Obesity and foot pain

Studies of non-mechanical and mechanical mechanisms

by

Tom Philip Walsh

MHSc(Pod), BPod

Thesis
Submitted to Flinders University
for the degree of

Doctor of Philosophy

College of Medicine and Public Health

18th September 2018

Table of Contents

Summary

Musculoskeletal pain is common, it is a leading cause of burden of disease and it is strongly associated with obesity. There is a particularly high prevalence of frequent, disabling musculoskeletal pain in the feet in the community, affecting nearly one in four adults aged over 45 years in Australia and the United States of America. Whilst much attention is directed towards the effect of obesity causing mechanical overload of single regions, there is a growing body of evidence that highlights the systemic effects of obesity, including non-mechanical factors such as inflammation and a reduction in psychological health that may manifest as pain throughout the human body, including the feet.

This thesis examines the relationship between obesity and foot pain.

The systemic effects of obesity are largely attributed to the metabolic activity of adipose tissue. Adipose tissue secretes a variety of cytokines and inflammatory mediators that have been linked with joint disease and also a deterioration in psychological health. Given excessive adipose tissue is not merely a passive load, it does question the usefulness of measuring body *weight* as opposed to body *composition,* when there is clear heterogeneity in the metabolic activity of both adipose tissue and lean tissue. The association between musculoskeletal pain and body fat was reviewed and analysed in a systematic review and meta-analysis (chapter 2). The systematic review suggested that the volume or percentage of body fat is an important distinction when considering the effect of obesity on pain across multiple sites in the body including the foot. Whether body fat or inflammatory mediators / adipokines were associated with pain was also investigated in a secondary analysis of a community cohort (chapter 3). The results of this study suggested that participants with higher body fat (and depression) had increased risk of having prevalent and future foot pain. Whether the location of fat or different aspects of

psychological health were important factors for foot pain was investigated for both the presence and the severity of foot pain (chapter 4). This study again reinforced that psychological health and body fat are both associated with foot pain.

Despite the known association of obesity and foot pain, there has been very limited research on the effects of weight loss on foot pain. As a means of analysing a group that is over-represented with foot pain, a cohort of people awaiting bariatric surgery were recruited. This study was able to analyse both the role of weight loss and the impact of baseline depression and body composition on a change in foot pain (chapter 5), finding that bariatric surgery was associated with a reduction in foot pain, while baseline body composition was significantly associated with a change in foot pain, independent of bariatric surgery.

The mechanical effects of body weight on foot pain were also studied. The association of foot pain with small changes in both body weight and regional plantar pressures were explored longitudinally over two-year period (chapter 6). This was the first study to explore the temporal relationships between plantar pressure and foot pain. Plantar pressure data from the bariatric cohort in chapter 5 was used to determine the impact of mechanical and non-mechanical factors in both baseline and a change of foot pain (chapter 7). These studies on plantar pressures, which also included foot posture, do not support a strong association between foot posture and foot pain.

Clinicians should be aware that musculoskeletal foot pain is associated with obesity through mechanisms beyond mechanical overload and local foot changes. Foot pain, psychological health and obesity are a triad of factors, each amplifying the other. As both obesity and foot pain (and hence depression) increase in the community, improving the understanding of how this relationship exists and how this may be overcome is discussed.

The association of obesity with foot pain is not surprising, but the studies that comprise this thesis highlight factors that are beyond mechanical overload.

Publications arising from this research

Peer-reviewed journals

Walsh TP, Arnold JB, Evans AM, Yaxley A, Damarell RA, Shanahan EM. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. [In press].

Walsh TP, Quinn SJ, Evans AM, Yaxley A, Chisholm JA, Kow L, Shanahan EM. Fat mass, but not fat-free mass, predicts increased foot pain with morbid obesity, independent of bariatric surgery. *Surg Obes Relat Dis*. [In press].

Walsh TP, Gill TK, Evans AM, Yaxley A, Chisholm JA, Kow L, Arnold JB, Shanahan EM. Changes in foot pain, structure and function following bariatric surgery. *J Foot Ankle Res*. [In press].

Walsh TP, Butterworth PA, Urquhart DM, Cicuttini FM, Landorf KB, Wluka AE, Shanahan EM, Menz HB. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. *J Foot Ankle Res*. 2017;10:31.

Walsh TP, Arnold JB, Gill TK, Evans AM, Yaxley A, Hill CL, Shanahan EM. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *Rheum Int*. 2017;37(7):1175-1182.

Walsh TP, Gill TK, Evans AM, Yaxley A, Shanahan EM, Hill CL. Association of Fat Mass and Adipokines With Foot Pain in a Community Cohort. *Arthritis Care Res (Hoboken)*. 2016;68(4):526-533.

Oral presentations

Walsh TP, Quinn SJ, Evans AM, Yaxley A, Chisholm JA, Kow L, Shanahan EM. Fat mass, but not fat-free mass, predicts increased foot pain with morbid obesity, independent of bariatric surgery. *ANZOS-OSSANZ-AOCO Joint Annual Scientific Meeting*, held 4-6 October 2017 in Adelaide, Australia ***Best paper award***

Walsh TP, Arnold JB, Gill TK, Evans AM, Yaxley A, Hill CL, Shanahan EM. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *Flinders Research Week*, held 4-8 September 2017 in Adelaide, Australia

Walsh TP, Arnold JB, Gill TK, Evans AM, Yaxley A, Hill CL, Shanahan EM. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *Australasian Podiatry Conference Biennial Scientific Meeting*, held 24-26 May 2017 in Melbourne, Australia

Walsh TP, Gill TK, Evans AM, Yaxley A, Shanahan EM, Hill CL. The association of fat mass and adipokines with foot pain. *Australian Podiatry Association (SA) Biennial Scientific Meeting*, held 2-4 June 2016 in Adelaide, Australia

Walsh TP. Foot pain and obesity: too heavy or too fat? *Repatriation General Hospital Medical Grand Round,* held 8 April 2016 in Adelaide, Australia

Walsh TP, Gill TK, Shanahan EM, Hill CL. The association of fat mass and adipokines with foot pain in a community cohort. *Australian Rheumatology Association Annual Scientific Meeting*, held 23-26 May 2015 in Adelaide, Australia

Poster presentations

Walsh TP, Arnold JB, Gill TK, Evans AM, Yaxley A, Hill CL, Shanahan EM. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *ANZOS-OSSANZ-AOCO Joint Annual Scientific Meeting*, held 4-6 October 2017 in Adelaide, Australia

Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

I am the primary author on all published manuscripts including in this thesis. The contribution made by my co-authors is stated at the beginning of each chapter.

Tom P Walsh

25th June 2018

Acknowledgements

There are a number of people and groups that deserve acknowledgement.

Firstly, thank you to Flinders University for giving me the opportunity to complete this PhD. I always felt well supported throughout my candidature, from the courses and training you facilitated to the financial support provided by the publication awards and travel grants. A special thanks to Mr Pawel Skuza, who provided statistical advice on two projects and whose workshops enlightened my understanding of statistics.

I would also like to acknowledge the financial support I received from Services for Australian Rural and Remote Allied Health, who funded my post-graduate scholarship. A very big thank you to Arthritis Australia and the Australian Podiatry Education and Research Foundation for providing project funding.

To the participants, thank you for taking time out of your lives to help me complete my studies.

To my supervisors;

- *Dr Angela Evans;* thank you for your ongoing support of both my career and my studies. You gave me great guidance throughout, from beginning to end, particularly early on in my PhD when it really mattered and your advice on oration was invaluable
- *Dr Alison Yaxley;* thank you for teaching me that attention to detail matters. I hope one day to be as eagle-eyed as you! I also appreciate the opportunity you gave me to supervise three nutrition and dietetics Honours students during my candidature

- *Prof Michael Shanahan*; thank you for being my primary supervisor and first port-of-call. You were always accessible and provided me with the opportunity to explore topics and projects that I was interested in, but you kept me focussed on the task at hand.

You all provided insightful, constructive, challenging and speedy advice throughout my candidature. I am richer for the experience of working with you all.

To my co-authors; *Dr Tiffany Gill*, *Prof Catherine Hill*, *Mr Jacob Chisholm, A/Prof Lilian Kow, Dr Paul Butterworth, Dr Donna Urquhart, Prof Flavia Cicuttini, A/Prof Karl Landorf, A/Prof Anita Wluka, Prof Hylton Menz, Dr Steve Quinn* and *Ms Raechel Damarell*. It was a real privilege to work with you all. A very special thanks to *Dr John Arnold.*

A number of the projects in this thesis required in-kind support from clinical and administrative staff at the Repatriation General Hospital and Flinders Medical Centre. A big thank you to *A/Prof Steve Stranks* and *Mr Con Kapsis* for providing access to your departments for the body composition and radiographic examinations. To *Ms Necia Bulgin, Ms Kirsty Czechowicz, Ms Angela Frangoulis, Ms Rebecca Pearce* and *Ms Nicole D'Agostino,* thank you for your help in recruiting, scheduling and analysing the participants. I would also like to thank the chief-investigators of the North-West Adelaide Health Study for enabling me to access data used for chapter 3.

And finally to my wife, *Maja*. Your continued support and encouragement for me to scratch this and the many itches I have is deeply appreciated. Our wonderful boys, *Edward* and *Louis,* are lucky to have such a patient, endearing and supportive woman to call, mum.

List of Tables

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

List of Figures

Chapter 1

Chapter 2

Chapter 6

Chapter 7

List of Appendices

List of Abbreviations

BIA	Bioelectrical impedance analysis
BMI	Body Mass Index
CATI	Computer Assisted Telephone Interview
CES-D	Center for Epidemiologic Studies Depression scale
CI	Confidence Interval
cm	centimetre
CRP	C-reactive Protein
CSI	Central Sensitization Inventory
DXA	Dual-energy X-ray Absorptiometry
EAI	Epidemiology Appraisal Instrument
ELISA	Enzyme Linked Immunosorbent Assay
FFM	Fat-free Mass
FFMI	Fat-free Mass Index
FM	Fat Mass
FMI	Fat Mass Index
GE	General Electric
ICC	Intraclass Correlation Coefficient
IL-6	Interleukin-6
IQR	Interquartile Range
kg	kilogram
kg / m^2	kilograms per metre squared

kPa	kilopascal
m	metre
MFPDI	Manchester Foot Pain and Disability Index
μg / ml	micrograms per mililitre
MOXFQ	Manchester-Oxford Foot Questionnaire
ms	millisecond
ng / ml	nanograms per millilitre
NJ	New Jersey
NWAHS	North West Adelaide Health Study
OA	Osteoarthritis
OR	Odds Ratio
PCS	Pain Catastrophizing Scale
PD-Q	PainDETECT questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROM	range of motion
RR	Relative Risk
SAT	Subcutaneous Adipose Tissue
SD	Standard Deviation
SMD	Standardised Mean Difference
SPSS	Statistical Package for the Social Sciences
TGF-β	Transforming growth factor-beta
TNF-α	Tumour necrosis factor-alpha

TX	Texas
USA	United States of America
VAS	Visual Analogue Scale
VAT	Visceral Adipose Tissue
VIF	Variance Inflation Factor
vs	versus
WHR	Waist to hip ratio

1

Thesis overview and introduction

1 INTRODUCTION

1.1 Background

The aim of this thesis was to investigate how both mechanical and non-mechanical factors of obesity relate to foot pain. Intuitively, the association between foot pain and obesity is not surprising, although the underlying mechanisms are largely unexplored. The presumption that excessive body weight in people with obesity places additional and excessive load onto weight-bearing joints and connective tissues is plausible. This, however, may not sufficiently explain the strong association of obesity with pain, given that pain in non-weight-bearing structures (such as the hand) is also associated with obesity [1]. Painful, radiographic-defined osteoarthritis of the hand cannot be explained through mechanical load mechanisms alone and so suggests that there may be a non-mechanical link between joint pain and obesity.

Degenerative and inflammatory changes in tissues, such as joints and tendons, are more prevalent in people with obesity [2,3], which may explain why people with obesity have more pain, but there is known discordance between joint and soft tissue changes and pain [4,5]. Pain, particularly chronic pain, is a complex, multi-faceted experience that is influenced by factors such as past experiences, gender and psychological health (for example depression) [6]. Hence, a painful joint or region may not necessarily be fully explained by an organic complaint. People with obesity have heightened pain sensitivity to pressure [7] and therefore pain may also be a manifestation of excessive adiposity acting on the nervous system, including the central nervous system [8]. The association between obesity and pain is complex. Despite its anatomical location, the presentation of foot pain in people with obesity is unlikely to be adequately explained as tissues bearing excessive mechanical loads.

1.1.1 The foot and foot pain

The foot is a complex mechanical structure: it has 20 intrinsic muscles, 28 bones and 34 joints [9]. It must have the capacity to adapt to terrain during locomotion, by both flexibly absorbing shock following heel strike and then becoming a rigid lever during propulsion [10]. There are 18 joints which comprise complementary curved surfaces and 16 plane joints (Figures 1 and 2), functioning as a unit to enable bipedal ambulation.

This figure has been removed due to copyright restrictions

Figure 1: Dorso-plantar view of the bones of the right foot

This figure has been removed due to copyright restrictions

Figure 2: Lateral view of the bones of the right foot

Given a vital role in ambulation, the foot is subjected to a variety of bending and torsional loads, predisposing the connective tissues and joints of the foot to trauma [11]. Indeed, macroscopic and microscopic changes found in neural [12] and ligamentous structures [13] on the plantar surface of the foot may be confused with pathology, but are likely signs

of adaptive, non-pathological change, reflective of the hostile environment of the foot. Furthermore, whilst there are associations between the severity of foot deformities and pain [14], strong associations also exist between the severity of depressive symptoms and foot pain [15]. Therefore, if pain is not necessarily a linear reflection of structural change, it does pose the question, why is pain present in some feet and not others?

Foot pain may not be viewed as being as troublesome as other lower-limb joints such as the hip and the knee, but it is not a trivial complaint. Foot pain has a detrimental effect on quality of life [16] and has been associated with falls [17,18]. Symptomatic foot osteoarthritis is as prevalent, if not more so, than knee osteoarthritis [19] and health-related quality of life in those with end-stage ankle arthrosis is comparable to those with end-stage hip arthrosis [20]. Unlike other larger joints in the lower-limb, foot joints are not routinely replaced when diseased and disabling pain affecting the foot may ensue. Frequent, disabling foot pain affects nearly one in four adults aged over 45 years [21] in Australia and the United States of America (USA) and this figure is likely to increase as the prevalence of obesity increases.

1.1.2 Obesity

Obesity is a growing epidemic, affecting 28% [22] of Australian adults, and over 35% of the global population are either overweight or obese [23]. The age-standardised mean BMI globally in women and men are depicted in Figures 3 and 4.

Obesity is usually defined as a body mass index (BMI) of ≥ 30 kg / m^2 [24] and is typified by an accumulation of adipose tissue [25]. Obesity is linked to a number of comorbidities, including type 2 diabetes, cardiovascular disease and cancer [26]. It has a substantial

impact on the health system and the economy [27], in both the developed and the developing world [28].

This figure has been removed due to copyright restrictions

Figure 3: The global prevalence of mean body mass indices (women) [29]

This figure has been removed due to copyright restrictions

Figure 4: The global prevalence of mean body mass indices (men) [30]

1 INTRODUCTION

Whilst obesity is most commonly defined by the BMI (≥ 30 kg / m^2), this definition has limitations [31] and does not account for differences in body composition. The BMI effectively treats all tissue as homogeneous and does not provide any details on how much lean tissue or how much adipose tissue is present, despite the known differences in the metabolic activity between these tissues [32]. It also fails to account for changes in body composition that occur with age and is not stratified by gender, despite known differences between men and women [33]. Other measures of obesity exist, such as waist circumference and hip circumference, however, not unlike the BMI these provide estimates of body composition. The perpetuated use of the BMI in defining obesity is likely due to its ease and accessibility, however its use in musculoskeletal research may implicitly confuse how obesity and pain are linked.

1.2 Non-mechanical factors and musculoskeletal pain

1.2.1 Body composition

A growing body of research has identified associations between musculoskeletal pain, including the foot, and body composition [34,35]. The analysis of body composition allows not just for the assessment of body weight, but also for the stratification of mass depending on its type. It can also provide data on the location of the tissue on the body, and in some cases what depth it exists within the abdominal cavity [36]. There are various methods of measuring and estimating body composition in musculoskeletal research, including underwater weighing [37], skin fold thickness [38], bioelectrical impedance analysis (BIA) [39] and dual-energy X-ray absorptiometry (DXA).

Measures of body composition can provide estimated data on the volume of fat mass and fat-free mass, enabling the distinction to be drawn between body mass, and the type of

body mass. Body composition is often expressed as the percentage of body fat or fat-free mass, or normalised to body height using fat mass index (FMI) and fat-free mass index (FFMI). Evidence indicates that fat mass may be the main perpetrator linking increased body mass and musculoskeletal pain [40], while FFMI may be protective.

1.2.2 Adipose tissue

Once considered a passive storage of energy, adipose tissue is now recognised as an active endocrine organ. It is responsible for the production and secretion of an array of hormones, proteins and cytokines [41] and obesity is associated with chronic low-grade inflammation [42]. Body fat accumulation may also be stratified by its location, with deposits around the abdomen referred to as ‘android’ and deposits around the thighs and buttocks regarded ‘gynoid’ [43]. Men and women selectively deposit body fat in different regions, with women storing fat in the gynoid region, and men storing fat in the android region [44] (Figure 5). The distinction between android and gynoid adipose tissue is important metabolically. Gynoid adipose tissue is only subcutaneous, whereas android adipose tissue is a combination of both subcutaneous and visceral adipose tissue.

This figure has been removed due to copyright restrictions

Figure 5: Gynoid and android body fat distributions [45]

Subcutaneous and visceral adipose tissue have different developmental origins and it has been proposed that they be considered as different organs [46]. They are structurally and functionally different, with distinctive anatomical, physiological, clinical and prognostic differences [47], which may explain why central obesity (high waist circumference) is linked to cardiovascular disease, whereas a high hip circumference is not [48]. Whilst adipose tissue is responsible for the regulation of a number of proteins and hormones, there is increasing interest in musculoskeletal medicine and a group of cytokines secreted by adipose tissue namely adipokines [40].

1.2.3 Adipokines

Adipokines may be pro- or anti-inflammatory [40] and have both local and systemic effects. The exact role of adipokines in osteoarthritis and musculoskeletal disease is unknown, but the three that have gained the most interest and attention are leptin, adiponectin and resistin [49,50].

Leptin is a hormone responsible for regulating energy expenditure, chiefly through inhibiting hunger [51]. It controls hunger centrally, and there is a strong correlation between subcutaneous adipose tissue and serum leptin [52]. Despite leptin being partially responsible for the regulation of hunger, there are functional leptin receptors found on human chondrocytes [53] and these may be downregulated by obesity through a negative feedback loop [54]. Interestingly, whilst leptin may be involved with chondrocyte generation, excessive leptin in the sera may blunt expression of functional receptors. Leptin has been associated with both upper- and lower-limb musculoskeletal pain [55], as well as generalised musculoskeletal pain [56], with one study finding that leptin mediates the relationship between BMI and knee osteoarthritis [57].

Adiponectin and resistin have also been targeted for investigation, albeit less than leptin. Whilst resistin is upregulated with adiposity, adiponectin is downregulated [58]. Both have been associated with knee osteoarthritis [49], and adiponectin has receptors on human chondrocytes which are down-regulated with osteoarthritis [59]. In clinical studies of musculoskeletal pain the effect of serum adiponectin appears to be protective, with higher levels associated with less progression of hand osteoarthritis [50]. Resistin is a pro-inflammatory cytokine which has its effects mediated by tumour necrosis factor-alpha (TNF-α) [60], and whilst it is not associated with the progression of hand osteoarthritis, it has been associated with the presence and incidence of radiographic knee osteoarthritis, even after adjusting for age, gender and BMI [61].

1.2.4 Pro-inflammatory cytokines / mediators

Other cytokines, not predominately released from adipose tissue, may also be involved in the pathway linking obesity with musculoskeletal pain. Tumour necrosis factor-alpha is a cytokine involved in the inflammatory cascade. It is a therapeutic target for the management of inflammatory arthropathies, and is primarily produced by activated macrophages, but it is also secreted by adipose tissue [41]. Systemic inflammation is upregulated with obesity with the acute inflammatory phase marker C-reactive protein (CRP) noted to be higher in obese people [62]. The increase in inflammation may be in response to over-nutrition initiating an immune response [63], and is particularly positively associated to the consumption of dietary fats [64]. Moreover, elevated TNF-α, along with other inflammatory mediators and markers are associated with chronic pain [65]. Elevated synovial TNF-α levels are also predictive of pain severity and a poor outcome following temporomandibular joint surgery [66]. Higher levels of inflammatory mediators TNF-α and interleukin-6 (IL-6) are associated with less improvement to treatment in those with chronic

pain [67] and TNF-α may moderate the relationship between chronic back pain and depressive symptoms [68]. The underlying mechanism is unknown but there is clearly an association between adipokines and pain and an association may also exist between adipokines and reduced psychological health, such as depression [69].

