity</td>
<td>Weight explained some of the variance of lumbar degeneration signs (LSUM) ($\beta$ weight 0.086 kg; SE 0.02).</td>
<td>NA</td>
</tr>
</tbody>
</table>
Obesity and LBP

A study by Williams et al. [28], 2011, investigated the association between obesity and LBP (OR 0.9; 95% CI 0.3–2.6) [29] (Fig. 3).

Association between obesity and LDD

Despite seven studies [14,23–28] having investigated the association between obesity-related measures and signs of LDD, a meta-analysis was not feasible because of the heterogeneity in study estimates of association or lack of outcome data.

Results of studies reporting total sample analyses

Signs of LDD such as disc height narrowing, bulging, and signal intensity were associated with increased body weight [23,25,28]. Body weight and intrinsic load in the L1–L4 discs explained between 1.4% [26] and 17% [23] of the variance in signs of lumbar degeneration. Three longitudinal studies investigating the effect of obesity in the progression of LDD did not find any increase in risk of developing LDD over 5 [14,27] or 10 years [28].

Results of studies reporting analyses that accounted for genetic and early environmental factors

Only two studies, both cross-sectional, that investigated the relationship between obesity-related measures and LDD accounted for genetic and early environmental factors [24,28]. One study used a within-pair MZ case-control analysis and found that heavier twin had 5.4% higher disc signal variation (a measure of water concentration in intervertebral discs) in L1–L4 intervertebral discs compared with the lighter co-twin [24].

In pairs of same-sex twins [28], a positive association between BMI and LDD was found for the total twin sample (OR 1.2; 95% CI 1.1–1.4) and for dizygotic (DZ) twins (OR 1.2; 95% CI 1.2–1.7), but not for MZ twins (OR 0.9; 95% CI 0.6–1.3) [28]. A cross-sectional analysis of the 10-year follow-up data showed that BMI was associated with LDD in the total sample analysis (OR 1.3; 95% CI 1.2–1.5) and MZ (OR 1.6; 95% CI 1.1–2.3) twins.

Discussion

Main findings

It is known that familial factors (genetic and early environment) play a significant role in obesity, LBP, and LDD [15,16,32]. However, there is limited evidence to examine whether familial factors affect a potential relationship between obesity and both LBP and LDD [33]. Twin studies, particularly using a within-pair twin case-control design, have the potential to provide less biased estimates of risk for a condition by controlling for possible confounding from genetic factors and early shared environment [34]. We aimed to review and summarize the evidence from twin studies that investigated the effect of obesity-related
measures on LBP and LDD when familial influences were or were not controlled for. The results of this systematic review suggest that individuals who are obese or overweight are more likely to have LBP and LDD than those who are in the normal weight range or underweight. However, after controlling for familial factors, the associations between obesity-related measures and LBP appear to diminish and are no longer evident after full adjustment in MZ twins. Results from the longitudinal studies showed evidence that obesity-related measures do not increase the risk for LBP or LDD, irrespective of adjustment for familial effects.

**Obesity and LBP**

The magnitude of association between obesity and LBP found in this review was weak (OR=1.8) according to the benchmarks used for observational studies [35]. However, results tended to be consistent in all five twin studies with samples from four different countries and participants’ ages ranging from 12 to 84 years. Our meta-analysis also identified a dose-response relationship between obesity and LBP. These findings are consistent with results from previous metaanalyses, in which a similar effect size was found for the association between obesity and prevalence of LBP in individuals from the general population [34,36] and a similar dose-response relationship [36]. Although these results tend to support the potential for a causal relationship between obesity and LBP, the criteria for the temporal relationship required to demonstrate causation has not been fulfilled in our review. We identified only one longitudinal study and that study did not identify any increased incidence of LBP in obese individuals. Similarly, no effect was found of obesity on LBP incidence in samples from the general population [37,38].

The obesity-LBP association is only apparent in cross-sectional studies, however, the inverse relationship, that is, LBP leading to obesity, should not be disregarded. Evidence from a nontwin study suggests that individuals with LBP, particularly chronic pain, tend to gain more weight than those with no symptoms of pain [39]. Therefore, to better understand the interaction between obesity and LBP, further investigation of the direction of the association should be conducted in longitudinal studies using a twin design.

Another interesting finding of our review was the small and nonsignificant association (OR 1.4; 95% CI 0.8–2.3; p=.26) between obesity and LBP observed in the MZ analysis when compared with the total sample analysis. This pattern of reduced association was consistent across all included studies that adjusted for genetic factors and with our own unpublished data from our research group in 156 MZ Spanish twins dissimilar for LBP status. Although we cannot rule out the possibility of this finding being a reflection of smaller samples and larger CIs, the imprecision of the data is unlikely to be the reason. The pooled MZ analysis...
included a large sample of 469 twin pairs (938 individuals). These twin pairs were matched for age, sex, and genetic factors, in addition to twins’ early shared environmental factors. By controlling for these confounders, the MZ analysis potentially provides a more precise estimate than the total sample analysis. In sum, the trend toward progressive reduction in the association across the phases (total sample: OR 1.8; DZ/MZ twins together: OR 1.5; MZ twins: OR 1.4) suggests that genetic factors and early environment shared by twins are possibly confounding the association between obesity and LBP.

**Obesity and LDD**

Positive associations between body weight and LDD were consistently present in the total sample analyses of all four cross-sectional studies included in our review [23,25,26,28]. However, there was no temporal effect of body weight on the progression of LDD; the risk of LDD was not increased in overweight or obese individuals in any of the three longitudinal studies [14,27,28]. Our results are partially in agreement with observational studies that used samples from the general population. Although one longitudinal study with a 20-year follow-up concluded that body weight did not increase the risk of LDD measured using plain X-ray (OR 1.1; 95% CI 0.3–3.6; p = .90) [40], another study with a four-year follow-up showed that overweight individuals (BMI > 25 kg/m²) at the age of 25 years had higher risks of developing LDD 4 years later (OR 4.3; 95% CI 1.3–14.3) [10].

In the present review, the effects of familial factors on the obesity-LDD relationship were only examined in two cross-sectional studies [24,28]. While one study found that the heavier MZ twin (at least 8 kg heavier than the co-twin) had a lower prevalence of LDD, the other study [28] found the body weight-LDD association to be present in the total sample and in DZ twins, but the association disappeared in MZ twins at a younger age. It is plausible to suggest that the effects of genetic factors on the obesity-LDD relationship are stronger earlier in life. Interestingly, the heritability of progression of LDD has been found to be mainly influenced by genetic factors at younger age [28].
Interpretation and implications for clinical practice and research

Currently there is uncertainty regarding the significance of obesity as a risk factor for LBP and LDD. Therefore, a recommendation to intervene to reduce obesity for the purpose of reducing LBP is not yet warranted in clinical guidelines. Inadequate control for familial factors is a possible explanation for conflicting results in this field. We found evidence that familial factors potentially influence the obesity-LBP association. The results of this review provide a different perspective on the relationship between obesity and LBP. The identification, in future research, of specific genes or early shared environmental factors (eg, diet, engagement in physical activity) that influence both obesity and LBP might reveal new mechanisms underlying this relationship and could, in turn, lead to effective preventative strategies. We advocate that future high-quality longitudinal research, preferably using a within-pair twin case-control design, is an ideal method to understand this relationship more precisely.

Strengths and limitations

One of the main strengths of this review is the inclusion of twin studies that facilitates insights into causal relationships between variables. The case-control analysis of twin studies allows the investigation of a more direct relationship between obesity and both LBP and LDD by controlling for possible genetic and early environmental confounding. This design also has the potential to provide more precise estimates of risks for a disease. The inclusion of a dose-response analysis was a unique feature in our review, which provides further insights into a possible causal relationship between obesity and LBP. Overall, the quality of included studies was high (mean: 83.3%) for LBP and LDD. We were also able to provide an efficient summary of results of twin studies by pooling the estimates of the relationship between obesity-related measures and LBP. Unfortunately, included studies were too heterogeneous for the measures of LDD and this precluded pooling of data. Also, the effect of familial factors was mostly available in cross-sectional studies that assessed LBP as the outcome.

Conclusion

Although obesity is commonly reported to be a risk factor for LBP, our results do not support a direct causal relationship between obesity and LBP. Genetic factors and early environment are possible factors influencing this relationship. Further longitudinal studies using the twin design are needed to better understand the complex mechanisms underlying the association between obesity and LBP and obesity and LDD.

References

Are obesity and body fat distribution associated with low back pain in women? A population-based study of 1128 Spanish twins

AUTHORSHIP STATEMENT

The co-authors of the paper “Are obesity and body fat distribution associated with low back pain in women? A population-based study of 1128 Spanish twins” confirm that Amabile Borges Dario has made the following contributions:

- Conception and design of the research
- Extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript and critical appraisal of content

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the above authorship attribution statement is correct.

Associate Professor Paulo Henrique Ferreira
The University of Sydney
December 2016
Are obesity and body fat distribution associated with low back pain in women? A population-based study of 1128 Spanish twins

Amabile B. Dario 1 · Manuela L. Ferreira 2 · Kathryn Refshauge 1 · Juan F. Sánchez-Romera 3,4 · Alejandro Luque-Suarez 5 · John L. Hopper 6 · Juan R. Ordoñana 3,4 · Paulo H. Ferreira 1

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Abstract

Purpose To investigate the relationship between different measures of obesity and chronic low back pain (LBP) using a within-pair twin case–control design that adjusts for genetics and early shared environment.

Methods A cross-sectional association between lifetime prevalence of chronic LBP and different measures of obesity (body mass index-BMI; percent body fat; waist circumference; waist–hip ratio) was investigated in 1128 female twins in three stages: (i) total sample analysis; (ii) within-pair case–control analysis for monozygotic (MZ) and dizygotic (DZ) twins together; (iii) within-pair case–control analysis separated by DZ and MZ. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated.

Results BMI (OR 1.12; 95 % CI 1.02–1.26) and percent body fat (OR 1.15; 95 % CI 1.01–1.32) were weakly associated with lifetime prevalence of chronic LBP in the total sample analysis but were absent when shared environment and genetic factors were adjusted for using the within-pair case–control analysis. Greater waist–hip ratios were associated with smaller prevalence estimates of chronic LBP in the within-pair case–control analysis with both MZ and DZ twins (OR 0.67; 95 % CI 0.47–0.94). However, this association did not remain after the full adjustment for genetic factors in the MZ within-pair case–control analysis.

Conclusions BMI, percent of fat mass and greater depotsitions of fat and mass around the hips are associated with increases in chronic LBP prevalence in women but these associations are small and appear to be confounded by the effects of genetics and early shared environment. Therefore, our results do not support a causal direct relationship between obesity and chronic LBP.

Keywords Obesity · Low back pain · Genetics · Twins

Introduction

Obesity is a pandemic and growing public health concern [1]. It is recognized as the main public health problem in industrialized countries [2] and is linked to morbidity and high mortality rates [1]. Obesity has also been found to be associated with various musculoskeletal disorders, including low back pain (LBP) [3].

LBP is common with the 1-month prevalence being estimated as 23.2 % (95 % CI 20.3–26.1). It is the highest contributor to the number of years that people live with disability in the world [4]. LBP is more common in women...
than in men [5] and little is understood about its etiology [6]. There is a consensus in the field that research efforts need to be allocated to the investigation of causes and risk factors for LBP, as this understanding is crucial for effective prevention [7]. From a public health perspective, it would be important to know if lifestyle factors, such as excessive body weight, are contributors to LBP incidence especially when considering that obesity is a potential modifiable risk factor.

Although it is generally assumed that obesity and LBP are associated, the actual path between these conditions remains controversial [6, 8]. For instance, whereas some studies have shown that obesity increases LBP prevalence [9, 10], others have failed to observe any association between the two [11, 12]. Moreover, in a study that used a twin sample [10], the positive association between body mass index (BMI) and LBP found in the total sample analysis disappeared in monozygotic twins dissimilar in body weight, suggesting that genetics possibly influence this relationship.

One of the limitations of the studies investigating the relationship between obesity and LBP is how obesity has been assessed. The frequent measure used to classify obesity in previous studies was BMI [2, 8, 13] which does not account for the distribution of fat in the body. Although there is evidence that body fat distribution rather than absolute total fat is associated with increases in the risk of diseases such as diabetes and coronary artery disease [14], most studies [2, 8, 13] have not investigated it. To our knowledge, only two studies have looked at the relationship between body fat distribution (where the excessive adipose tissue is stored) and LBP and found higher prevalence of LBP in women with a predominant central obesity, measured by waist circumference and waist–hip ratio [15, 16]. Although familial factors (genetics and early environment) were not investigated in these studies, the findings indicate that body fat distribution, in addition to total fat, should be considered when analyzing the obesity–LBP relationship.

In this current study, we aim to investigate the relationship between chronic LBP and different measures of obesity that account for body fat distribution in female twins. Previous evidence has indicated that women are more likely to report back pain [5, 17], seek medical care more frequently [18], and suffer from pain for longer periods [17] than men. It is likely that women represent a specific subgroup of patients with LBP and deserves special attention particularly when investigating factors such as body fat distribution. By performing a within-pair twin case–control analysis (where one twin has chronic LBP while the co-twin does not), we are able to control for possible genetic and early shared environmental effects on the obesity–LBP relationship.

### Methods

#### Design

Cross-sectional observational study with a within-pair twin case–control design.

#### Study sample and data collection

All twins included in this study were registered in the Murcia Twin Registry (MTR), a population-based twin registry of adult multiples born between 1940 and 1966 in the region of Murcia, Southeast Spain. Information regarding the MTR characteristics and recruitment procedures can be found elsewhere [19]. All registry and data collection procedures involved in this study were approved by the Murcia University Ethics Committee, and informed consent was obtained from all twins.

#### Assessment of chronic LBP

The main outcome of this study was lifetime prevalence of chronic LBP with participants being asked the following question: “Have you ever suffered from chronic low back pain?”, based on the corresponding item from the Spanish National Health Survey. The Survey defines ‘chronic’ as a health problem lasting for at least 6 months to screen and eliminate isolated acute processes. This includes seasonal or recurrent episodes. Participants answering “yes” to this question were categorized as having a history of chronic LBP.

#### Measures of obesity-related measures

Self-reported measures of weight and height were obtained for 38 % of the sample (430 participants). For the other 62 % of the sample (698 participants), standardized anthropometric measurements were obtained on participants by a blinded research assistant for weight, height, waist circumference and percent body fat. BMI was calculated by dividing the individuals’ body weight in kilograms by the square of their height in meters. Percentage of body fat was measured by bioelectrical impedance using TANITA BC-420 MA (Tanita Corporation of America, USA) equipment. A single new and calibrated device was used during the whole study. Subjects were instructed to fast and not practise physical exercise during the previous 4 h, refrain from drinking alcoholic beverages during the last 24 h, and urinate closely prior to the appointment. Waist circumference was measured at the narrowest torso circumference or, alternatively, at the midpoint between the inferior border of the ribcage and the superior aspect of
the iliac crest using an inelastic measuring tape. Hip circumference was measured at the widest point or, alternatively, over the buttocks". Waist–hip ratio (WHR) was calculated as the ratio between their respective components.

**Statistical analysis**

The analysis was conducted in three stages: (i) total sample analysis; (ii) within-pair case–control analysis for monozygotic (MZ) and dizygotic (DZ) twins together; (iii) within-pair case–control analysis separated by DZ (iii.a) and MZ (iii.b) (Fig. 1). BMI, percent body fat, waist circumference and waist-hip ratio were classified in four categories according to percentile distributions of the data (i.e., category one ≤25th lowest percentile; 25th percentile < category two ≤50th percentile; 50th < category three ≤75th percentile; category four > 75th percentile). The specific cut-off points used to define the quartiles for obesity-related measures are defined in Table 1.

Potential confounders for the total sample analysis included age, engagement in leisure physical activity, engagement in daily physical activity (work and domestic related) and smoking. The same confounders were investigated for the within-pair twin case–control analyses, except age. Leisure physical activity was dichotomised into low/no physical activity engagement in recreational physical activity (mainly sedentary) or moderate/vigorous physical activity engagement (regular physical activity or training several times a week/month, ex: jogging, swimming, cycling). Daily physical activity was dichotomised into low/no engagement in work-related physical activity (mainly sitting or light physical efforts) or moderate/vigorous physical activity engagement (doing tasks that require a strong physical effort). Smoking was dichotomized as ex/never smoker or current smoker. We included confounders in the multivariate logistic regression models if p values for associations in univariate models were <0.2.

**Total sample analysis**

For the total sample analysis, we investigated the association between obesity-related measures (BMI, percent body fat, waist circumference and waist-hip ratio) and lifetime prevalence of chronic LBP using separate multivariate unconditional regression models for each obesity measure. All participants were included and twins were analyzed as individuals rather than pairs.

**Within-pair twin case–control analyses**

To control for the effect of genetics and early shared environment on a possible association between obesity-related measures and the lifetime prevalence of chronic LBP, we performed a subsequent within-pair twin case–control analysis on all complete and discordant pairs for LBP status (one twin reported chronic LBP while the other did not) using conditional logistic regression. In addition, separated analyses were conducted for DZ and MZ twin pairs. Theoretically, when the magnitude of the association between two variables (i.e., BMI and LBP) increases sequentially from the total sample analysis (no adjustment for genetics or early shared environment) to a DZ within-pair case–control analysis (adjustment for early shared environment and approximately 50 % of genetics occurs) and then to a MZ within-pair case–control analysis (adjustment for early shared environment and approximately 100 % of genetics), the relationship between the two variables is more direct and possibly more consistent with a direct causal path [20].

We set p < 0.05 as our level of significance for the estimates of association in the multivariate models and presented estimates as odds ratios (OR) and 95 % confidence intervals (CI). OR represents the odds of having chronic LBP per quartile step. Data analyses were performed using STATA statistical software (version 12.0).

**Results**

**Sample characteristics**

Data on lifetime prevalence of chronic LBP for the total sample of 1128 females was estimated as 41.3 % (95 % CI 38.4–44.2) with the prevalence for MZ and DZ estimated as 43.1 % (95 % CI 38.3–47.9) and 40.3 % (95 % CI 36.7–43.9), respectively. Among all twins, the mean age was 54 years with 64 % of the twins being DZ (Table 2). Results for the obesity-related measures for twins with and without chronic LBP are described in Table 3.
### Table 1: Cut-off points used for the obesity-related measures

<table>
<thead>
<tr>
<th>Obesity related measures</th>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>3rd Quartile</th>
<th>4th Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>≤23.71</td>
<td>&gt;23.71 to ≤26.40</td>
<td>&gt;26.40 to ≤30.11</td>
<td>&gt;30.11</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>≤29.64</td>
<td>&gt;29.64 to ≤34.93</td>
<td>&gt;34.93 to ≤39.55</td>
<td>&gt;39.55</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>≤76</td>
<td>&gt;76 to ≤84</td>
<td>&gt;84 to ≤93</td>
<td>&gt;93</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>≤0.78</td>
<td>&gt;0.78 to ≤0.84</td>
<td>&gt;0.84 to ≤0.89</td>
<td>&gt;0.89</td>
</tr>
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</table>

### Table 2: Study sample characteristics of anthropometric data and lifestyle factors

<table>
<thead>
<tr>
<th>Variables</th>
<th>LBP absent</th>
<th>LBP present</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) or %</td>
<td>n</td>
<td>Mean (SD) or %</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.23 (7.38)</td>
<td>662</td>
<td>53.59 (7.38)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.57 (0.07)</td>
<td>662</td>
<td>1.57 (0.07)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.19 (11.24)</td>
<td>662</td>
<td>67.79 (12.39)</td>
</tr>
<tr>
<td>Smoking habits a</td>
<td>38.75 %</td>
<td>255</td>
<td>42.12 %</td>
</tr>
<tr>
<td>Daily physical activity b</td>
<td>15.58 %</td>
<td>103</td>
<td>11.83 %</td>
</tr>
<tr>
<td>Leisure physical activity b</td>
<td>53.34 %</td>
<td>351</td>
<td>43.44 %</td>
</tr>
<tr>
<td>DZ twins</td>
<td>59.69 %</td>
<td>428</td>
<td>43.07 %</td>
</tr>
<tr>
<td>MZ twins</td>
<td>56.93 %</td>
<td>234</td>
<td>43.07 %</td>
</tr>
</tbody>
</table>

LBP: low back pain, DZ: dizygotic, MZ: monozygotic, BMI: body mass index, SD: standard deviation, n: number of participants.
a Percentage who smoked
b Percentage engaged in physical activity

### Table 3: Study sample characteristics of obesity-related measures for the total sample and cases and controls within a twin pair

<table>
<thead>
<tr>
<th>Variables</th>
<th>LBP absent</th>
<th>LBP present</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) or %</td>
<td>n</td>
<td>Mean (SD) or %</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>26.81 (4.59)</td>
<td>662</td>
<td>27.68 (5.23)</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>27.42 (4.88)</td>
<td>155</td>
<td>27.68 (5.65)</td>
</tr>
<tr>
<td>DZ pairs</td>
<td>27.75 (4.83)</td>
<td>77</td>
<td>28.48 (5.42)</td>
</tr>
<tr>
<td>MZ pairs</td>
<td>27.09 (4.95)</td>
<td>78</td>
<td>26.90 (5.80)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>34.14 (7.03)</td>
<td>374</td>
<td>34.93 (7.60)</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>34.85 (7.40)</td>
<td>128</td>
<td>35.71 (7.18)</td>
</tr>
<tr>
<td>DZ pairs</td>
<td>35.14 (7.14)</td>
<td>65</td>
<td>36.77 (7.06)</td>
</tr>
<tr>
<td>MZ pairs</td>
<td>34.55 (7.71)</td>
<td>63</td>
<td>34.62 (7.20)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>84.64 (11.94)</td>
<td>378</td>
<td>85.40 (12.50)</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>85.79 (11.25)</td>
<td>132</td>
<td>86.42 (12.59)</td>
</tr>
<tr>
<td>DZ pairs</td>
<td>86.92 (10.85)</td>
<td>67</td>
<td>88.98 (12.46)</td>
</tr>
<tr>
<td>MZ pairs</td>
<td>84.63 (12.15)</td>
<td>65</td>
<td>83.77 (12.27)</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>0.85 (0.08)</td>
<td>371</td>
<td>0.85 (0.08)</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>0.85 (0.07)</td>
<td>132</td>
<td>0.85 (0.08)</td>
</tr>
<tr>
<td>DZ pairs</td>
<td>0.86 (0.08)</td>
<td>67</td>
<td>0.87 (0.08)</td>
</tr>
<tr>
<td>MZ pairs</td>
<td>0.85 (0.07)</td>
<td>65</td>
<td>0.84 (0.07)</td>
</tr>
</tbody>
</table>

LBP: low back pain, SD: standard deviation, n: number of participants, MZ: monozygotic, DZ: dizygotic.
BMI

BMI (OR 1.13; 95 % CI 1.02–1.26) was weakly associated with lifetime prevalence of chronic LBP in the total sample analysis but no association was found between BMI and chronic LBP in any of the within-pair twin case–control analyses (Table 4).

Percent body fat

Percent body fat (OR 1.15; 95 % CI 1.01–1.32; p = 0.05) was weakly associated with lifetime prevalence of chronic LBP but no association was identified in any of the within-pair case–control analyses.

Waist circumference

No association was found between waist circumference and lifetime prevalence of chronic LBP for the total sample or the within-pair case–control analyses.

Table 4 Total sample analysis and within-pair twin case–control analysis for chronic low back pain

<table>
<thead>
<tr>
<th>Multivariate models</th>
<th>OR (95 % CI)</th>
<th>p value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>1.13 (1.02–1.26)</td>
<td>0.026*</td>
<td>1123</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>1.12 (0.83–1.51)</td>
<td>0.449</td>
<td>310</td>
</tr>
<tr>
<td>DZ pairs</td>
<td>1.04 (0.69–1.58)</td>
<td>0.842</td>
<td>154</td>
</tr>
<tr>
<td>MZ pairs</td>
<td>1.19 (0.78–1.83)</td>
<td>0.444</td>
<td>156</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>1.15 (1.01–1.32)</td>
<td>0.047*</td>
<td>682</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>1.27 (0.93–1.75)</td>
<td>0.138</td>
<td>256</td>
</tr>
<tr>
<td>DZ pairs</td>
<td>1.41 (0.88–2.26)</td>
<td>0.149</td>
<td>130</td>
</tr>
<tr>
<td>MZ pairs</td>
<td>1.23 (0.78–1.94)</td>
<td>0.369</td>
<td>126</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>1.06 (0.93–1.22)</td>
<td>0.378</td>
<td>689</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>0.84 (0.62–1.15)</td>
<td>0.277</td>
<td>264</td>
</tr>
<tr>
<td>DZ pairs</td>
<td>0.83 (0.54–1.26)</td>
<td>0.374</td>
<td>134</td>
</tr>
<tr>
<td>MZ pairs</td>
<td>0.89 (0.56–1.42)</td>
<td>0.638</td>
<td>130</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>1.02 (0.89–1.17)</td>
<td>0.779</td>
<td>677</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>0.67 (0.47–0.94)</td>
<td>0.022*</td>
<td>264</td>
</tr>
<tr>
<td>DZ pairs</td>
<td>0.59 (0.35–0.98)</td>
<td>0.040*</td>
<td>134</td>
</tr>
<tr>
<td>MZ pairs</td>
<td>0.77 (0.48–1.25)</td>
<td>0.289</td>
<td>130</td>
</tr>
</tbody>
</table>

OR odds ratio, CI confidence interval, MZ monozygotic, DZ dizygotic, n number of participants in each analytical step

* Statistically significant p < 0.05

Waist-hip ratio

No association was found between waist–hip ratio and lifetime prevalence of chronic LBP for the total sample analysis. Waist–hip ratio was associated with chronic LBP in the within-pair case–control analysis with MZ and DZ twins included (OR 0.67; 95 % CI 0.47–0.94). When the analyses were performed separately for zygosity, a stronger association was found for DZ twins (OR 0.59; 95 % CI 0.35–0.98) and the association disappeared when the analysis was conducted for MZ twins (OR 0.77; 95 % CI 0.48–1.25).

Discussion

To our knowledge, this is the first study investigating the obesity–LBP relationship in females that considered not only traditional measures of obesity such as BMI but also measures of body fat distribution and explored the effects of genetics and early shared environment. We found that lifetime prevalence of chronic LBP was weakly associated with measures of obesity. However, the association was no longer present after the full adjustment for genetics and early shared environmental factors in MZ twins dissimilar for LBP status. These results suggest that a causal direct link between obesity and chronic LBP is unlikely.

BMI and percent body fat

Our results demonstrated that lifetime prevalence of chronic LBP was associated with BMI and percent body fat when the total sample of twins (with no adjustment for genetics or early shared environment among twins) was used. The association was small (OR 1.1 and OR 1.2 for BMI and percent body fat, respectively), in agreement with previous cross-sectional studies [21–23].

Obesity and LBP are complex traits resulting from multiple interactions between genetic and environmental factors. For example, 35–60 % of the body fat [24], and 67 % of LBP [25] variances can be accounted for the transmission of genetic and familial environmental factors. Consequently, the true extent of the effect of obesity on LBP is difficult to estimate, and for a clear and more direct identification of obesity–LBP relationship other factors, including familial factors, should be considered.

We found that after the adjustment for familial factors, using the within-pair twin case–control design, the significant association between chronic LBP and both BMI and percent body fat did not persist. This pattern of attenuated associations after controlling for familial factors is in agreement with the previous twin studies that investigated the obesity and LBP relationship using a within-pair twin.
case–control design [10, 21]. It suggests that genetics and common shared environment facts play an important role when measures such as BMI and percent body fat are investigated as part of the obesity–LBP relationship.

Waist circumference and waist–hip ratio

Our results did not reveal any association between waist circumference and lifetime prevalence of chronic LBP for the total sample analysis or for any of the within-pair case–control analyses. In addition, no association was found between waist–hip ratio and lifetime prevalence of chronic LBP for the total sample analysis. However, the within-pair twin case–control analysis, with both MZ and DZ twins included, showed a significant inverse relationship between waist–hip ratio and chronic LBP (OR 0.7; 95 % CI 0.5–0.9), meaning that women with greater waist–hip ratios had lower estimates of prevalence of chronic LBP.

When we sequentially separated the analysis for DZ and then MZ twins pairs, even though the pattern of association remained the same (inverse relationship between waist–hip ratio and chronic LBP), the association was significant only in DZ twins (OR 0.6; 95 % CI 0.4–1.0), disappearing after the full adjustment for genetic factors in the MZ twins (OR 0.8; 95 % CI 0.5–1.3). The pattern of a significant relationship being observed in the within-pair twin case–control analysis and in the within-pair twin DZ only case–control analysis but not in the total sample analysis indicates that when genetics and early shared environment among twins are considered, a relationship between waist–hip ratio and chronic LBP is stronger and possibly more direct. This association is attenuated and was not statistically significant when only MZ twins are analyzed (OR 0.8; early shared environment and genetic component are fully controlled for) as opposed to DZ twins only (OR 0.6; early shared environment fully controlled for but genetic component only partially controlled for). Although there is not a clear explanation for this effect, this finding could point to the possibility that when a full adjustment for genetics and early environment is implemented, the significant relationship initially observed in DZ twins disappears. Thus, genetics could be responsible for the possible relationship between waist–hip ratio and chronic LBP.

The direction of the relationship between waist–hip ratio and chronic LBP were somewhat unexpected. Our findings suggest that chronic LBP prevalence is smaller in women with a higher waist–hip ratio. Thus, those individuals with greater hip circumferences (accumulation of fat and corresponding weight around the hip bones) were more likely to have chronic LBP. Our results are in agreement with a population-based cross-sectional study in middle-aged women, which showed that even after the adjustment of many possible confounder factors such as work-related and physical activity, high waist-to-hip ratio was still inversely associated with the risk of severe LBP [26]. However, this study did not control for genetics factors and early shared environment. These findings are in contrast to other earlier studies that used samples of women from the general population where greater levels of central obesity were associated with LBP [15, 16]. From a biomechanical perspective, it is plausible that greater fat mass around the waist area loads the spine through gravity. However, it is also mechanically plausible that greater hip to waist mass could potentially unbalance the forces around the spine, leading to lumbar–pelvic instability and LBP [27]. It is important to note that the assessment of waist–hip ratio not only incorporates the distribution of fat but also is a reflection of bony anatomical features such as the shape of the pelvis. However, it is possible that the results found in the intermediate analytical steps are a result of genetics confounding the association between waist–hip ratio and chronic LBP. It is important to note that this finding was only present in the intermediate analytical steps (MZ/DZ analysis and DZ analysis) where DZ pairs are included, and consequently 50 % of genetics are not controlled for.

Limitations

We acknowledge several limitations in our study design. Firstly this was a cross-sectional analysis, which limits possible insights on a causation path between the variables of interest. Secondly, the measure of chronic LBP used in this study was somewhat simple and did not include additional assessments of the severity, frequency, as well as disability levels associated with LBP. This assessment of LBP might have influenced the results as patients’ understanding of what constitutes chronic LBP and degrees or patterns of chronicity may vary. Thirdly, the accuracy of BMI data could have been affected by the combination of self-reported with a direct measure of weight and height used to calculate BMI given that self-reported assessment methods seem to underestimate weight and overestimate height values [28]. In our sample, the difference between the subgroups for BMI data, measured (27.53 kg/m²) and self-reported (26.58 kg/m²), was 0.96 kg/m². We have tested the association between LBP and both subgroups for BMI for all analytical steps, and the difference in OR found were very small (≠OR < 0.2) and clinically not significant. Therefore, we believe that the combination of self-reported with a direct measure of weight and height have little or no effect in our results.

Also, in spite of being a practical and widely used assessment method, uncertainty has been raised regarding the validity and reliability of bioelectrical impedance measurements for estimation of body fat [29]. However, we should take into account the homogeneous character of our
sample and the measurement conditions, and the fact that the objective of this study is not to determine the exact value of body fat percentage but analyzing its possible association with LBP. Consequently, we believe that the method of body fat measurement does not have a relevant effect on our results and conclusions. Lastly, we recognize that the smaller sample size in the case–control analyses reduced the power required to identify a relationship between obesity-related measures and chronic LBP, if in fact, the relationship exists. Therefore, we cannot exclude that a much larger twin sample would show a significant result. Although smaller samples and larger confidence intervals observed in the case–control analyses could add uncertainty to the results of our study, the imprecision of the data is unlikely to be the explanation for this finding. Firstly, the average values between LBP and non LBP groups are very small for all variables in all analysis steps. Furthermore, the magnitude of the ORs for the significant predictors in the total sample (BMI and percent body fat) is still similar to the all within-pair twin case–control analyses, which points to the fact that the association between obesity-related measures and chronic LBP in fact was weak and non-reliable when twins were considered as individuals. Secondly, according to a systematic review recently published, the reduced association between LBP and obesity seems to be consistent across studies when genetics and the environment factors are considered [30]. Pooled results of two MZ case–control studies with greater sample sizes than ours, 442 [10] and 413 [21] pairs, has shown no association between obesity and LBP (OR 1.4; 95 % CI 0.8–2.3) [30]. Notwithstanding, this study represents a step forward in the investigation of the relationship between obesity and chronic LBP relationship because we used a comprehensive assessment of obesity that accounts for body fat distribution and employed a within-pair case–control design to allow for more direct and precise estimates of obesity–LBP relationship.

In summary, BMI, percent of fat mass and greater depositions of fat and mass around the hips are associated with increases in chronic LBP prevalence in women. However, these associations are small and disappear with the full adjustment for genetics and early shared environment effects. Therefore, our results do not support a causal direct relationship between obesity and chronic LBP. We advocate that the results observed in this study should be tested in the future in a longitudinal twin research design.

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Conflict of interest None.

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Obesity does not increase the risk of chronic low back pain when genetics is considered. A prospective study of Spanish adult twins.

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AUTHORSHIP STATEMENT

The co-authors of the paper “Obesity does not increase the risk of chronic low back pain when genetics is considered. A prospective study of Spanish adult twins” confirm that Amabile Borges Dario has made the following contributions:

- Conception and design of the research
- Extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript and critical appraisal of content

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the above authorship attribution statement is correct.

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Associate Professor Paulo Henrique Ferreira
The University of Sydney
December 2016
Basic Science

Obesity does not increase the risk of chronic low back pain when genetics is considered. A prospective study of Spanish adult twins

Amable Borges Dario, MSc\textsuperscript{a,*}, Manuela Loureiro Ferreira\textsuperscript{bc}, Kathryn Refshauge\textsuperscript{a}, Alejandro Luque-Suárez\textsuperscript{a}, Juan Ramon Ordoñana\textsuperscript{c}, Paulo Henrique Ferreira\textsuperscript{a}

\textsuperscript{a}Discipline of Physiotherapy, Faculty of Health Sciences, University of Sydney, PO Box 170, Lidcombe, Sydney 1825, Australia
\textsuperscript{b}The George Institute for Global Health, Sydney Medical School, University of Sydney, PO Box 170, Lidcombe, Sydney 1825, Australia
\textsuperscript{c}Institute of Bone and Joint Research, The Kolling Institute, Sydney Medical School, University of Sydney, PO Box 170, Lidcombe, Sydney 1825, Australia
\textsuperscript{d}Discipline of Physiotherapy, University of Málaga, Spain

*Murcia Twin Registry, Department of Human Anatomy and Psychobiology, University of Murcia, Spain

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Abstract

\textbf{BACKGROUND CONTEXT:} Obesity is commonly investigated as a potential risk factor for low back pain (LBP); however, current evidence remains unclear. Limitations in previous studies may explain the inconsistent results in the field, such as the use of a cross sectional design, limitations in the measures used to assess obesity (e.g., body mass index—BMI), and poor adjustment for confounders (e.g., genetics and physical activity).

\textbf{PURPOSE AND DESIGN:} To better understand the effects of obesity on LBP, our aim was to investigate in a prospective cohort whether obesity-related measures increase the risk of chronic LBP outcomes using a longitudinal design. We assessed obesity through measures that consider the magnitude as well as the distribution of body fat mass. A within-pair twin case-control analysis was used to control for the possible effects of genetic and early shared environmental factors on the obesity-LBP relationship.

\textbf{PATIENT SAMPLE AND OUTCOME MEASURES:} Data were obtained from the Murcia Twin Registry in Spain. Participants were 1,098 twins, aged 43 to 71 years, who did not report chronic LBP at baseline. Follow-up data on chronic LBP (>6 months), activity-limiting LBP, and care-seeking for LBP were collected after 2 to 4 years.

\textbf{RISK FACTORS:} The risk factors were BMI, percentage of fat mass, waist circumference, and waist-to-hip ratio.

\textbf{METHODS:} Sequential analyses were performed using logistic regression controlling for familial confounding: (1) total sample analysis (twins analyzed as independent individuals); (2) within-pair twin case-control analyses (all complete twin pairs discordant for LBP at follow-up); and within-pair twin case-control analyses separated for (3) dizygotic and (4) monozygotic twins.

\textbf{RESULTS:} No increase in the risk of chronic LBP was found for any of the obesity-related measures: BMI (men/women, odds ratio [OR]: 0.99; 95% confidence interval [CI]: 0.86–1.14), % fat mass (women, OR: 0.87; 95% CI: 0.66–1.14), waist circumference (women, OR: 0.98; 95% CI: 0.74–1.30), and waist-to-hip ratio (women, OR: 1.05; 95% CI: 0.81–1.36). Similar results were found for activity-limiting LBP and care-seeking due to LBP. After the adjustment for genetics and early environmental factors shared by twins, the non-significant results remained unchanged.

\textbf{CONCLUSION:} Obesity is not a risk factor for chronic LBP.

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\textbf{Conflicts of interest:} All authors declare that they have no competing interests.

\textbf{Author contributions:} All authors contributed to the study design and data collection. All authors contributed to the data analysis. The manuscript was written by all authors.

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CONCLUSIONS: After 2 to 4 years, obesity-related measures did not increase the risk of developing chronic LBP or care-seeking for LBP with or without adjustment for familial factors such as genetics in Spanish adults. © 2016 Elsevier Inc. All rights reserved.

Keywords: Anthropometric measures; Body mass index; Case-control; Genetics; Low back pain; Obesity; Twin

Introduction

Low back pain (LBP) is the most frequent musculoskeletal condition experienced worldwide [1] and is ranked the leading cause of disability in 2013 [2]. The global lifetime prevalence of LBP has been estimated to be 35.3% in women and 29.4% in men [1]. Despite abundant research on the risk factors for LBP, the etiology is still poorly understood [3], and the lack of consistent and strong risk factors for LBP limits the design of effective preventive strategies [4].

Numerous risk factors have been investigated in LBP, including lifestyle [3,5] behavioral [6], and genetic [3,7] factors. Obesity is commonly investigated as one of the factors that could potentially increase the risk of LBP [8,9]. Excessive mechanical loading of the spine [10], spine degeneration [7], and systemic chronic inflammation [11] are proposed mechanisms that could explain why obese individuals could be at higher risk of developing LBP. Nevertheless, the biological plausibility of these mechanisms, as well as the current evidence of the link between obesity and LBP, remains inconclusive [12].

One limitation in previous studies that assessed obesity as a risk factor for LBP is the use of a cross-sectional study design [12,13]. Another limitation is that nearly all previous studies assessed obesity through body mass index (BMI). Body mass index is regarded as a surrogate measure of body fatness [14] and does not account for the distribution of fat in the body. There is preliminary evidence that body fat distribution, rather than absolute total fat, is associated with LBP [15–17]. It is likely that the use of BMI as a sole measure of obesity is not sufficient [15], and other anthropometric measures that consider not only the amount but also the distribution of body fat should be used to reach valid conclusions on the effects of obesity on LBP. As a consequence, the establishment of a causal path between obesity and LBP is likely to be premature.

Inadequate control for familial factors in previous studies has also contributed to the conflicting evidence in the field. It is known that the obesity-LBP relationship is influenced by familial factors [18]. A recent meta-analysis conducted by our group has shown that genetic factors confound the relationship between obesity and LBP, with these conditions being associated only when the effects of genetics and early shared environment are not controlled for [18]. The majority of the studies included in our review employed a cross-sectional design. The results suggest that a direct relationship between obesity (mainly assessed through BMI) and LBP is questionable, and these conditions may be, in fact, linked by mutually shared genetic factors.

To better understand the effects of obesity on LBP, we aimed to investigate whether obesity, assessed through measures that consider the magnitude as well as the distribution of body fat, increases the risk of chronic LBP using a longitudinal design. As previous evidence suggests that obesity may have a stronger link with more severe types of LBP [13,17], we have investigated whether obesity-related measures increase the risk of chronic LBP associated with disability and care-seeking. We also aimed to conduct a within-pair twin case-control analysis to control for the possible effects of genetic and early shared environmental factors on the obesity-LBP relationship.

Materials and Methods

Design

This is a prospective cohort study with a within-pair twin case-control design.

Study sample and data collection

The study sample included twins registered in the Murcia Twin Registry (MTR). This population-based twin registry comprises adults born between 1940 and 1966 in the region of Murcia, Southeast Spain. Further description on the MTR, recruitment procedures, and data collection is provided elsewhere [19]. Due to logistic constraints, baseline data used in this study were collected sequentially for woman-woman, man-man, and opposite sex twin pairs in 2009, 2010, and 2011, respectively. Data were collected face to face or via telephone interviews by a blinded research assistant. Twins were included in this study if they did not report chronic LBP at baseline when asked the following question: “Have you ever suffered from chronic LBP?” Chronic LBP was defined and explained to the participants as the presence of pain in the lower back area that lasted for 6 months or longer, including seasonal or recurrent episodes. Follow-up was conducted by phone interview for all the participants in 2013. The research ethics committee of Murcia University approved the MTR protocols, and the participants provided written informed consent when interviewed in person or oral consent when a telephone interview was used.

LBP outcomes

Information related to LBP outcomes was collected using adapted questions from consensual definitions of the prevalence of LBP in population-based studies [20].
Chronic LBP

Information on chronic LBP at follow-up was obtained by asking twins the same question used in the baseline assessment: “Have you ever suffered from chronic LBP?” Participants answering “yes” to this question were categorized as having chronic LBP.

Activity-limiting LBP and care-seeking for LBP

Participants who answered positively to the chronic LBP question were asked two additional questions to gather information on disability and care-seeking associated with chronic LBP. Activity-limiting LBP was investigated with the following question: “Was this pain bad enough to limit your usual activities or change your daily routine for more than one day?”, whereas for care-seeking associated with chronic LBP participants were asked: “Did you seek medical help because of this pain?”