1.2.5 Psychological health

Depression, obesity and pain are all strongly related [70-73] There are positive relationships between all three factors, and these factors may effectively form a triad that causes each to propagate and amplify the other two. The relationship between obesity and pain is complex, but it may be mediated metabolically through depression. Indeed, it has been proposed that depression is an inflammatory condition [74]. It is important that depression is measured and considered when analysing pain, particularly in the context of obesity, given that it may be a mediator. Depression is undoubtedly the most common psychological health complaint measured in relation to pain, but there are other important features to assess in relation to pain including pain catastrophising and central sensitisation.

Pain catastrophising is the exaggerated negative orientation toward noxious stimuli [75]. It has been shown to predict chronic pain after total knee replacement [76] and is associated with non-musculoskeletal complaints such as migraine, a relationship that exists following adjustment for obesity [77]. Pain catastrophising may predict activity intolerance which in turn feeds into a fear-avoidance cycle that may create future avoidance, anxiety and failure to recover [78]. Interestingly there are higher levels of pain catastrophising in borderline morbidly obese or morbidly obese people awaiting total knee replacement when compared to less obese cohorts [79] and thus there may be interaction between obesity and catastrophising. While pain catastrophising is responsible for

excessive negative feelings toward pain, some people develop an over-reaction to even normal stimuli, central sensitisation.

Central sensitisation is a phenomena that manifests as hyperalgesia, allodynia, expansion of the receptive field, and poor sleep, fatigue, and cognitive deficits [80]. Fibromyalgia is considered a syndrome that has features of central sensitisation, resulting in an unpleasant or exaggerated response to a stimulus [81]. People with central sensitisation may respond negatively to normal stimuli, contorting the lines of investigation regarding obesity and pain. Indeed, elevated BMI has been associated with neuropathic pain [82], which whilst different to central sensitisation does suggest a non-mechanical, non-musculoskeletal related relationship between obesity and pain.

1.3 Mechanical factors and musculoskeletal pain

The obvious link between obesity and foot pain is via mechanical overload. There is undoubtedly a relationship between excessive weight acting directly on weight-bearing structures. Soft tissue or joint disease can develop following excessive loading, which may occur when a single load is too high (acute), or when a normal load is sustained in a repetitive manner over a long duration (chronic) [83,84]. Indeed, osteoarthritis (of the knee in particular) has been described as a mechanical complaint [85], caused by malalignment and overload of physical forces acting on the joint and the surrounding tissues. How mechanical factors relate to foot pain may be both systemic (bodyweight) and local (foot posture and foot function).

1.3.1 Body weight

Elevated body weight has been associated with foot pain, in both athletic and non-athletic populations [86]. Obesity increases the risk of developing both specific and non-specific regional foot pain [87], with the plantar heel particularly susceptible to pain in people with obesity [88]. Excessive body weight increases ground reaction forces, which are dose-dependent as weight increases [89]. The increased ground reaction forces may place additional (and excessive) loads through the pedal joints and connective tissues, although interestingly the reaction forces may be negatively related to lean body mass [90]. The proposed and accepted mechanically mediated relationship between obesity and pain is depicted in Figure 6.

Despite the known associations between obesity and foot pain, literature investigating the effect of weight loss as an effective treatment is scarce. There have been observational studies of multi-site pain in people undergoing bariatric surgery, finding gross improvement in both foot and ankle pain [91,92], but these studies did not include control groups and there have been no randomised controlled trials investigating the effectiveness of either surgical or non-surgical weight loss on foot and ankle symptoms.

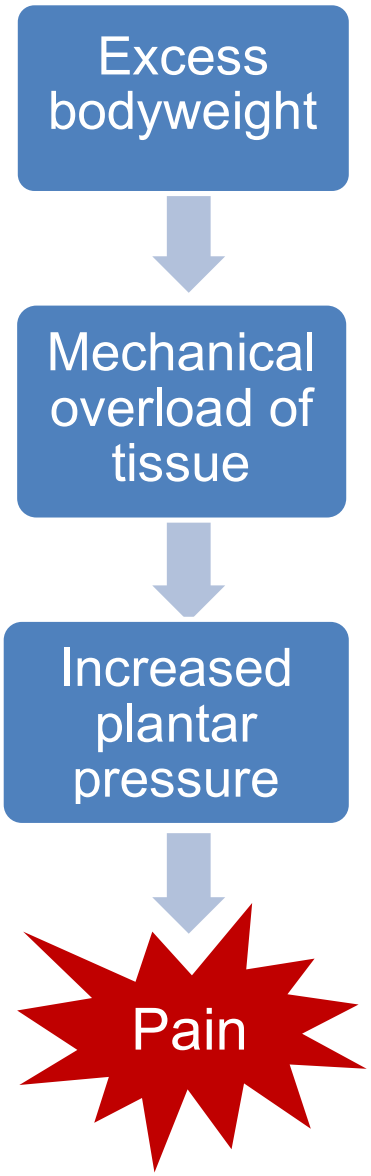


Figure 6: The common proposed pathway linking elevated BMI and musculoskeletal pain

1.3.2 Foot function and plantar pressure

A foot functioning in a pronated posture is frequently associated with foot pain. A large community-based study found that a pronated foot function is associated with foot pain [93] and low-back pain [94], and impairs weight bearing activity [95]. As obesity increases, accurately measuring foot function becomes a challenge.

1 INTRODUCTION

Sophisticated, three-dimensional biomechanical analyses of people with obesity is difficult, as traditional reference sites (often bony landmarks) are less accessible and the accuracy of marker placement and therefore outcome data is questionable [96]. At the other end of the spectrum, static footprints are considered too rudimentary, offering little in the way of foot function assessment. Plantar pressure systems provide a measure that is clinically relevant [97] and can be used as a proxy for foot function and walking speed. Plantar pressure systems capture the pressure between the plantar foot and the supporting surface, each footprint can be stratified into various regions, which can provide useful data for mapping if painful areas correspond with excessive pressure. The systems may be in-shoe or pressure mats, with both able to analyse specific regions; whole foot, heel, midfoot, forefoot, lesser toes and the hallux [98]. A plantar pressure mat system is depicted in Figure 7.

This figure has been removed due to copyright restrictions

Figure 7: Plantar pressure system, Matscan ® (Tekscan, USA) that is used to assess dynamic foot function [99]

Plantar pressure systems can provide useful data, but there are limitations to what they can capture. These systems are unable to measure intra-articular pressures, nor do they provide data that can be extrapolated to inform three-dimensional movement analysis.

Studies have found that asymptomatic people with obesity display increases in plantar pressures that are not uniform, with the areas of highest pressure being the midfoot and forefoot, when compared to non-obese people [98,100,101]. Given that obesity is strongly associated with plantar heel pain [88,102], increased pressure elsewhere is discordant with that which would be expected if pain was strongly related to excessive pressure. Furthermore, people with chronic plantar heel pain paradoxically display reduced loading (effectively offloading the painful region) under the heel when compared to controls, often shifting pressure to the lateral forefoot [103]. Clearly, understanding the link between plantar pressure and foot pain is important as it may help guide therapies that could be implemented at a local level to change pressures and possibly pain. There is currently scant evidence on how the change in weight and change in plantar pressure are associated with foot pain.

1.3.3 Foot posture

A number of measurement tools are available for the assessment of foot posture, which are used both clinically and in the research setting [104]. The rigour and clinical usefulness of traditional measures of foot posture are frequently challenged [105-107] and assessing foot posture in adults with both obesity and morbid obesity, where there may be an accumulation of intra pedal fat that appears to artificially ‘flatten’ a foot, is an even greater task. Indeed, there has been no specific study assessing the reliability and validity of foot posture measures in obese populations has been conducted.

Plain film radiographs are considered the ‘gold standard’ for assessing foot posture [108]. Given the unknown reliability or validity of foot posture measures using existing clinical tools, it may be most suitable to measure foot posture in people with obesity with plain film radiographs. Four measures are used to assess foot posture across multiple planes, known to be useful in describing foot posture [109]. Two weight bearing radiograph views are used; dorso-plantar and lateral (Figure 8 and 9). Using these measures in obese cohorts allows for the measurement of foot posture that is not confounded by soft tissue.

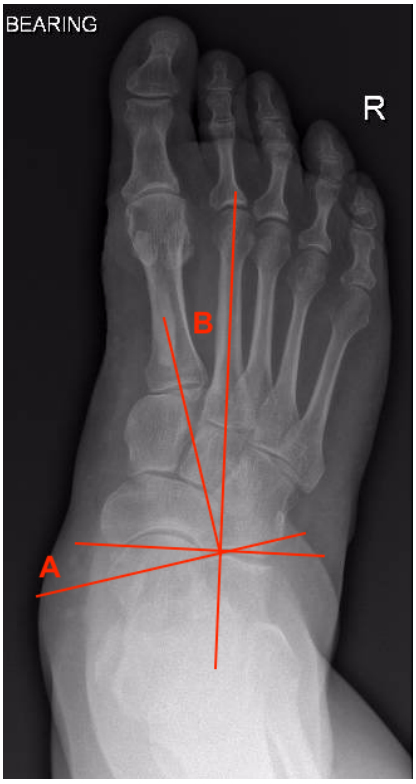


Figure 8: A weight-bearing dorso-plantar radiograph, A: talo-navicular coverage angle B: talus-second metatarsal angle

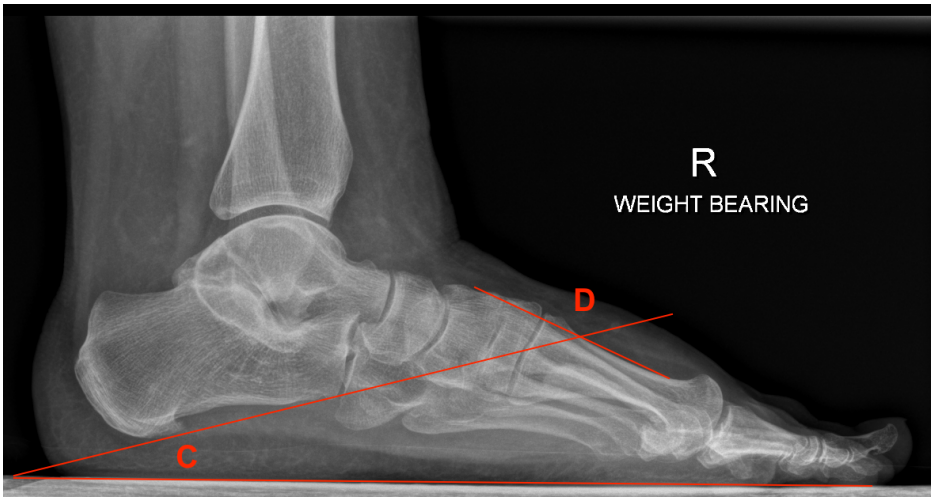


Figure 9: A weight-bearing lateral radiograph of the right foot, C: calcaneal inclination angle D: calcaneal-first metatarsal angle

1.4 Research objectives

The objectives of this thesis are to address and explore the following questions through a variety of study designs:

- Is there an association between body fat and musculoskeletal pain?
- Are there differences in body composition between those with and those without foot pain in a community cohort?
- Are regional fat deposits e.g. subcutaneous or visceral fat associated differentially with either the presence or the severity of foot pain?
- Is the severity of foot pain reduced following bariatric surgery, and if so can the change in foot pain be predicted by body mass or body composition or both?
- Does the severity of foot pain change with increase in weight and regional plantar pressures?

- Does bariatric surgery have an effect on foot pain, foot structure or foot function?

1.5 Clinical importance

Improving the understanding of how obesity and foot pain are related is important to guide therapy. It may indeed be that foot pain is a manifestation of excessive *adiposity*, rather than excessive *weight*. Clearly, if body weight is found to be a significant factor, then modifying or modulating forces and pressures through the foot is a possible treatment method. If body composition, however, is found to be a significant factor, then this may need addressing through methods beyond local (foot) therapy.

This thesis assesses both non-mechanical (FMI, FFMI, psychological health, adipokines) and mechanical (BMI, foot function, plantar pressure, foot posture) factors in relation to foot pain. In most chapters the analysis accounts for at least one mechanical and non-mechanical factor. This was not, however, possible in Chapter 6, as only mechanical measures were available.

Chapter 2 reviews the existing literature that examines the association between body fat and musculoskeletal pain. That is, what do we currently understand about the association between the mass of body fat and the presence or risk of developing pain? This provides a basis for further studies assessing body fat and foot pain.

Chapter 3 reports on a study of a community cohort to determine any associations between prevalent and future foot pain with both body composition and adipokines. This chapter specifically examines whether fat mass or body mass is associated with foot pain.

Chapter 4 examines the question of whether location or psychological health impacts on either the presence or the severity of foot pain, building on the work from Chapter 3. The groups in this study are matched on BMI, such that body weight cannot confound the results.

Chapter 5 is an observational study, but does include an intervention, bariatric surgery, and assesses the effect of weight loss on foot pain, whilst also accounting for body composition and depression.

Chapter 6 is chiefly an exploration into mechanical factors and foot pain. The association of weight gain and plantar pressure on foot pain is explored, examining whether foot mechanics may explain the change in foot pain.

Chapter 7 is concerned with the change in foot structure and function following bariatric surgery and how these changes may relate to foot pain. This chapter explicitly analyses the effect of mechanical (BMI, foot posture and foot function) and non-mechanical (depression) measures on foot pain severity before and following bariatric surgery.

Chapter 8 summarises the findings and provides directions for future research.

2

Chapter 2: Literature review

2.1 Introduction to publication

Walsh TP, Arnold JB, Evans AM, Yaxley A, Damarell RA, Shanahan EM. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. [In press]

Purpose

The purpose of this study was to investigate the association between body fat and musculoskeletal pain.

A number of studies have investigated the association between single-site or multi-site pain and body fat, but there had not been a systematic review or meta-analysis of the literature. This paper aimed to provide a 'state of play' from which future studies could be directed.

Accepted in

BMC Musculoskeletal Disorders

2016 Impact Factor: 1.739

5-year Impact Factor: 2.268

2 LITERATURE REVIEW

Contribution from primary author

Primary Author – Tom Walsh

This review was written by the primary author, which followed consultation and review by the listed co-authors. The primary author conceived the research question and completed the data analysis with a consultant statistician (Pawel Skuza) at Flinders University.

2.2 Abstract

Background: Obesity and musculoskeletal pain are strongly related, but there is emerging evidence that body fat, not body weight, may be a better indicator of risk. There is, therefore, a need to determine if body fat is associated with musculoskeletal pain as it may improve management strategies. The aim of this systematic review was to investigate the association between body fat and musculoskeletal pain.

Methods: Seven electronic databases were searched from inception to 8th January 2018. Cross-sectional and longitudinal studies investigating the association between measures of body fat and musculoskeletal pain were included. All included articles were assessed for methodological rigour using the Epidemiology Appraisal Instrument. Standardised mean differences (SMDs) and effect estimates were pooled for meta-analysis.

Results: A total of 10,221 citations were identified through the database searching, which after abstract and full-text review, yielded 28 unique articles. Fourteen articles were included in the meta-analyses, which found significant cross-sectional associations between total body fat mass and widespread pain (SMD 0.49, 95% CI 0.37 to 0.61, $p < 0.001$). Individuals with low-back pain and knee pain had a higher body fat percentage than asymptomatic controls (SMD 0.34, 95% CI 0.17 to 0.52, $p < 0.001$ and SMD 0.18, 95% CI 0.05 to 0.32, $p = 0.009$, respectively). Fat mass index was significantly, albeit weakly, associated with foot pain (SMD 0.05, 95% CI 0.03 to 0.06, $p < 0.001$). Longitudinal studies (n = 8) were unsuitable for meta-analysis, but were largely indicative of elevated body fat increasing the risk of incident and worsening joint pain. There was conflicting evidence for an association between body fat percentage and incident low-back pain (3 studies, follow-up 4-20 years). Increasing knee pain (1 study) and incident foot pain

(2 studies) were positively associated with body fat percentage and fat mass index. The percentage of items in the EAI graded as ‘yes’ for each study ranged from 23-85%, indicating variable methodological quality of the included studies.

Conclusions: This systematic review and meta-analysis has identified positive cross-sectional associations between increased body fat and widespread and single-site joint pain in the low-back, knee and foot. Longitudinal studies suggest elevated body fat may infer increased risk of incident and worsening joint pain, although further high-quality studies are required.

2.3 Background

Musculoskeletal conditions, manifesting as pain in soft tissues and joints, are a leading cause of disability [110]. Worldwide, they are second only to mental and behavioral problems in contributing to the total years lived with disability [111]. Musculoskeletal pain can lead to an avoidance of physical activity [112] and weight gain [113]. Excessive weight gain may result in the development of obesity and there is a strong bidirectional relationship between obesity and musculoskeletal pain [73], but understanding how excessive body weight and pain are related is important as it guides therapy.

The implication that excessive loading of joints is directly related to pain likely oversimplifies the complex relationship between obesity and pain. This is demonstrated by an abundance of studies with often conflicting findings regarding the nature of the relationship between mechanical loading and pain [103,114-117]. Moreover, whilst ground impact forces are positively related to obesity, lean mass (i.e. muscle) is negatively associated with impact force and may be protective, suggesting that body tissues should not all be considered homogeneous [90].

Obesity is commonly defined as ≥ 30 kg / m^2 on the body mass index (BMI) scale, which is calculated by dividing body weight (kg) by body height (m) squared. This scale, however, treats all body tissue as homogeneous and it does not account for either the type or the distribution of body weight [118]. The BMI is not a good measure of adiposity (body fatness) as it does not account for age or gender differences [33]. Furthermore, given the association between BMI-defined obesity and musculoskeletal pain extends to both weight-bearing [119] and non-weight-bearing joints [1], it follows that the mechanism underpinning this relationship may extend beyond excessive mechanical loading alone, which is implied with the BMI. Fat mass index (FMI) is a more relevant measure in having

or predicting pain [120], suggesting the type of tissue is important. It is also now well-recognised that adipose tissue is an active endocrine organ that secretes many active cytokines and hormones [41], some of which may be related to the development of musculoskeletal pain.

Recent cross-sectional and longitudinal studies are beginning to highlight the important role of body composition in the development and worsening of joint pain [34,35,121]. Body composition can be analysed using a number of techniques including dual energy x-ray absorptiometry, bioelectrical impedance analysis and skin-fold thickness, although this method has challenges with increasing levels of obesity [38]. Whilst much attention is directed toward the strong association between BMI-defined obesity and musculoskeletal pain, there are metabolic [122,123], structural [124] and psychological mechanisms [72] that may link adiposity and pain. There is, therefore, a need to determine whether body fat is associated with musculoskeletal pain as this understanding may improve management strategies. The aim of this systematic review was therefore to investigate the association between body fat and musculoskeletal pain.

2.4 Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [125]. This systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) on 12th August 2017 (http://www.crd.york.ac.uk/PROSPERO/), registration number: CRD42017074289.

2.4.1 Search strategy for identification of studies

The following databases were searched on 9th August 2017: Medline (Ovid); PubMed (non-Medline content only); Embase (OVID); Scopus; CINAHL (EBSCOhost); Cochrane Central Register of Controlled Trials; and Web of Science. All databases were searched from inception to current date. Reference lists from suitable papers were also investigated and included prior to applying exclusion and inclusion criteria. Broad MeSH terms and keywords were used, combining musculoskeletal pain and body composition. The search terms were broad to ensure capture of all relevant studies. Table 1 illustrates the full search strategy used for this systematic review, and minor modifications to search terms were required depending on the database searched. Database searching and registration for automatic e-alerts were also continued until the review was finalised (8th January 2018).

Table 1: Ovid Medline search strategy

#	Searches
1	adipocytes/ or adipose tissue/ or adipose tissue, beige/ or adipose tissue, brown/ or adipose tissue, white/ or abdominal fat/ or intra-abdominal fat/ or subcutaneous fat, abdominal/ or subcutaneous fat/
2	Anthropometry/ or body composition/ or body fat distribution/ or adiposity/
3	obesity, abdominal/
4	(body adj4 composition).tw,kw.
5	(Anthropometr* or "Lean to fat").tw,kw.
6	(Adipos* or adipocyte*).tw,kw.
7	((Body or trunk or subcutaneous or visceral or abdominal or android or gynoid) adj3 fat).tw,kw.
8	(fat adj (mass or deposit* or content or accumulat* or muscle or tissue or volume* or percentage or distribut* or thickness or ratio?)).tw,kw.
9	((Trunk or subcutaneous or visceral or abdominal or android or gynoid) adj obesity).tw,kw.
10	or/1-9
11	musculoskeletal pain/ or myalgia/ or fibromyalgia/ or arthralgia/
12	shoulder pain/ or back pain/ or low back pain/ or pelvic girdle pain/ or neck pain/
13	Muscles, skeletal/ or Joints/ or tendons/ or ligaments/ or ligaments, articular/ or "bone and bones"/ or exp cartilage/
14	hip/ or hip joint/ or knee/ or knee joint/ or foot/ or heel/ or leg/ or lower extremity/

#	Searches
15	upper extremity/ or arm/ or elbow/ or forearm/ or hand/ or shoulder/ or neck/ or back/ or lumbosacral region/ or sacrococcygeal region/
16	"bones of lower extremity"/ or "bones of upper extremity"/ or spine/
17	cervical vertebrae/ or coccyx/ or intervertebral disc/ or lumbar vertebrae/ or sacrum/ or thoracic vertebrae/
18	pain/ or acute pain/ or breakthrough pain/ or chronic pain/ or metatarsalgia/ or morton neuroma/ or exp neuralgia/ or pain, intractable/
19	Pain Measurement/
20	or/13-17
21	or/18-19
22	20 and 21
23	((muscular or muscle* or joint* or musculo* or bone* or skeletal or tendon* or ligament* or cartilage) adj3 pain).tw,kw.
24	(myalgi* or fibromyalgi* or arthralgi* or metatarsalgi*).tw,kw.
25	((((shouder* or back or pelvic or spine or spinal or neck or vertebrae or vertebral or intervertebral or arm* or hand* or elbow* or forearm* or upper extremit* or limb* or widespread) adj3 pain*) or backache).tw,kw.
26	((hip or hips or knee* or foot or feet or heel or heels or leg or legs or lower extremit*) adj3 pain*).tw,kw.
27	or/23-26
28	11 or 12 or 22 or 27
29	10 and 28
30	exp animals/ not humans/
31	(mice or mouse or murine or rat or rats or rabbit* or equine or horse*).ti.
32	(case reports or comment or editorial or legal cases or legislation or letter or news or newspaper article or patient education handout).pt.
33	or/30-32
34	29 not 33
35	limit 34 to english language

Notes: / = Medical Subject Heading (MeSH) search; tw = search on title and abstract fields; kw = search on author keywords; ti = search on title field only; pt = publication type search; exp = exploded MeSH term search to include narrower headings; adj = adjacency operator, restricting search terms on either side to occur within a designated number of spaces from each other.

Following removal of duplicates, two reviewers (TPW and JBA) applied the predetermined selection criteria to all articles by reading the title and abstract alone. Where discrepancies between article selections existed, the reviewers discussed these discrepancies to form a

consensus, a third reviewer was not required to arbitrate a consensus for this review. Articles were then assessed for eligibility by full-text review.

2.4.2 Eligibility criteria

Articles from English language, peer-reviewed, scientific journals were eligible for inclusion in this review if they reported studies that examined the association between body composition and musculoskeletal pain were eligible. Studies were included if all participants were aged at least 18 years, had musculoskeletal pain recorded via self-report or questionnaire (or were controls) and had an assessment of body fat. Studies specifically investigating participants with inflammatory conditions or autoimmune diseases were excluded. Further exclusion criteria were; unclear assessment of musculoskeletal pain or body composition, letters to the editor and editorials, opinion pieces and non-English language publications.

2.4.3 Assessment of methodological quality

All included articles were assessed for methodological rigour using the Epidemiology Appraisal Instrument (EAI) [126]. This tool has been shown to demonstrate good reliability and content validity [127]. A number of items from the EAI were omitted as they were not applicable to non-interventional studies (Questions 10, 12, 20, 22-24, 35, 37, 40) as per previous reviews of observational studies investigating musculoskeletal disorders [128,129]. The covariates considered important for questions 11 and 36 were age, gender and a measure of psychological health. As it is not known if each question of the EAI is equally weighted, rather than providing a quality assessment score for each study, a summary score for each question is reported. A summary (%) of the number of questions a study scored ‘yes’ on is also reported.

2.4.4 Data extraction and analysis

To reduce the risk of bias, author and publication details were removed prior to data extraction. Where available the relevant data (means, medians, standard deviations (SDs), odds ratios (ORs), relative risks (RRs), confidence intervals (CIs) and *p* values) were recorded for each study. Where available, multivariable OR (95% CI) were extracted in preference to unadjusted OR (95% CI). For studies reporting means and standard deviations, effect sizes (Cohen's *d*) and CIs were calculated. According to Cohen [130], effect sizes were interpreted as 0.2, small; 0.5, medium; and 0.8, large. Widespread pain was defined as ≥ 5 painful joints, which is modeled on the criteria of the American College of Rheumatology [131]. Multi-site pain was defined as > 1 but < 5 painful joints. For those studies investigating multi-site or widespread pain, the differences were calculated between the no pain group and the multi-site / widespread pain group. Meta-analysis was performed where more than one study reported on the same parameter, grouped by widespread or single-site pain location. Only the gender-specific sample size was used when entering gender-stratified data into the meta-analysis.

The OR and CIs, and SMDs (Cohen's *d*) were pooled for meta-analysis by the standard approach, weighted by the inverse variance method. Odds ratios and CIs were converted to SMDs for meta-analysis [132]. Statistical heterogeneity was assessed for each site using the I^2 statistic. Potential publication bias was assessed graphically using a funnel plot [133] and Egger's regression intercept for low-back pain, knee pain and foot pain. Both heterogeneity and publication bias were considered, accepting the fact that the power was low because of the small number of studies for each site. Sensitivity analysis was performed via the one-study removed test (removal of individual studies out of the model in turn), which gauges each study's impact on the overall pooled effect size. A p-value less

than 0.05 (two-tailed) was considered statistically significant. All analyses were conducted using Comprehensive Meta Analysis v3.0 (Biostat, NJ, USA).

2.5 Results

The initial literature search yielded a total of 10,221 citations, which was reduced to 5,026 following the removal of duplicates. These 5,026 articles were screened based on their title and abstract, where a further 4,945 articles were excluded, leaving 81 articles that underwent full-text review. After 53 articles were excluded, 28 unique articles included in this review [34,35,120,121,134-157]. Twenty-two articles reported cross-sectional data [35,120,121,134-152] and eight articles [34,120,134,153-157] provided longitudinal data (two articles reported both cross-sectional and longitudinal data [120,134]). Four articles used participants from the same study [34,35,121,139], and there were three other instances of articles using data, reporting different outcomes, from the same study [146,156], [134,138,154] and [137,141], leaving 21 unique studies. The regions with multiple studies using the same parameter were widespread, low-back, knee and foot and thus these were included in the quantitative analysis (n = 14) [120,134-136,138-142,146-148,150,151]. All of the studies included in the meta-analysis were cross-sectional. There were fewer longitudinal studies, with most studies only investigating one site (other than low-back) with variable follow up time, therefore these data did not undergo meta-analysis. Details of study selection have been recorded (Figure 1) following the guidelines set by PRISMA.

2.5.1 Study characteristics

A variety of sites for musculoskeletal pain were investigated, including the neck, low-back, knee and foot. The low-back was the most common region investigated, with 15 studies including this site in their analysis [35,121,134-137,142,145-147,150,151,155-157]. Three

studies investigated the association between multi-site / widespread pain and body composition [121,134,135], while another investigated multiple regions, but stratified the analysis by these regions [136]. One study [153] used body composition as a predictor for any injury and thus a specific region was not investigated. Body composition was analysed with dual energy x-ray absorptiometry in 13 studies [34,35,120,121,134,135,137-142,154], bioelectrical impedance analysis in 10 studies [136,143-149,155,156], and skin fold thickness in 5 studies [150-153,157]. Body composition was generally reported as a percentage of body fat (17 / 28 studies) [136,138,142-151,153-157]. The cross-sectional studies consisted of; population-based (n = 7), clinic-based (n = 7), musculoskeletal pain study (n = 5), occupational-based (n = 2) and unknown (n = 1). The longitudinal studies were largely population-based (n = 6) along with occupational-based (n = 1) and military-based (n = 1). The longitudinal studies varied in follow-up from 3 months [153] to > 20 years [157], but most were between 3 – 5 years.

2.5.2 Participant characteristics

The studies included in this systematic review reported on 12,942 participants, with studies from Asia, Europe, South America and Australia. Both men and women were represented in most studies, although gender-specific studies accounted for > 35% of the total [137,140,141,145,146,148,151,153,156,157]. Mean age in the cross-sectional studies ranged from 20.7 years [149] to 74.4 years [39], while the longitudinal studies ranged from 19.0 years [153] to 64.6 years [120]. Most cross-sectional studies included participants with mean BMIs of < than 30 kg / m^2, however four included participants with a mean BMI of > 30 kg / m^2 [35,121,139,152]. The mean BMI of the participants from the longitudinal studies ranged from 20.8 kg / m^2 [153] to 29.6 kg / m^2 [34].

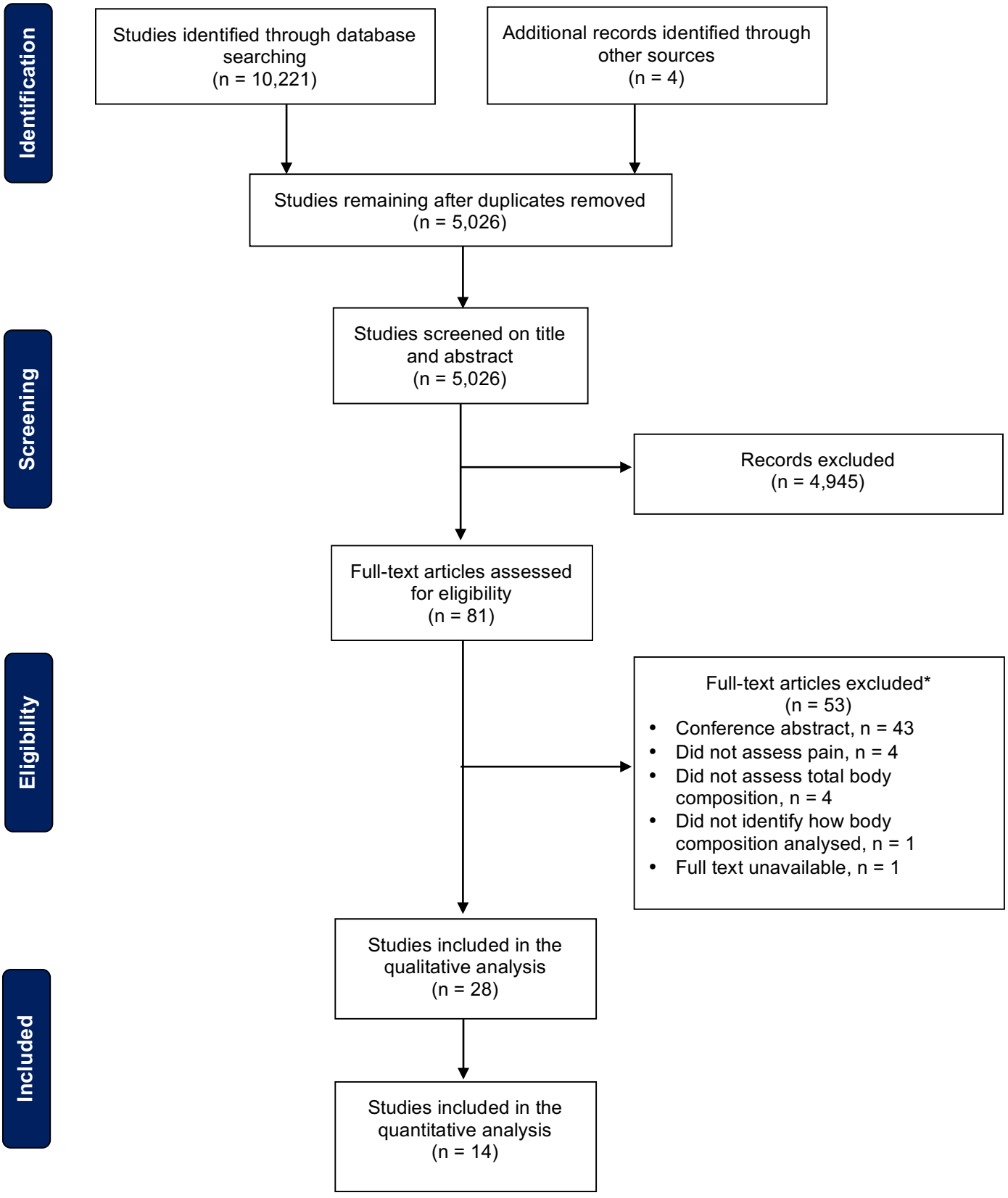


Figure 1: Selection process for inclusion of articles in this review of the association between body fat and musculoskeletal pain

2.5.3 Methodological quality assessment

The results of the methodological quality assessment are provided in Table 2. The summary scores for each question ranged from 4% to 96%, with 14 / 34 questions scoring above 50%. The percentage of items in the EAI graded as 'yes' for each study ranged from 23-85%, indicating variable methodological quality of the included studies. There were common, strong themes among the studies with the clear descriptions of the aims, study design and results reported in most studies (> 85%). There were, however, a number of consistent methodological limitations; the reliability and validity of the instruments used was often under-reported, a sample size calculation was mostly not reported (96%) and the generalisability of the findings was questionable in over 80% of the included studies. Whilst there was adjustment for a number of other variables e.g. smoking, physical activity, self-reported arthritis, adjustment for all of the important confounding variables was reported in less than 30% of the articles [34,120,121,134,137,139,141,155]. One article considered psychological health alone [143], one article considered age alone [157], six articles considered both age and gender [35,135,136,140,154,156]. Only three articles [120,139,141] provided data that were adjusted for the important confounding variables (age, gender, psychological health) that were also used in the meta-analyses.

Table 2: Quality assessment

Study	1. Hypothesis/aim/objective	2.Exposure	3. Outcome	4. Study design	5.Study population	6. Inclusion criteria clearly described	7.Participation rates reported	8.Characteristics of participants described	9.Characteristics of subjects lost or unavailable reported	11. Important covariates described	13.Statistical methods described	14.Results clearly described	15.Variability in data reported	16.Statistical parameters reported	17. Sample size calculation	18.Comparability of groups	19. Adequate participation rate	21.Drop-out characteristics reported*	25.Exposure variables reliable	26.Exposure variables valid	27.Exposure methods comparable	28. Exposure conducted prior to symptoms	29.Observers blind to subject grouping	30.Subjects blinded	31.Outcome measures reliable	32.Outcome measures valid	33.Standardised assessment of variables	34.Same time period of observations	36. Adequate adjustment for covariates	38. Minimum time to follow-up to detect relationship	39. Adjustment for different lengths of follow-up	41. Exposure data reported by subgroup	42.Generalisability of results to study population	43.Generalisability of results to greater population	Summary of questions answered 'yes' (%)
Brady [121]	y	y	y	p	p	p	n	y	n	y	p	y	y	n	n	na	utd	n	utd	utd	na	na	na	na	utd	utd	na	na	y	na	na	y	utd	utd	36
Butterworth [34]	y	y	y	p	p	p	y	y	y	y	y	y	y	y	n	y	utd	p	utd	utd	y	y	utd	utd	utd	y	y	utd	y	y	utd	y	y	y	62
Butterworth [141]	y	y	y	y	y	n	y	y	y	y	y	y	y	y	n	na	y	y	utd	utd	na	na	na	na	utd	y	na	na	y	na	na	y	y	y	80
Celan [145]	n	p	p	y	p	p	y	n	n	n	p	n	n	n	n	y	utd	n	utd	utd	y	y	na	utd	utd	utd	y	utd	n	na	na	y	utd	utd	23
Chou [137]	y	y	y	y	y	p	y	y	p	y	y	y	y	y	n	na	y	p	utd	utd	na	na	utd	utd	utd	y	na	na	y	na	na	y	y	y	67
Dario [146]	y	y	y	y	y	p	n	y	n	n	p	y	y	y	n	na	utd	n	utd	utd	na	na	utd	utd	utd	utd	na	na	p	na	na	y	utd	utd	37
Dario [156]	y	y	y	y	y	n	y	y	y	p	y	y	y	y	n	na	utd	y	utd	utd	na	y	na	na	utd	utd	na	na	p	y	y	y	y	y	68
Hashimoto [157]	y	y	y	p	y	n	y	n	n	n	y	p	y	y	n	y	utd	utd	utd	utd	y	n	utd	utd	utd	utd	y	y	p	y	y	n	p	n	41
Hodselmans [150]	y	y	p	y	y	n	n	y	n	n	y	y	y	n	n	p	utd	utd	utd	utd	utd	na	n	n	utd	utd	utd	utd	n	na	na	p	utd	utd	26
Hussain [155]	y	y	y	y	y	n	y	y	y	y	y	y	y	y	n	y	y	y	utd	utd	y	y	y	y	y	y	y	y	y	y	utd	y	y	y	85
Iizuka [136]	y	y	y	y	y	p	y	y	n	p	y	y	y	y	n	na	n	y	utd	utd	na	na	na	na	utd	utd	na	na	p	na	na	n	n	n	48
Jin [154]	y	y	y	y	y	p	y	y	n	p	y	y	y	y	n	y	p	y	utd	utd	y	y	utd	y	utd	y	y	y	p	y	utd	y	p	p	62
Jordani [143]	y	y	p	n	y	y	p	y	n	y	y	y	y	y	n	y	utd	y	utd	utd	y	na	utd	utd	utd	utd	y	p	p	na	na	y	utd	utd	48
Kodesh [153]	y	y	p	p	y	p	n	y	n	n	y	y	y	y	n	y	utd	n	y	utd	y	y	y	y	utd	utd	y	y	n	y	na	y	utd	utd	55
Ozer Kaya [148]	y	y	y	y	y	p	y	y	n	n	y	y	y	n	n	y	p	n	utd	utd	y	na	utd	utd	y	p	y	utd	n	na	na	y	p	p	48
Pan [134]	y	y	y	y	y	n	n	y	n	y	y	y	y	y	n	y	utd	p	utd	utd	y	utd	utd	utd	utd	utd	y	y	y	y	y	y	utd	utd	56
Sabeti [149]	y	y	y	p	n	p	n	y	n	n	p	p	p	n	n	utd	utd	y	utd	utd	y	na	n	utd	utd	utd	y	utd	n	na	na	y	p	utd	37

Study	1. Hypothesis/aim/objective	2.Exposure	3. Outcome	4. Study design	5.Study population	6. Inclusion criteria clearly described	7.Participation rates reported	8.Characteristics of participants described	9.Characteristics of subjects lost or unavailable reported	11. Important covariates described	13.Statistical methods described	14.Results clearly described	15.Variability in data reported	16.Statistical parameters reported	17. Sample size calculation	18.Comparability of groups	19. Adequate participation rate	21.Drop-out characteristics reported*	25.Exposure variables reliable	26.Exposure variables valid	27.Exposure methods comparable	28. Exposure conducted prior to symptoms	29.Observers blind to subject grouping	30.Subjects blinded	31.Outcome measures reliable	32.Outcome measures valid	33.Standardised assessment of variables	34.Same time period of observations	36. Adequate adjustment for covariates	38. Minimum time to follow-up to detect relationship	39. Adjustment for different lengths of follow-up	41. Exposure data reported by subgroup	42.Generalisability of results to study population	43.Generalisability of results to greater population	Summary of questions answered 'yes' (%)
Sakai [142]	y	y	y	y	y	p	n	y	n	p	y	y	y	n	n	y	utd	n	utd	utd	y	na	utd	utd	utd	utd	y	y	n	na	na	y	utd	utd	45
Scott [138]	y	y	y	y	y	p	p	y	n	n	y	y	y	y	n	y	p	n	utd	utd	y	na	utd	utd	utd	y	y	y	n	na	na	y	p	p	52
Spyropoulos [151]	y	y	y	n	y	p	n	y	n	n	p	y	y	n	n	y	utd	n	utd	utd	y	na	y	n	utd	utd	y	y	n	na	na	y	utd	utd	42
Sutbeyaz [152]	y	y	y	p	y	y	n	y	n	p	y	y	y	n	n	y	utd	n	utd	utd	y	na	utd	utd	utd	y	y	utd	n	na	na	y	utd	utd	45
Tanamas [139]	y	y	y	p	p	p	n	y	n	y	y	y	y	y	n	na	utd	n	utd	utd	na	na	na	na	utd	y	na	na	y	na	na	y	utd	utd	48
Toda [147]	p	y	y	p	p	p	n	y	n	p	y	y	y	n	n	y	utd	n	utd	y	y	na	utd	utd	utd	utd	y	y	n	na	na	y	utd	utd	39
Urquhart [35]	y	y	y	y	p	p	n	y	n	y	n	y	y	y	n	na	utd	n	utd	utd	na	na	na	na	y	y	na	na	p	na	na	y	utd	utd	48
Walsh [120]	y	y	y	p	y	n	n	y	n	y	y	y	y	y	n	y	utd	n	utd	utd	y	y	utd	utd	utd	utd	y	y	y	y	utd	y	utd	utd	53
Walsh [140]	y	y	y	y	y	y	n	y	n	y	y	y	y	y	y	p	utd	n	y	utd	y	na	n	n	y	p	y	utd	p	na	na	y	utd	utd	58
Yalcinkaya [144]	y	y	y	p	y	y	n	y	n	y	y	y	y	n	n	p	utd	n	utd	utd	y	na	n	n	y	y	y	utd	n	na	na	y	utd	utd	48
Yoo [135]	y	y	y	y	y	y	y	y	y	p	y	y	y	y	n	y	p	n	utd	utd	y	na	na	na	utd	utd	y	na	p	na	na	y	p	p	61
Studies scoring 'Yes' (%)	93	96	86	57	75	18	39	93	18	43	79	89	93	64	4	57	11	25	7	4	68	25	11	11	18	37	68	36	29	29	11	89	18	18	

y conditions met, *p* conditions partially met, *n* conditions not met, *utd* unable to determine, *na* not applicable

2.5.4 Meta-analysis

Meta-analysis of cross-sectional single-site and widespread pain studies that underwent meta-analysis found significant associations between body fat and pain (Figures 2-5), summarised in Table 3. There was a positive medium effect size between total body fat mass and widespread pain (SMD 0.49, 95% CI, 0.37 to 0.61, $p < 0.001$ and $I^2 < 0.001$, $p = 0.366$). Single-site musculoskeletal pain also had positive associations with body fat. Low-back pain and body fat percentage had a combined small-medium effect size (SMD 0.34, 95% CI 0.17 to 0.52, $p < 0.001$), but there was a significant level of heterogeneity ($I^2 = 91.21$, $p < 0.001$). Body fat percentage and knee pain had a small effect (SMD 0.18 95% CI, 0.05 to 0.32, $p = 0.009$ and $I^2 < 0.001$, $p = 0.941$), while the pooled FMI and foot pain had a small effect (SMD 0.05, 95% CI, 0.03 to 0.06, $p < 0.001$ and $I^2 < 0.001$, $p = 0.564$).