Obesity-related measures

Self-reported measures of weight and height were obtained from all male participants and 39% of the female participants. For the remaining female participants, standardized anthropometric measurements were collected for weight, height, percent body fat (% body fat), and waist and hip circumference. BMI was calculated by dividing the individuals' body weight in kilograms by the square of their height in meters. % Body fat was measured by bioelectrical impedance using the Tanita BC-420 MA equipment (Tanita Corporation of America, Arlington Heights, IL, USA). This method estimates body composition, including % body fat, by measuring the bioelectrical resistive impedance based on the principle that lean mass electrical conductivity is far greater than fat mass [21]. Waist circumference was measured at the narrowest torso circumference or, alternatively, at the midpoint between the inferior border of the rib cage and the superior aspect of the iliac crest, using an inelastic measuring tape. Hip circumference was measured at the widest point or, alternatively, over the buttocks. Waist-to-hip ratio (WHR) was calculated as the ratio of the waist to hip components.

Statistical analysis

We investigated the association between obesity-related measures and LBP outcomes using separate multivariate logistic regression and assuming a linear effect in our model. All obesity measures were classified into four categories (quartiles) according to percentile distributions of the data (ie, category 1 ≤ 25th lowest percentile). To verify the effect of confounding factors such as genetics and early environment shared by twins on these associations, we performed the analyses in four stages. The first stage, total sample analysis, included the whole sample regardless of the concordance of twins for LBP status, with twins being analyzed as individuals rather than pairs. To control for similarities shared by twins, intra-cluster correlation was used (cluster command in Stata). For the subsequent analysis, only complete and discordant twin pairs for each LBP outcome (eg, one twin reported activity-limiting LBP, whereas the co-twin did not) were included as follows: within-pair case-control analysis included monozygotic (MZ) and dizygotic (DZ) twins (second stage); and within-pair case-control analysis separated by DZ twins only (third stage) and MZ twins only (fourth stage). The Figure describes each analytical stage and the confounding variables considered, including the measurement methods [22–24]. Theoretically, the levels of adjustment for confounding factors increase in the analytical stages. Further information about this method can be found elsewhere [25,26]. Only a proportion of the female participants (61%) were included in the analysis for % body fat, waist circumference, and WHR due to data availability. We set p<.05 as our level of significance for the estimates of association in the multivariate models and present estimates as odds ratios (OR) and 95% confidence intervals (CI). Data analyses were performed using Stata statistical software (version 12.0).

Results

Sample characteristics

Of the 1,454 twins who did not report chronic LBP symptoms at baseline, the MTR could only contact 1,098 twins (76%) at follow-up due to budget constraints. All twins contacted at follow-up answered the questions on LBP (100%). No differences were found for age, gender, weight, height, and obesity-related measures between those twins who were contacted (and therefore were entered in the analysis) and those who were not contacted by the MTR in the 2013 follow-up (p>0.05) (Table 1). Twins included in the analyses aged between 43 and 71 years, with the average estimated at 53.7 (standard

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline a</th>
<th>Twins not contacted at follow-up</th>
<th>Follow-up b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>1,454 53.7 (7)</td>
<td>356 53.9 (8)</td>
<td>1,098 53.7 (7)</td>
</tr>
<tr>
<td>Male</td>
<td>759 52.2</td>
<td>182 51.1</td>
<td>577 52.6</td>
</tr>
<tr>
<td>Female</td>
<td>695 47.8</td>
<td>174 48.9</td>
<td>521 47.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>1,443 73.3 (13)</td>
<td>351 74.2 (14)</td>
<td>1,098 73.6 (13)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1,416 27.3 (4)</td>
<td>339 27.2 (4)</td>
<td>1,077 27.3 (4)</td>
</tr>
<tr>
<td>% Fat mass</td>
<td>375 34.1 (7)</td>
<td>61 34.1 (8)</td>
<td>314 34.1 (7)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>378 84.6 (12)</td>
<td>61 85.9 (13)</td>
<td>317 84.4 (11)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>378 0.85 (0.8)</td>
<td>61 0.85 (0.9)</td>
<td>317 0.85 (0.8)</td>
</tr>
<tr>
<td>Monozygotic twins</td>
<td>467 31.7</td>
<td>96 27.0</td>
<td>371 33.8</td>
</tr>
<tr>
<td>Dizygotic twins</td>
<td>987 68.3</td>
<td>260 73.0</td>
<td>727 66.3</td>
</tr>
</tbody>
</table>

a, mean; BMI, body mass index; LBP, low back pain; SD, standard deviation.

b Twins free of chronic LBP at baseline.

c Twins free of chronic LBP at baseline who answered the questions on LBP at follow-up.

d Female participants only.
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<table>
<thead>
<tr>
<th>Statistical design</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Stage. Total Sample Analysis</td>
</tr>
<tr>
<td>- All participants.</td>
</tr>
<tr>
<td>- Genetics and early shared environment factors are not accounted for. Results can be considered similar to those from a general non-twin population;</td>
</tr>
<tr>
<td>- Unconditional multivariate logistic regression models used for each obesity measure and LBP outcome;</td>
</tr>
<tr>
<td>- Intra-cluster correlation used to control for similarities shared by twins.</td>
</tr>
</tbody>
</table>

To investigate the influence of genetics and early environment shared by twins |

2nd Stage. Within-pair twin case-control analysis |
| - Monozygotic and Dizygotic complete and discordant twin pairs for LBP outcome (i.e. one twin reported LBP while the other did not); |
| - Genetic and early shared environmental factors are accounted for; |
| - Conditional multivariate logistic regression used for each obesity measure and LBP outcome. |

Analysis separated by zygosity for further insights about the effect of genetics and early shared environment by twins |

3rd Stage. Dizygotic within-pair twin case-control analysis |
| - Complete and discordant dizygotic twin pairs for LBP outcome; |
| - Adjustment for 50% of genetics and early environmental factors shared by dizygotic twins; |
| - Conditional multivariate logistic regression used for each obesity measure and LBP outcome. |

4th Stage. Monozygotic within-pair twin case-control analysis |
| - Complete and discordant monozygotic twin pairs for LBP outcome; |
| - Adjustment for approximately 100% of genetics and early environmental factors shared by monozygotic twins; |
| - Conditional multivariate logistic regression used for each obesity measure and LBP outcome. |

To investigate the influence of other possible confounding factors |
| - Potential confounders: age, sex, engagement in physical activity (work-related and leisure), smoking, depression and sleep quality. |
| - Age and sex was included in the total sample models to be comparable with the within-pair twin case-control analyses; |
| - Other confounders included if the p-values for the associations between the potential confounders and both outcome and exposure were <0.2. Same confounders were used for all stages. |
| - Differences in follow-up length were adjusted in the models when appropriate. |

Work-related physical activity: Dichotomised into low/no engagement in work related physical activity (mainly sitting or light physical efforts) or moderate/vigorous physical activity engagement (doing tasks that require a strong physical effort). |

Leisure physical activity: Dichotomised into no physical activity engagement in recreational physical activity (sedentary) or low/moderate/vigorous physical activity engagement (regular physical activity). |

Smoking habits: Dichotomised as ex/never smoker or occasional/current smoker. |

Depression/Anxiety: Dichotomised into not depressed or anxious (question 1) and moderately/very depressed/anxious (question 2 and 3) based on the scores of the depression/anxiety domain of the EuroQol-5 dimension [22]. |

Sleep quality: Dichotomised into poor sleep quality (>5) or good sleep quality (<5) based on the scores of the Spanish version of the Pittsburgh Sleep Quality Index [23, 24]. |

Figure. Statistical scheme describing the four stages used to adjust for possible confounding factors on the obesity-LBP relationship, including genetics and early environment factors shared by twins. LBP, low back pain.

deviation [SD]: 7.3 years. Male participants accounted for 52.6% of the sample, and 68% of the sample was overweight or obese. The cutoff points used for the obesity-related measures are presented in Table 2. The incidences of chronic LBP, activity-limiting LBP, and care-seeking due to chronic LBP at follow-up were 22.3% (95% CI: 19.9–24.8), 15.6% (95% CI: 13.5–17.8), and 18.7% (95% CI: 16.4–21.0), respectively. In the case-control analysis, the largest
Table 2
Cutoff points used for the obesity-related measures

<table>
<thead>
<tr>
<th>Obesity-related measures</th>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>3rd Quartile</th>
<th>4th Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>&lt;24.33</td>
<td>&gt;24.33 to &lt;26.67</td>
<td>&gt;26.67 to &lt;29.87</td>
<td>&gt;29.87</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>&lt;29.12</td>
<td>&gt;29.12 to &lt;34.44</td>
<td>&gt;34.44 to &lt;39.09</td>
<td>&gt;39.09</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>&lt;75.5</td>
<td>&gt;75.5 to &lt;84</td>
<td>&gt;84 to &lt;93</td>
<td>&gt;93</td>
</tr>
<tr>
<td>Waist-to-hip ratio (%)</td>
<td>&lt;0.79</td>
<td>&gt;0.79 to &lt;0.84</td>
<td>&gt;0.84 to &lt;0.90</td>
<td>&gt;0.90</td>
</tr>
</tbody>
</table>

* Female participants only.

available dataset of complete and discordant twin pairs was for the outcome of chronic LBP (111 pairs). Among those, 81 twin pairs were DZ and 30 twin pairs were MZ.

BMI

The results from the total sample analysis showed that BMI did not increase the risk of chronic LBP (OR: 0.99; 95% CI: 0.86–1.14) (Table 3). Similar non-significant results were found for the other LBP outcomes (activity-limiting LBP and care-seeking for LBP). When the analyses were performed separately for male and female twins, the results did not differ (data not shown).

The results were similar when the analyses were adjusted for genetic and shared environmental factors using complete twin pairs discordant for chronic LBP (OR: 0.89, 95% CI: 0.65–1.20 [111 DZ and MZ pairs]; OR: 0.91, 95% CI: 0.56–1.26 [81 DZ pairs]; OR: 0.75, 95% CI: 0.31–1.79 [30 MZ pairs]). Similar non-significant results were found when the relationship between BMI and the other LBP outcomes (activity-limiting LBP and care-seeking for LBP) was investigated using the within-pair twin case-control analysis.

% Body fat, waist circumference, and waist-to-hip ratio

In the total sample analysis, the % body fat did not increase the risk of chronic LBP in women (OR: 0.87; 95% CI: 0.66–1.14), with similar results observed for the variables of waist circumference (OR: 0.98; 95% CI: 0.74–1.30) and WHR (OR: 1.05; 95% CI: 0.81–1.36). When the other LBP outcomes (activity-limiting LBP and care-seeking for LBP) were investigated, similar and non-significant results were found for all these obesity-related measures (Table 3).

After adjusting for genetic and shared environmental factors using 23 complete twin pairs discordant for chronic LBP (13 DZ and 10 MZ pairs), the % body fat (OR: 1.00; 95% CI: 0.35–2.85), waist circumference (OR: 0.48; 95% CI: 0.16–1.50), and WHR (OR: 0.47; 95% CI: 0.18–1.21) did not increase the risk of chronic LBP. When the other LBP outcomes (activity-limiting LBP and care-seeking for LBP) were investigated using the within-pair twin case-control analysis, similar non-significant results were found. Because of the small sample sizes of MZ and DZ twin pairs discordant for chronic LBP, we could not stratify the analyses by zygosity.

Discussion

Summary of our findings

This is the first longitudinal study investigating the relationship between obesity-related measures and chronic LBP outcomes accounting for a large number of possible confounding factors, including genetics. We used a comprehensive

Table 3
Total sample analyses and within-pair twin case-control analyses according to low back pain outcomes

<table>
<thead>
<tr>
<th>Multivariable models</th>
<th>Chronic LBP</th>
<th>Activity-limiting LBP</th>
<th>Care-seeking due to LBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>0.99 (0.86–1.14)</td>
<td>1.077</td>
<td>0.93 (0.78–1.10)</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>0.89 (0.65–1.20)</td>
<td>222</td>
<td>0.89 (0.60–1.31)</td>
</tr>
<tr>
<td>DZ pairs</td>
<td>0.91 (0.56–1.26)</td>
<td>162</td>
<td>0.92 (0.60–1.41)</td>
</tr>
<tr>
<td>MZ pairs</td>
<td>0.75 (0.31–1.79)</td>
<td>60</td>
<td>0.69 (0.26–1.87)</td>
</tr>
<tr>
<td>Percentage of fat mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>0.87 (0.66–1.14)</td>
<td>314</td>
<td>0.85 (0.62–1.53)</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>1.00 (0.35–2.85)</td>
<td>46</td>
<td>0.80 (0.21–3.0)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>0.98 (0.74–1.30)</td>
<td>317</td>
<td>0.97 (0.72–1.31)</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>0.48 (0.16–1.50)</td>
<td>46</td>
<td>0.48 (0.10–2.16)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>1.05 (0.81–1.36)</td>
<td>316</td>
<td>1.08 (0.81–1.44)</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>0.47 (0.18–1.21)</td>
<td>46</td>
<td>0.48 (0.15–1.56)</td>
</tr>
</tbody>
</table>

LBP, low back pain; OR, odds ratio; CI, confidence interval; MZ, monozygotic; DZ, dizygotic; n, number of participants in each analysis stage.

* Adjusted for depression/anxiety levels.

# Adjusted for daily physical activity.

! Adjusted for sleep quality.

* Female participants only.

& Adjusted for age and sex.
assessment of general (BMI and % fat mass) and central (waist circumference and WHR) obesity to explore the extent to which the quantity and distribution of body fat affect the risk of chronic LBP and related outcomes. Our findings demonstrate that none of the obesity measures investigated increased the risk of developing chronic LBP, activity-limiting LBP, or care-seeking for LBP in adult twins with and without adjustment for genetic and early shared environmental factors.

Comparison of findings with previous research

In our previous cross sectional study, using a sample of female twins from Spain, positive associations between chronic LBP and both BMI (OR: 1.12; 95% CI: 1.02–1.26) and % fat mass (OR: 1.15; 95% CI: 1.01–1.32) were found [26]. However, the modest and significant associations did not persist after further adjustment for the effects of genetics and early environmental factors in MZ twins with dissimilar LBP status. The results of our cross sectional study suggested a non-causal relationship between obesity and LBP. The initial association observed in the total sample analysis could be, in fact, explained by underlying familial factors affecting both obesity and LBP. This pattern of attenuated association between these conditions is consistent across all twin studies that adjusted for genetic and early shared environmental factors when investigating the obesity-LBP relationship [5,27,28].

A closer look at the previously published systematic reviews that investigated the relationship between obesity and LBP reveals that the findings of previous studies are somewhat in agreement with those of our current study [3,9,13,18,29]. Although positive and significant associations have been reported in a meta-analysis of systematic reviews [3,13,18], the authors of these reviews concluded that the evidence for a possible causal path between obesity and LBP is inconclusive. First, most of the evidence in these reviews was driven by inclusion of a large number of cross sectional studies, a study design that limits the inference on causality [13,18,29]. Second, the magnitude of the pooled estimates in the previous reviews was, in general, small (eg, risk estimates expressed as odds or risk ratios usually smaller than 2), thereby providing weak evidence for the association between obesity and LBP [9,13,18,29]. Third, the presence of publication bias was reported in a recent review, suggesting that studies in favor of positive associations were more likely to be published [13]. Furthermore, the majority of the evidence supporting a positive association between obesity and LBP still rests essentially on non-twin data, which precludes the consideration of genetic and environmental factors that could interfere with the obesity-LBP relationship [18].

Recent findings from a cross sectional study suggested that the association between obesity and LBP is not consistent across countries [30]. Whereas in countries such as Finland (OR: 3.33; 95% CI: 2.09–5.30) and Russia (OR: 2.20; 95% CI: 1.15–4.21) the association was high, in others the association appeared to be weak (eg, Spain—OR: 1.56; 95% CI: 1.03–2.35; South Africa—OR: 1.48; 95% CI: 1.02–2.16) or absent (eg, Mexico—OR: 1.17; 95% CI: 0.54–2.57; China—OR: 1.00; 95% CI: 0.65–1.55) [30]. If cultural differences play a role in the obesity-LBP relationship, this may explain why our results differ in part from those in a recent longitudinal Finnish study [31]. Body mass index did not increase the risk of LBP in either study. However, whereas central obesity assessed by waist circumference increased the risk of non-specific LBP in Finnish women (OR: 1.2 per 1 cm change; 95% CI: 1.01–1.04), no increase in the risk of chronic LBP was found in Spanish women in our study (OR: 0.98 per quartile change; 95% CI: 0.74–1.30) [31]. The reasons for the relationship between obesity and LBP to be, potentially, culturally or geographically dependent are unknown, yet different factors could be speculated. It is well known that pain perception is affected by culture, the environment, and genetic factors [30,32,33]. In addition, the prevalence of obesity and the age of obesity onset may differ among countries due to sociocultural, economic, and transport and environment factors [34]. These findings reinforce the importance of a comprehensive approach that also considers the environment and genetic factors when investigating the obesity-LBP relationship.

In our current study, we have chosen outcomes that reflect the disability and severity of LBP (eg, activity-limiting LBP and care-seeking due to LBP). A previous meta-analysis with cross sectional data suggested that the association between obesity and LBP is stronger in patients with longer lasting symptoms who seek care for LBP (OR: 1.43; 95% CI: 1.28–1.60) than in those with general symptoms of LBP (OR: 1.33; 95% CI: 1.14–1.54) [13]. Yet our data did not reveal any increase in the risk of developing chronic LBP outcomes for the obesity-related measures investigated. Therefore, it is possible that the association found in previous cross sectional studies was the result of inadequate control of potential confounders. For example, physical inactivity has been associated with both obesity and LBP, and this possible shared common risk factor could lead to both conditions [35–38]. Consistent with this hypothesis, most of the studies included in the meta-analysis [13] did not adjust for important confounders, including physical activity and genetic factors.

Strengths and limitations

The present study has considerable strengths, such as the use of within-pair case-control analysis, a longitudinal design, and a comprehensive assessment of obesity [3,18,25]. However, certain limitations should be taken into consideration when interpreting the results. First, the follow-up length varied depending on the type of twin pair, which could bias our results for BMI. To overcome this issue, we used the follow-up length as a covariate in our multivariate models. The other outcome measures were not affected by follow-up length as they were only obtained in same-sex female pairs. Furthermore, 24% of the twins could not be contacted at follow-up due to limited resources in the MTR, which could potentially increase the risk of bias. This represents the nature of a twin registry, which implements a sequence of data collection waves and the
number of twins recruited is a function of resources and funding in the registry. Nevertheless, as presented in Table 1, we did not observe any significant differences in the characteristic of participants included in the analysis (n=1098) and those who were not recruited at follow-up (n=356).

In our case-control analysis, we found only a small number of twin pairs discordant for LBP. Because LBP has moderate to high heritability (up to 67%) [3], it is difficult to identify discordant twin pairs for LBP status. Our case-control analyses included between 17 and 111 MZ and DZ twin pairs. Although these numbers might be small, it is important to note that this limitation could be circumvented by the use of the twin design. Studies with smaller samples of twins discordant for an outcome have been able to identify causal (and protective) risk factors for other conditions. For example, differences in body composition measures (eg, % fat mass) and glucose homeostasis were shown in 10 MZ discordant twin pairs dissimilar for physical activity habits. This suggests a causal relationship between physical activity and improved glucose homeostasis [39]. Furthermore, a previous longitudinal twin study of over 300 MZ twin pairs found similar results to ours where BMI was not found to increase the risk of LBP [3].

Potential limitations arise from the data available in the twin registry. First, the assessment of chronic LBP did not include the assessment of radiating peripheral symptoms. Previous studies have found that both general and abdominal obesity are associated with radiating (sciatica) but not with non-specific LBP [16,31]. As a consequence, LBP symptoms related to different spinal anatomical diagnoses might be differently affected by obesity. Second, we had data available on % body fat, waist circumference, and WHR only for women, and therefore the results could be only generalized to women. However, the relationship between LBP and obesity does not appear to be affected by gender when a longitudinal study design is employed [13]. Moreover, we combined self-reported (39%) and objective data (61%) for height and weight, which could potentially affect the accuracy of our results for BMI in women. To investigate this issue as a potential source of bias, we have compared the characteristics of these subgroups at baseline. We found small differences between groups with those who self-reported their height and weight being on average 2.2 years older (SD: 0.57), 1.01 kg heavier (SD: 0.25), 4 cm taller (SD: 0.5), and 1 point greater in the BMI scale (kg/m²) (SD 0.36). When comparing the subgroups using independent t-tests, although we found that age (p<0.001), height (p=0.001), and BMI (p=0.001) were statistically different, we regarded these differences as not clinically meaningful and likely to be a result of our large sample. Consequently, we believe that the combination of self-reported and direct measures of weight and height has little or no effect on our BMI results.

In our models, we assumed a linear effect of obesity on chronic LBP. It is biologically plausible that obesity has a progressive effect on chronic LBP (ie, greater effects on chronic back pain with greater levels of obesity) if, in fact, a true relationship between these conditions exists. Previous studies have proposed a dose-response relationship between obesity and LBP based on cross sectional data [8,40]; however, to our knowledge, no evidence supports a clear linear progressive effect of obesity on LBP. Because of the lack of such evidence, we have performed further exploratory analyses testing the models independently. The first quartile was used as a reference and was compared with other quartiles. The effects have been estimated separately (Supplementary Table S1). Furthermore, to compare the results of our current longitudinal analyses with our previous cross sectional study [26], we used the same data-driven approach to categorize our sample into different levels of obesity. According to Shiri et al. [13], differences in the classification of obesity could potentially lead to the underestimation of the association between obesity-related measures and LBP outcomes. To investigate this issue, we performed additional analyses using the World Health Organization (WHO) recommendations for BMI (normal: ≤25; overweight: >25–30; obese: >30), waist circumference (normal: ≤80 cm; increased risk: >80–88 cm; substantial increased risk: >88 cm), and WHR cutoffs (increased risk: >0.85) [41] (Supplementary Table S2). Because WHO has no proposed threshold for the % of fat mass, we used 35% of fat mass as the cutoff point to identify obese women. This cutoff point has been suggested as one of the best estimates available in the literature [42]. Regardless of the cutoff points (quartiles or WHO categorization) or models assumption (linear or independent effect) applied, the results from our main and supplementary analyses are mostly consistent, pointing to no effect of the obesity-related measures on the risk of chronic LBP outcomes in this Spanish sample. However, when independent models for WHR were investigated, we found significant associations between intermediate quartiles and activity-limiting LBP (quartile one vs. quartile three: OR: 3.64; 95% CI: 1.05–12.62) and care-seeking due to chronic LBP (quartile one vs. quartile two: OR: 2.72; 95% CI: 1.06–6.99). This finding suggests that activity-limiting chronic LBP is more common in women with a smaller or intermediate WHR. It is likely that these significant results are coincidental findings and do not represent a true causal relationship. First, of the 100 regressions performed, only these two associations were significant. The sample for independent models is small (approximately 160 individuals), resulting in large CIs and imprecise estimates. In addition, these associations are somewhat biologically implausible and no evidence of a dose-response relationship was found (significant results only appeared for intermediate quartiles). These findings, therefore, do not meet the criteria for causality.