2.5.5 Sensitivity analysis

The association between knee pain and body fat percentage was not significant when the data pertaining to women from Scott et al [138] was removed from the meta-analysis, (SMD 0.16, 95% CI -0.02 to 0.34, $p = 0.075$), suggesting that the relationship may be mediated by gender. All other sites remained significant when one study was removed from the respective model.

2.5.6 Publication bias

No significant publication bias was detected for studies reporting foot pain or knee pain, with Egger's regression intercept (95% CI) of 0.75 (-2.38 to 3.87), $p = 0.412$ and -0.61 (-10.87 to 9.66), $p = 0.589$, respectively. There was however a potential for publication bias detected for studies reporting low-back pain with Egger's regression intercept (95% CI) of 3.44 (1.57 to 5.33), $p = 0.004$. Widespread pain was reported in only two studies and was therefore not amenable for the funnel plot test or Egger's regression intercept

Table 3: Selected characteristics of the cross-sectional articles included in the review (n = 22)

Study / country / reference	Sample size, n	Age, y	BMI, kg / m^2	Body composition assessment	Parameter investigated	Body composition (Case, control)	Effect size (CI) Cohen's *d*	OR (CI)	Included in the meta-analyses
Widespread pain (≥ 5 sites)									
Pan, Australia [134] [#]	336 widespread pain, 137 no pain	Baseline 63.3 (7.7) widespread pain, 62.2 (7.2) no pain	Baseline 28.8 (5.3) widespread pain, 26.2 (3.9) no pain	DXA	Total fat mass	30.0 (9.5) kg, 25.0 (7.1) kg	0.56 (0.36 to 0.76)	N/A	Yes
Yoo, Republic of Korea [135]	229 widespread pain, 618 no pain	60.8 (8.6)	24.3 (3.2)	DXA		19.1 (6.1) kg, 15.9 (7.5) kg	0.45 (0.29 to 0.60)	N/A	Yes
Multi-site pain (3 sites)									
Brady, Australia [121]	133 (104 women), 42 multi-site pain 27 no pain	47.9 (45.0, 50.7)[$] multi-site pain 46.3 (42.8, 50.0) no pain	36.6 (34.1, 39.2)[$] multi-site pain 28.4 (25.2, 31.6) no pain	DXA	FMI	16.2 (14.5-17.9) kg / m^2 multi-site pain, 11.0 (8.8-13.1) kg / m^2 no pain	N/A	N/A	No
Temporomandibular joint pain									
Jordani, Brazil [143]	299 (229 women), 159 pain, 70 no pain	37.7 (12.2) pain 35.9 (13.6) no pain	Not stated	BIA	Body fat percentage	N/A	N/A	1.58 (0.72 to 3.48)	No
Neck pain									
Yalcinkaya, Turkey [144]	160 (80 women), 40 case, 40 control	44.6 (10.2) case 40.8 (8.0) control	28.4 (4.3) case 28.3 (3.9) control	BIA	Body fat percentage	Case Women: 46.6 (9.6)% Men: 37.6 (6.0)% Control Women: 46.0 (9.8)% Men: 34.2 (6.0)%	Women 0.06 (-0.38 to 0.50) Men 0.57 (0.11 to 1.01)	N/A	No
Neck and shoulder pain									
Iizuka, Japan [136][‡]	273 (179 women)	64.3 (13.2)	23.4 (2.9)	BIA	Body fat percentage	N/A	N/A	0.98 (0.94 to 1.03)	No
Low-back pain									
Hodselmans, Netherlands [150]	101 (47 women)	39.2 (9.6)	Not stated	Skin fold		30.4 (8.2)%, 26.4 (6.1)%	0.55 (0.27 to 0.83)	N/A	Yes
Spyropoulos, Greece [151]	60 (all women), 30 case, 30 control	41.7 (7.3) case 42.2 (7.3) control	27.1 (3.4) case 25.3 (3.1) control	Skin fold	Body fat percentage	34.7 (5.1)%, 31.3 (5.2)%	0.66 (0.13 to 1.17)	N/A	Yes

Study / country / reference	Sample size, n	Age, y	BMI, kg / m^2	Body composition assessment	Parameter investigated	Body composition (Case, control)	Effect size (CI) Cohen's *d*	OR (CI)	Included in the meta-analyses
Iizuka, Japan [136]‡	273 (179 women)	64.3 (13.2)	23.4 (2.9)	BIA		N/A	N/A	0.97 (0.93 to 1.02)	Yes
Dario, Spain [146]	687 (all women), 313 pain, 374 no pain	53.6 (7.4) pain 52.2 (7.4) no pain	27.7 (5.2) pain 26.8 (4.6) no pain	BIA		N/A	N/A	1.15 (1.01 to 1.32)	Yes
Toda, Japan [147]	330 (206 women), 203 case 127 control	Men: 55.6 (8.8) case, 57.7 (9.8) control Women: 60.0 (9.2) case, 57.6 (8.1) control	Men: 23.9 (2.4) case, 23.9 (3.1) control Women:22.7 (3.4) case, 22.7 (3.3) control	BIA		Women 29.7 (6.8)%, 27.9 (6.7)% Men 23.8 (5.2)%, 22.3 (6.1)%	Women 0.27 (-0.01 to 0.54) Men 0.27 (-0.10 to 0.64)	N/A N/A	Yes
Sakai, Japan [142]	660 (311 women), 100 case, 560 control	74.4 (6.0) case, 73.2 (7.6) control	23.6 (3.2) case, 24.2 (3.5) control	DXA	Body fat percentage	Women: 41.1 (4.1)%, 34.3 (8.8)% Men: 35.8 (6.7)%, 27.7 (7.6)%	Women: 0.83 (0.09 to 1.54) Men: 1.08 (0.76 to 1.40)	N/A N/A	Yes
Celan, Slovenia [145]	112 (all men), 76 pain 36 no pain	44.2 (5.6), range 31-56	27.7 pain, 27.9 no pain	BIA		Case 26.4% Control 25.5%	N/A	N/A	No
Urquhart, Australia [35]	135 (113 women), 29 high pain, 106 no or low pain	47.4 (9.0) range 25-62	32.6 (8.7), range 18-55	DXA	Total fat mass	N/A	N/A	Pain intensity 1.19 (1.04 to 1.38) Disability 1.41 (1.20 to 1.67)	No
Chou, Australia [137]	820 (all men), 124 high pain, 696 no or low pain	62.9 (14.0) high pain 58.1 (17.1) no or low pain	28.6 (4.5) high pain 27.2 (4.1) no or low pain	DXA	Total fat mass	High pain disability / intensity 25.9 (7.9) kg No or low disability / intensity 23.0 (8.6) kg	0.34 (0.15 to 0.53)	N/A	No

Study / country / reference	Sample size, n	Age, y	BMI, kg / m^2	Body composition assessment	Parameter investigated	Body composition (Case, control)	Effect size (CI) Cohen's *d*	OR (CI)	Included in the meta-analyses
Knee pain									
Ozer Kaya, Turkey [148]	149 (all women), 52 cases, 97 controls	42.6 (4.1) case 41.7 (4.2) control	30.5 (5.3) case 29.4 (4.6) control	BIA		39.3 (7.9)%, 38.1 (7.7)%	0.15 (-0.19 to 0.49)	N/A	Yes
Scott, Australia [138]	709 (357 women), 311 pain, 398 no pain	Men: 62.0 (7.2) pain, 63 (7.3) no pain Women: 61.7 (7.5) pain, 62.0 (7.0) no pain	Men: 28.2 (3.8) pain 27.0 (3.5) no pain Women: 28.2 (5.6) pain, 27.0 (4.4) no pain	DXA	Body fat percentage	Women 40.1 (5.5)%, 39.0 (5.0)% Men 28.0 (5.2)%, 27.2 (4.4)%	Women 0.21 (0.00 to 0.42) Men 0.17 (-0.04 to 0.38)	N/A N/A	Yes
Sutbeyaz, Turkey [152]	56 (32 women), 28 cases 28 control	44.0 (10.2) case 43.7 (10.0) control	33.3 (3.7) case 34.8 (3.5) control	Skin fold	Total fat mass	Case 29.4 (7.2) kg Control 33.6 (7.5) kg	-0.57 (-1.10 to -0.03)	No	No
Shin pain									
Sabeti, Iran [149]	35 (gender not stated), 17 cases 18 control	21.1 (2.3) case 20.7 (2.5) control	21.7 (2.7) case 20.7 (2.2) control	BIA	Body fat percentage	Case 27.8 (7.2)% Control 23.4 (5.8)%	0.68 (-0.02 to 1.34)	N/A	No
Foot pain									
Walsh, Australia [140]	88 (all women), 44 cases, 44 control	56.6 (10.3) case 56.7 (6.5) control	29.3 (9.9) case 27.6 (10.5) control	DXA		12.5 (5.1) kg / m^2, 12.0 (4.9) kg / m^2	0.10 (-0.32 to 0.52)	N/A	Yes
Walsh, Australia [120]	1066	64.6 (10.3)	28.4 (5.1)	DXA	FMI	N/A	N/A	1.08 (1.04 to 1.12)	Yes
Tanamas, Australia [139]	136 (114 women), 75 pain, 61 no pain	47.5 (9.2) pain 47.7 (8.8) no pain	35.1 (7.8) pain 28.4 (7.6) no pain	DXA		N/A	N/A	1.16 (1.06 to 1.28)	Yes
Butterworth, Australia [141]	796 (all men), 177 pain, 619 no pain	68 (24-90)^ pain 57 (25-98)^ no pain	28.0 (4.3) pain 27.1 (3.8) no pain	DXA		N/A	N/A	1.08 (1.01 to 1.15)	Yes

* Values are mean (SD) unless otherwise stated, ^ median (range), $ mean (95% CI), # cross-sectional and longitudinal study, ‡ Duplicate study

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *kg* kilogram, m^2 metres squared, *DXA* Dual-energy X-ray absorptiometry, *FMI* fat mass index, *BIA* bioelectrical impedance analysis, *N/A* not applicable

Study name and reference		SMD	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Pan	[134]	0.563	0.103	0.011	0.361	0.765	5.463	0.000
Yoo	[135]	0.446	0.078	0.006	0.293	0.599	5.707	0.000
Pooled effect estimate		0.488	0.062	0.004	0.366	0.610	7.848	0.000

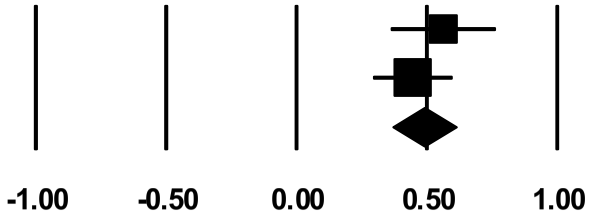


Figure 2: Forest plot of effect sizes and 95% confidence intervals for widespread pain and total body fat relative to controls

Study name	Subgroup within study and reference	SMD	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hodselmans	[150]	0.540	0.143	0.021	0.259	0.821	3.770	0.000
Spyropoulos	[151]	0.661	0.265	0.070	0.141	1.180	2.492	0.013
Dario	[146]	0.077	0.038	0.001	0.003	0.151	2.047	0.041
Toda	Men [147]	0.271	0.188	0.036	-0.099	0.640	1.435	0.151
	Women	0.267	0.143	0.020	-0.013	0.546	1.870	0.062
Sakai	Men [142]	1.087	0.165	0.027	0.764	1.410	6.591	0.000
	Women	0.334	0.149	0.022	0.042	0.627	2.240	0.025
Iizuka	[136]	-0.017	0.013	0.000	-0.042	0.009	-1.286	0.198
Pooled effect estimate		0.343	0.089	0.008	0.169	0.518	3.859	0.000

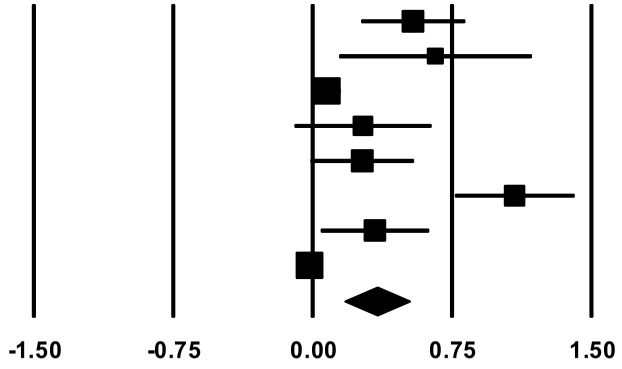


Figure 3: Forest plot of effect sizes and 95% confidence intervals for low-back pain and body fat percentage relative to controls

Study name	Subgroup within study and reference	SMD	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ozer Kaya	[148]	0.150	0.172	0.030	-0.187	0.487	0.871	0.384
Scott	Men [138]	0.167	0.108	0.012	-0.044	0.378	1.555	0.120
	Women	0.210	0.107	0.011	0.000	0.420	1.961	0.050
Pooled effect estimate		0.182	0.069	0.005	0.046	0.318	2.627	0.009

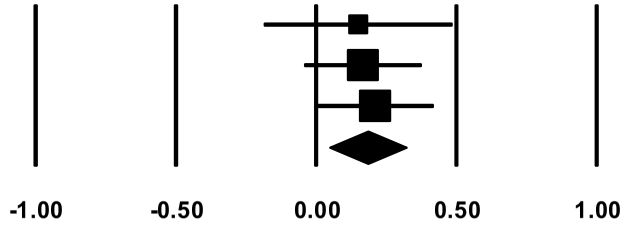


Figure 4: Forest plot of effect sizes and 95% confidence intervals for knee pain and body fat percentage relative to controls

Study name	Reference	Statistics for each study						
		SMD	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Walsh	[140]	0.100	0.213	0.046	-0.318	0.518	0.469	0.639
Walsh	[120]	0.042	0.010	0.000	0.022	0.063	4.071	0.000
Tanamas	[140]	0.082	0.027	0.001	0.030	0.134	3.085	0.002
Butterworth	[141]	0.042	0.018	0.000	0.007	0.078	2.324	0.020
Pooled effect estimate		0.047	0.009	0.000	0.030	0.063	5.447	0.000

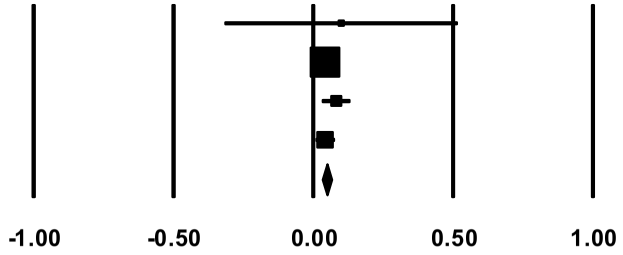


Figure 5: Forest plot of effect sizes and 95% confidence intervals for foot pain and fat mass index relative to controls

2.5.7 Cross-sectional studies not included in the meta-analysis

The cross-sectional studies not included in the meta-analysis (due to the type of data or the parameter used) were generally concordant with the overall findings (Table 3), with the reasons for exclusion in Table 4. Multi-site pain (3 sites) was associated with FMI in the study by Brady et al [121]. Neck pain was associated with body fat percentage in one study [144], while temporomandibular pain was not [143]. The large study by Chou et al [137] that investigated low-back pain used the same sample as reported by Butterworth et al [141] who investigated foot pain, with both finding FMI, but not FFMI, to be significantly associated with pain. Celan et al [145] studied the relationship between body fat percentage and low-back pain, but the only data provided were mean body fat percentage, without confidence intervals or standard deviations and therefore these data were not amenable for the meta-analysis. Iizuka et al [136] investigated multiple regions separately (neck / shoulder, back and low-back) and their associations between body fat percentage. Whilst we felt it appropriate to include the low-back region in the meta-analysis, we did not include the neck / shoulder and the back region with the other studies given the difficulty with delineating these regions, particularly the low-back region from the back region, but we did include the neck / shoulder region in Table 1. Other studies investigating low-back pain generally found increased fat mass was associated with pain. The smaller studies that investigated both knee and shin pain found non-significant associations between pain and body fat mass.

2.5.8 Longitudinal studies

Findings from the longitudinal studies (Table 5) were consistent with the overall theme identified in the cross-sectional studies, finding increased levels of body fat predicted future musculoskeletal pain. Higher baseline FMI was predictive of foot pain in the short

term (less than three years) [34,120] in data from both a community cohort (OR 1.06, 95% CI 1.02 to 1.11) and a musculoskeletal study (OR 1.28, 95% CI 1.04 to 1.57). In the knee, Jin et al [154] found an association between increased fat mass and an increased relative risk (RR) of pain in either lying in bed, (RR 1.47, 95% CI 1.12 to 1.93) or sitting (RR 1.46, 95% CI 1.10 to 1.95), although knee pain when weight-bearing was not associated with fat mass. More frequent knee pain at 5.1 years follow-up was positively associated with higher total fat mass, and there was an increased risk (95% CI) of consistent (RR 1.89, 95% CI 1.43 to 2.51) and fluctuating knee pain (RR 1.78, 95% CI 1.41 to 2.25). A 5-year longitudinal study by Pan et al [134] found a significant trend across three time-points for fat mass and multisite pain, with the number of painful sites significantly associated with total body fat mass over 5 years. There was, however, some discordance between the relationship of body composition and low-back pain, but the larger studies found fat mass to be a predictor of increased pain and disability following multiple adjustments [155-157]. A twin study by Dario et al [156] did not find a significant relationship between body fat and the risk of chronic low-back pain in women (n = 314), however a larger study (n = 4986) by Hussain et al [155] found higher body fat at baseline to be predictive of both high pain intensity and high disability in women and men at five years follow-up. Hashimoto et al [157] also found that men in the fourth quartile of body fat percentage had a significant risk of chronic back pain at >20 years follow-up when adjusting for age, smoking, alcohol consumption and maximal oxygen uptake (OR 2.12, 95% CI 1.13 to 3.98). One study found that the risk of developing injury during a three-month training program increased in women with an increased body fat percentage (OR 1.16, 95% CI 1.00 to 1.34) [153].

Table 4: Reasons for exclusion from meta-analysis

Study	Reason for exclusion
Brady [121]	This study did not stratify each body site by body composition and it was the only study to report up to three body sites.
Celan [145]	Unable to calculate effect size or odds ratio from the data provided
Chou [137]	The other studies assessing low-back pain measured body fat %, rather than fat mass or fat mass index
Iizuka [136]	Only study to report neck and shoulder pain
Jordani [143]	The participants with and without pain were compared according to their body fat %, but were stratified into four categories
Sabeti [149]	Only study to report shin pain
Sutbeyaz [152]	The other studies assessing knee pain measured body fat %, rather than fat mass or fat mass index
Urquhart [35]	Pain reported is not binary and is stratified into disability and intensity, unlike the other studies that reported low-back pain
Yalcinkaya [144]	Only study to report neck pain

Table 5: Characteristics of longitudinal articles included in the review (n = 8)

Study / country / reference	Follow-up time	Sample size, n	Age, y	BMI, kg / m^2 (Baseline)	Body composition assessment	Parameter investigated	Body composition (Baseline)	OR (CI)
Multi-site pain (0-7 joints)								
Pan, Australia [134] #	2.6 and 5.1 years	336 widespread pain, 137 no pain	Baseline 63.3 (7.7) widespread pain, 62.2 (7.2) no pain	Baseline 28.8 (5.3) widespread pain, 26.2 (3.9) no pain	DXA	Total fat mass	30.0 (9.5) kg, 25.0 (7.1) kg	1.06 (1.02 to 1.10)
Incident low-back pain								
Hussain, Australia [155]	5 years	No intensity: 900 Low intensity: 3085 High intensity: 1001	49.2 (10.9)	26.6 (4.7)	BIA		Pain intensity No: 31.7 (11.8)% Low: 32.6 (11.6)% High 36.2 (13.3)%	Men Low intensity: 1.28 (1.09 to 1.27) High Intensity: 1.45 (1.19 to 1.77) Low disability: 1.11 (0.92 to 1.32) High disability: 1.37 (1.10 to 1.72)
		No disability: 3061 Low disability: 651 High disability: 482				Body fat percentage	Pain disability No: 32.1 (11.5)% Low: 33.7 (12.6)% High 37.4 (13.3)%	Women Low intensity: 1.41 (1.25 to 1.59) High intensity: 1.39 (1.22 to 1.57) Low disability: 1.20 (1.07 to 1.35) High disability: 1.48 (1.31 to 1.68)
Dario, Spain [156]	4 years	314 (all women)	53.7 (7.0), range 43-71	27.3 (4.0)	BIA		34.1 (7)%	Chronic pain: 0.87 (0.66 to 1.14) Activity-limiting pain: 0.85 (0.62 to 1.53) Care-seeking due to pain: 0.79 (0.59 to 1.05)
Hashimoto, Japan [157]	> 20 years	1152 (all men)	28.0 (4.6)	22.6 (2.7)	Skin fold		14.7 (3.5)%	Q1: referent Q2: 0.86 (0.43 to 1.71) Q3: 1.46 (0.79 to 2.72) Q4: 2.12 (1.13 to 3.98)
Increasing knee pain								
Jin, Australia [154]	5.1 years	767 (380 women)	62.4 (7.2) pain increase 61.9 (7.0) no pain increase	29.1 (5.3) pain increase 27.3 (4.3) no pain increase	DXA	Body fat percentage	Pain increase: 30.2 (7.8)%, no pain increase: 27.0 (7.8)%	1.36 (1.20 to 1.55)$
Incident foot pain								
Butterworth, Australia [34]	3 years	51 (37 women), 11 incident pain, 40 no pain	48.3 (9.8) incident pain, 49.5 (7.9) no pain	29.6 (7.9) incident pain, 26.3 (5.4) no pain	DXA	FMI	12.1 (6.4) kg / m^2 incident pain, 8.7 (4.2) kg / m^2 no pain	1.28 (1.04 to 1.57)

Study / country / reference	Follow-up time	Sample size, n	Age, y	BMI, kg / m^2 (Baseline)	Body composition assessment	Parameter investigated	Body composition (Baseline)	OR (CI)
Future foot pain								
Walsh, Australia [120]	4 years	1066	64.6 (10.3)	28.4 (5.1)	DXA	FMI	10.2 (3.9) kg / m^2	1.06 (1.02 to 1.11)
Multi-site injuries								
Kodesh, Israel [153]	3 months	158 (all women)	19.0 (18.1-20.2)	20.8 (16.1-32.0)	Skin fold	Body fat percentage^	Injured 23.7 (20.5-29.2)% Non injured 22.5 (14.9-31.5)%	1.16 (1.00 to 1.34)

* Values are mean (SD) unless otherwise stated, ^ median (range), $ Relative risk (CI), # cross-sectional and longitudinal study

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *kg* kilograms, m^2 metres squared, *Q* quartile, *DXA* Dual-energy X-ray absorptiometry, *FMI* fat mass index, *BIA* bioelectrical impedance analysis

2.6 Discussion

This is the first review to systematically appraise and synthesise studies examining the relationship between body fat and musculoskeletal pain. This review included single- and multi-site joint pain and the meta-analyses demonstrated significant associations between increased fat mass and widespread pain, low-back pain, knee pain and foot pain. There was also emerging evidence from longitudinal studies that elevated body fat may infer an increased risk of incident or worsening joint pain. Thus, musculoskeletal pain may be a manifestation of excessive fat mass, which exists beyond excessive mechanical loading.

The association between fat mass and widespread pain is perhaps the most important finding of this review. Single-site pain may be confounded by local biomechanical factors or trauma, whereas widespread pain may be due to the pervasive nature of excessive adipose tissue on pain, extending beyond local tissue disease to include how pain may be perceived centrally [158]. The study by Pan et al [134] found both cross-sectional and longitudinal associations with widespread pain and they adjusted for psychological health in the longitudinal analysis, which is particularly important given the bidirectional relationship between depression and pain [72]. Whilst depressive symptoms are undoubtedly more common in those with excessive adiposity, there were independent associations between body fat and pain, particularly in the foot [120,139,141]. The foot is the first site in the body to modulate ground reaction forces, where the bones and soft tissues are subjected to bending and torsional loads [11]. The weak pooled estimate for the association between foot pain and body fat may be attributed to the fact that three of the four articles included in the meta-analysis adjusted for age, gender and depression and normalised fat mass for height, while the other article also matched on age, gender and BMI. This therefore suggests that unless FMI is associated with specific changes to

foot mechanics, which seems unlikely, that the association of foot pain with obesity may be metabolically mediated. It is important to note that the magnitude of the effects were small to medium in size, suggesting a relatively modest potential contribution of fat mass to musculoskeletal pain amongst other known physiological and psychological factors.

A number of proposed pathways can explain the association between body fat and musculoskeletal pain, including the up-regulation of cytokines secreted by adipose tissue, referred to as adipokines. Leptin, a pro-inflammatory adipokine predominately expressed by subcutaneous adipose tissue [159] is associated with bodily pain in women [56] and leptin levels in both serum [160] and synovial fluid [161] are associated with osteoarthritis, particularly in women. Leptin has functional receptors on articular chondrocytes, and may be involved with cartilage generation [53]. Leptin signaling, however, may be blunted with adiposity, through a regulative negative feedback loop [54]. Interestingly, excessive adiposity may increase leptin secretion, which in turn may compromise its ability to repair joint cartilage by a down-regulation in receptor expression [162]. This theory is supported by an observational study investigating knee joint changes using magnetic resonance imaging, where reduced cartilage volume, a hallmark of osteoarthritis, is associated with increased leptin [163]. Thus, leptin may be associated with structural joint changes that, at the very least may predispose the joint to further cartilage failure and pain.

Other suggested mechanisms linking adipose tissue with pain, including subclinical inflammation [164,165]. Tumour necrosis factor-alpha (TNF-α) is a cytokine involved in the inflammatory cascade. It is a therapeutic target for the management of inflammatory arthropathies, and is primarily produced by activated macrophages, but it is also secreted by adipose tissue [41]. Systemic inflammation is up-regulated with obesity with the acute inflammatory phase marker, C-reactive protein (CRP), higher in obese people [62]. The

increase in inflammation may be in response to over-nutrition initiating an immune response [63], particularly linked to the consumption of dietary fats [64]. Moreover, elevated TNF-α, along with other inflammatory mediators and markers are associated with chronic pain [65]. Elevated synovial TNF-α levels are also predictive of pain severity and a poor outcome following temporomandibular joint surgery [66]. Furthermore, elevated serum levels of TNF-α and interleukin-6 (IL-6) are associated with less improvement to treatment in those with chronic pain [67] and TNF-α may moderate the relationship between chronic back pain and depressive symptoms [68].

Systemic inflammation related to adiposity has been linked to other structural joint changes and this may be one phenotype that contributes to osteoarthritis [166]. In the knee, both TNF-α and IL-6 have been associated with knee cartilage loss [124] and elevated IL-6 is a predictor of radiographic osteoarthritis [167], suggesting a link between low-level inflammation and osteoarthritis pathogenesis. Tendinopathy has also been linked with dietary fats, adiposity and inflammation [2,168], highlighting that obesity may not necessarily be only related to excessive load. Clearly elevated body fat is linked with structural changes and pain in multiple regions and may explain the known link between elevated BMI and osteoarthritis in non-weight-bearing joints such as the hands [1]. Future work to investigate if there is a true discordance between fat mass and fat-free mass may help strengthen the notion that body composition is more meaningful measure of risk for musculoskeletal pain.

This review should be considered in light of certain limitations. Firstly, given the lack of homogeneity in follow-up time, we were unable to undertake a meta-analysis on longitudinal associations between musculoskeletal pain and body fat. Secondly, despite the considerable variability in the quality of the articles included in this study, a number of

items assessed with the EAI would have scored higher had they been explicitly reported, such as the reliability and validity of the tools used to assess pain and body composition. A number of the tools are known to be both reliable and valid, but unfortunately this was not reported by the authors. Thirdly, the case-definition for pain did vary between studies and thus while we did perform a meta-analysis by region those with stricter criteria may under-report the prevalence, incidence or progression of pain. Fourthly, the pooled estimates of the meta-analyses are small to medium in size, suggesting a weak to moderate effect which should be taken into consideration. Finally, this review focused on the association between body fat and pain, but it did not investigate whether lean mass was inversely related to pain. However, this is the first review to systematically appraise and synthesise studies examining the relationship between body fat and musculoskeletal pain.

2.7 Conclusion

This systematic review has demonstrated that increased body fat is positively associated with widespread pain, low-back pain, knee pain and foot pain. Meta-analysis found positive cross-sectional associations between increased body fat and widespread and single-site joint pain in the low-back, knee and foot. Evidence from longitudinal studies suggests elevated body fat may infer increased risk of incident and worsening joint pain, although further high-quality studies are required.

3

Chapter 3: Association of Fat Mass and Adipokines with Foot Pain in a Community Cohort

3 FAT MASS AND ADIPOKINES

3.1 Introduction to publication

Walsh TP, Gill TK, Evans AM, Yaxley A, Shanahan EM, Hill CL. Association of Fat Mass and Adipokines With Foot Pain in a Community Cohort. *Arthritis Care Res (Hoboken)*. 2016;68(4):526-533.

Purpose

The purpose of this study was to investigate whether body composition or adipokines / inflammatory mediators are associated with foot pain in a community cohort. Previous studies have investigated body composition and foot pain, but they have used smaller samples and they have not used fat mass and body mass in the same statistical model – limiting the conclusions that can be drawn regarding the effect of weight or body composition on pain. No previous study has investigated the association of adipokines / inflammatory mediators on foot pain. Thus, this study explores the associations between foot pain and both mechanical and non-mechanical factors.

Published in

Arthritis Care & Research

2016 Impact Factor 3.319

5-year Impact Factor 4.862

Contribution from primary author

Primary Author – Tom Walsh

This study was performed with data made available from the North West Adelaide Health Study, a longitudinal study which commenced in 1999. These data used in this study were collected in Stage 2 (2004-6) and Stage 3 (2008-10). The candidate was given permission to use these data by the Chief Investigators.

The manuscript was written by the primary author, which followed consultation and review by the listed co-authors. The primary author conceived the research questions and completed the initial data analysis with the study statistician, the final analyses reported in the publication were conducted by the study statistician.

3.2 Abstract

Objective: To determine if fat mass index (FMI) or fat-free mass index (FFMI) and serum adipokines, tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are (1) associated with prevalent (Stage 2) foot pain, and (2) are predictive of future (Stage 3) foot pain.

Methods: A subset of participants aged ≥ 50 years (n = 1462) from The North West Adelaide Health Study were used for this study. Participants from this community cohort were asked in Stage 2 (2004 – 2006) and Stage 3 (2008 – 2010) if they had foot pain, aching or stiffness. In Stage 2, serum adipokines and anthropometry were measured, while body composition was analysed with dual-energy X-ray absorptiometry. These variables, along with comorbidities and social history were used in logistic regression analysis to determine if FMI, FFMI and serum adipokines were associated with foot pain.

Results: Prevalent and future foot pain was present in 20.2% and 36.4%, respectively. Following multivariable modelling, the odds of having pain at Stage 2 increased by 8% for each FMI unit (odds ratio (OR) 1.08 (95% confidence interval (95% CI) 1.04 to 1.12), while the odds of having pain at Stage 3 increased by 6% for each FMI unit at Stage 2 (OR 1.06, 95% CI 1.02 to 1.11). Tumour necrosis factor-α, IL-6 and FFMI were not associated with pain.

Conclusion: Increased FMI, but not BMI, FFMI, TNF-α or IL-6, was associated with both prevalent and future foot pain. These results suggest that body fat may be more important than body weight with respect to foot pain. The role of other adipokines requires further investigation.

3.3 Background

Frequent foot pain affects 24% of adults aged 45 years and older [21] and is associated with a reduced quality of life, increased age, female gender and depression [169]. Along with these factors, studies have also found obesity to be associated with the presence and development of foot pain [34,86,139]. A systematic review found that increased body mass index (BMI) was strongly associated with non-specific foot pain [86] and a recent longitudinal analysis of middle-aged women found increased BMI can increase the odds of developing foot pain, independent of age [87].

Obesity is a global pandemic, affecting both developed and developing countries and is strongly associated with diet and physical inactivity [170,171]. The worldwide prevalence of overweight or obese adults has increased from 28% to 37% over the past 30 years, with some countries reporting obesity rates of over 50% [23]. Furthermore, high obesity rates have been identified using the BMI calculation (kg / m^2), a measure which probably underestimates the prevalence of adiposity (body fat) when compared with a more accurate measure of body composition evaluation, dual-energy X-ray absorptiometry (DXA) [172]. The BMI is an arbitrary measure of weight/height and cannot account for body composition, namely fat (adipose) mass and lean soft tissue mass nor can it account for the location or activity of these tissues.

Whilst once considered a passive reservoir for energy storage, adipose tissue is now recognised as an active endocrine organ, responsible for many bioactive cytokines [41]. Some of the cytokines secreted by adipose tissue (adipokines) are associated with the development of chronic pain, inflammatory states and OA [40,49,173]. This suggests that the activity within adipose tissue may be as important as the weight of the tissue.

Pain in weight bearing joints such as the hip [174], knee [119], or foot [88] have been associated with obesity, where the presumption of mechanical overload seemed the most logical pathological pathway. This is further supported by studies which find increased plantar pressures in the foot as obesity increases [98] and a reduction of pain with weight loss [175]. The association of obesity with painful, non-weight bearing joints such as the hand [176] is not in keeping with the mechanical overload pathway and suggests that the metabolic effect of obesity may be an important consideration systemically. Despite investigations into the significance of adipokines in other regions of the body [177,178], the association with foot pain has not been formally investigated. The aim of this study was therefore to investigate the association of fat mass and adipokines with prevalent and future foot pain in a large community dwelling cohort of adults.

3.4 Patients and Methods

3.4.1 Study participants

The North-West Adelaide Health Study (NWAHS) is a representative cohort study of randomly selected adults initially aged 18 years and over (n = 4056), from the north-west region of Adelaide. The region is representative of the wider community with varied socio-economic distributions and comprises nearly one half of the population of the city of Adelaide and one third of the state of South Australia [179]. The study commenced in 1999 to 2003 (Stage 1), Stage 2 was conducted between 2004 and 2006 and Stage 3 was conducted between 2008 and 2010. The inception, recruitment and purpose have been previously described [169,179]. During all three stages data have been collected using a Computer Assisted Telephone Interview (CATI), a self-completed questionnaire and a clinical assessment. This study focuses on data collected primarily as part of Stage 2 and aims firstly to examine the factors associated with prevalent foot pain in Stage 2.

Secondly, these covariates from Stage 2 are then used to determine the predictors of future foot pain in Stage 3. Participants aged ≥ 50 years at Stage 2 were the focus of this analysis as these were the only participants to have had the option of undertaking DXA. The potential sample size was thus 1462, however while age and sex was obtained for all of these participants, not all participated in every aspect of testing (e.g. unable to provide blood, unable to attend an appointment for DXA testing, "don't know" response provided to questions).

3.4.2 Foot pain

As part of Stage, 2 CATI participants were asked: "On most days, do you have pain, aching or stiffness in either of your feet?" and in Stage 3: "Over the past month, have you had pain, aching or stiffness in either of your feet on most days?"

Prevalent foot pain was defined as having answered 'yes' at Stage 2. Future foot pain was defined as having answered 'no' at Stage 2, but yes at Stage 3.

3.4.3 Anthropometric measures

During the clinic assessment in Stage 2 height and weight were measured using standardised protocols. All clinic staff were trained in clinical assessment including height and weight measurements. Height was measured to the nearest 0.5 centimetre (cm) using a wall mounted stadiometer and weight was measured to the nearest 0.1 kilogram (kg) using electronic scales. Body mass index (weight (kg) / height $(m)^2$) was then calculated. Waist and hip circumference were measured (cm) with an inelastic tape, in triplicate, and the means calculated. Waist:hip ratio (WHR) was calculated by dividing the mean waist measurement by the mean hip measurement. There were 1348 respondents whose BMI and 1337 whose WHR could be calculated.

3.4.4 Inflammatory markers / adipokines

Fasting blood samples were collected and centrifuged, with the serum aliquoted and stored at -80°C until final analysis. Tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) were quantified with an enzyme linked immunosorbent assay (ELISA) and Cobas autoanalyser (Roche Diagnostics, Florham Park, NJ, USA). The inter-assay coefficients of variation were 10.6% for TNF-α and 7.8% for IL-6 [180]. Tumour necrosis factor-alpha and IL-6 were the only adipokines included in the analysis as these had both been measured for a previous investigation and data were available for use in this study. Overall 825 participants aged ≥ 50 years provided blood for adipokine analysis.

3.4.5 DXA measurements

Body composition was measured by two GE Lunar machines; Prodigy DXA using acquisition and analysis software Encore version 9.15, or DPX+ DXA using Lunar DPX version 4.7e software. Calibration of the machine was performed at the beginning of each day of scanning. Whole body phantom scans were performed 10 times to determine precision of scan for total body composition. The coefficients of variation were 0.48% for fat mass (FM) and 0.44% for fat-free mass (FFM) [181]. The analysis determined whole body fat and fat-free mass which was then normalised for height by calculating fat mass index (FMI) (total body fat (kg) / height $(m)^2$ and fat-free mass index (FFMI) (lean body mass + bone mineral content (kg) / height $(m)^2$). Participants aged ≥ 50 years who attended the clinic assessment were offered the opportunity to undertake a DXA scan. Overall n = 1066 provided data for use in this analysis.

3.4.6 Covariates

Age, BMI, WHR and gender of participants was determined during the clinical assessment, while smoking status, general health, physical activity and alcohol consumption were

determined from responses to the self-completed questionnaire. The level of physical activity was determined from questions used in the Australian National Health Survey (2001) [182], which asked participants for frequency, duration and intensity of physical activity over the last two weeks. Walking, moderate exercise and vigorous exercise were weighted for intensity by 3.5, 5.0 and 7.5 respectively and was multiplied by the frequency of exercise and time in minutes for each exercise. A score of < 100 was classified as sedentary. General health was obtained using the first question from the Short Form-36; SF1 [183], a valid measure of general health [184] and alcohol consumption was determined from questions based on the National Heart Foundation Risk Factor Prevalence Study undertaken in 1989 [185].

Depression was determined from the CATI responses to the Center for Epidemiologic Studies-Depression (CES-D) scale with a score of ≥ 16 indicating depressive symptoms [186]. Participants were asked if they had been told by a doctor that they had arthritis. If they responded “yes”, they were then asked what type of arthritis they had. The presence of diabetes was determined from self-report of doctor diagnosed diabetes and/or a fasting plasma glucose level of greater than or equal to 7.0mmol / L [187].

3.4.7 Data weighting

At the conclusion of Stage 1 of the NWAHS, data were weighted by region (Western and Northern health regions of South Australia). Age group, gender and probability of selection of the household to the Australian Bureau of Statistics 1999 Estimated Resident Population and the 2001 Census data was used to reflect the population of interest. Stage 2 and 3 were reweighted using the 2004 and 2009 Estimated Resident Population for South Australia respectively, incorporating participation in the three components, while at

the same time retaining the original weight from Stage 1 in the calculation. All analyses undertaken in this paper are weighted where possible. Ethics approval was obtained from the Human Research Ethics committee of The Queen Elizabeth Hospital, Adelaide, South Australia and all participants in the study provided written informed consent.