**Implications of study findings for research and clinical practice**

The LBP field has experienced a significant shift with efforts being aligned toward the identification of possible causal mechanisms. Without such understanding, the development of effective preventive interventions is likely to be impeded.
Obesity is a recognized risk factor for chronic diseases, such as type II diabetes and cardiovascular diseases [43]. The maintenance of a healthy weight is relevant and recommended for the prevention of these health conditions. For instance, landmark clinical trials have shown that lifestyle modification programs focused on weight loss are effective for decreasing the incidence of diabetes [44,45]. However, our data suggest that obesity-related measures do not increase the risk of chronic LBP outcomes. Consequently, weight reduction might not reduce new cases of chronic LBP or reduce care-seeking from new cases of LBP among adults. These findings may explain the findings of an interesting trial that failed to show the benefit of lifestyle modification, including weight reduction, in the reduction of the prevalence of LBP and related disability [46]. Although obesity might still deserve attention in managing patients who suffer from LBP with the aim of improving the prognosis [47], we recommend that well-conducted prospective risk studies in LBP should focus on additional modifiable risk factors. The twin case-control approach, a design that allows for the adjustment of genetic and environmental influences, should be considered as an attempt to reach more conclusive evidence on the risk factors for LBP.

Conclusions

This study demonstrated that BMI does not increase the risk of chronic LBP, activity-limiting LBP, or care-seeking due to LBP in a population of adult Spanish twins after 2 to 4 years. Similar non-significant results were found for % fat mass, waist circumference, and WHR in women. The consideration of familial factors such as genetic and early shared environment factors did not alter these relationships.

Acknowledgments

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Supplementary material

Supplementary material related to this article can be found at http://dx.doi.org/10.1016/j.spinee.2016.10.006.

References

Title: Obesity-related measures do not seem to be determinants for low back pain: Insights from Australian identical twins.

Background

Recent evidence suggests the association between obesity and low back pain (LBP) is not consistent across cultures [1]. In some countries, obese individuals are over three times more likely to experience LBP (e.g. Finland: OR 3.33; 95% CI 2.09 to 5.30), while in other countries the association between obesity and LBP is weak (e.g. Spain: OR 1.56; 95% CI 1.03 to 2.35), or absent (e.g. China: OR 1.00; 95% CI 0.65 to 1.55) [1]. These findings suggest that the obesity-LBP relationship appears to be dependent on the underlying genetic make-up of the population investigated and the environmental variation at play. Therefore, to get a clearer understanding of whether obesity is a risk factor for LBP the influence of genetic and environmental factors should be taken into account.

In Chapters Three and Four of this thesis, the association between obesity-related measures and LBP were investigated in twins. The twin design represents a unique method to overcome genetic and environmental confounding, in particularly when investigating pairs of identical twins. Identical twins, also called monozygotic twins (MZ), are considered nearly genetically identical - “a natural clone” - as they are from the same fertilized ovum. Moreover, MZ twins tend to be exposed to a common environment (e.g. diet, education) until early adulthood [2]. Consequently, the use of identical twin pairs discordant for LBP (co-twin design) represents a robust approach when investigating whether obesity-related measures are risk
factors for LBP, as this method allows us to control for a number of important confounders (e.g. genetics and early shared environment).

The results of the cross-sectional (Chapter Three) and longitudinal (Chapter Four) analyses, which utilized a co-twin design, indicated that obesity-related measures are unlikely to be risk factors for LBP. However, both studies used a sample of Spanish twins from Murcia, a Mediterranean region with high prevalence of obesity [3], and therefore little variance in obesity-related measures, which may compromise the generalizability of these findings to other populations. Then, to further explore the relationship between obesity-related measures and LBP, we used a sample of twins from Australia to compare the concordance rates of obesity-related measures within MZ twin pairs discordant or concordant for LBP. We hypothesized that the degree of concordance in obesity-related measures would not differ considerably between twin pairs discordant or concordant for LBP. These findings would indicate that obesity-related measures are unlikely to be risk factors for LBP, consistent with the results of the previous chapters.

Methods

Design: Cross-sectional observational study.

Study sample and data collection: The study sample comprised adult MZ twin pairs from Australia, ranging from 18 and 72 years old. Data were collected on the 22nd March 2015, during the Twins Festival in Melbourne. This festival was a national event organised by the Australian Twin Registry attracting over 2000 Australian twins (http://www.twinsfestival.com.au/). During the event, twins were informed about the objectives of the study. Twins interested in
participating signed the consent form and provided self-reported information about their demographics and medical history. To collect obesity-related measures, participants were invited to attend a physical examination. The University of Sydney and Australia Twin Registry ethics committees approved all data collection procedures involved in this study.

**Anthropometric measures.** Standardized anthropometric measures such as height, weight, percentage of fat mass, and waist and hip circumference were assessed by trained researchers. Percentage of fat mass was measured by bioelectrical impedance using TANITA equipment (model TISC330S, Tanita Corporation of America, USA). Waist circumference was measured at the point on the torso where the circumference would be the smallest or at the midpoint between the inferior border of the ribcage and the superior aspect of the iliac crest using an inelastic measuring tape. Hip circumference was measured either at the widest point or over the buttocks. Waist-hip ratio was calculated from the respective components. Body mass index (BMI) was calculated by dividing the individuals’ body weight in kilograms by the square of their height in meters.

**Assessment of LBP.** Data on the presence of LBP within the past four weeks was self-reported and obtain from the following question: “In the past 4 weeks, have you had pain in your low back? Please do not report pain from feverish illness or menstruation”. This question was derived from a standardized definition of LBP for the use in epidemiological studies [4].

**Statistical analysis.** We used descriptive statistics to present the characteristics of the cohort, including demographic characteristics, LBP prevalence, and anthropometric measures. For each anthropometric measure, we calculated the differences within-pair and the intraclass correlation coefficients (ICC) [95% Confidence Intervals (CI)] for the total sample and subgroups according
to the concordance (or discordance) of LBP status. STATA 13 software was used to perform the analysis.

Results

Sample characteristics

A total of 31 twin pairs had demographic and anthropometric data available and were included in this analysis (Table 1). The mean age of twins was 43.4 [range: 19 to 73; standard deviation (SD): 16.1] years, and the majority of the sample was composed of females (84%). Twins, on average, were overweight (BMI: 26.7 kg/m$^2$), and 51% reported having LBP in the last four weeks. When analyzing all twin pairs regardless of concordance (or discordance) for LBP, we observed high intrapair correlations for most of the obesity-related measures with coefficients greater than 0.85. The only obesity-related measures that presented a fair (ICC< 0.6) intrapair correlation was waist-hip ratio (ICC: 0.57, 95% CI 0.27 to 0.78) (Table 2).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (SD) or %</th>
<th>Range</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.4 (16.1)</td>
<td>19 to 73</td>
<td>62</td>
</tr>
<tr>
<td>Female</td>
<td>83.9</td>
<td>-</td>
<td>62</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.66</td>
<td>1.50 to 1.86</td>
<td>62</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.1 (16.4)</td>
<td>44 to 119</td>
<td>62</td>
</tr>
<tr>
<td>Body mass index (m/h$^2$)</td>
<td>26.7 (5.7)</td>
<td>18.4 to 45.9</td>
<td>62</td>
</tr>
<tr>
<td>% Fat mass</td>
<td>31.7 (9.6)</td>
<td>9.6 to 49.7</td>
<td>62</td>
</tr>
<tr>
<td>% Lean mass</td>
<td>65.0 (9.0)</td>
<td>47.8 to 86.0</td>
<td>62</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>91.7 (15.6)</td>
<td>68 to 144</td>
<td>56</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.89 (0.1)</td>
<td>0.75 to 1.09</td>
<td>56</td>
</tr>
</tbody>
</table>

LBP: low back pain; SD: standard deviation; n: number of participants.
**Obesity-related measures and LBP concordance within twin pairs**

The majority of twin pairs (77.4%) reported being concordant for LBP status in the past four weeks: 12 (38.7%) twin pairs did not have LBP while 12 (38.7%) twin pairs had LBP (Table 2). Only 7 (22.6%) pairs reported being discordant for LBP status. When observing the mean difference for obesity-related measures within twin pairs, the differences within twin pairs discordant for LBP were not greater than the differences within twin pairs concordant for LBP. For example, among twin pairs discordant for LBP the mean difference for BMI within the pairs was $0.3 m/h^2$ compared to $3.5 m/h^2$ in twin pairs concordant for not having LBP. Similar results were found for weight, percentage of fat mass, waist circumference and waist-hip ratio (Table 2).

A similar pattern was found for the intrapair correlations. For most obesity-related measures, the intrapair correlations were similar across twin pairs concordant and discordant for LBP. For instance, intrapair correlations ranged from 0.73 to 0.93 for weight, BMI and % fat mass, irrespective of the concordance for LBP. However, twin pairs discordant for LBP had a lower concordance for their waist circumference (ICC = 0.36) when compared to twin pairs concordant for having (ICC = 0.84) or not having LBP (ICC = 0.87).
Table 2. Obesity-related measures of intrapair concordance in monozygotic twins for the total sample and according to low back pain status.

<table>
<thead>
<tr>
<th>Obesity-related measures</th>
<th>Within-pair difference</th>
<th>Correlation ICC (95% CI)</th>
<th>N pairs</th>
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<tbody>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>6.6</td>
<td>0.86 (0.72 to 0.93)</td>
<td>31</td>
</tr>
<tr>
<td>Concordant - no LBP</td>
<td>9.3</td>
<td>0.89 (0.66 to 0.97)</td>
<td>12</td>
</tr>
<tr>
<td>Concordant - LBP</td>
<td>4.6</td>
<td>0.73 (0.28 to 0.92)</td>
<td>11</td>
</tr>
<tr>
<td>Discordant - LBP</td>
<td>5.0</td>
<td>0.93 (0.68 to 0.99)</td>
<td>7</td>
</tr>
<tr>
<td><strong>BMI (m/\text{m}^2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>2.3</td>
<td>0.85 (0.71 to 0.92)</td>
<td>31</td>
</tr>
<tr>
<td>Concordant - no LBP</td>
<td>3.5</td>
<td>0.91 (0.74 to 0.97)</td>
<td>12</td>
</tr>
<tr>
<td>Concordant - LBP</td>
<td>1.6</td>
<td>0.75 (0.34 to 0.93)</td>
<td>11</td>
</tr>
<tr>
<td>Discordant - LBP</td>
<td>0.3</td>
<td>0.87 (0.49 to 0.98)</td>
<td>7</td>
</tr>
<tr>
<td><strong>% Fat mass</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>3.6</td>
<td>0.90 (0.80 to 0.95)</td>
<td>31</td>
</tr>
<tr>
<td>Concordant - no LBP</td>
<td>5.1</td>
<td>0.93 (0.77 to 0.98)</td>
<td>12</td>
</tr>
<tr>
<td>Concordant - LBP</td>
<td>3.2</td>
<td>0.82 (0.49 to 0.95)</td>
<td>11</td>
</tr>
<tr>
<td>Discordant - LBP</td>
<td>0.0</td>
<td>0.89 (0.53 to 0.98)</td>
<td>7</td>
</tr>
<tr>
<td><strong>Waist Circumference (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>6.2</td>
<td>0.86 (0.72 to 0.93)</td>
<td>28</td>
</tr>
<tr>
<td>Concordant - no LBP</td>
<td>7.8</td>
<td>0.84 (0.51 to 0.96)</td>
<td>10</td>
</tr>
<tr>
<td>Concordant - LBP</td>
<td>7.0</td>
<td>0.87 (0.60 to 0.96)</td>
<td>11</td>
</tr>
<tr>
<td>Discordant - LBP</td>
<td>2.8</td>
<td>0.36 (-0.47 to 0.87)</td>
<td>7</td>
</tr>
<tr>
<td><strong>Waist-hip ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>0.05</td>
<td>0.57 (0.27 to 0.78)</td>
<td>28</td>
</tr>
<tr>
<td>Concordant - no LBP</td>
<td>0.05</td>
<td>0.83 (0.48 to 0.95)</td>
<td>10</td>
</tr>
<tr>
<td>Concordant - LBP</td>
<td>0.04</td>
<td>0.28 (-0.38 to 0.71)</td>
<td>11</td>
</tr>
<tr>
<td>Discordant - LBP</td>
<td>0.03</td>
<td>0.93 (0.66 to 0.99)</td>
<td>6</td>
</tr>
</tbody>
</table>

LBP: low back pain; BMI: body mass index; r: correlation within-pair; ICC: intraclass correlation coefficients; CI: Confidence interval.
Discussion

Our data from Australian twins showed no evidence of major dissimilarities in those twins discordant for LBP for any of the obesity-related measures. Interestingly, within-twin pair differences in measures of obesity were often smaller in twin pairs discordant for LBP. Although there are some limitations in this supplementary analysis, such as the small sample size, the results nevertheless question the hypothesis that obesity is a strong risk factor for LBP, consistent with the previous findings presented in Chapters Two, Three, and Four [5, 6]. This supplementary analysis also provided evidence of close agreement for both obesity-related measures and LBP within MZ twin pairs. Twenty-four (77%) of the 31 pairs were concordant for LBP status, and, irrespective of the concordance status for LBP, the ICCs for most obesity-related measures were higher than 0.7. These findings are not surprising as they are consistent with other studies in suggesting that genetic factors play a significant role in obesity and in LBP status [7-10].

The high concordance rates in both traits also reinforce the possibility of shared familial determinants (both genetic and environmental) underlying the occurrence of obesity and LBP. Although not tested in this thesis, it is likely that there might be some overlap of familial determinants that are common to both obesity and LBP. Using a sample of 1452 females twin pairs (756 MZ and 696 DZ pairs) from England, the effects of share common genetics and environmental components in the obesity-LBP relationship were quantified [11]. The English study reported a significant, but modest, additive genetic correlation [r 0.205 (± 0.015)] and environmental correlation [r 0.101 (± 0.064)] for the association between obesity (assessed by BMI) and LBP.

In summary, the findings from this supplementary analysis, using a small sample of
Australian twins, reinforces the familial resemblance of both obesity-related measures and LBP status. Furthermore, it demonstrated that the concordance for obesity-related measures does not differ according to the presence or absence of LBP. These results further question a direct causal path between obesity-related measures and LBP, when the influences of genetic and shared environmental factors are considered.
References


CHAPTER FIVE

Mapping the association between back pain and type 2 diabetes:
A cross-sectional and longitudinal study of adult Spanish twins

This Chapter has been under review in *PLOS ONE* since 13 October 2016, and it is in the format required by this journal.
AUTHORSHIP STATEMENT

The co-authors of the paper “Mapping the association between back pain and type 2 diabetes: A cross-sectional and longitudinal study of adult Spanish twins” confirm that Amabile Borges has made the following contributions:

- Conception and design of the research
- Extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript and critical appraisal of content

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the above authorship attribution statement is correct.

Associate Professor Paulo Henrique Ferreira
The University of Sydney
December 2016
Mapping the association between back pain and type 2 diabetes:
A cross-sectional and longitudinal study of adult Spanish twins

Short title: Association between back pain and type 2 diabetes: a twin study

Amabile B Dario¹#, Manuela L Ferreira²,³, Kathryn Refshauge¹, Alison R Harmer¹, Juan F. Sánchez-Romera⁴,⁵, Francisco Pérez-Riquelme⁴,⁵, Ligia L Cisneros⁶, Juan R. Ordoñana⁴,⁵*, Paulo H Ferreira¹*

¹Faculty of Health Sciences, The University of Sydney, Sydney, NSW, Australia.
²The George Institute for Global Health, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia.
³Institute of Bone and Joint Research, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia.
⁴Murcia Twin Registry, Department of Human Anatomy and Psychobiology, University of Murcia, Spain.
⁵Biomedical Research Institute of Murcia (IMIB-Arrixaca-UMU), University Clinical Hospital “Virgen de la Arrixaca”, Murcia, Spain.
⁶Department of Physiotherapy, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.

The authors contributed equally to this work.
*These authors share senior authorship

# Corresponding author
E-mail: adar3900@uni.sydney.edu.au
Abstract

**Background:** Back pain and type 2 diabetes often co-occur, resulting in greater impact on people’s health and complexity in their care. Plausible causal mechanisms for this association have been proposed, yet the nature of the link remains unclear. We therefore explored the direction of the association between type 2 diabetes and chronic back pain in twins, controlling for genetics and early environmental confounding.

**Methods:** 2,096 and 1,098 twins were included in the cross-sectional and longitudinal analyses, respectively. Any or severe (≥ 9) low back pain (LBP), neck pain (NP), and spinal pain (concurrent LBP and NP) and type 2 diabetes were investigated. Sequential analyses were performed using logistic regression. Firstly, twins were analysed unpaired (adjusted age and gender): total sample analyses. Then, to control for genetic and shared environmental factors, a co-twin case-control analysis was performed including monozygotic and dizygotic twin pairs discordant for back pain (cross-sectional only).

**Results:** In the cross-sectional total sample analyses, type 2 diabetes was associated with chronic spinal pain (OR 1.61; 95%CI 1.12 to 2.31), severe chronic spinal pain (OR 3.33; 95%CI 1.47 to 7.53), chronic NP (OR 1.37; 95%CI 1.01 to 1.85), severe chronic NP (OR 2.28; 95%CI 1.24 to 4.21), and severe chronic LBP (OR 1.63; 95%CI 1.00 to 2.64). After further adjustment for genetic and shared environmental factors, none of the associations remained significant. The longitudinal analyses indicated that the presence of type 2 diabetes did not increase the risk of future back pain, or vice-versa, after two to four years.

**Conclusions:** Chronic back pain (spinal pain, NP, or LBP) was associated with the prevalence of type 2 diabetes. Associations are stronger for severe cases of pain. Future research should investigate the temporal relationships between these conditions with longer follow up in twins.
Introduction

Diabetes, low back pain (LBP) and neck pain (NP) are all recognized major public health problems (1-3). They are common and costly conditions, ranking among the top seven causes of years lived with disability worldwide (1). Recent studies have reported that diabetes commonly coexists with LBP and NP (4-7). The prevalence of LBP among people with diabetes is twice as high as among age- and gender-matched controls (8). Importantly, patients with concurrent diabetes and LBP have more frequent recurrence of pain, higher levels of LBP-specific disability, and poorer general health than those with LBP in isolation (6, 9). Furthermore, those presenting with both conditions are twice as likely to be admitted to hospital [OR: 2.02; 95% confidence interval (CI): 1.69 to 2.40] and to have surgery for cervical or lumbar disc disease, which incurs significant health care expenditure (7, 9-11).

Recent evidence suggests that diabetes and back pain, including LBP, NP and spinal pain (concurrent LBP and NP), not only co-exist, but may in fact be bi-directionally linked. The hyperglycemia and altered fat metabolism commonly present in diabetes have been linked to pathoanatomical changes of the spine, such as early degeneration of vertebrae, cartilage, and intervertebral discs (12-16). These changes are a frequent finding in osteoarthritic spinal joints and have been associated with pain (17-20). Conversely, chronic pain is well known to have an adverse impact on health behaviours such as physical activity and diet, and these lifestyle choices may induce type 2 diabetes (21-23).

Apart from a possible bi-directional relationship between diabetes and back pain, it is also plausible that these health conditions coexist due to common risk factors, such as genetic...
influences, on their pathogeneses (24). Family-based studies have consistently suggested the presence of a major genetic component underlying the variation (heritability) of LBP (52%; 95% CI 33 to 72%), NP (48%; 95% CI 29 to 67%) and type 2 diabetes (72%; 95% CI 61 to 78%) (25, 26). Therefore, genetics should be taken into account to obtain more precise estimates when investigating a possible direct path between back pain and diabetes.

Considering that the global population is ageing and becoming more obese, a future increase in the burden of diabetes and back pain is likely to occur, as these conditions are commonly observed in the older and obese populations (27-29). Understanding potential causal risk factors for diabetes and back pain is therefore paramount for optimizing treatment and prevention of these conditions. Thus, we explored the bi-directional association, in terms of precision and magnitude, between type 2 diabetes and chronic back pain [chronic LBP, chronic NP, and chronic spinal pain] using a Spanish twin sample. The use of twin pairs discordant for a health condition, in this case back pain, allows the influence of critical potential confounders such as genetic and early environmental factors to be controlled.

Method

Study design: Cross-sectional and longitudinal observational study with a co-twin case-control design.