3.4.8 Data analysis

Descriptive statistics (frequencies and means) were initially undertaken. Prior to undertaking bivariable and multivariable logistic regression analyses, continuous variables (BMI, FMI, FFMI, WHR, age, IL-6 and TNF-α) were checked to determine whether they were normally distributed. As these variables were not normally distributed, the Mann-Whitney *U* test was used to examine the association between these variables and those with and without foot pain. Logistic regression analysis was used to determine the association between foot pain and each of the categorical variables. Variables with a significance probability of $p \leq 0.25$ were then included in the multivariable logistic regression analysis [188]. Prior to inclusion in the multivariable model, it was also necessary to test the continuous predictors for linearity in the logit, to ascertain whether the variables should be included as continuous or categorical. This was done using the Box-Tidwell transformation, as recommended by Hosmer & Lemeshow [188]. Those that were not linear in the logit were grouped into ordinal variables and included in the model as categorical predictors. All variables were then included in multivariable logistic regression analysis and non-significant variables were removed in a backwards stepwise elimination to determine the factors ($p < 0.05$) associated with foot pain. The final models were tested for goodness of fit using the Hosmer and Lemeshow goodness-of-fit test. For this test, if the value of the chi square (χ^2) statistic in this test is low, the p-value is not significant and indicates that the model is a good fit for the data [188]. Analysis was

conducted using SPSS V21 (IBM SPSS Statistics, New York) and STATA V13.1 (StataCorp LP, College Station, Texas).

3.5 Results

The characteristics of the sample are presented in Table 1 and co-morbidities are presented in Table 2.

3.5.1 Prevalent foot pain

Overall, 20.2% (95% CI 18.33 to 22.28) of the participants reported that they had foot pain in Stage 2. Both FMI and BMI were significantly different between those with and without foot pain (Table 3) while gender (female), general health, depression, diabetes, OA, arthritis (type unknown) and rheumatoid arthritis were associated with foot pain at Stage 2 in univariable analysis (Table 4). Physical activity (some level of activity) was found to be protective of foot pain (odds ratio (OR) 0.76, 95% CI 0.58 to 0.99), $p = 0.048$. All of these variables, IL-6 and WHR ($p \leq 0.25$ at a univariable level) were initially included in the multivariable model.

Depression, FMI, poor general health, diabetes, OA, arthritis (type unknown) and rheumatoid arthritis remained significantly associated with prevalent foot pain after multivariable analysis (Hosmer and Lemeshow goodness of fit $\chi^2 = 3.51$, df = 8, $p = 0.90$, Table 5).

Table 1: Overall descriptive statistics for NWAHS cohort (≥ 50 years)

	n	Mean (SD)	Range
Age (years)	1463	64.99 (10.58)	50-93
BMI (kg / m^2)	1348	28.37 (5.07)	14.6-52.0
WHR (waist (cm):hip (cm))	1337	0.90 (0.09)	0.68-1.43
TNF-α (pg / mL)	825	1.82 (3.51)	0-76.78
IL-6 (pg / mL)	825	1.99 (1.69)	0.18-21.43
FMI (kg / m^2)	1066	10.18 (3.89)	1.08-28.40
FFMI (kg / m^2)	1066	18.02 (2.48)	10.89-27.68
	n	%	(95% CI)
Gender			
Male	682	46.61	(44.20 to 49.03)
Female	781	53.39	(50.97 to 55.80)
*Prevalent foot pain**			
No	1162	79.76	(77.72 to 81.67)
Yes	295	20.24	(18.33 to 22.28)
Future foot pain^*			
No	617	63.58	(60.81 to 66.27)
Yes	353	36.42	(33.73 to 39.19)
*Smoking status**			
Non-smoker	650	47.67	(45.21 to 50.13)
Ex-smoker	550	40.40	(38.01 to 42.80)
Current smoker	163	11.95	(10.45 to 13.64)

	n	%	(95% CI)
*Alcohol use**			
Non-drinker	756	57.33	(54.84 to 59.78)
Low risk of harm from alcohol	494	37.43	(35.05 to 39.88)
Intermediate to very high risk of harm from alcohol	69	5.24	(4.24 to 6.46)
*Physical activity**			
Sedentary	401	33.31	(30.88 to 35.83)
Undertakes some activity	803	66.69	(64.17 to 69.12)
*General health**			
Excellent/ very good/good	1071	78.44	(76.32 to 80.41)
Fair or poor	294	21.56	(19.59 to 23.68)

*Don't know / not stated category excluded from the analysis, ^Future foot pain measured in Stage 3, all other variables are from Stage 2 data collection

SD standard deviation *IL-6* interleukin-6, *TNF-α* tumour necrosis factor-alpha, *FMI* fat mass index, *FFMI* fat-free mass index, *BMI* body mass index, *WHR* waist:hip ratio, *pg* picogram, *mL* millilitre, *kg* kilogram, *cm* centimetre, m^2 meters squared, *CI* confidence interval

Table 2: Prevalence of comorbidities at Stage 2

	n	% (95% CI)
*Depression**		
No depressive symptoms	1300	89.65 (88.10 to 91.01)
Depressive symptoms	150	10.35 (8.99 to 11.90)
*Diabetes**		
No diabetes	1149	85.79 (83.99 to 87.42)
Diabetes	190	14.21 (12.58 to 16.01)
*Arthritis**		
No	1241	84.85 (83.04 to 86.50)
Osteoarthritis	222	15.15 (13.50 to 16.96)
No	1388	94.87 (93.65 to 95.87)
Rheumatoid arthritis	75	5.13 (4.13 to 6.35)
No	1453	99.32 (98.83 to 99.60)
Other type of arthritis	10	0.68 (0.40 to 1.17)
No	1167	79.76 (77.79 to 81.60)
Don’t know type of arthritis	296	20.24 (18.40 to 22.21)

*Don’t know / not stated category excluded from the analysis

CI confidence interval

3.5.2 Future foot pain

Future foot pain was present in 36.4% (95% CI 33.73 to 39.19) of the participants aged ≥ 50 years. As with prevalent foot pain, FMI and BMI were also significantly different between those with and without foot pain ($p < 0.05$, Table 3), gender (female), poor general health, arthritis (unknown type) and depression demonstrated univariable significance, increasing the risk of developing foot pain (Table 4). All of these variables and risk of harm from alcohol and self-reported OA (both significant at $p \leq 0.25$) were included in the initial multivariable model. Only FMI ($p < 0.005$), arthritis (unknown type) ($p < 0.001$) and depression ($p < 0.035$) remained significant following multivariable analysis (Hosmer and Lemeshow goodness of fit $\chi^2 = 7.67$, df = 8, $p = 0.47$, Table 6).

Table 3: Comparison between participants with and without foot pain for continuous variables

Prevalent foot pain					
	Mean rank	Median	IQR	Z-score	*p* value
IL-6					
No foot pain	598.08	1.53	1.03-2.38	-1.90	0.057
Foot pain	646.33				
TNF-α					
No foot pain	604.77	1.34	0.95-1.90	-0.55	0.581
Foot pain	618.77				
FMI					
No foot pain	750.23	9.54	7.35-12.35	-5.73	<0.001
Foot pain	913.56				
FFMI					
No foot pain	787.45	17.91	16.00-19.85	-0.78	0.436
Foot pain	762.25				
BMI					
No foot pain	930.36	27.70	24.80-31.00	-4.76	<0.001
Foot pain	1082.03				
WHR					
No foot pain	962.02	0.90	0.83-0.97	-1.38	0.169
Foot pain	918.24				
Age					
No foot pain	1025.75	64.00	57.00-73.00	-1.13	0.258
Foot pain	988.58				

Future foot pain					
	Mean rank	Median	IQR	Z-score	*p* value
IL-6					
No foot pain	460.76	1.51	1.01-2.31	-1.14	0.253
Foot pain	483.32				
TNF-α					
No foot pain	464.24	1.34	0.94-1.89	-0.51	0.613
Foot pain	474.21				
FMI					
No foot pain	469.81	9.31	7.21-11.94	-2.67	0.008
Foot pain	523.67				
FFMI					
No foot pain	486.18	17.96	16.04-19.87	-0.31	0.760
Foot pain	480.01				
BMI					
No foot pain	559.01	27.45	24.80-30.70	-2.00	0.046
Foot pain	602.58				
WHR					
No foot pain	564.04	0.91	0.83-0.97	-0.58	0.565
Foot pain	576.58				
Age					
No foot pain	588.00	64.00	57.00-73.00	-0.49	0.621
Foot pain	577.08				

IQR interquartile range, *IL-6* interleukin-6, *TNF-α* tumour necrosis factor-alpha, *FMI* fat mass index, *FFMI* fat-free mass index, *BMI* body mass index, *WHR* waist:hip ratio

Table 4: Univariable logistic regression for association of categorical variables with foot pain

		Prevalent foot pain		Future foot pain	
Variable		OR (95% CI)	*p* value	OR (95% CI)	*p* value
Gender	Female	1.50 (1.17 to 1.93)	0.002	1.40 (1.05 to 1.87)	0.020
	Male	1.00		1.00	
General health	Fair/poor	2.37 (1.79 to 3.13)	<0.001	1.70 (1.14 to 2.56)	0.010
	Excellent/very good/good	1.00		1.00	
Depression	Yes	3.43 (2.46 to 4.79)	<0.001	2.12 (1.29 to 3.48)	0.003
	No	1.00		1.00	
Diabetes	Yes	1.53 (1.10 to 2.13)	0.011	0.96 (0.61 to 1.51)	0.863
	No	1.00		1.00	
Osteoarthritis	Yes	1.90 (1.40 to 2.56)	<0.001	1.38 (0.92 to 2.07)	0.117
	No	1.00		1.00	
Rheumatoid arthritis	Yes	2.50 (1.55 to 4.05)	<0.001	1.31 (0.60 to 2.82)	0.497
	No	1.00		1.00	

Variable		Prevalent foot pain OR (95% CI)	*p* value	Future foot pain OR (95% CI)	*p* value
Arthritis (unknown type)	Yes	1.57 (1.18 to 2.07)	0.002	1.90 (1.35 to 2.67)	<0.001
	No	1.00		1.00	
Arthritis (other)	Yes	0.49 (0.09 to 2.52)	0.392	1.13 (0.22 to 5.87)	0.882
	No	1.00		1.00	
Physical activity	Some level of activity	0.76 (0.58 to 1.00)	0.048	0.96 (0.68 to 1.34)	0.815
	Sedentary	1.00		1.00	
Smoking	Current smoker	0.78 (0.49 to 1.22)	0.275	0.85 (0.52 to 1.39)	0.524
	Ex smoker	1.09 (0.84 to 1.41)	0.530	0.96 (0.71 to 1.30)	0.781
	Non smoker	1.00		1.00	
Alcohol	Intermediate - very high risk	0.94 (0.53 to 1.66)	0.837	1.35 (0.71 to 2.56)	0.364
	Low risk	1.09 (0.83 to 1.41)	0.534	1.21 (0.89 to 1.64)	0.221
	Non-drinker	1.00		1.00	

OR odds ratio, *CI* confidence interval

Table 5: Variables significantly associated with prevalent foot pain following multivariable analysis

	OR (95% CI)	*p* value
FMI	1.08 (1.04 to 1.12)	< 0.001
Depression	2.47 (1.63 to 3.74)	< 0.001
General Health	1.92 (1.37 to 2.68)	< 0.001
Diabetes	1.55 (1.04 to 2.31)	0.033
Osteoarthritis	1.92 (1.31 to 2.80)	0.001
Rheumatoid arthritis	2.68 (1.53 to 4.69)	0.001
Arthritis (unknown type)	1.73 (1.22 to 2.46)	0.002

FMI fat mass index, *OR* odds ratio, *CI* confidence interval

Table 6: Variables significantly associated with future foot pain following multivariable analysis

	OR (95% CI)	*p* value
FMI	1.06 (1.02 to 1.11)	0.005
Depression	1.90 (1.05 to 3.45)	0.035
Arthritis (unknown type)	1.99 (1.37 to 2.91)	< 0.001

FMI fat mass index, *OR* odds ratio, *CI* confidence interval

3.6 Discussion

In this large community cohort, FMI, but not BMI, FFMI, IL-6 or TNF-α, was associated with prevalent and future foot pain in people aged ≥ 50 years after adjusting for multiple confounding variables. Prevalent and future foot pain was increased by 8% and 6% respectively, for every unit increase of FMI.

A recent study has found that both BMI and FMI were independent predictors of prevalent foot pain, suggesting there are likely both biochemical and biomechanical factors in the development of foot pain [139]. Results of the current study also support the utility of FMI, with BMI losing its significance when fat mass added to the multivariable model. This finding is consistent with another study investigating fat mass and foot pain [34]. These results suggest that body *weight* may be less important than body *fat* in promoting foot pain, particularly given the lack of association of FFMI with pain.

The association with reduced general health, depression, diabetes, osteoarthritis, arthritis (unknown type) and rheumatoid arthritis with prevalent foot pain is in keeping with other studies which have found systemic inflammation [189] and reduced mental health [190] with musculoskeletal complaints. Interestingly, when body composition is considered, BMI and female gender were no longer predictive of foot pain but FMI continued to be so. Given women typically have more body fat then men for the same body weight [191], body fat (and possibly adipokines) may explain why women experience more pain. Fewer variables were associated with the development of future foot pain than prevalent foot pain. The predictors of future foot pain after multivariable analysis were FMI, depression and arthritis.

3 FAT MASS AND ADIPOKINES

Whilst it was not the aim of this study to investigate the relationship of depression with foot pain, it was one variable that strongly featured. Depression has previously been found to be associated with musculoskeletal pain, while pain itself promotes depression [190] suggesting a positive feedback cycle. Interestingly, while we did not find association between adipokines and foot pain, major depression has been proposed to be a consequence of systemic inflammation [192] and is associated with an increase in TNF-α and IL-6 [193]. The association of a reciprocal relationship between obesity and depression [71] provides further evidence that metabolic disease and chronic pain are profoundly entwined, with this study providing evidence that pain may develop from carrying excessive fat, not weight. These interrelationships require further examination.

The adipokines, TNF-α and IL-6 were not associated with foot pain after adjustment for confounding variables. They are not exclusively secreted by adipose tissue, however, and are therefore not solely adipokines. The presence of these cytokines may reflect other pro-inflammatory states in the general population that may have produced this result. Elevated fat mass is clearly associated with foot pain, but this association may be mediated by other adipokines.

The presence of receptors for other adipokines on chrondrocytes, synoviocytes and subchondral osteoblasts [53,194,195] does suggest that adipokines may influence joint structure and could be involved with both degenerative and inflammatory processes, from which pain may result. Clinically, adiposity is also associated with tendinopathy [168] and adipokines, such as leptin and adiponectin, have been associated with OA [196,197]. Furthermore, another adipokine (visfatin), has been found to be associated with upper extremity pain intensity [177] and with predicting recovery following upper extremity injury.

Recovery was also positively associated with resistin, while elevated leptin may prevent timely recovery from injury and may provide a link between fat mass and musculoskeletal pain [55]. We are unable to report on these other adipokines, but the association with FMI suggests their involvement with foot pain to be a plausible pathway.

The strengths of this study are that the data is sourced from a large community based cohort. The clinical implications of our findings are that, FMI but not BMI, is associated with both prevalent and the development of foot pain after multivariable analysis in adults aged ≥ 50 years. Overweight or obese patients presenting with foot pain may be best instructed that fat mass is likely more important than body mass alone and given the limitations of the BMI, the use of DXA may be encouraged to determine body composition to appropriately inform patients regarding risk. Given the association of FMI with future foot pain, patients with increased fat are at risk of developing foot pain and should be counselled as such, particularly given increased fat mass is modifiable and should not be considered as a chronic condition. A weight loss trial with body composition analysis could confirm hypotheses regarding fat mass and resolution of foot pain and this would be highly relevant for clinicians.

There are some limitations of our study. Firstly, the question posed to define foot pain could have excluded people with non-disabling foot pain and therefore under estimate the prevalence of foot pain *per se*. Secondly, there was no clinical or radiographic examination of the feet and therefore we are unable to report on foot structure or function and presence or absence of OA nor the implications these may have on pain. Thirdly, the data on fat mass is only available on people aged ≥ 50 years and is cross-sectional. We are unable to report the effects of body composition in younger adults or on how body composition may

have changed over time. Fourthly, whilst we have included a number of comorbidities in the analysis, we did not include socio-economic status, which may have had a mediation effect on pain. Finally, due to financial constraints we are only able to report on a limited number of adipokines, TNF-α and IL-6, and additional analysis of others such as visfatin, resistin, leptin or adiponectin would highly relevant given the findings.

3.7 Conclusion

In conclusion, FMI is positively associated with both prevalent and future foot pain. BMI, FFMI, TNF-α and IL-6 were not associated with either prevalent or future foot pain after adjusting for multiple confounding variables. These results suggest that body composition may be more important than body weight in determining and predicting foot pain. The role of other adipokines requires further investigation.

4

Chapter 4: Body fat distribution and psychological health in women with and without foot pain

4 BODY FAT DISTRIBUTION AND PSYCHOLOGICAL HEALTH

4.1 Introduction to publication

Walsh TP, Arnold JB, Gill TK, Evans AM, Yaxley A, Hill CL, Shanahan EM. The severity of chronic, disabling foot pain in middle-aged women is correlated with visceral adipose tissue, fat mass index and depression. *Rheum Int*. 2017;37(7):1175-1182.

Purpose

The primary purpose of this study was to investigate differences in the body composition or psychological measures between middle-aged women with and without foot pain. The secondary purpose is to investigate whether these measures impact on the severity of foot pain. Given the known associations between pain and both psychological health and body composition, this study aims to build on previous work from chapter 3, but will explore if pain is associated with the location of fat, or an aspect of psychological health.

Published in

Rheumatology International

2016 Impact Factor 1.824

5-year Impact Factor 1.670

4 BODY FAT DISTRIBUTION AND PSYCHOLOGICAL HEALTH

Contribution from primary author

Primary Author – Tom Walsh

The Australian Podiatry Education & Research Foundation provided a research grant for this study. The successful grant application was led by the primary author, but included consultation with the listed co-authors and a statistical consultant (Pawel Skuza) from Flinders University.

The manuscript was written by the primary author, which followed consultation and review by the listed co-authors. The primary author conceived the research questions and completed the initial data analyses, the study statistician conducted the final regression analyses reported in the publication.

4 BODY FAT DISTRIBUTION AND PSYCHOLOGICAL HEALTH

4.2 Abstract

Introduction: Body composition and poor mental health are risk factors for developing foot pain, but the role of different fat deposits and psychological features related to chronic pain are not well understood. The aim of this study was to investigate the association between body composition, psychological health and foot pain.

Method: Eighty-eight women participated in this study: 44 with chronic, disabling foot pain mean (standard deviation (SD)) age 55.3 (7.0) years, body mass index (BMI) 29.5 (6.7) kg / m^2), and 44 age and BMI matched controls. Disabling foot pain was determined from the functional limitation domain of the Manchester Foot Pain and Disability Index. Body composition was measured using dual x-ray absorptiometry and psychological health (catastrophisation, central sensitisation and depression) was measured using three validated questionnaires.

Results: Between-group analyses found that foot pain was not significantly associated with body composition variables, but was significantly associated with all psychological health measures (p < 0.001 - 0.047). Within-group analyses found that the severity of foot pain was significantly correlated with body composition measures: fat-mass (total, android, gynoid, visceral), fat-mass ratios (visceral / subcutaneous (VAT / SAT), visceral / android), fat-mass index (FMI), and depression. In multivariable analysis, VAT / SAT (β 1.3, 95% CI 0.3 to 2.3), FMI (β 0.1, 95% CI 0.0 to 0.3) and depression (β 0.1, 95% CI 0.0 to 0.1) were independently associated with foot pain severity.

Conclusions: Psychological health, not body composition, was associated with prevalent foot pain. For women with foot pain, VAT / SAT, FMI and depression were associated with severity. Further work is needed to determine if a reduction in fat-mass reduces the severity of foot pain.

4 BODY FAT DISTRIBUTION AND PSYCHOLOGICAL HEALTH

4.3 Introduction

Foot pain affects one in five adults aged over 45 years [21] and has a significant negative impact upon performing activities of daily living [198] and health-related quality of life [199]. Women are disproportionately affected by foot pain, particularly during and after middle age. After 45 years, women are 60% more likely to report foot pain than men and are more commonly troubled by persistent foot pain [21,200]. Despite the disparity in the prevalence of foot pain between women and men, and the spike in prevalence in women during middle-age, investigations of foot pain specifically in this group have not been performed [21].

Obesity is a significant risk factor for foot pain, with body mass index (BMI) strongly associated with non-specific foot pain in the general population [86]. In middle-aged women, a higher BMI yields a significantly increased likelihood of developing and sustaining foot pain over a five-year period, independent of age [87]. It has traditionally been thought that increased body mass in overweight or obese individuals mechanically overloads the feet, leading to foot pain [201]. More recently, it has been identified that the amount of fat mass as opposed to fat-free mass, is associated with prevalent foot pain [139] and is predictive of incident foot pain over a three-year period [34]. Moreover, a study using a large community sample found a relationship between fat mass and foot pain [120]; this same study found significant associations with depression and foot pain, reconfirming findings [15,202,203]. Furthermore this effect appears to be stronger in women [204]. Indeed, in other musculoskeletal conditions there are associations between obesity and other aspects of psychological health such as pain catastrophising [79] and central sensitisation [81], which to date have not been explored in people with foot pain.

These findings have led to an increase in interest in both, metabolic and psychological factors, rather than purely mechanical mechanisms.

Further exploration of body composition, finds both body fat mass and body fat percentage increase with age in both men and women [205]. Women typically have more body fat than men across all age groups, and have more fat around the hips and thighs (gynoid) than men who typically have increased abdominal fat mass (android) [206]. Along with different regional fat storage, a study specifically investigating android adiposity found whilst there was no difference in the sagittal diameter between genders, men had more visceral abdominal tissue (VAT), women had more subcutaneous abdominal tissue (SAT) [207]. Moreover, the volume of VAT in women is associated with depression [208,209], and is suggestive that the links between pain, depression and obesity are closely entwined. However, no study has specifically investigated the role of these factors in middle-aged women with chronic, disabling foot pain.

Both depression [210] and obesity [211] are associated with low-grade inflammation, a state considered ripe for chronic pain to develop. These relationships may be bidirectional, with causation difficult to ascertain, but they are likely to be synergistic and symbiotic [212]. Determining the volume, location and type of adipose tissue, and how this may interact with psychological health, and chronic, disabling foot pain will improve our understanding of potential mechanisms and future therapeutic targets.

Therefore, the aim of this study was to investigate the association of body composition and psychological health with chronic, disabling foot pain in middle-aged women.

4.4 Materials and Methods

4.4.1 Study participants

Participants with and without chronic, disabling foot pain were recruited for this cross-sectional, matched-pairs study from the community via advertisements placed in newspapers, local general practitioner clinics and online via social media.

4.4.2 Inclusion and exclusion criteria

Inclusion criteria for the disabling foot pain group were: females aged between 40 and 65 years, the presence of foot pain for at least three-months (and assessed as 'disabling' for the past month) with the Manchester Foot Pain and Disability Index (MFPDI) [213], with regular daily foot pain severity of at least 30-mm on a 100-mm visual analogue scale. Participants must not have received or be undergoing treatment for their foot pain from a health professional. Healthy community-dwelling women without chronic foot pain were recruited and matched to the case-group participants for age (within 2 years) and BMI (within 2 kg / m^2).

Exclusion criteria for all participants included: living in a residential aged care facility, current or previous foot ulceration, previous foot surgery, previous trauma to foot, the presence of any medical condition impacting mobility, a body mass greater than 220 kg (the upper safety limit for the body composition scanner [iDXA]), pregnancy, current medication for depression, a diagnosis by a medical practitioner of any arthropathy affecting the back or lower limbs, peripheral neuropathy, cognitive impairment, or the inability to understand English. The study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (Project number 431.15). All participants provided written informed consent.

4.4.3 Anthropometric data

Age, height and body mass were recorded at the time of the body composition assessment. Body weight was measured to the nearest 0.1 kg using electronic scales and height was measured to the nearest 0.1 cm using a stadiometer (with shoes, socks, and bulky clothing removed). From these data, BMI (weight (kg) / height (m^2)) was calculated.

4.4.4 Body composition assessment

Body composition was measured using a dual x-ray absorptiometry machine (Lunar iDXA, GE Healthcare, Madison, WI, USA) by an experienced operator to identify VAT, android fat mass, gynoid fat mass, total body fat mass, total fat-free mass (total lean body mass plus total bone mineral content mass) and android / gynoid fat ratio. Whole body fat and fat-free mass were then normalised for height by calculating fat mass index (FMI) (total body fat (kg) / height (m^2) and fat-free mass index (FFMI) (total lean body mass plus total bone mineral content (kg) / height (m^2)). Visceral adipose tissue was normalised to the abdominal region by dividing VAT / android fat and SAT was calculated by (android – VAT), enabling the use of VAT / SAT ratio. All participants were scanned in the morning after an overnight fast. The precision of repeat iDXA measurements of VAT is excellent with a coefficient of variation of 5.1%, and highly related to fat mass derived from computed tomography (r^2 = 0.957) [214,215]. Test-retest reliability of all body composition variables was assessed in this study by repeating scans on 10 participants with repositioning, and indicated excellent reliability (ICC > 0.98).

4.4.5 Psychological health

The Center for Epidemiologic Studies-Depression scale (CES-D) consists of 20-items designed to assess depressive symptoms [186]. All items are graded via four-point Likert scale, which are later graded between 0 – 3. A score of ≥ 16 has been shown to be sensitive to detect depressive symptoms [216].

The Central Sensitization Inventory (CSI) is a two-part questionnaire used to determine if those with pain have central sensitisation [217]. Part A was used for this study; it assesses 25 health-related symptoms common to central sensitisation syndromes. Questions are graded via five-point Likert scale with total scores ranging from 0 to 100. A score of ≥ 40 in Part A has been found to be clinically significant in identifying those with and without a central sensitisation syndrome [80].

The Pain Catastrophizing Scale (PCS) is a 13-item questionnaire that was developed to identify the degree to which catastrophising impacts on pain experience [75]. The PCS asks participants to reflect on past painful experiences, and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on five-point scales with the end points (0) not at all and (4) all the time. The PCS yields a total score (range 0 – 52) and three subscale scores assessing rumination, magnification and helplessness. The total score underwent Rasch transformation [218] to allow it to be used as a continuous variable.

The CES-D, CSI and PCS were used to measure various aspects of psychological health in both the foot pain group and the control group.

4.4.6 Foot pain and disability

The MFPDI was administered to measure disabling foot pain, and consists of 19 items that are preceded with the phrase, ‘‘*because of pain in my feet,*’’ formalised under four domains: functional limitation (10 items), pain intensity (5 items), personal appearance (2 items), and difficulties with work or leisure activities (2 items). Each item is documented as being present ‘none of the time’ (0 points), ‘on some days’ (1 point), or ‘on most / everyday’ (2 points) The entire questionnaire was asked of participants with foot pain, but

for the purposes of defining disabling foot pain, only questions relating to functional limitation (questions 1 – 10) were considered. This modification of the MFPDI is based upon the case definition proposed by Roddy et al [219] and participants must answer 'on most / everyday' to qualify as having disabling foot pain, and the degree of disability was measured by the sum score of the functional limitation domain. The raw score for functional limitation underwent a Rasch transformation as previously described [220], enabling the resultant value to be treated as a continuous variable for statistical analysis. Functional limitation is graded on a 0 – 20 scale. Other joint pain in both hands, elbows, shoulders, hips, knees, along with the neck and lower back was also recorded and the total number of joints affected were summed (range 0 – 12).

Participants completed the PainDETECT questionnaire (PD-Q) to determine if the foot pain group had nociceptive or neuropathic components to pain. The questionnaire consists of nine items (seven with Likert-scale scoring, graded 0 to 5, and two separate questions, scored -1 to +2, total maximum score of 38). The PD-Q questionnaire has been used to identify neuropathic pain components in a range of conditions [221] and has good reliability with high sensitivity and specificity for detecting neuropathic pain [222].

4.4.7 Sample size calculation

A sample size calculation was performed based on a previous investigation of regional fat mass in middle-aged women [223]. Eighty-eight women (44 cases and 44 controls) provided 80% power to detect an effect size of 0.37 using the VAT / SAT ratio, assuming a mean ratio of 0.4 and 0.48 in each respective group, assuming a standard deviation of 0.17. A conservative estimate for type 1 error of 0.01 and a correlation between groups of 0.2.

4.4.8 Data analysis

Descriptive statistics (frequencies, means, medians and ranges) were initially undertaken. All data distributions were checked for normality via the inspection of histograms and the Shapiro-Wilks test prior to interferential statistical analysis. Fat mass and fat mass index were normally distributed and differences between groups were analysed with independent samples t-test, the remaining body composition data and the number of painful joints (external to the foot), along with the CSI and PCS were not-normally distributed and were analysed with Mann-Whitney *U* test. Differences between groups with the CES-D score and the site of painful joints (external to the foot) was analysed with the chi-squared (χ^2) test. As functional limitation was not normally distributed, univariate correlations between other joint pain, body composition and psychological health were explored with Spearman's rank correlation coefficient. Body composition variables with significant univariate association with foot pain and all psychological variables were used in multivariable regression modelling for the Rasch-transformed functional limitation subscale. Regression diagnostics indicated that there were outliers in the sample however due to the nature of the study these were kept in the analysis. All independent variables (age, psychological and body composition variables) were examined for collinearity within the model using the variance inflation factor (VIF). All variables had a VIF < 4 and remained within the final model. A p value < 0.05 (2 - tailed) were regarded as statistically significant. All data analyses were performed with SPSS V24 (IBM SPSS Statistics, New York) and STATA V14.2 (StataCorp LP, College Station, Texas).

4.5 Results

4.5.1 Participant characteristics

Eighty-eight women completed the study. The foot pain group and the control group were similar in age, physical characteristics and menopause status, as shown in Table 1. The foot pain group and the control group had a median (range) age of 56.6 (40.6 – 65.9) years and 56.6 (41.6 – 64.4) years, respectively ($p > 0.05$). The median (range) BMI for the foot pain group control group was similar, 29.3 (18.5 – 44.1) kg / m^2 versus 27.6 (17.2 – 42.2) kg / m^2, $p > 0.05$.

4.5.2 Foot pain and disability

The results of the PD-Q and MFPDI are detailed in Table 1. There was a low prevalence in neuropathic pain and the functional limitation subscale score from the MFPDI had a median (range) of 8.8 points (6.7 – 15.2). There were significant correlations between the Rasch-transformed functional limitation score and body composition measures: total body fat mass, fat mass index (FMI), android fat mass, gynoid fat mass, VAT, VAT / android fat mass ratio, and VAT / SAT, while the only psychological health measure to correlate with functional limitation was the total CES-D score. There was no statistically significant correlation with number of other joints with pain and functional limitation.

Table 1: Participant characteristics (median (IQR) unless otherwise specified)

	Foot pain group (n = 44)	Control group (n = 44)
Age, yrs	56.6 (10.3)	56.7 (6.5)
Height, m, mean (SD)	1.6 (0.1)	1.6 (0.1)
Weight, kg, mean (SD)	78.1 (18.1)	76.1 (18.8)
BMI, kg / m^2	29.3 (9.9)	27.6 (10.5)
Menopause status		
Pre-menopausal, n	7	9
Peri-menopausal, n	5	6
Post-menopausal, n	31	29
Unsure of menopause status, n	1	0
Painful joints (external to foot), n	2 (4)	0.5 (2)
MFPDI subscale score[#]		
Functional limitation	8.8 (2.1)	
PD-Q category		
Negative, n (%)	29 (65.9)	
Unclear, n (%)	10 (22.7)	
Positive, n (%)	5 (11.4)	

[#] Rasch transformed MFPDI subscale score

IQR interquartile range, *SD* standard deviation, *yrs* years, *m* metres, *kg* kilograms, *BMI* body mass index; *MFPDI* Manchester Foot Pain and Disability Index, *PD-Q* PainDETECT Questionnaire

4.5.3 Other joint pain

The foot pain group had significantly more painful joints (external to the foot) than the control group, with a median (IQR) of painful joints of 2 (4) and 0.5 (2) (p = 0.001), respectively. The foot pain group reported significantly more hand, elbow, hip and low back pain. There was no difference the prevalence of knee, shoulder or neck pain between the two groups.

4.5.4 Body composition

There were no statistically significant differences in any measure of body composition between the foot pain group and the control group, as detailed in Table 2.

Table 2: Differences in body composition between foot pain group and control group (median (IQR) unless otherwise specified)

	Foot pain group (n = 44)	Control group (n = 44)	*p* value
Fat mass, kg, mean (SD)	33.1 (13.6)	31.5 (13.4)	0.578[a]
Fat mass index, kg/m^2, mean (SD)	12.5 (5.1)	12.0 (4.9)	0.632[a]
Fat-free mass, kg	43.5 (7.1)	42.7 (7.2)	0.520[b]
Fat-free mass index, kg / m^2	16.7 (2.6)	16.3 (2.5)	0.993[b]
Android fat, g	2787 (2115)	2511 (2192)	0.806[b]
Gynoid fat, g	5724 (3380)	5217 (2866)	0.582[b]
Android / gynoid ratio	0.4 (0.1)	0.5 (0.2)	0.531[b]
Visceral fat, g	958 (871)	661 (960)	0.383[b]
Visceral / android ratio	0.3 (0.2)	0.3 (0.2)	0.110[b]
VAT / SAT ratio	0.5 (0.3)	0.4 (0.3)	0.098[b]

[a] *p* calculated for differences between groups analysed with independent samples t-test

[b] *p* calculated for differences between groups analysed with Mann-Whitney *U* test

IQR Interquartile range, *SD* standard deviation, *kg* kilograms, *m* meters, *g* grams, *SAT* subcutaneous adipose tissue, *VAT* visceral adipose tissue

4.5.5 Psychological health

There were significant differences between the foot pain group and the control group across all measures of psychological health (depressive symptoms, central sensitisation, catastrophisation), as shown in Table 3. Thirteen participants (29.5%) in the foot pain group were characterised as having depressive symptoms, compared to zero participants in the control group (χ^2 = 15.253, $p < 0.001$). There were significant differences in central sensitisation between the foot pain group and the control group of mean (standard deviation (SD)) 31.5 (12.0) versus 24.0 (14.5), $p = 0.002$, respectively, although neither group scored a clinically significant mean score of > 40 with the CSI. The Rasch transformed PCS scores of the foot pain group were significantly different to the control group, with median (range) 14.9 (0 – 26.1) versus 9.3 (0 – 21.7), $p < 0.001$. The three domains of the PCS; rumination, magnification and helplessness were all significantly higher in the foot pain group compared to the control group.

4.5.6 Multivariable analysis

In multivariable analyses, after adjusting for age, FFMI, central sensitisation and pain catastrophisation, functional limitation was positively correlated VAT / SAT ratio (β 1.3, 95% CI 0.3 to 2.3), FMI (β 0.1, 95% CI 0.0 to 0.3) and depression (β 0.1, 95% CI 0.0 to 0.1), (Table 4). Fat-free mass index was negatively associated with functional limitation, suggesting a possible protective effect, although not statistically significant.

Table 3: Differences in psychological health between foot pain group and control group (median (IQR) unless otherwise specified)

	Foot pain group (n = 44)	Control group (n = 44)	*p* value
PCS			
Rumination	3.0 (4.0)	1.0 (4.0)	0.047[a]
Magnification	2.0 (2.0)	0.0 (2.0)	0.001[a]
Helplessness	4 0 (5.0)	0.5 (2.0)	< 0.001[a]
Total score[#]	14.9 (5.5)	9.3 (13.5)	< 0.001[a]
CES-D			
No depressive symptoms, n	31	44	
Depressive symptoms, n	13	0	< 0.001[b]
CSI-A total score, mean (SD)	31.5 (12.0)	24.0 (14.5)	0.002[c]

[#] Rasch transformed PCS total score

[a] *p* calculated for differences between groups analysed with Mann-Whitney *U* test

[b] *p* calculated for differences between groups analysed with χ^2 test

[c] *p* calculated for differences between groups analysed with independent samples t-test

SD standard deviation, *PCS* Pain Catastrophizing Scale, *CES-D* Center for Epidemiologic Studies-Depression Scale, *CSI-A* Central Sensitization Inventory – Part A

Table 4: Multivariable relationship between foot pain severity with age, body composition and psychological variables

	β-coefficients (95% CI)	*p* value
Functional limitation sub-scale^		
Age	0.0 (-0.0 to 0.1)	0.582
FMI	0.1 (0.0 to 0.3)	0.019
FFMI	-0.3 (-0.6 to 0.0)	0.087
VAT / SAT ratio	1.3 (0.3 to 2.3)	0.014
CES-D	0.1 (0.0 to 0.1)	0.046
CSI-A	0.0 (-0.1 to 0.1)	0.938
PCS	0.1 (-0.0 to 0.1)	0.220

^ All variables listed were included in the multivariable model

CI confidence interval, *FMI* fat mass index, *FFMI* fat-free mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue, *CES-D* Center for Epidemiologic Studies-Depression Scale, *CSI-A* Central Sensitization Inventory – Part A, *PCS* Pain Catastrophizing Scale

4.6 Discussion

This study demonstrates that there are significant increases in depressive symptoms, central sensitisation and pain catastrophisation between groups of middle-aged women with and without chronic, disabling foot pain. There were no significant differences in body composition between the two, matched groups, but our results suggest that once foot pain has developed, the severity of disabling foot pain may increase as VAT / SAT ratio, fat mass, and to a lesser extent, depressive symptoms increase.

The concordance between psychological health and chronic pain is high and considered bidirectional [224]. The mechanisms are not entirely understood, but the association of low-grade inflammation, depression and pain suggests a metabolic pathway. Our results suggest that lower levels of depressive symptoms, central sensitisation and catastrophisation may be protective of developing disabling foot pain, but once developed it is depression, rather than pain catastrophisation or central sensitisation, that influences the severity. Given participants were excluded if they reported a current diagnosis of depression, and given 13 / 44 (29.5%) of the foot pain group had depressive symptoms, according to the CES-D, there may be a high level of undiagnosed depression in people with chronic, disabling foot pain.

The higher prevalence of multi-site pain (external to the foot) in the foot pain group compared to the control group in univariable analysis suggests that poor psychological health may be associated with widespread pain. Indeed, given the relationship between psychological health and chronic pain is considered bidirectional, further study specifically in people with foot pain to fully determine the temporal nature of these relationships is warranted.

4 BODY FAT DISTRIBUTION AND PSYCHOLOGICAL HEALTH

The link between obesity and the manifestation of chronic pain in women may be as a result of low-grade inflammation [225] produced by excessive adiposity [67] or by other metabolic processes involving adipokines. The absence of statistically significant differences in body composition in the between group analysis, however, suggests that body composition alone may not be associated with having foot pain. Body composition, including the location and degree of adiposity, does appear to more related to the severity of pain once it has developed.

The increase in disabling foot pain severity with an increase in VAT / SAT and FMI, along with the inverse correlation with FFMI (although not statistically significant) suggests that body composition may be a more important consideration than body weight alone. Previous authors have hypothesised that a reduction in ghrelin, a hormone with antinociceptive properties and inversely related to obesity could be responsible, at least in part [226]. There is also evidence that proinflammatory cytokines, such as leptin are associated with both the presence and the severity of pain [56]. Visfatin is an adipokine preferentially expressed from VAT and has been associated with pain severity with incipient upper limb soft tissue disorders [177]. Indeed, there is mounting evidence that the association between pain and obesity may go beyond excessive mechanical loading, and this study's findings support this premise. This study is the first to report that the location of adipose tissue, specifically the ratio between VAT / SAT, does appear to influence the severity of foot pain.

The correlation between VAT / SAT ratio and the severity of disabling foot pain suggests that the location of adipose tissue does affect the experience of pain, and is independent of other measures of body composition. Given the known association of low-grade

inflammation and visceral adiposity [227], it is possible that our results are in accordance with the premise that the presence of low-grade inflammation is related to chronic pain, although the added analysis of sera inflammatory markers would have provided stronger evidence to support this.

There are limitations with this study that require acknowledgement. Firstly, the study is cross-sectional and therefore we are unable to determine causality between pain, body composition and psychological health. Secondly, participants were not diagnosed with local foot pathology, but were recruited on the basis of the duration and degree of pain. Thirdly, whilst we were able analyse the fat mass distribution, direct measurement of serum cytokines released by this tissue may have been more informative with respect to the influence of adiposity on pain. Finally, there were subjects identified as outliers, which may influence the results of the regression analysis and the sample size in this study may have limited the ability to detect differences in the outcome variables between groups. Further investigation with larger samples is required.

This study has strengths when compared to similar work. By using body composition assessment with iDXA, this study was able to explore different fat deposits (visceral and subcutaneous) along with the traditional body composition variables enabling the study to report the effect of fat mass distribution on pain. Given the groups were matched for age and BMI, we were able to adequately control for these variables in between-group analyses, which is an improvement on previous investigations that did not match age and BMI. The results of this study are generalisable to middle-aged women; menopause status was evenly matched (a potential confounding variable for pain [228]), there was a wide range of age and BMI, and a low prevalence of neuropathic pain.