Participants and data collection: The study sample comprised adult twins from the Murcia Twin Registry (MTR) in Spain who were born between 1940 and 1966 in the region of Murcia. For the present study, twins recruited by the MTR in the second data wave (baseline: 2009 to 2011) and
third data wave (follow-up: 2013) who provided information on diabetes and back pain were included. Data were collected face-to-face or via telephone interviews conducted by research assistants who were blinded to the predictors and outcomes of the study. Recruitment and data collection procedures for the MTR were approved by the University of Murcia ethics committee (30).

Zygosity evaluation: Twin zygosity was assessed by DNA in 338 pairs and by a 12-item questionnaire in the remainder of the sample. The questionnaire, which identifies the degree of similarity among twin pairs, is in agreement with DNA testing in approximately 96% of cases (30).

Assessment of LBP, NP, and spinal pain: Information on chronic LBP and chronic NP was drawn from self-reported responses derived from the Spanish National Health Survey (31). At baseline, participants were asked “Have you ever suffered from chronic LBP (or NP)?”, followed by, in case of an affirmative answer “Has it been diagnosed by a doctor?” The definition of chronic pain used in the survey was the presence of pain in the lower back or neck area lasting for six months or longer, including seasonal or recurrent episodes. Participants were fully apprised of this definition during the process of data collection. Participants answering “yes” to either or both the LBP or NP questions were categorized as having chronic LBP alone, chronic NP alone, or chronic spinal pain (concurrent LBP and NP). At follow-up, participants who answered positively to the same chronic LBP and chronic NP questions that were administered at baseline were asked additional questions to gather information on pain intensity: “How intense was your pain in the last episode (0= no pain at all; 10 = the worst pain ever)?”
Assessment of type 2 diabetes: Similar to the assessment of back pain, information on diabetes was assessed using self-reported responses to the Spanish National Health Survey (31). Participants were asked the following questions “Have you ever suffered diabetes?” and when the answer was affirmative, “Has it been diagnosed by a doctor?” An additional question was asked about medication: “Did you take medication for diabetes in the previous month?” Initially, those who answered “yes” to one or more of these questions were categorized as having diabetes. This information was then linked to the regional databases of the Murcia Health Council, which include data about virtually all patients using the public health system in the geographical area of the MTR. Only participants for whom the diagnosis of type 2 diabetes could be confirmed (diagnosed by a physician) were considered as cases. Participants with type 1 diabetes or non-confirmed self-reported type 2 diabetes were excluded (0.5% and 1.9% of the total sample, respectively).

Assessment of covariates: Potential confounders were selected based on plausible associations with back pain and diabetes, as well as data availability. Variables investigated included age, sex, body mass index (BMI), engagement in physical activity (work-related and leisure), and smoking history. To assess engagement in physical activity and smoking history we used categorical self-reported responses to the Spanish National Health Survey (31). BMI was calculated from self-reported height and weight, and used as a continuous variable. For smoking history, participants were categorized as current smoker or never smoker/ex-smoker. For leisure-time physical activity, participants were categorized as sedentary (no engagement in recreational physical activity) or regularly physically active (low/moderate/vigorous physical activity engagement). For work-related physical activity, participants were categorized as sedentary (low/no...
engagement in work related physical activity such as mainly sitting or light physical efforts) or
as doing tasks that require a strong physical effort (moderate/vigorous physical activity
engagement).

Statistical Analysis: Descriptive analyses were performed on demographic and clinical
characteristics of the cohort at baseline and follow-up. We then investigated the cross-sectional
and longitudinal associations between diabetes and back pain using univariate and multivariable
regression models. To adjust the models for the similarities shared by twins (i.e. to control for
data dependence due to twin sample), we used a robust sandwich estimator (cluster command in
STATA) in the total sample analyses. In the multivariable regression analyses, we adjusted the
total sample models by age and sex to ensure comparability with the co-twin case-control
models. Possible additional confounders (BMI, engagement in physical activity, and smoking
history) were only included in the models when the p-values were <0.2 for the associations with
both the outcome and exposure. Figure 1 describes the statistical analysis schema.

Figure 1. Statistical analysis schema and sample size. The level of adjustment for confounding
factors increases throughout the analytical stages.

Cross-sectional analyses: To explore a possible association between type 2 diabetes and spinal
pain, NP or LBP, we conducted cross-sectional analyses using the baseline data. In addition, with
the availability of data on pain intensity collected at the follow-up assessment (2013), we
investigated the potential association between type 2 diabetes and severe cases of spinal pain (or
NP, or LBP). Participants in the upper quartile of the distribution of the pain intensity variable,
reporting pain equal to or higher than 9/10, were classified as having severe pain. To control for
the possible effects of genetic and early shared environmental factors on the relationship between type 2 diabetes and chronic spinal pain (or NP, or LBP), we conducted a co-twin case-control analysis. Only complete and discordant twin pairs (i.e. one twin reported chronic spinal pain, whereas the co-twin did not) for each back pain outcome were included. Theoretically, the co-twin control design enables adjustment of the estimates for a large number of confounding factors that twins share, including genetics, as monozygotic and dizygotic twin pairs share approximately 100% and 50% of their genes, respectively. Furthermore, twins tend to be exposed to a common environment until early adulthood.

Longitudinal analysis: (i) To investigate type 2 diabetes as a risk factor for chronic spinal pain (or NP, or LBP), twins were included when they did not report chronic spinal pain (or NP, or LBP) at baseline and had complete data available at both baseline and follow-up. A similar method was used to investigate whether type 2 diabetes increased the risk of severe cases of chronic spinal pain (or NP, or LBP) with twins being included only if they did not report severe spinal pain (or NP, or LBP) at baseline. (ii) To investigate chronic spinal pain (or NP, or LBP) as risk factors for type 2 diabetes, twins were included when they did not report diabetes at baseline and had complete data available at both baseline and follow-up.

Results

Sample characteristics

At baseline, a total of 2,096 twins were included in our cross-sectional analysis. The mean age of twins was 53.6 [standard deviation (SD) 7.3] years, and the majority of the sample was composed of female twins (55%). On average, twins were overweight (BMI 27.4kg/m², SD 4.5),
with 18.8% reporting engagement in work-related physical activity and 54.2% in leisure-time physical activity. The prevalence of chronic spinal pain, NP, and LBP was 18.2% (95% CI 16.5 to 19.8), 28.4% (95% CI 26.5 to 30.3), and 32.2% (95% CI 30.2 to 34.2) respectively, while 10.9% (95% CI 9.6 to 12.3) of twins had a confirmed diagnosis of type 2 diabetes (Table 1).

At follow-up, 1613 twins from the original sample had complete data for back pain and type 2 diabetes. The mean age of the twins was 56.7 (SD 7.1) years and their mean BMI was classified as overweight (BMI 27.2 kg/m^2; SD 4.3). The proportion of those engaged in work-related and leisure-time physical activity were 20.8% and 66.0%, respectively. The prevalence of chronic spinal pain, NP, and LBP was 14.8% (95% CI 13.1 to 16.6), 24.8% (95% CI 22.8 to 27.0), and 36.8% (95% CI 34.5 to 39.2); with 13% (95% CI 11.4 to 14.7) of twins presenting with type 2 diabetes (Table 1). The proportions of incident cases of chronic spinal pain, NP, and LBP at follow-up were 9.0% (95% CI 7.5 to 10.6), 14.7% (95% CI 12.7 to 16.8), and 22.3% (95% CI 19.8 to 24.8), respectively. Incident cases of type 2 diabetes comprised 2.4% (95% CI 1.6 to 3.3) of the twins over two to four years follow-up (Table 1).

[Table 1]
Table 1 Characteristics of study sample, including anthropometric data, lifestyle factors, and type 2 diabetes and back pain status at baseline and follow-up.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th></th>
<th>Baseline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) or % n</td>
<td></td>
<td>Mean (SD) or % n</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.6 (7.3) 2096</td>
<td></td>
<td>56.7 (7.1) 1613</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 (1.0) 2049</td>
<td></td>
<td>1.64 (9.2) 1502</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.2 (14.1) 2082</td>
<td></td>
<td>73.2 (13.7) 1575</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>27.4 (4.5) 2041</td>
<td></td>
<td>27.2 (4.3) 1491</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44.8% 940</td>
<td></td>
<td>44.9% 725</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>36.2% 759</td>
<td></td>
<td>30.8% 496</td>
<td></td>
</tr>
<tr>
<td>Work-related physical activity$^a$</td>
<td>18.8% 393</td>
<td></td>
<td>20.8% 336</td>
<td></td>
</tr>
<tr>
<td>Leisure-time physical activity$^a$</td>
<td>54.2% 1137</td>
<td></td>
<td>66.0% 1064</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes$^b$</td>
<td>10.9% 229</td>
<td></td>
<td>13.0% 210</td>
<td></td>
</tr>
<tr>
<td>Low back pain$^b$</td>
<td>32.2% 675</td>
<td></td>
<td>36.8% 593</td>
<td></td>
</tr>
<tr>
<td>Neck pain$^b$</td>
<td>28.4% 595</td>
<td></td>
<td>24.8% 400</td>
<td></td>
</tr>
<tr>
<td>Spinal pain$^{\text{^ab}}$</td>
<td>18.2% 381</td>
<td></td>
<td>14.8% 239</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Spinal pain: concurrent lower back and neck pain; SD: standard deviation; n: number of participants; $^a$ Percentage engaged in physical activity within group; $^b$ Prevalence.
Type 2 diabetes and chronic spinal pain (both LBP and NP)

The analyses, including cross-sectional data from the total sample, demonstrated that type 2 diabetes was associated with chronic spinal pain [unadjusted odds ratio (OR) 1.49; 95% CI 1.07 to 2.09; adjusted OR 1.61; 95% CI 1.12 to 2.31] and severe chronic spinal pain (unadjusted OR 2.94; 95% CI 1.44 to 5.99; adjusted OR 3.33; 95% CI 1.47 to 7.53) (Table 2). When the analyses were separated by sex, type 2 diabetes was associated with chronic spinal pain in females only (unadjusted OR 1.76; 95% CI 1.17 to 2.66; adjusted OR 1.64; 95% CI 1.06 to 2.53). However, for severe chronic spinal pain, type 2 diabetes was strongly associated among both females (unadjusted OR 2.71; 95% CI 1.03 to 7.11), and males (unadjusted OR 3.46; 95% CI 1.13 to 10.59; adjusted OR 4.80; 95% CI 1.37 to 16.84). After adjusting for genetic and shared environmental factors using 201 and 26 twin pairs discordant for chronic spinal pain and severe chronic spinal pain respectively, the magnitude of association reduced and was no longer significant.

The longitudinal analysis for the total sample showed no association between type 2 diabetes and risk of developing severe chronic spinal pain after two to four years follow-up. Likewise, presence of chronic spinal pain did not increase the risk of future type 2 diabetes.

[Table 2]
Table 2: Association between type 2 diabetes and chronic spinal pain (concurrent low back pain and neck pain) for all participants and by sex.

<table>
<thead>
<tr>
<th>Models</th>
<th>All participants</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Cross-sectional analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic SP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.49 (1.07 to 2.09)</td>
<td>2096</td>
<td>1.76 (1.17 to 2.66)</td>
</tr>
<tr>
<td>Adjusted&lt;sup&gt;1, 2, 3&lt;/sup&gt;</td>
<td>1.61 (1.12 to 2.31)</td>
<td>2084</td>
<td>1.64 (1.06 to 2.53)</td>
</tr>
<tr>
<td>MZ and DZ pairs&lt;sup&gt;2, 3, *&lt;/sup&gt;</td>
<td>1.12 (0.58 to 2.15)</td>
<td>402</td>
<td>1.07 (0.43 to 2.64)</td>
</tr>
<tr>
<td>Severe Chronic SP#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.94 (1.44 to 5.99)</td>
<td>1485</td>
<td>2.71 (1.03 to 7.11)</td>
</tr>
<tr>
<td>Adjusted&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3.33 (1.47 to 7.53)</td>
<td>1485</td>
<td>2.60 (0.87 to 7.82)</td>
</tr>
<tr>
<td>MZ and DZ pairs*</td>
<td>2.90 (0.48 to 17.42)</td>
<td>52</td>
<td>-</td>
</tr>
<tr>
<td><strong>Longitudinal analysis:</strong></td>
<td>Type 2 diabetes as a risk factor for SP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic SP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.95 (0.49 to 1.84)</td>
<td>1293</td>
<td>0.78 (0.30 to 2.05)</td>
</tr>
<tr>
<td>Adjusted&lt;sup&gt;1, 2&lt;/sup&gt;</td>
<td>0.85 (0.42 to 1.73)</td>
<td>1284</td>
<td>0.60 (0.20 to 1.81)</td>
</tr>
<tr>
<td>Severe Chronic SP#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>3.80 (0.91 to 15.82)</td>
<td>98</td>
<td>7.17 (0.89 to 57.47)</td>
</tr>
<tr>
<td>Adjusted&lt;sup&gt;1, 2&lt;/sup&gt;</td>
<td>3.67 (0.84 to 16.03)</td>
<td>98</td>
<td>7.16 (0.91 to 56.41)</td>
</tr>
<tr>
<td><strong>Longitudinal analysis:</strong></td>
<td>SP as a risk factor for type 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.80 (0.31 to 2.11)</td>
<td>1399</td>
<td>1.63 (0.54 to 4.93)</td>
</tr>
<tr>
<td>Adjusted&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.01 (0.39 to 2.59)</td>
<td>1399</td>
<td>1.52 (0.50 to 4.65)</td>
</tr>
</tbody>
</table>

SP: Spinal pain; OR: Odds ratio; CI: Confidence interval; MZ: Monozygotic; DZ: Dizygotic; n: Number of participants in each analysis stage; <sup>1</sup> Adjusted for age and sex; <sup>2</sup> Adjusted for work-related physical activity; <sup>3</sup> Adjusted for body mass index; <sup>#</sup> Severe pain: pain ≥ 9 on visual analogical scale (0 to 10) in the last episode; * Case-control analysis: twins are discordant for spinal pain status. Analyses stratified by gender only include same-sex pairs.
Type 2 diabetes and chronic NP

The cross-sectional analysis of the total sample demonstrated that type 2 diabetes was associated with chronic NP (unadjusted OR 1.35; 95% CI 1.02 to 1.79; adjusted OR 1.37; 95% CI 1.01 to 1.85) (Table 3). When the analysis was separated by sex, type 2 diabetes was only associated with chronic NP in females (unadjusted OR 1.72; 95% CI 1.18 to 2.51; adjusted OR 1.58; 95% CI 1.07 to 2.34). The positive associations in the total and female only samples did not remain significant after adjustment for genetic and shared environmental factors using 276 and 139 twin pairs discordant for chronic NP, respectively.

We also found that type 2 diabetes was strongly associated with higher prevalence of severe chronic NP (unadjusted OR 2.11; 95% CI 1.17 to 3.79; adjusted OR 2.28; 95% CI 1.24 to 4.21). When the analyses were separated by sex, type 2 diabetes was associated with severe chronic NP in females only in the unadjusted analysis (OR 2.28; 95% CI 1.04 to 5.04) and was close to statistical significance in the adjusted analysis (OR 2.19; 95% CI 0.99 to 4.87). The positive associations for severe chronic NP in the total and female only samples did not remain after adjustment for genetic and shared environmental factors in 43 and 15 discordant twin pairs, respectively. In the total sample analysis using longitudinal data, type 2 diabetes did not increase the risk of developing chronic NP, or vice-versa, after two to four years.

[Table 3]
Table 3 Association between type 2 diabetes and chronic neck pain for all participants and by sex.

<table>
<thead>
<tr>
<th>Models</th>
<th>All participants</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Cross-sectional analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic NP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.35 (1.02 to 1.79)</td>
<td>2096</td>
<td>1.72 (1.18 to 2.51)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.37 (1.01 to 1.85)</td>
<td>2074</td>
<td>1.58 (1.07 to 2.34)</td>
</tr>
<tr>
<td>MZ and DZ pairs</td>
<td>1.23 (0.62 to 2.27)</td>
<td>552</td>
<td>1.69 (0.66 to 4.32)</td>
</tr>
<tr>
<td>Severe Chronic NP*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.11 (1.17 to 3.79)</td>
<td>1511</td>
<td>2.29 (1.04 to 5.04)</td>
</tr>
<tr>
<td>Adjusted 1</td>
<td>2.28 (1.24 to 4.21)</td>
<td>1511</td>
<td>2.19 (0.99 to 4.87)</td>
</tr>
<tr>
<td>MZ and DZ pairs*</td>
<td>0.91 (0.30 to 2.78)</td>
<td>86</td>
<td>1.00 (0.06 to 15.99)</td>
</tr>
<tr>
<td>Longitudinal analysis: Type 2 diabetes as a risk factor for NP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic NP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.29 (0.77 to 2.18)</td>
<td>1126</td>
<td>1.27 (0.56 to 2.89)</td>
</tr>
<tr>
<td>Adjusted 1,2,4</td>
<td>1.16 (0.65 to 1.91)</td>
<td>1111</td>
<td>0.82 (0.34 to 2.01)</td>
</tr>
<tr>
<td>Severe Chronic NP#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.88 (0.58 to 6.11)</td>
<td>138</td>
<td>5.33 (0.92 to 31.06)</td>
</tr>
<tr>
<td>Adjusted #1,2</td>
<td>1.91 (0.52 to 6.95)</td>
<td>138</td>
<td>6.42 (0.92 to 44.53)</td>
</tr>
<tr>
<td>Longitudinal analysis: NP as a risk factor for type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.80 (0.31 to 2.11)</td>
<td>1399</td>
<td>1.63 (0.54 to 4.93)</td>
</tr>
<tr>
<td>Adjusted 1</td>
<td>1.01 (0.39 to 2.59)</td>
<td>1399</td>
<td>1.52 (0.50 to 4.65)</td>
</tr>
</tbody>
</table>

NP: Neck Pain; OR: Odds ratio; CI: Confidence interval; MZ: Monozygotic; DZ: Dizygotic; n: Number of participants in each analysis stage; ^1 Adjusted for age and sex; ^2 Adjusted for work-related physical activity; ^3 Adjusted for body mass index; ^4 Adjusted for smoking; # Severe pain: pain ≥ 9 on visual analogical scale (0 to 10) in the last episode; * Case-control analysis: twins are discordant for neck pain status. Analyses stratified by gender only include same-sex pairs.
Type 2 diabetes and chronic LBP

The cross-sectional analysis of the total sample showed that type 2 diabetes was only associated with higher prevalence of severe chronic LBP in the adjusted total sample analysis (OR 1.63; 95% CI 1.00 to 2.64). After adjusting for genetic and shared environmental factors using 73 twin pairs discordant for severe chronic LBP, the association was no longer significant. The longitudinal analyses showed that type 2 diabetes did not increase the risk of developing chronic LBP, or vice-versa, after two to four years.

[Table 4]
Table 4 Association between type 2 diabetes and chronic low back pain for all participants and by sex.

<table>
<thead>
<tr>
<th>Models</th>
<th>All participants</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Cross-sectional analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic LBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.07 (0.80 to 1.45)</td>
<td>2096</td>
<td>1.38 (0.93 to 2.04)</td>
</tr>
<tr>
<td>Adjusted(^1,2)</td>
<td>1.18 (0.86 to 1.60)</td>
<td>2084</td>
<td>1.35 (0.90 to 2.03)</td>
</tr>
<tr>
<td>MZ and DZ pairs*</td>
<td>0.84 (0.45 to 1.55)</td>
<td>610</td>
<td>0.89 (0.34 to 2.30)</td>
</tr>
<tr>
<td><strong>Severe Chronic LBP</strong>#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.36 (0.86 to 2.15)</td>
<td>1525</td>
<td>1.52 (0.83 to 2.81)</td>
</tr>
<tr>
<td>Adjusted(^1)</td>
<td>1.63 (1.00 to 2.64)</td>
<td>1525</td>
<td>1.88 (0.99 to 3.58)</td>
</tr>
<tr>
<td>MZ and DZ pairs*</td>
<td>2.75 (0.54 to 13.91)</td>
<td>146</td>
<td>-</td>
</tr>
<tr>
<td><strong>Longitudinal analysis</strong>: Type 2 diabetes as a risk factor for LBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic LBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.76 (0.47 to 1.22)</td>
<td>1084</td>
<td>0.87 (0.41 to 1.85)</td>
</tr>
<tr>
<td>Adjusted(^1,2,3)</td>
<td>0.84 (0.51 to 1.40)</td>
<td>1077</td>
<td>0.73 (0.32 to 1.63)</td>
</tr>
<tr>
<td><strong>Severe Chronic LBP</strong>#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.88 (0.71 to 5.02)</td>
<td>218</td>
<td>1.25 (0.23 to 6.85)</td>
</tr>
<tr>
<td>Adjusted(^1,2)</td>
<td>1.91 (0.67 to 5.46)</td>
<td>218</td>
<td>1.38 (0.24 to 7.99)</td>
</tr>
<tr>
<td><strong>Longitudinal analysis</strong>: LBP as a risk factor for type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.92 (0.45 to 1.90)</td>
<td>1399</td>
<td>2.03 (0.70 to 5.94)</td>
</tr>
<tr>
<td>Adjusted(^1)</td>
<td>1.10 (0.54 to 2.22)</td>
<td>1399</td>
<td>1.92 (0.66 to 5.60)</td>
</tr>
</tbody>
</table>

LBP: Low back pain; OR: Odds ratio; CI: Confidence interval; MZ: Monozygotic; DZ: Dizygotic; n: Number of participants; \(^1\)Adjusted for age and sex; \(^2\) Adjusted for work-related physical activity; \(^3\)Adjusted for body mass index; \(^\#\) Severe pain: pain ≥ 9 on visual analogical scale (0 to 10) in the last episode; * Case-control analysis: twins are discordant for low back pain status. Analyses stratified by gender only include same-sex pairs.
Discussion

Main findings

Our findings suggest a positive association between type 2 diabetes and chronic back pain in the cross-sectional analyses. Those in our cohort with type 2 diabetes were more likely to report chronic low back, neck, and spinal pain. The associations tended to be stronger for severe cases of chronic pain (e.g. severe chronic spinal pain: adjusted OR 3.33) than any pain (chronic spinal pain: adjusted OR 1.61). Nevertheless, our findings do not provide strong and conclusive evidence of a causal relationship between type 2 diabetes and back pain. Firstly, none of the associations remained significant after further adjusting for the genetic and early environmental factors shared by twins. Moreover, no statistically significant association was found in the bi-directional longitudinal analyses, although large magnitudes in risks were produced when diabetes was investigated as a risk factor for severe spinal pain. The presence of positive associations only in the cross-sectional analyses, in which confounders are partially controlled, suggest that type 2 diabetes and back pain could be linked by other mutually shared common risk factors (e.g. genetics).

Association of back pain and type 2 diabetes

Back pain and other musculoskeletal pain disorders are common among patients with diabetes (7, 8, 11, 32-34). Despite this, there is a scarcity of well controlled studies that have attempted to disentangle this relationship. This may be due to back pain possibly being considered a trivial comorbidity compared with other major health problems associated with diabetes, such as heart disease or stroke (33). Nevertheless, compelling evidence suggests that people who suffer from type 2 diabetes and back pain usually present with greater signs of poor general health (e.g.
hypertension and dyslipidemia) and progress to worse outcomes such as increased pain severity
(6, 33, 35, 36). In agreement with previous studies, we found that type 2 diabetes was more
strongly associated with severe cases of chronic spinal pain (adjusted OR 3.33, 95% CI 1.47 to
7.53), NP (adjusted OR 2.28, 95% CI 1.24 to 4.21), and LBP (adjusted OR 1.63, 95% CI 1.00 to
2.64).

Our cross-sectional results also indicated the association between diabetes and chronic neck and
spinal pain tended to be more consistent, and often stronger, among females than in males. The
underlying mechanisms for this difference is still unknown, but several reasons could be
speculated. For example, sex hormones that are predominant in females (e.g. estrogen) can affect
the immune system and increase the inflammatory response, which may result in a greater
predisposition to develop diabetes and spine degeneration (37-42). Higher prevalence of back
pain and more rapid changes in spine degeneration have been reported in females after
menopause (38, 40-44). In our sample, most females were in their mid-life period (mean age: 54
years), which coincides with the timing of menopausal age (45). As the majority of women with
type 2 diabetes are older and frequently diagnosed during or after menopause (38), the
understanding of underlying mechanisms of back pain and degeneration in this population may
deserve further exploration.

Causal relationship between type 2 diabetes and back pain
In light of the findings from the cross-sectional co-twin and the longitudinal analyses, the
relationship between type 2 diabetes and back pain might not be as simple or direct as previously
believed. After further adjustment for a large number of potential disease confounders, such as
genetics and early environmental factors shared by twins, the significant associations between
type 2 diabetes and back pain did not persist suggesting that a causal relationship between the
two diseases is not likely. Our findings are consistent with results from two other twin studies
that investigated lumbar spine degeneration in twin pairs discordant for diabetes status (24, 46).
One of these studies (24) investigated lumbar spine degeneration and bone density, using
magnetic resonance imaging, among nine MZ twin pairs discordant for insulin-dependent
diabetes. No difference was observed in lumbar disc degeneration or bone density scores
between twins with or without a diagnosis of diabetes (24). Likewise, a recent co-twin study
including 33 MZ and DZ pairs discordant for type 2 diabetes reported that twins with type 2
diabetes did not present with higher lumbar degeneration scores than those without (46). The
findings from our study and these other co-twin studies (24, 46) indicate that a causal link
between these health conditions are unlikely. Similarly, our longitudinal analyses showed that
type 2 diabetes possibly does not increase the risk of back pain, or vice-versa, suggesting no
temporal effect, one of the important indicators of a causal relationship between variables (47).
However, we acknowledge that the lack of significant associations in our co-twin and
longitudinal analyses may be due to the small sample size, which reduces the power required to
identify a relationship, if in fact, it exists. Some large magnitude in risks were identified (e.g.
diabetes as a risk factor for severe spinal pain, particularly in women), and might reveal as
statistically significant if larger samples of twins were available.

Implications of study findings for clinical practice and research

Although our results question a possible causal relationship between type 2 diabetes and back
pain, this study suggests that LBP and NP are associated with type 2 diabetes. Our findings
provide guidance for health professionals that people with both diabetes and back pain are more likely to present with more severe levels of pain compared to those without diabetes. Screening for back pain in patients with diabetes could be incorporated in clinical settings as an approach to avoid subsequent pain-related disability and minimize the progression of back pain and diabetes. At present, to our knowledge, only one study has investigated the efficacy of an intervention for this population, and found that osteopathic manual treatment resulted in a clinically relevant reduction of LBP severity over 12 weeks (medium effect size; Cohen d=0.7) compared to sham treatment. Interestingly, better metabolic profile was also observed in the intervention group after treatment as serum concentration of TNF-α significantly reduced. TNF-α is considered a contributing factor for metabolic disturbances such as insulin resistance and dyslipidemia in type 2 diabetes (48). Consequently, studies are needed to investigate interventions that can be delivered to patients suffering from both back pain and diabetes with the aim of minimizing diseases’ progression and their related complications.

Strengths and Limitations

The strengths of our study include the use of a co-twin design, allowing for within-twin pair comparisons naturally adjusted for genetics and other shared childhood factors such as diet and parental characteristics (e.g. socioeconomic status and lifestyle), that could affect both diabetes and back pain. In addition, we only included participants with a confirmed diagnosis of diabetes (via the Spanish Health Registry), which adds validity to the ascertainment of the presence of diabetes. An investigation of causality using longitudinal data accompanied the cross-sectional analyses, to assess whether there was a bi-directional relationship between type 2 diabetes and back pain.
There are also potential limitations that should be taken into account when interpreting our results. Firstly, as expected due to the moderate back pain heritability (25, 26), there were few twin pairs discordant for back pain identified in our sample. As a result, it is possible that some co-twin analyses were underpowered. Nevertheless, the matching generated by the co-twin design may have the potential to overcome this limitation (49, 50). Furthermore, our findings were consistent with two other previously published co-twin studies (24, 46). Inadequate power could have also affected the statistical significance and confidence intervals observed in our longitudinal analyses. Secondly, two to four years follow up may be short considering the chronic and progressive deleterious effect that type 2 diabetes and back pain can have on health. Therefore, the temporal relationship between these conditions may need to be explored over longer period of time. Lastly, the generalizability of our results to global populations needs to be undertaken with caution. Our sample comprised older Spanish people from a Mediterranean region (Murcia) with a high prevalence of obesity and type 2 diabetes (51). Therefore, before drawing definitive conclusions, we emphasize the need for further prospective twin studies using a more heterogeneous and larger cohort.

In summary, chronic back pain (NP, LBP and both) was associated with the prevalence of type 2 diabetes. Stronger associations were observed for more severe cases of pain. Genes or environmental factors that influence both conditions should not be excluded as factors confounding these associations. Given the increasing global prevalence of back pain and diabetes, further studies are warranted to understand the mechanisms behind these associations, as well as the strategies to optimize management and healthcare utilization in this population.
Acknowledgements: The Murcia Twin registry is grateful to the Murcia Health Council for data validation accessibility (CMBD and OMI-AP).

References


Twins from the Murcia Twin Registry with data available for type 2 diabetes and chronic back pain [low back pain (LBP), neck pain (NP) or both].
Number of participants: 2096

**Baseline (Data collected between 2009 and 2011)**
Cross-sectional analysis. Type 2 diabetes and *chronic back pain* (chronic NP, or LBP, or both independently). All participants with data available for back pain and type 2 diabetes were included, except for the case-control analysis where only complete and discordant pairs for chronic NP, or LBP or both were included. Analysis stages:
1. Total sample analysis unadjusted
2. Total sample analysis adjusted (Confounding factors investigated: age, sex, BMI, smoking, engagement in physical activity)
3. Within-pair twin case-control analysis (confounding factors investigated age, sex, BMI, smoking, engagement in physical activity, genetics and early environmental factors shared by twins)

**Follow-up (Data collected in 2013)**
Cross-sectional analysis. Type 2 diabetes and *chronic severe back pain* (chronic NP, or LBP, or both independently). All participants with data available for severe back pain and type 2 diabetes were included. Analysis stages:
1. Total sample unadjusted
2. Total sample adjusted (confounding factors investigated age, sex, BMI, smoking, engagement in physical activity)
3. Within-pair twin case-control analysis (confounding factors investigated age, sex, BMI, smoking, engagement in physical activity, genetics and early environmental factors shared by twins)

Longitudinal analysis. Type 2 diabetes as a predictor for *chronic back pain* (chronic NP, or LBP, or both independently). All participants with data available for back pain and type 2 diabetes who were free of chronic NP (or LBP, or both) at baseline. Analysis stages:
1. Total sample unadjusted
2. Total sample adjusted (confounding factors investigated age, sex, BMI, smoking, engagement in physical activity)

Longitudinal analysis. *Chronic back pain* (chronic NP, or LBP or both independently) as a predictor for type 2 diabetes. All participants with data available for back pain and type 2 diabetes who were free of diabetes type II at baseline. Analysis stages:
1. Total sample unadjusted
2. Total sample adjusted (confounding factors investigated age, sex, BMI, smoking, engagement in physical activity)
Conclusions
6.1 Purpose of the thesis

The broad aim of this thesis was to contribute to a better understanding of whether obesity-related measures - *general obesity, abdominal obesity,* and *type 2 diabetes* - are risk factors for the development of low back pain (LBP), particularly chronic LBP. To date, much research examining potentially modifiable risk factors for LBP has been conducted. Identifying potentially modifiable risk factors, such as obesity, could lead to the development and implementation of evidence-based preventive strategies for LBP and associated disability. However, minimal progress has been made in identifying potentially modifiable risk factors and developing preventive approaches. As such, the evidence on the relationship between obesity-related risk factors and LBP remains conflicting. Methodological flaws, such as the lack of adjustment for important confounders and the use of suboptimal obesity measures, likely explain the controversial findings.

To investigate the link between obesity-related risk factors and LBP, the studies that compose this thesis used a twin case-control design. The highly matched twin case-control design accounts for a range of potential confounders, including genetics and early environmental factors. Theoretically, this methodology can shed more light on the nature of the association between obesity and LBP by determining whether there is a direct (causal) relationship between these conditions. To overcome the limitation of previous studies that used suboptimal measures of obesity, the studies in this thesis used a comprehensive assessment of obesity that considered the *magnitude* of fatness as well as the body fat *distribution.* This thesis also sought to investigate whether obesity-related risk factors fulfil several criteria that are considered decisive
for confirming a direct (causal) link between exposure and an outcome, including the strength of association, consistency, and temporality [1, 2].

6.2 Overview of main findings

The initial objective of this thesis was to investigate whether obesity is a risk factor for LBP and lumbar disc degeneration. A comprehensive literature search and appraisal was conducted to summarise the findings of twin studies in a systematic review with a meta-analysis approach (Chapter Two). This study revealed a positive association between obesity and both LBP and lumbar disc degeneration in the least adjusted models (unpaired analyses in which familial factors were not taken into account). Most (four out of five) of the cross-sectional twin studies included in this review reported positive associations between obesity and LBP, suggesting consistency of findings and therefore enhancing the possibility of obesity being a risk factor for LBP. Nonetheless, the pooling of these five studies showed that obesity was weakly (odds ratio <2.0) associated with LBP (odds ratio [OR] 1.8; 95% confidence interval [CI] 1.6 to 2.0)[2]. Additionally, pooling of the studies that controlled for familial factors, including 469 identical (monozygotic - MZ) twins discordant for body weight status, revealed a reduction in the strength of association which was then no longer significant (OR 1.4; 95% CI 0.8 to 2.3). The findings of this systematic review with meta-analysis provided a different perspective to the LBP field, suggesting the possibility of genetics and familial factors confounding the relationship between obesity and LBP. Furthermore, Chapter Two highlighted limitations in previous studies such as imprecise measures used to define obesity (e.g. body mass index - BMI) and a lack of longitudinal twin studies.
Chapters Three and Four have attempted to address the limitations revealed in Chapter Two by evaluating the effect of four measures of obesity that consider the effects of magnitude (BMI; percentage of fat mass) and distribution of body fat mass (waist circumference - WC; waist-hip ratio - WHR) on chronic LBP. Cross-sectional and longitudinal data from Spanish twins were used to conduct the studies reported in Chapters Three and Four, respectively. Results from Chapter Three demonstrated that greater magnitude of fat (measured by BMI and percent of fat mass), as well as higher distribution of fat mass around the hips (measured by WHR), were associated with higher prevalence of chronic LBP in females. However, the associations were weak and did not remain significant after further control for the effects of familial factors shared by MZ twins. Chapter Four showed that obesity-related factors did not increase the risk of chronic LBP, activity-limiting LBP, or care-seeking for LBP after two to four years follow-up. Furthermore, no evidence of a dose-response relationship was found in any of the analyses. The lack of temporal effect and dose-response relationship are in agreement with the findings reported in Chapters Two and Three, suggesting that a direct link between obesity measures and chronic LBP outcomes is unlikely.

A Supplementary Analysis presented in Chapter Four further questioned obesity-related measures as strong risk factors for LBP, when the influences of genetic and shared environmental factors are considered. The results revealed that the within-pair concordance rates within-pair for obesity-related measures did not differ according to the presence or absence of LBP in 31 Australian MZ twin pairs. Essentially, twins with LBP were not generally heavier than their co-twins without LBP. Furthermore, due to the high concordance rates in obesity measures and LBP phenotypes within-pairs, the findings reinforced the possibility of shared genetics and familial factors confounding the link between obesity-related measures and LBP.
The final study of this thesis reported in Chapter Five investigated the relationship between chronic back pain (including LBP, neck pain, or both) and another obesity-related health risk factor: type 2 diabetes. Results of the cross-sectional analysis indicated that chronic back pain was associated with the prevalence of type 2 diabetes. Importantly, for the first time, evidence of stronger associations between type 2 diabetes and severe concurrent chronic LBP and neck pain were reported (OR 3.3; 95% CI 1.5 to 7.5). However, similar to the findings of Chapters Two, Three, and Four, none of the associations remained significant after further adjustment for genetics and early environmental factors shared by twins. The longitudinal analyses also showed that the presence of type 2 diabetes did not increase the risk of future back pain, or vice-versa, after two to four years of follow up. Ultimately, the findings of Chapters Two to Five show that obesity-related measure are unlikely to be directly linked to chronic LBP. Genetics and early environmental factors are plausible confounding factor for the link between obesity-related measures and LBP.

6.3 Limitations of the thesis

When interpreting the findings of this thesis, potential limitations should be taken into consideration. First, an assumption presented earlier in this thesis in regards to MZ and dizygotic (DZ) twin pairs sharing a similar environment may not be entirely correct. MZ twins tend to share demographic and lifestyle factors (e.g. education, smoking habits, and exercise habits) to a greater degree than DZ twins [3]. Although this issue does not affect the estimates presented in the thesis, the greater concordance rates of environmental exposures in MZ twins should be considered when interpreting the results. For example, the differences in MZ and DZ case-control estimates should not be interpreted as purely genetically driven. Second, in the MZ case-
control analyses presented in Chapters Three, Four, and Five, the number of twin pairs discordant for chronic LBP was often less than 50 pairs, which may reduce the precision of the estimates. While these numbers are relatively small, the use of a highly matched twin case-control design may reduce the demand on large sample sizes. Furthermore, results from the case-control analyses (Chapter Three, Four, and Five) are consistent with the meta-analysis (Chapter Two) that included a greater number of MZ twin pairs (>400 MZ pairs) and other twin studies in the field [4, 5]. This suggests that the findings of Chapters Three, Four and Five are plausible.

Third, another potential limitation of the thesis is related to the effect of the duration of the exposures (obesity or type 2 diabetes) on LBP. It is possible that the proposed biological mechanisms underlying the link between obesity or type 2 diabetes and spinal degeneration (e.g. overload or low-grade systemic inflammation) are slow and progressive. The follow-up duration in the longitudinal analyses of this thesis (Chapters Four and Five) were no longer than four years. As such, the temporality effect (time frame of a potential cause and effect) may need to be explored with longer follow-ups. In addition, objective obesity-related data (percentage of body fat, and waist and hip circumference) presented in Chapters Three and Four were available only for females. Hence, this can affect the generalisability of the study findings to males.

Finally, in Chapter Four, the investigation of a dose-response relationship between obesity and LBP revealed that higher levels of obesity did not result in greater risk of chronic LBP. However, in this study, severe obesity was not distinguished from overweight or obesity. According to a recent cross-sectional MZ twin case-control study, not overweight or obese twins, but those twins with severe obesity have a higher chance of reporting chronic LBP (OR 3.7; 95% CI 1.2 to 11.4) compared to co-twins who are of normal weight [4]. This indicates the need for
further studies using twin pairs who are highly discordant for obesity levels. Nevertheless, despite the uncertainty around the role of obesity being regarded as a risk factor for chronic LBP, from a public health perspective, preventing severe levels of obesity should be recommended as an attempt to reduce the risk of a number of obesity-related comorbidities (e.g. cardiovascular disease, type-2 diabetes, and some cancers) [6-9].

6.4 Implications of the thesis and directions for future research

The main results of this thesis reveal that obesity-related factors are unlikely to be strong, direct, and consistent risk factors for the development of chronic LBP. This new evidence likely explains the lack of effectiveness of interventions targeting weight reduction to reduce LBP incidence in adults [10]. The relevance of familial factors such as genetics and environmental factors, and perhaps the interactions between these factors, as plausible risk factors for the development of both obesity and chronic LBP, should not be disregarded. The genetic architecture and gene-environment interactions that influence obesity and chronic LBP are likely complex [5]. However, genetic testing for these highly prevalent and multi-dimensional chronic health conditions is neither clinically applicable nor cost-effective [11, 12]. Therefore, considering the implications and applicability of the findings of this thesis to guide best practice and future research, several key topics will now be considered.

6.4.1 Prevention: Early family-based interventions

A recognised characteristic of LBP, particularly for chronic LBP, is that it tends to cluster in families [13, 14]. The studies that compose this thesis and the vast majority of twin and family research in the field have consistently indicated genetics and familial factors, and perhaps their
interaction, as contributing factors for LBP [4, 13-22]. In light of the strong evidence for familial factors influencing chronic LBP, preventive interventions that are narrowly focused on one health/environmental aspect (e.g. weight loss) later in life, without changing fundamental characteristics of the early family environment, are likely to be insufficient to reduce the risk of chronic LBP. A novel strategy warranting evaluation in future research is early family-based preventive interventions for chronic LBP. Individuals at risk would be identified through their family history of chronic LBP [13, 14]. Targeting the family unit as a means to improve lifestyle behaviours (e.g. physical activity, diet, and cognitive coping skills) has been proven successful to reduce the risk and impact of other chronic health conditions such as obesity, diabetes (type 1 and 2), and chronic pain [23-28]. These results from other fields highlight the value of family-based interventions that could potentially be applied in chronic LBP. Interventions of this nature provide an innovative and promising approach to reduce the risk of chronic LBP, as well as other chronic health conditions that often coexist with chronic LBP such as obesity and type 2 diabetes.

6.4.2 Management of chronic low back pain

Taken in isolation, chronic LBP or obesity (and/or type 2 diabetes) pose enormous challenges to patients, clinicians, and the healthcare system. Importantly, negative impacts on health seem to be exacerbated further when these conditions present concomitantly. Multimorbidity has a greater impact on physical deterioration, quality of life and mortality compared to having one health condition in isolation [29, 30]. The coexistence of chronic health conditions increases the complexity of healthcare services needed by patients [31]. The presence of comorbidities has also been associated with significant longer duration of LBP-related work
disability and higher healthcare costs [32-34]. Furthermore, disability retirement due to LBP is twice more common in overweight or obese individuals than those with normal weight (OR 2.0; 95% CI 1.6 to 2.6) [35]. Therefore, although the main findings of this thesis suggest no direct causal link between obesity and LBP, the importance of obesity and type 2 diabetes as comorbidities for chronic LBP is not diminished.

The studies reported in Chapters Two, Three, and Five revealed a consistent positive association between obesity-related factors and chronic LBP in cross-sectional analyses (unpaired analysis). Importantly, Chapter Five showed that individuals with type 2 diabetes were three times more likely to present with concurrent severe pain (visual analogue scale for pain ≥ 9 out of 11 points) in both the lower back and cervical regions. Hence, the understanding of mechanisms underlying these association (e.g. metabolic mediators), as well as the design of healthcare interventions considering obesity-related comorbidities, should be considered in future research to enhance management of chronic LBP.

6.4.2.1 Metabolic mediators

The mechanisms underlying the associations between obesity, type 2 diabetes, and chronic LBP are likely to be diverse and multifactorial [5, 12]. Familial factors may partially explain these associations, yet it is also likely that other metabolic mediators could play a role in these links. Growing evidence suggests metabolically driven inflammation as a possible pathophysiological link between obesity, type 2 diabetes, and chronic pain [36, 37]. Preliminary evidence suggests that LBP and obesity-related factors are often associated with a low-grade systemic inflammatory phenotype, indicated by higher levels of pro-inflammatory markers (IL-1β and TNF-α). This could affect both pain perception and disease progression in conditions
such as LBP and diabetes [38-40]. Importantly, the pro-inflammatory mediator C-reactive protein (CRP) is elevated in obese individuals [41-43], and obese adults with elevated CRP are more likely to report LBP than those with normal CRP levels [44, 45]. Moreover, greater signs of spinal degeneration are present in individuals with chronic LBP who have high serum CRP levels [46]. Given this evidence, it is likely that low-grade inflammation due to obesity and type 2 diabetes could influence chronic LBP outcomes. A better understanding of endocrine and metabolic mediators providing a mechanistic link between LBP and obesity-related factors would yield a stronger physiological basis to inform the design of novel therapies such as anti-inflammatory or analgesic drugs. Consequently, future research should determine the significance of metabolic pathways to control the progression of chronic LBP in individuals with concurrent obesity and/or type 2 diabetes, in particular individuals with severe pain.

6.4.2.2 Novel approaches to managing individuals with concurrent chronic LBP and obesity (and/or type 2 diabetes)

Traditional models of care are failing to significantly reduce care-seeking and costs associated with the management of chronic LBP [47-51]. This unsatisfactory success may be due to the limitations of conventional clinical management of chronic LBP that often relies on monotherapies which involve face-to-face interactions between the healthcare provider and the patient [52, 53]. Most monotherapies for chronic LBP such as physiotherapy, analgesics, and non-steroidal anti-inflammatory drugs have limited efficacy in LBP [53, 54]. As chronic LBP often coexists with other comorbidities such as obesity and type 2 diabetes, increasing complexity of care, focusing on the management of individual chronic conditions may not be sufficient to achieve treatment success [31, 55]. Efforts towards developing management
approaches that are effective across different chronic illnesses (e.g. chronic LBP and obesity) should be emphasised to ensure integration of healthcare, which could also impact health expenditure [34]. Put simply, this approach would minimise costs due to the elimination of duplication of healthcare services, thereby optimising limited resources [34, 55].

Considering high costs associated with care and limited access to treatment for those with chronic LBP and obesity, innovative methods for healthcare delivery such as telehealth-based interventions should be encouraged [31, 56, 57]. Currently, telehealth-based interventions are successfully used to manage obesity and type 2 diabetes [58-61]. However, the benefits of telehealth-based interventions are limited for individuals with chronic LBP. This evidence is from an unpublished systematic review conducted by our group (Appendix B). This systematic review demonstrates that telehealth-based interventions implemented as a unique management strategy for chronic LBP are not effective in reducing pain and disability (Appendix B). The small effect size identified may be explained by the inherent complexity of chronic LBP management which was not considered in the telehealth-based models. For example, none of the interventions included in the review addressed other common LBP-related comorbidities such as obesity or type 2 diabetes.

To promote optimal patient care focussing on maximising health goals, integration of interventions using telehealth should be explored for individuals with chronic LBP and obesity-related comorbidities. Notably, the protocol of the first randomised clinical trial designed to evaluate the effectiveness of a telephone-based lifestyle behavioural intervention for patients with concurrent LBP and obesity has recently been published [31]. Lifestyle behavioural interventions delivered remotely by phone will be compared to usual care among patients on a waiting list for spinal surgery [31]. Participants will receive ten individually tailored coaching
calls over a six-month period including brief advice and education about the benefits of weight loss and physical activity. Likewise, trials exploring the potential of telehealth-based interventions for individuals with concurrent chronic LBP and type 2 diabetes are needed. Individuals with type 2 diabetes commonly present with poor glycaemic control that may lead to worsening of frequency and severity of LBP and other related comorbidities [62-64]. Telehealth-based interventions are effective in improving glucose control [59, 65-68]. Hence, another important future direction is to explore whether integrated healthcare through telehealth can enhance patient care at a lower costs while improving health outcomes related to chronic LBP and obesity-related comorbidities.

6.5 Final conclusions

Taken together, the results of the twin studies presented in this thesis provide novel information that generate a better understanding of the complex relationships between obesity and LBP. Although obesity and chronic LBP often coexist, a direct link between them is questionable as the associations are mostly weak with no evidence of temporality. Additionally, findings from the twin analyses indicate that these health conditions coexist possibly due to common genetics and early shared environmental influences on their pathogenesis. In light of this new evidence, innovative studies have been proposed. An important future consideration for the prevention of LBP is to investigate whether early family-based interventions targeting modifiable lifestyle behaviours can reduce the incidence of chronic LBP and related disability in youth. This would present an advanced step in a field which urgently requires novel, evidence-based, cost-effective approaches to minimise the individual and societal burden of LBP.
6.6 References


APPENDIX A

Media coverage of Chapter Two and Three
Is there a link between obesity and back pain?

A big belly isn’t necessarily a pain in the back

AUGUST 4, 2015 BY BIM

Over 80% of Australians experience back pain at some point in their lives, which is one of the most common reasons people miss work and seek health care. Despite the efforts of the scientific community to identify risks factors for back pain, the cause of this condition is still poorly understood. Knowing what causes low back pain might help us prevent its occurrence.

The Back Pain Group from the University of Sydney’s Faculty of Health Sciences is currently investigating different factors that increase the risk of back pain such as genetics and obesity related measures. Extra loading on the spine and inflammation are proposed mechanisms that could explain why obese individuals could be at higher risk of developing back pain. However, the evidence is still unclear.

According to our new research investigating twins it could be our genes – not those extra kilos – that are causing back pain. We have recently published two novel twin studies, in The Spine Journal and in The European Spine Journal that debunk the direct link between obesity and low back pain. The articles show that the relationship between obesity and low back pain is more likely the result of shared genetic factors.

The first study, including 1128 Spanish female twins, is the result of collaboration between researchers from the University of Sydney and Spain’s Murcia Twin Registry [1]. The second is a paper summarizing the findings from twin studies conducted in four different countries with participants ranging from 12 to 84 years-of-age [2].

Studying obesity and back pain in twins gives us a unique opportunity to control for various shared genetic factors that can influence people’s health. The strongest results are seen when investigating these health conditions in identical twins because these twins share almost one hundred percent of their genes.

Twin studies give us a less biased estimate of risk for conditions like back pain by controlling for possible confounding from genetic factors and early shared environment. On the surface, it appears that overweight and obese people are twice as likely to have lower back pain. However this association diminishes when factoring in genetic and familial confounders among twins.
Is there a link between obesity and back pain?

The studies suggest that genes common to both low back pain and obesity might be responsible for the relationship between these conditions. From here, where do we go? Currently, to confirm these results, we are conducting a new study that follows the Spanish twins and checks if those who are obese have a higher risk of developing back pain over time. The project is underway and the results will soon be available.

For a long time we thought targeting obesity and prescribing weight loss could help alleviate the prevalence of back pain in the community but these studies call for a rethink. Hopefully these results will contribute to the field and inform policy makers on whether obesity increases, or not, the risk of back pain. This knowledge has the potential to help the design of future preventative strategies for back pain. We think the proverb from 17th century is still valid for today: “An ounce of prevention is worth a pound of cure – Benjamin Franklin”.

About Amabile Borges Dario

Amabile completed her physiotherapy and honours degrees at Santa Catarina State University in Brazil. At the same university, she undertook a Master degree on the effect of aquatic exercise in people with active rheumatoid arthritis. At the University of Sydney, Amabile is conducting a PhD focusing on risk factors for low back pain and was lead author on these twin studies.

Her research career has focused on chronic pain and she is currently a member of the Arthritis and Musculoskeletal Research Group at the Faculty of Health Sciences – University of Sydney.

References


Effectiveness of telehealth-based interventions in the management of non-specific low back pain: a systematic review with meta-analysis.

This systematic review has been under review in *The Spine Journal* since 18 August 2016, and it is in the format required by this journal.
Effectiveness of telehealth-based interventions in the management of non-specific low back pain: a systematic review with meta-analysis

Abstract: Background: Telehealth has emerged as a potential alternative to deliver interventions for low back pain (LBP), however its effectiveness has not been investigated.

Purpose: The aim of this review was to evaluate whether interventions delivered by telehealth improve pain, disability, function, and quality of life in non-specific LBP.

Study Design: Systematic review with meta-analysis

Methods: Seven databases were searched from the earliest records to August 2015. Eligible studies were randomized controlled trials that investigated the effectiveness of telehealth-based interventions, solo or in combination with other interventions, for non-specific LBP compared to a control group. Trials deemed clinically homogeneous were grouped in meta-analyses.

Results: Eleven studies were included (N = 2280). In chronic LBP, telehealth interventions had no significant effect on pain at short [four trials; 1,089 participants; weighted mean difference (WMD) -2.61 points; 95% CI: -5.23 to 0.01] or medium-term follow-up (two trials; 441 participants; WMD: -0.94 points; 95% CI: -6.71 to 4.84) compared to a control group. Similarly, there was no significant effect for disability. Results from three individual trials showed that telehealth was superior to a control intervention for improving quality of life. Interventions combining telehealth and usual care were more beneficial than usual care alone in people with recent onset of LBP symptoms.
Conclusion: There is moderate-quality evidence that current telehealth interventions, alone, are not more effective than minimal interventions for reducing pain and disability in chronic LBP. To date, modern telehealth media (e.g. apps) and telehealth as an adjunct to usual care remain understudied.
Effectiveness of telehealth-based interventions in the management of non-specific low back pain: a systematic review with meta-analysis

Amabile Dario(MSc)\textsuperscript{1}, Anelise Moreti (Physiotherapy Student)\textsuperscript{2}, Lisandra Almeida (Physiotherapy Student)\textsuperscript{3}, Manuela L Ferreira (PhD)\textsuperscript{4}, Kathryn Refshauge (PhD)\textsuperscript{1}, Milena Simic (PhD)\textsuperscript{1}, Evangelos Pappas (PhD)\textsuperscript{1}, Paulo H Ferreira(PhD)\textsuperscript{1}

\textsuperscript{1}Discipline of Physiotherapy, Arthritis and Musculoskeletal Research Group, Faculty of Health Sciences, The University of Sydney, Sydney, Australia.

\textsuperscript{2}Discipline of Physiotherapy, Center of Biological Sciences and Health, Federal University of São Carlos, São Carlos, Brazil.

\textsuperscript{3}Discipline of Physiotherapy, Institute of Health Sciences, Federal University of Bahia, Salvador, Brazil.

\textsuperscript{4}The George Institute for Global Health, Sydney Medical School, The University of Sydney, Sydney, Australia.

Corresponding author: Ms. Amabile Borges Dario

Tel: 61 2 93519562 Fax: 61 2 93519601

E-mail: adar3900@sydney.edu.au

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Introduction

Low back pain (LBP) is a major public health problem with lifetime prevalence estimated at 39% worldwide, affecting people across the whole age spectrum[1,2]. LBP is the leading cause of years lived with disability[3] with costs associated with treatment being extremely high, exceeding €12 billion a year in the European Union[4,5]. As the population ages, a substantial increase in the disease burden of LBP is expected[6].

It is recognized that traditional healthcare models have failed to significantly reduce care-seeking and costs associated with treatment[7-11]. Conventionally, clinical management of LBP relies on face-to-face interactions between the health care provider and the patient[12]. However, this approach is not affordable or accessible for a large number of individuals, particularly those living in remote locations. Given the increase in use of technologies to enhance health services[13], telehealth has emerged as a potential alternative to deliver interventions for LBP.

Telehealth refers to health services delivered remotely via electronic communication media (e.g. websites, telephone) aimed at improving individuals’ health status by providing education and services, reducing healthcare cost, and overcoming geographic barriers[14-16]. Potentially, interventions listed in the most recent clinical practice guidelines for LBP (i.e. patient education, behavior therapy, and exercise programs)[17] could be delivered through telehealth.

The use of telehealth is growing in popularity and has shown to be effective in the management of a variety of other health conditions (e.g. obesity and asthma)[13,18-20]. Despite the growing interest in telehealth for people with LBP[19,21,20], little is known about the clinical effectiveness of this approach. Therefore, we conducted a systematic review and a meta-analysis to determine whether telehealth-based interventions are effective for reducing pain and disability, and for improving function and quality of life for people with LBP.

Methods

A protocol for this review was registered a priori in PROSPERO (CRD42014010007). We also used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement) recommendations to guide the review[22].
Search. MEDLINE, Embase, Web of Science, Scopus, CINAHL, PEDro, and Cochrane databases were searched using a combination of key words related to LBP, telehealth, and randomized controlled trials (RCTs) from earliest records to August 2015. Additionally, citation tracking was conducted of the reference lists of the included studies and relevant publications in the field. The search strategy used for each database can be found in the supplementary Appendix 1.

Selection of studies. The assessment process involved screening of titles, followed by abstracts, and finally full text by two investigators (LA, AM) independently. In cases of disagreement, consensus was reached with a third investigator (AD).

Eligibility criteria. Eligible studies were RCTs that investigated the effectiveness of any telehealth-based intervention, in isolation or in combination with other interventions, for non-specific LBP, compared to a control group. Non-specific LBP is defined as pain arising from the lumbar spine structures with no relevant neural compromise or serious spinal pathology such as fracture or cancer. Relevant outcomes were: pain, disability, function, and quality of life. No restriction on participants' age and sex was applied. Telehealth strategies were defined as any type of health-related service (e.g. health education, exercise prescription, or goal-setting) delivered via telecommunication technologies such as telephone [call, short message service (SMS), applications (apps)] and internet (websites, e-mail). The control group could include no intervention, a waiting list, minimal intervention (i.e. non-health-related or LBP information), or usual care. Studies that included participants with a history of spinal surgery or serious spinal pathologies (i.e. cancer, fracture and systemic diseases) were excluded.

Data extraction. Two reviewers (LA, AM) independently extracted the data, including demographic information, intervention and control group characteristics, and outcomes. A third reviewer (MH) extracted data for non-English studies. Outcome data included mean scores, mean difference between groups, odds ratios, standard deviations (SD), and standard errors (SE). Outcomes were extracted for short-term (immediate effect post-treatment to ≤ 3 months follow-up), medium-term (> 3 months to 1 year follow-up), and long-term (>1 year follow-up) evaluations. When more than one assessment was performed in an interval (e.g. at 4 and 12 weeks), data from the longest period to follow-up were extracted. Results from intention-to-treat analyses were preferentially extracted.
Data synthesis and analysis. For the meta-analyses, the outcomes were converted to a 0-100 scale and described as weighted mean differences (WMD) with 95% confidence interval (CI). The average pain score was used when trials evaluated more than one pain outcome (e.g. worst pain and average pain). When SD was not reported we calculated it from available SE (SE = SD/√n). Trials deemed clinically homogeneous were grouped according to: (i) outcome; (ii) follow-up length (i.e. short and medium-term); (iii) telehealth strategy (i.e. delivered in isolation or added to other intervention; and (iv) LBP chronicity (i.e. acute or chronic). Between-trial heterogeneity was evaluated by visual inspection of the forest plots and the I² Statistic (I²<50%: low to moderate; 50%< I²<75%: substantial; I²>75% considerable heterogeneity)[23]. Pooled effects were calculated using fixed-models when low to moderate heterogeneity was found (i.e. I² ≤ 50), otherwise random-models were used. Analyses were conducted with comprehensive Meta-Analysis software (Biostat, Englewood, NJ, version 2).

Assessment of trial methodological quality. Two independent reviewers (LA, AM) assessed the methodological quality of individual studies using the PEDro scale (0 - 10). This scale is a valid tool to assess the methodological quality of clinical trials, with acceptable reliability [24-26]. Scoring disagreements were resolved by consensus, however, if consensus could not be reached, the issue was resolved by a third reviewer (AD). When available, quality scores were extracted from the PEDro database (www.pedro.org.au). Studies with a PEDro score of 7 or greater were considered ‘high quality’, those with a score of 6 or less were considered low quality [27].

Quality of evidence. Two independent reviewers (AD, MS) used an adapted version of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) classification, to evaluate the quality of evidence and the strength of the recommendation in high, moderate, low, and very low [28,29]. For each pooled estimate, the quality of evidence was initially considered as high and downgraded by one level based on five criteria: poor study design (>25% of participants from studies with low quality methods - PEDro score <7 points), inconsistency of results (I2>50%), publication bias (funnel plot), imprecision (sample size <400 for each outcome), and indirectness (i.e. comparison of different populations and interventions).
Results

Description of included studies.

Screening of titles and abstracts yielded 93 potentially eligible articles with 11 articles included after reviewing full-text (Figure 1)[18,30-32,13,33-38]. Eight original RCTs were included (n = 2280 participants), as more than one publication reported data from the same trial[32,36,38,33,30]. Ten articles were published in English [18,32,36,34,37,38,33,30,35,13], and one was published in German [31]. The earliest publication was in 2002[18], while eight were published in 2010 or later[34,37,38,33,30,35,31,13].

Characteristics of participants. Age of participants ranged from 18 to 82 years and originated from countries such as the United States[13,18,36,32,34,35], Australia[37], Germany[31], and Spain[33,30,38] (Table 1). Participants were recruited at healthcare centers[30,35,31,32,36,37,33,38,39], workplaces[18], or used mixed recruitment strategies (e.g. workplace and online recruitment) [13]. Except for one study, which included patients with mixed symptom duration[13], remaining studies included participants with acute-subacute[37,33,30,38,32,36], or chronic[18,34,35,31] LBP symptoms only. Trials defined acute and subacute LBP as symptoms in the lower back lasting for less than eight weeks, [37] or eight to 12 weeks[32,36,38,33,30] respectively. Chronic LBP was identified by medical records[31], symptoms lasting longer than 12 weeks[34], or having at least one[18], or two[35] outpatient visits in the previous year.

Methodological quality. The overall quality of included studies ranged from four to eight, with the mean score being seven (0-10 PEDro score) (Table 1). The control and intervention groups did not differ at baseline in any study. Four studies (36%) had inadequate (<85%) retention of participants at follow up[18,32,36,31], and three studies (27%) did not conduct an intention-to-treat analysis[32,36,40]. The most common methodological limitation was the lack of blinding of assessor (4/11; 36%), participants (0/11; 0%), and therapist (1/11; 9%), mostly impossible in clinical studies.

Characteristics of telehealth-based interventions. Interventions varied in their length and components (Table 1). However, the aim of the interventions was primarily to support and educate participants in self-managing their
symptoms. Most trials included an educational component to improve the knowledge regarding LBP and to encourage an active life-style\cite{13,18,36,32,34,33,30,38,35}. One study used a health tracker device (pedometer) to encourage physical activity \cite{35}. Behavioral change approaches such as cognitive behavioral therapy and health coaching principles were utilized in five studies\cite{13,36,32,34,37,35}. Trials used website\cite{34,35,33,30,38}, mobile website\cite{13}, online chat-group discussion\cite{35,31}, e-mail discussion\cite{18}, phone calls (i.e. health coaching via telephone)\cite{36,32,37}, or a combination of these telehealth strategies\cite{35,38,33,13} to deliver interventions.

Telehealth interventions were used in isolation\cite{13,31,35,34,18}, or in addition to other interventions (i.e., usual care plus web-based program)\cite{30,33,38,37,36,32}. Intervention length ranged from four weeks\cite{34} to one year\cite{18,35}. Trials compared telehealth interventions to usual care\cite{31,36,32,37,33,30,38} or minimal interventions such as non-health-related\cite{18,35} or LBP information\cite{34,35,13}.

**Efficacy of telehealth to reduce pain.** Six original trials investigated the effect of telehealth on pain reduction\cite{13,31,35,30,33,38,34,18} (supplementary Table 1). Comparison groups consisted predominantly of minimal interventions (i.e. non-health-related or LBP information) in people with chronic LBP. Pooled analysis of four trials\cite{18,29,32,33} revealed a WMD for pain at short-term of -2.61 (95\%CI: -5.23 to 0.01; p = 0.05; $I^2 = 0\%$) on a 100-point scale, where negative values favor telehealth interventions. For the medium-term follow-up, two studies\cite{29,32} were pooled and the WMD was -0.94 (95\%CI: -6.71 to 4.84; p = 0.75; $I^2 = 40\%$) (Figure 2). According to the GRADE classification, there is moderate quality of evidence that telehealth is not superior to minimal interventions for reducing pain in chronic LBP at the short or medium-term follow-ups (publication bias, through the inspection of a funnel plot, not investigated as fewer than ten studies were pooled\cite{41}) (Table 2). Remaining trials that could not be pooled demonstrated that telehealth strategies, when delivered in combination with usual care, or as an unique intervention, reduced pain in patients with sub-acute symptoms,\cite{30} and with mixed length of symptoms\cite{13}, respectively.

**Efficacy of telehealth to reduce disability.** Seven original trials investigated the effect of telehealth interventions on disability\cite{31,35,30,33,38,37,34,36,32,18} (supplementary Table 2). For chronic LBP, four trials compared telehealth strategies mostly to minimal interventions at short-\cite{34,35,18,31} and two at medium-term\cite{34,31} follow-ups. Pooled analysis showed that telehealth was not superior to minimal interventions at short-term (WMD = -1.85 points;
95% CI: -4.32 to 0.62; p = 0.14; $I^2 = 0\%$) or medium-term follow-ups (WMD = 0.13 points; 95% CI: -4.1 to 4.4; p = 0.94; $I^2 = 0\%$). Based on the GRADE classification, there is ‘moderate quality evidence’ that telehealth is not superior to minimal interventions for reducing disability in chronic LBP. Due to considerable heterogeneity, results for acute[32,36], and sub-acute[38,33,30,37] LBP could not be pooled. Nevertheless, findings from three individual trials indicate that telehealth combined with usual care was superior to usual care alone for reducing disability at short[33,30,38], and medium-term[32] follow-ups.

**Efficacy of telehealth in improving physical function and quality of life.** Five[36,32,37,30,35,31] and three[13,18,33,30,38] original trials investigated the effect of telehealth-based interventions on functional status and quality of life, respectively (supplementary Table 3). Meta-analysis was not feasible due to differences in LBP chronicity, outcome measurements, and follow-up length. Overall, trials reported that telehealth combined with other interventions were superior to minimal interventions in improving function for people with acute and sub-acute LBP at short[37,30], and medium-term[32] follow-ups. For chronic LBP, no effect on function was found at short[35], or medium-term[31], when telehealth was used as a sole intervention and compared to minimal interventions. For improving quality of life, the three trials[13,18,33,30] reported that telehealth was superior to a control intervention regardless of duration of LBP symptoms or follow-up length.

**Discussion**

**Summary of findings**

Given the rapid advances in communication technology, telehealth has become increasingly popular for the delivery of health-related interventions for various patient groups[42]. Our results suggest that the evidence supporting the use of current telehealth-delivered interventions in the management of LBP is limited. For chronic LBP, findings from our meta-analysis provide moderate quality evidence that telehealth-based interventions are not superior to minimally-based interventions in reducing pain and disability. For acute and sub-acute LBP, a meta-analysis could not be performed. However, findings from individual studies suggest that telehealth intervention, when used as an adjunct to usual care, appear to optimize the effects of usual care in patients with recent onset of LBP symptoms. Furthermore, telehealth was superior to a control intervention for improving quality of life regardless of duration of LBP symptoms or follow-up length. Telehealth-based interventions for non-specific LBP are in their early stages of
development. Only a limited number of trials have been published, and it remains to be determined if the content of the interventions or the technology approach can explain the lack of effectiveness in chronic LBP.

**Chronic LBP**

Current telehealth-based interventions (mainly based on supporting patients’ behavior change or to self-manage their condition) are not more effective than minimal interventions (i.e. health or non-health-related information) for reducing pain and disability in chronic LBP when used as a sole treatment strategy. The evaluated telehealth-based interventions demonstrated a treatment effect of less than three points on a 100-point scale. As function[35,31] and quality of life[18] were not often reported, we could not quantify the effect of telehealth-based interventions on these outcomes. Individual studies have shown no benefit in function[35,31], yet the only trial that assessed quality of life demonstrated a positive effect of telehealth at short-term follow-up[18].

Although limited benefit of current telehealth interventions was demonstrated for people with chronic LBP, other systematic reviews have shown favorable outcomes of telehealth-based interventions for people with cardiovascular disease, diabetes, obesity, and osteoarthritis[43-46]. The small effect identified in our review may be due to the inherent complexity of chronic LBP management and the low effectiveness of current traditional interventions for management of LBP on which telehealth strategies are built on. Another plausible reason for discrepant results may be the predominantly isolated telehealth interventions implemented for LBP management, whereas many studies of other conditions included telehealth as adjunct therapy[43-46].

Poor patient compliance is often reported in internet-based trials[47]. In our review, only two studies evaluated patient adherence to the telehealth interventions, reporting that compliance was lower than recommended[18,35]. For instance, Krein et al.[35] reported that participants logged into the website only 38% of the recommended time. It is likely that poor treatment adherence may have resulted in small treatment effects associated with telehealth for LBP. Limitations in the technology used to deliver the telehealth interventions may have also contributed to the small effects found in our review. Of the four trials included in our meta-analysis, participants could not access information though their mobile devices which could have interfered with service utilization and its efficacy. For
instance, in other chronic diseases such as asthma and type 2 diabetes, the use of cell phone and text messaging showed significant improvements in intervention acceptance and compliance[42,48].

Another factor likely to explain the small treatment effects of telehealth for LBP is the limited efficacy of the base interventions (i.e. behavioral strategies, exercise prescription, and education) delivered through the telehealth medium. For instance, past research has shown that exercise and cognitive behavioral therapy have small effects on pain relief or function improvements (<10 points on the 100-point scale or 0.3 standard mean deviation) even when delivered face to face to patients with LBP[49-52]. Thus, it is possible that the limitations associated with telehealth are not entirely related to the medium but perhaps to the components of the intervention upon which they are based.

**Acute and subacute LBP**

For acute and sub-acute LBP, we found three small trials, with less than 400 participants in total[36,30,37], where telehealth was carried out in addition to a usual care intervention (e.g.) and compared to usual care alone. Meta-analysis was not feasible. The treatment effects across the trials were inconsistent. For instance, the treatment effect for disability based on standardized effect size ranged from non-significant to large at short-term follow-up. However, in at least one of the three trials, one positive finding was reported when telehealth was added to usual care for all outcomes investigated (pain[30], disability[32,30], function[32,30,37], and quality of life[30]). The variability in results may be explained by the differences in design and contents of the interventions. For instance, the trial with the largest effect size for pain and disability used the longest intervention (9 months)[38]. This is not surprising as behavior change is difficult and time consuming and may in fact be dependent on the length of the intervention.

**Interpretation and implications for clinical practice and research**

Despite the spike in interest and usage of telehealth, this study highlights the limited evidence supporting the use of telehealth for non-specific LBP. To date, most telehealth-based interventions have not shown significant clinically important benefits in the outcomes investigated, in particular for chronic LBP. Future research should focus on improving the design of interventions, drawing on recent guidelines for the management of LBP, and the implementation of telehealth. As telecommunication technology improves and becomes a major source of health
information and social support [53], our findings should encourage interest in researching telehealth for non-specific LBP and its potential to enhance healthcare delivery.

For people with non-specific LBP, telehealth interventions have been delivered via telephone calls[32,36,37], online chat[31], websites[34,35,38,30,33], and email[18,35,38,30,33,13]. However, more recent technology such as smartphone apps, SMS, and health trackers was rarely investigated. Only one trial used a website where participants could access self-tailored strategies through their smartphones[13]. One of the major findings of our review was that those who participated in a tailored self-management web-based program based on education and behavior strategies were almost two times less likely (OR: 1.7) to experience LBP two months after the intervention compared to the control group. Benefits from mobile phone interventions have been observed in the management of chronic diseases such as diabetes, asthma, and hypertension[20,54,55]. The accessibility to smartphones and their use is increasing in both developed and developing countries [56]. Therefore, studies exploring the effectiveness of telehealth-based interventions using more recent wireless mobile technology such as apps and fitness trackers are required.

Another area currently under-investigated is the integration of telehealth using modern communication technology with face-to-face management for LBP. The supplementation of traditional face-to-face interventions by telehealth strategies would allow multimodal interventions by combining treatments which cannot be delivered remotely (e.g. specific forms of exercises or spinal manual therapy techniques) with those which can be effectively delivered remotely such as behavioral change program[57,58]. The combination of behavioral change programs with spinal manual therapy techniques, both delivered face to face, has been shown to improve patient outcomes in chronic LBP[59,60]. Therefore, telehealth-based interventions used as an adjunct, rather than a sole intervention, could potentially optimize the effects of current treatments for LBP.

The profile of patients who are more likely to benefit from telehealth interventions is another area that deserves further attention. Telehealth trials included in this review reported data on recruitment sources, age, and baseline pain and disability levels – all of which affected the effectiveness of telehealth interventions[35,34]. Telehealth interventions appear to be more effective for people with acute and sub-acute LBP symptoms, although this is only a tentative finding based on the limited evidence from three small trials[36,30,37].
Strengths and Limitations

This is the first review to synthesise the findings and quantify the effectiveness of telehealth-based interventions in nonspecific LBP. We evaluated important clinical outcomes, used well-established methods to assess trial methodological quality and strength of evidence, and did not restrict our search on language. However, some weaknesses need to be acknowledged. The scope of our findings are limited due to the small number of trials and variability in the design, content, populations investigated, and measurement of outcomes. As a result, the quantitative synthesis was limited to the outcomes of pain and disability. Furthermore, due to limited research conducted in this area, we were unable to investigate factors that explain the efficacy of telehealth, such as individual patient characteristics (e.g. level of disability, patients’ personal preferences towards treatments) and intervention details (e.g. technology medium, content of intervention). As the best evidence level observed was of moderate quality, future studies with larger sample sizes may provide different estimates of the effects of telehealth for all comparisons.

In summary, this review provides moderate quality-evidence that telehealth-based interventions used in isolation are not more effective than minimal interventions for the reduction of pain and disability in chronic non-specific LBP. Whether the limited effectiveness is explained by the content and nature of the interventions still needs to be explored. For acute and sub-acute LBP, preliminary evidence for the potential of telehealth as an adjunct to usual care has been demonstrated in small individual trials. Larger and higher quality studies with longer follow-ups are crucial for the evaluation of the effectiveness of telehealth-based interventions. Ideally, future trials should investigate which intervention content (e.g. CBT, education, reminders about self-management), and type of telehealth delivery (e.g. SMS, apps) provides the greatest clinical improvements and which subgroup of patients would benefit most from telehealth.
Reference


doi:http://dx.doi.org/10.2519/jospt.2012.3980


doi:10.1111/j.1365-2702.2011.03743.x

doi:10.1097/md.0000000000000312


doi:10.1093/rheumatology/ken470
Figure Legends

Figure 1. Process for the selection of included studies.

Figure 2. Pooled effect of trials that investigated the effect of telehealth on pain and disability for non-specific low back.

Figure 2 Footnote. CI - Confidence interval; I² - heterogeneity of studies. Squares represent each individual study. Diamonds represent the pooled effect. Weight% represents the influence of each study in the overall meta-analysis.
### Table 1. Characteristics of the included studies according to intervention types.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Age Years</th>
<th>Women</th>
<th>Population and source</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
<th>Time points</th>
<th>PEDro scores</th>
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<td><strong>Telemedicine only</strong></td>
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<td>Lorig et al., 2002</td>
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<td>38%</td>
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<td>E-mail discussion group; Book; Videotape emphasizing health behavior change.</td>
<td>Subscription to a non-health-related magazine.</td>
<td>Pain Disability</td>
<td>Baseline and post-treatment</td>
<td>5/10</td>
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<tr>
<td>(United States)</td>
<td>THG: 296</td>
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<td>Chronic LBP (&gt;3 months) patients recruited at pain center and online</td>
<td>Web-based program (self-management and CBT). Intervention</td>
<td>LBP guide e-mailed.</td>
<td>Pain Disability</td>
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<td>(18-79)</td>
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<tr>
<td>Krein et al., 2013</td>
<td>Total: 229</td>
<td>51(13)</td>
<td>13%</td>
<td>Chronic LBP (≥2 outpatient visit in the past year) recruited at</td>
<td>Web-based walking program; E-community; email reminders to upload data.</td>
<td>Pedometer and Email reminders; goal settings.</td>
<td>Pain Disability</td>
<td>Baseline and post-treatment</td>
<td>7/10</td>
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<td>Study</td>
<td>Total</td>
<td>THG</td>
<td>CG</td>
<td>THG/CG</td>
<td>LBP Duration</td>
<td>Intervention</td>
<td>Usual Care</td>
<td>Pain Disability</td>
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<td>Moessner et al., 2013 (Germany)</td>
<td>334</td>
<td>169</td>
<td>165</td>
<td></td>
<td>12 months</td>
<td>Online chat-group; Self-monitoring goals through questionnaire.</td>
<td>Usual care</td>
<td>Pain Disability</td>
<td>Functional Status</td>
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<tr>
<td>Irvine et al., 2015 (United States)</td>
<td>597</td>
<td>199</td>
<td>199</td>
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<td>8 weeks</td>
<td>Self-management web-based program</td>
<td>CG 1. Links to 6 websites with information about LBP e-mailed.</td>
<td>CG2. Usual care</td>
<td>Pain Quality of life</td>
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<td>Damush et al., 2003a,b (United States of America)</td>
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<td>105</td>
<td>106</td>
<td></td>
<td></td>
<td>Usual care + Self-Management Program</td>
<td>Usual care</td>
<td>Disability</td>
<td>Functional Status</td>
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**Telemodecine in addition to other intervention**

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<tr>
<th>Study</th>
<th>Total</th>
<th>THG</th>
<th>CG</th>
<th>THG/CG</th>
<th>LBP Duration</th>
<th>Intervention</th>
<th>Usual Care</th>
<th>Disability</th>
<th>Measurements</th>
<th>Follow-ups</th>
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<td>105</td>
<td>106</td>
<td></td>
<td></td>
<td>Usual care + Self-Management Program</td>
<td>Usual care</td>
<td>Disability</td>
<td>Functional Status</td>
<td>Status and 12(b) months after baseline.</td>
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<td>Study, Year and Location</td>
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<td>CG</td>
<td>Sub-acute LBP Duration</td>
<td>Intervention Details</td>
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<td>Follow-up Period</td>
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<td>Iles et al., 2011 (Australia)</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>&lt;8 weeks</td>
<td>Sub-acute LBP patients recruited at hospital; Intervention length: 4 months</td>
<td>Physiotherapy + health coaching via telephone.</td>
<td>Baseline and 12 weeks after baseline</td>
<td>8/10</td>
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<tr>
<td>Del Pozo-Cruz et al., 2012 a,b,c (Spain)</td>
<td>100</td>
<td>50</td>
<td>50</td>
<td>&lt;12 weeks</td>
<td>Sub-acute LBP patients recruited at University’s Preventive Medicine Service; Intervention length: 9 months</td>
<td>Standard care + Web-based program (e-mail reminders; Videos with exercises and postural reminders). Intervention length: 7 weeks</td>
<td>Baseline and post-treatment</td>
<td>a) 8/10, b) 8/10, c) 8/10</td>
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LBP = Low Back Pain; n = number of participants; Mean, mean (standard deviation), or mean (range); THG = Telehealth Group; CG = Control Group.
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<td>CG: 104</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Krein et al., 2013</td>
<td>Total: 229</td>
<td>51(13)</td>
<td>13%</td>
<td>Chronic LBP (≥2 outpatient visit in the past year) recruited at</td>
<td>Web-based walking program; E-community; Pedometer and email reminders to upload data.</td>
<td>Pedometer; Email reminders; goal settings.</td>
<td>Pain Disability</td>
<td>Baseline and post-treatment</td>
<td>7/10</td>
</tr>
<tr>
<td>(United States of America)</td>
<td>THG: 111</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>CG: 118</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Total: 334</td>
<td>THG: 169</td>
<td>THG: 165</td>
<td>Chronic LBP patients recruited at hospitals</td>
<td>Online chat-group; Self-monitoring goals through questionnaire.</td>
<td>Usual care</td>
<td>Pain Disability</td>
<td>Baseline</td>
<td>Follow-ups</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Moessner et al., 2013 (Germany)</td>
<td>47 (10)</td>
<td>64%</td>
<td></td>
<td>12-15 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irvine et al., 2015 (United States)</td>
<td>597</td>
<td>NR</td>
<td>60%</td>
<td>Individuals with LBP within 90 previous days (chronicity not defined) recruited at workplace and online</td>
<td>Self-management web-based program (education, behavioral strategies). E-mail reminder to log on to FitBack. Intervention length: 8 weeks</td>
<td>CG 1. Links to 6 websites with information about LBP e-mailed. CG2. Usual care</td>
<td>Pain Quality of life</td>
<td>Baseline and 2 months post-treatment</td>
<td>7/10</td>
</tr>
<tr>
<td>Telemedicine in addition to other intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Damush et al., 2003a,b (United States of America)</td>
<td>211</td>
<td>46</td>
<td>74%</td>
<td>Acute and sub-acute LBP (&lt;12 weeks) patients recruited at health centers and</td>
<td>Usual care + Self-Management Program</td>
<td>Usual care</td>
<td>Disability</td>
<td>Baseline, post- treatment (a)</td>
<td>a) 5/10</td>
</tr>
</tbody>
</table>

...
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Total:</th>
<th>THG:</th>
<th>CG:</th>
<th>Recruitment</th>
<th>Intervention length</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iles et al., 2011</td>
<td>Australia</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>Sub-acute LBP (&lt;8 weeks) patients recruited at hospital</td>
<td>4 months</td>
<td>Disability, Functional Status, Baseline and 12 weeks after</td>
</tr>
<tr>
<td>Del Pozo-Cruz et al., 2012 a,b,c</td>
<td>Spain</td>
<td>100</td>
<td>50</td>
<td>50</td>
<td>Sub-acute LBP (&lt;12 weeks) patients recruited at University’s Preventive Medicine Service</td>
<td>9 months</td>
<td>Pain, Disability, Functional Status, Baseline and post-treatment</td>
</tr>
</tbody>
</table>

LBP = Low Back Pain; n = number of participants; *Mean, mean (standard deviation), or mean (range); THG = Telehealth Group; CG = Control Group.
Table 2. Summary of the quality of evidence and strength of recommendation according to GRADE scale.

<table>
<thead>
<tr>
<th>Metaanalyse</th>
<th>Quality Assessment</th>
<th>Patient, n</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk of Bias‡</td>
<td>Inconsistency§</td>
<td>Imprecision¶</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term¹ follow-up four</td>
<td>Serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Direct</td>
</tr>
<tr>
<td>studies 18,31,34,35</td>
<td>limitation (-1)</td>
<td>inconsistency</td>
<td>imprecision</td>
<td></td>
</tr>
<tr>
<td>Medium-term² follow-up two</td>
<td>Serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Direct</td>
</tr>
<tr>
<td>studies 31,34</td>
<td>limitation (-1)</td>
<td>inconsistency</td>
<td>imprecision</td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term¹ follow-up four</td>
<td>Serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Direct</td>
</tr>
<tr>
<td>studies 18,31, 34,35</td>
<td>limitation (-1)</td>
<td>inconsistency</td>
<td>imprecision</td>
<td></td>
</tr>
<tr>
<td>Medium-term² follow-up two</td>
<td>Serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Direct</td>
</tr>
<tr>
<td>studies 31,34</td>
<td>limitation (-1)</td>
<td>inconsistency</td>
<td>imprecision</td>
<td></td>
</tr>
</tbody>
</table>

‡ More than 25% of participants from studies with low methodological quality (Physiotherapy Evidence Database score <7 points); § I² > 50%; ¶ Fewer than 400 participants in the pooling; ** Patient-relevant outcome measures; ¹ Short-term: immediate effect post-treatment to ≤ 3 months follow-up; ² Medium-term: (> 3 months to 1 year follow-up.
Records identified through database searching
- MEDLINE: 262
- CINAHL: 123
- EMBASE: 809
- Web of Science: 461
- PEDro: 810
- Scopus: 980
- Cochrane: 143
  \( n = 3588 \)

Additional records identified through other sources
- Hand searching: 10

Records after duplicates removed
  \( n = 2052 \)

Records screened
  \( n = 2052 \)

Records excluded
  \( n = 1959 \)

Full-text articles assessed for eligibility
  \( n = 93 \)

Full-text articles excluded:
- Not RCT: 27
- Not non-specific LBP: 22
- Not Telemedicine: 13
- Not outcomes: 8
- Not a full text: 5
- Spinal surgery history: 7
  \( n = 82 \)

Studies included in the review
  \( n = 11 \)

Studies included in quantitative synthesis (meta-analysis)
  \( n = 4 \)
<table>
<thead>
<tr>
<th></th>
<th>Mean Differences (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Short-term (≤ 3 months)</strong></td>
<td></td>
</tr>
<tr>
<td>Chiauzzi et al., 2010</td>
<td>-4.0 (-9.5 to 1.6)</td>
<td>22.25</td>
</tr>
<tr>
<td>Moessner et al., 2013</td>
<td>-0.7 (-6.0 to 4.6)</td>
<td>24.03</td>
</tr>
<tr>
<td>Lorig et al., 2002</td>
<td>-3.4 (-8.2 to 1.1)</td>
<td>32.85</td>
</tr>
<tr>
<td>Krein et al., 2013</td>
<td>-2.0 (-7.7 to 3.7)</td>
<td>20.88</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>-2.6 (-5.2 to 0.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Medium-term (&gt; 3 months to 1 year)</strong></td>
<td></td>
</tr>
<tr>
<td>Chiauzzi et al., 2010</td>
<td>-4.0 (-10.5 to 2.5)</td>
<td>46.75</td>
</tr>
<tr>
<td>Moessner et al., 2013</td>
<td>1.9 (-4.2 to 8.0)</td>
<td>53.25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>-0.9 (-5.3 to 3.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Disability</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Short-term (≤ 3 months)</strong></td>
<td></td>
</tr>
<tr>
<td>Chiauzzi et al., 2010</td>
<td>-0.5 (-4.7 to 3.7)</td>
<td>35.30</td>
</tr>
<tr>
<td>Moessner et al., 2013</td>
<td>-2.4 (-8.5 to 3.8)</td>
<td>16.08</td>
</tr>
<tr>
<td>Lorig et al., 2002</td>
<td>-2.5 (-6.8 to 1.8)</td>
<td>32.81</td>
</tr>
<tr>
<td>Krein et al., 2013</td>
<td>-2.9 (-9.1 to 3.3)</td>
<td>15.82</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>-1.9 (-4.3 to 0.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Medium-term (&gt; 3 months to 1 year)</strong></td>
<td></td>
</tr>
<tr>
<td>Chiauzzi et al., 2010</td>
<td>-0.1 (-5.5 to 5.5)</td>
<td>59.90</td>
</tr>
<tr>
<td>Moessner et al., 2013</td>
<td>0.5 (-6.2 to 7.2)</td>
<td>40.10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0.2 (-4.1 to 4.4)</td>
<td></td>
</tr>
</tbody>
</table>

Disability Short-term (≤ 3 months)

Disability Medium-term (> 3 months to 1 year)

Disability Total; I² = 0% (fixed effects); p=0.94 0.2 (-4.1 to 4.4)