4.7 Conclusion

In conclusion, in this study of middle-aged women, the presence of chronic, disabling foot pain was more closely linked with psychological health than body composition. Once disabling foot pain had developed, however, the severity was more closely linked with VAT / SAT ratio and fat mass, suggesting a metabolic mechanism and potential role for visceral fat in the perception of foot pain severity. Further work is needed to determine if an improvement in psychological health reduces the risk of developing foot pain, or if a reduction in VAT / SAT ratio, fat mass index or depression reduces the severity of chronic, disabling foot pain.

5

Chapter 5: The effect of bariatric surgery and body composition on foot pain

5 BODY COMPOSITION, WEIGHT LOSS AND FOOT PAIN

5.1 Introduction to publication

Walsh TP, Quinn S, Evans AM, Yaxley A, Chisholm JA, Kow L, Shanahan EM. Fat mass, but not fat-free mass, predicts increased foot pain with obesity, independent of bariatric surgery. *Surg Obes Relat Dis*. [In press]

Purpose

The primary purpose of this study is to investigate whether bariatric surgery reduces foot pain in a morbidly obese cohort. The secondary purpose was to determine if there are baseline predictors for a change in foot pain, particularly whether there are differences in the prognostic value of either body mass index (body weight); or fat mass index and fat-free mass index (body composition). Whether a change in adipokines is associated with a change in pain will also be analysed. Thus, the study aims to assess potential mechanical and non-mechanical mechanisms underlying foot pain.

Accepted in

Surgery for Obesity and Related Diseases.

2016 Impact Factor 4.496

5-year Impact Factor 4.886

5 BODY COMPOSITION, WEIGHT LOSS AND FOOT PAIN

Contribution from primary author

Primary Author – Tom Walsh

Arthritis Australia provided a research grant for this study. The successful grant application was led by the primary author, but included consultation with the listed co-authors.

The manuscript was written by the primary author, which followed consultation and review by the listed co-authors. The primary author conceived the research questions and completed the initial data analysis with the study statistician, the final analyses reported in the publication were conducted by the study statistician.

5 BODY COMPOSITION, WEIGHT LOSS AND FOOT PAIN

5.2 Abstract

Introduction: The aim of this study was to investigate; i) if bariatric surgery is associated with a reduction in foot pain and; ii) if body mass index (BMI) or body composition predict a change in foot pain.

Material and Methods: Participants with foot pain awaiting bariatric surgery were recruited for this prospective study. Multivariable linear regression was used to determine predictors of change in foot pain between baseline and six-month follow-up using body composition (fat mass index (FMI) and fat-free mass index (FFMI)) or BMI, adjusting for, depression, age, gender and group (surgery versus control).

Results: Forty-five participants (38 female), mean (standard deviation (SD)) age of 45.7 (9.4) years, were recruited for this study. Twenty-nine participants mean (SD) BMI of 44.8 (7.0) kg underwent bariatric surgery, while 16 participants mean (SD) BMI of 47.9 (5.2) kg were on the waiting-list (control). One participant was lost to follow-up. The treatment group lost a mean of 24.3kg (95% CI 21.1 to 27.5), while the control group gained 1.2kg (95% CI -2.5 to 4.9), respectively. In multivariable analysis, bariatric surgery was significantly associated with reduced foot pain at six-month follow-up -32.6 points (95% CI -43.8 to -21.4, $p < 0.001$), while FMI was significantly associated with increased pain at follow-up 1.5 points (95% CI 0.2 to 2.8, $p = 0.027$), after controlling for FFMI, age, gender and depression.

Conclusion: Bariatric surgery was significantly associated with reduced foot pain. Higher baseline FMI, but not FFMI or BMI, was predictive of increased foot pain at follow-up. Foot pain may be mediated by metabolic, rather than mechanical, factors in bariatric surgery candidates.

5 BODY COMPOSITION, WEIGHT LOSS AND FOOT PAIN

5.3 Introduction

Musculoskeletal pain is strongly associated with obesity [229]. Obesity increases the risk of lower-limb complaints such as osteoarthritis, and affects the speed of recovery following injury [230]. Increased body mass index (BMI) is strongly associated with foot pain [86], with increased body weight excessively loading pedal joints and tissues, thought to be the underlying mechanism. Indeed, obesity is associated with hindfoot stiffness, increased plantar pressure and pronated foot posture, which may increase the risk of pain [98]. Whilst much attention is directed toward the effect of excessive mechanical loading, foot pain associated with obesity may also be due to metabolic dysfunction related to excessive fat. Further exploration of the relationship between obesity and foot pain is important as it may better inform more targeted management strategies.

Studies investigating the effect of body composition on musculoskeletal pain in the low-back [35], knee [231] and foot [120,232] are associated with fat mass, but not fat-free mass. These findings propose that the type of tissue present may be more important than the weight of the tissue. Furthermore, obesity has been associated with hand osteoarthritis [176,233], which as a non-weight bearing structure, suggests that the effect of obesity may extend beyond excessive mechanical loading. There is evidence that cytokines from adipose tissue, adipokines, may be upregulated with obesity with strong associations between adipose tissue and serum adipokines [52].

Leptin, a proinflammatory adipokine, chiefly secreted by subcutaneous adipose tissue, has been found to be a mediator between body weight and knee osteoarthritis [57] and is associated with generalised musculoskeletal pain in women [56]. Furthermore, higher serum leptin predicts a slower recovery from upper extremity soft tissue disorders [55].

Articular chondrocytes express receptors for leptin [53], providing a direct pathway for adipose tissue to interact with joint cartilage, beyond mechanical loading. This suggests that the link between obesity and joint pain may be mediated locally via the effects of systemic adiposity.

Despite the strong association between obesity and foot pain, there is a paucity of literature investigating the effectiveness of weight loss on reducing symptoms. Indeed, the effectiveness of bariatric surgery on the morbidly obese, a group plagued with foot pain, has been largely unexplored. Moreover, whether there are predictors or correlates for a change in foot pain, to suggest a possible underlying mechanism whether that be mechanical or metabolic are also undetermined.

This study aims to investigate whether; i) bariatric surgery is associated with a reduction in foot pain, ii) if baseline body mass index (BMI), body composition or a change in adipokines predict change in foot pain following bariatric surgery.

5.4 Materials and Methods

5.4.1 Study participants

This project was a prospective observational study conducted between January 2015 and June 2017. A convenience sample of people with foot pain was recruited from the surgical waiting lists at two tertiary hospitals in Adelaide, South Australia. The treatment group was recruited for baseline measures immediately prior to bariatric surgery and re-evaluated again six months post-operatively and underwent either a Roux-en-Y gastric bypass, a sleeve gastrectomy or a laparoscopic adjustable gastric band. The control group was recruited from the same waiting lists as the treatment group, but these patients were not scheduled to have surgery within six-months. Participants in the control group were re-evaluated at six-month follow-up. Ethics approval has been given for this project by

Southern Adelaide Clinical Human Research Ethics Committee (Project ID 211.14).

5.4.2 Inclusion and exclusion criteria

People on the waiting list for bariatric surgery were eligible for inclusion if they were aged ≥ 18 years and had reported foot pain for ≥ 3 months of ≥ 30mm on a visual analogue scale, as this has been shown to represent moderate (or greater) pain [234]. People were excluded if they had; a systemic inflammatory condition, clinically significant peripheral neuropathy, known infectious disease, cancer, previous bariatric or foot surgery, were non-ambulatory or were pregnant.

5.4.3 Anthropometric data

Age, body weight, height, and waist and hip circumference were recorded at the time of the body composition assessment. Body weight and height was measured to the nearest 0.1 kg and 0.1 cm, respectively using an electronic stadiometer (with shoes, socks, and bulky clothing removed) (Seca 284, Germany). From these data, BMI (weight (kg) / height (m^2)) was calculated [24]. Waist and hip circumference were measured using a flexible steel measuring tape (Lufkin, US) in duplicate to the nearest 0.1cm and the mean score was recorded.

5.4.4 Foot pain

Foot pain and disability was assessed with the Manchester-Oxford Foot Questionnaire (MOXFQ) [235]. The MOXFQ is a reliable and valid 16-item questionnaire that comprises three separate underlying dimensions: walking/standing problems (seven items), foot pain (five items), and social interaction (four items) [236]. Item responses are each scored from 0 – 4, with 4 representing the most severe state. The scale score representing each dimension was produced by summing the responses of each item within that dimension.

This produces raw scale scores, which were then transformed to a scale from 0 – 100 (100 most severe). The foot pain domain was used for this study, it has been previously recommended for measuring relief of pain [236].

5.4.5 Body composition

Participants underwent a dual-energy X-ray absorptiometry (DXA*)* scan, with the Lunar Prodigy Advance (GE Healthcare, WI, USA), at baseline and at six-months follow-up. The DXA was used to assess body composition; total fat mass (FM), total lean mass and total bone mineral content (BMC). Lean mass and BMC were combined to give fat-free mass (FFM). Fat mass and FFM were normalised for height by calculating fat mass index (FMI) (total body fat (kg) / height $(m)^2$) and fat-free mass index (FFMI) (FFM / height $(m)^2$) [205].

5.4.6 Adipokines

Fasting blood samples were collected and centrifuged, and aliquots of serum were stored at -80^{o}C until the final analysis. Serum concentrations of leptin, adiponectin and resistin were measured with the Millipore human adipokine kits on the MAGPIX machine and analysed with xPONENT software (Luminex Corporation, TX, USA). Samples were prepared at appropriate dilutions and assessed according to the manufacturer's instructions. Internal control samples supplied by the manufacturer were tested and duplicate analyses were used to ensure quality control.

5.4.7 Depressive symptoms

Given the bidirectional association of depression and pain [72], depression was measured. The Center for Epidemiologic Studies Depression scale (CES-D) consists of 20-items designed to assess depressive symptoms [186]. All items are graded via four-point Likert scale, which are later graded between 0 – 3. A score of ≥ 16 has been shown to be

sensitive to detect depressive symptoms [216] and this was used define depression in this cohort.

5.4.8 Sample size calculation

The primary outcome measure was the change in foot pain following bariatric surgery. Given we did not expect to see a significant change in foot pain in the control group [237,238], the sample size was based on a mean (standard deviation (SD)) of change in foot pain within the treatment group of 13 (25.1) based on previous studies [236,239]. A conservative sample size calculation required 34 participants in the treatment group to provide 80% power, assuming a Type I error of 5%.

5.4.9 Data analysis

All data distributions were checked for normality via the inspection of histograms and the Shapiro-Wilks test prior to interferential statistical analysis. Differences between treatment and control groups at baseline were assessed using chi-squared tests for categorical data and t-tests or Mann-Whitney *U* tests for continuous data that is normally or non-normally distributed, respectively. Given the low numbers and the fact that BMI is the sum of FMI and FFMI, two multivariable linear regressions were used to assess differences between baseline and follow-up. The dependent variable was foot pain at follow-up. The independent variables were foot pain at baseline, age, gender, group, depression and either BMI (model 1) or FMI and FFMI (model 2). We also used partial correlation, to investigate whether change in foot pain was associated with change in leptin, adiponectin or resistin. Standard homoscedasticity and normality checks of residuals were carried out to ensure model validation (using Stata's hettest and swilk commands). These models were also adjusted for age, gender, group, depression, FMI and FFMI. In all analyses, a p-value (two-sided) less than 0.05 was deemed to be statistically significant. Results are

reported with 95% confidence intervals (95% CI). All data analyses were performed with SPSS V24 (IBM SPSS Statistics, New York) and Stata V14.2 (StataCorp LP, College Station, Texas).

5.5 Results

5.5.1 Participant baseline characteristics

Baseline characteristics are described in Table 1. There were 45 participants (38 women), with a mean (SD) age of 45.7 (9.4) years, recruited for this study. Twenty-nine participants were in the treatment group and 16 were in the control group. All participants underwent baseline measures, one participant (from the treatment group) was lost to follow-up. The baseline mean (SD) BMI for the treatment and control group was 44.8 (7.0) and 47.9 (5.2) kg, respectively. Fat-free mass index was significantly different between groups, with a mean (SD) in the treatment group of 21.4 (3.2) versus 23.0 (2.3) in the control group, p = 0.041. Otherwise there were no statistically significant between-group differences in baseline characteristics. There were 13, 11, and 5 participants who underwent Roux-en-Y gastric bypass, sleeve gastrectomy or laparoscopic adjustable gastric band, respectively.

Table 1: Baseline characteristics of the treatment and control groups[a] (values are mean (SD) unless otherwise indicated)

	Treatment group (n = 29)	Control group (n = 16)	*p* value
Age, years	45.1 (9.0)	45.3 (10.4)	0.958
Gender, no. of women (%)	25 (86.2)	13 (81.3)	0.661
Height, m	1.7 (0.1)	1.7 (0.1)	0.906
Weight, kg	123.9 (19.4)	132.4 (15.5)	0.140
Waist circumference, cm	127.4 (11.7)	134.0 (13.2)	0.094
Hip circumference, cm	139.2 (13.2)	141.9 (13.8)	0.527
BMI, kg / m^2	44.8 (7.0)	47.9 (5.2)	0.120
FMI, kg / m^2	23.4 (5.7)	24.6 (4.1)	0.497
FFMI, kg / m^2	21.3 (3.2)	23.4 (3.0)	0.041
FMI / FFMI ratio	1.1 (0.2)	1.1 (0.2)	0.533
Adiponectin, μg / ml, median (IQR)[b]	12.5 (17.1)	8.5 (20.0)	0.445
Leptin, ng / ml, median (IQR)[b]	41.8 (26.8)	56.3 (32.7)	0.150
Resistin, ng / ml, median (IQR)[b]	31.9 (25.3)	29.0 (16.0)	0.471
Depressive symptoms, n (%)[c]	15 (51.7)	10 (62.5)	0.486
MOXFQ pain domain score	54.1 (16.2)	63.4 (17.5)	0.080

[a] *p* calculated for differences between the treatment and control groups analysed with the independent samples t-test

[b] *p* calculated for differences between the treatment and control groups analysed with the Mann-Whitney *U* test

[c] *p* calculated for differences between the treatment and control groups analysed with the chi-squared test

SD standard deviation, *m* metres, m^2 metres squared, *kg* kilogram, *μg* microgram, *ng* nanogram, *ml* millilitre, *cm* centimetre, *MOXFQ* Manchester-Oxford Foot Questionnaire, *IQR* Interquartile range

5.5.2 Multivariable linear regression

After adjusting for age, gender and depression, bariatric surgery was a significant predictor of change in foot pain, β = -30.7 (95% CI -41.9 to -19.5, $p < 0.001$), Table 2. Body mass index was not a significant predictor of a change in foot pain with β = 0.5 (95% CI -0.3 to 1.4, $p = 0.213$). Using a similar model, but substituting FMI and FFMI for BMI, bariatric surgery and FMI were significant predictors of a change in foot pain, β = -32.6 (95% CI -43.8 to -21.4, $p < 0.001$) and FMI β = 1.5 (95% CI 0.2 to 2.8, $p = 0.027$), respectively. The relationship between FFMI and a change in foot pain was not statistically significant, β = -1.4 (95% CI -3.4 to 0.5, $p = 0.145$), and was divergent from FMI, Table 3. There was no evidence of model violation in either model: Table 2 – swilk $p = 0.74$, hettest $p = 0.40$; and Table 3 – swilk $p = 0.21$, hettest $p = 0.93$. The within-group change in baseline variables can be found in Table 4.

5.5.3 Partial correlation of adipokines with change in pain

Change in foot pain was not significantly correlated with change in leptin or adiponectin, when adjusted for the same confounders in Table 3. On the other hand, change in pain and change in resistin were negatively correlated (ρ = -0.42, $p = 0.024$) when adjusted for the other confounders in Table 3.

Table 2: Multivariable relationship between baseline predictors for change in foot pain between baseline and follow-up, with BMI as a predictor

	β-coefficients (95% CI)	*p* value
Age	0.1 (-0.6 to 0.9)	0.677
Bariatric surgery	-30.7 (-41.9 to -19.5)	< 0.001
BMI	0.5 (-0.3 to 1.4)	0.213
Depressive symptoms	7.2 (-4.3 to 18.7)	0.214
Gender (female)	10.7 (-5.4 to 26.8)	0.186

CI confidence interval, *BMI* body mass index

Table 3: Multivariable relationship between baseline predictors for change in foot pain between baseline and follow-up, with FMI and FFMI as predictors

	β-coefficients (95% CI)	*p* value
Age	0.3 (-0.5 to 1.0)	0.480
Bariatric surgery	-32.6 (-43.8 to -21.4)	< 0.001
Depressive symptoms	3.6 (-8.5 to 15.6)	0.553
FMI	1.5 (0.2 to 2.8)	0.027
FFMI	-1.4 (-3.4 to 0.5)	0.145
Gender (female)	4.8 (-13.0 to 22.5)	0.588

CI confidence interval, *FMI* fat mass index, *FFMI* fat-free mass index

Table 4: Change in body size, body composition, foot pain and depression between baseline and follow-up for the treatment and control groups[a]

	Treatment group (n = 29)		Control group (n = 16)	
	Mean difference	95% CI	Mean difference	95% CI
Body size				
Waist circumference, cm	-17.2	-20.1 to -14.3*	-1.0	-6.1 to 4.2
Hip circumference, cm	-15.8	-18.8 to -12.8*	-0.8	-4.6 to 2.9
Body weight, kg	-24.3	-27.5 to -21.1*	1.2	-2.5 to 4.9
BMI, kg / m^2	-8.8	-10.0 to -7.6*	0.5	-0.8 to 1.8
Body composition				
FMI, kg / m^2	-6.7	-7.8 to -5.6*	0.1	-1.0 to 1.2
FFMI, kg / m^2	-1.9	-2.4 to -1.5*	0.4	-0.2 to 1.0
FMI / FFMI ratio	-0.2	-0.2 to -0.3*	0.0	-0.0 to 0.1
Adipokines				
Adiponectin, μg / ml	19.8	10.0 to 32.3*	11.9	2.4 to 24.8[$]
Leptin, ng / ml	-20.4	-27.4 to -13.3*	15.4	7.4 to 37.0[#]

	Treatment group (n = 29)		Control group (n = 16)	
	Mean difference	95% CI	Mean difference	95% CI
Adipokines				
Resistin, ng / ml	9.4	1.7 to 15.7[#]	10.9	-3.7 to 15.2
MOXFQ				
Pain domain	-34.5[b]	-41.0 to -27.9*	-6.3	-16.5 to 4.0
Depressive symptoms[c]	*Baseline*	*Follow-up*	*Baseline*	*Follow-up*
Yes, n	15	5	10	7
No, n	14	23[#]	6	9[#]

[a] *p* calculated for differences between baseline and follow-up measures analysed with the paired samples t-test

[b] *p* calculated for differences between baseline and follow-up measures analysed with the Wilcoxon signed-rank test

[c] *p* calculated for differences between baseline and follow-up measures analysed with the chi-squared test

[#] $p < 0.05$, [$] $p < 0.01$, * $p < 0.001$

CI confidence interval, *cm* centimetre, *kg* kilograms, m^2 metres squared, *ng* nanogram, μg microgram, *ml* millilitre, *MOXFQ* Manchester-Oxford Foot Questionnaire

5.6 Discussion

This study found clinically significant improvements in foot pain following bariatric surgery. Bariatric surgery rendered a marked decrease in foot pain severity between baseline and follow-up, while increased baseline FMI, but not FFMI or BMI, yielded increased foot pain at follow-up, after controlling for age, gender and depression.

The findings of this study are concordant with previous work investigating body composition predicting foot pain. A study evaluating incident foot pain in an overweight cohort [34] found that increased FMI, but not FFMI, predicts pain while a large community cohort study found that increased FMI was associated with a six per cent increase in future foot pain over four years [120]. Our study is the first to measure the change in foot pain severity in relation to body composition, rather than incident foot pain, and additionally our study adjusts for the affect of bariatric surgery. We found that fat mass, not fat-free mass (which had a negative correlation with foot pain severity), may potentially be the main perpetrator linking obesity and pain and does suggest that excessive mechanical loading may not be the exclusive interface between obesity and foot pain. The findings also suggest that details on body composition may be more clinically important than the BMI and that body fat may have affects on the musculoskeletal system that are not resolved with the reduction of in body weight e.g. degenerative joint or soft tissue changes.

Elevated BMI has been found to be a predictor of future foot pain over a two-year period in a community cohort [240] and indeed was a predictor of foot joint pain in a study of women over a five-year period [87]. The findings of our study, however, suggest that using the BMI alone may underestimate the impact of adiposity and it may not be a good predictor of future prognosis for bariatric cohorts with foot pain. Moreover, there is evidence that

examining fat mass alone may underestimate the effect of this tissue, a recent study of women with foot pain found the ratio of visceral to subcutaneous abdominal fat was associated with foot pain, suggesting that not only the amount of fat, but its location could impact on pain [140].

The challenge for addressing musculoskeletal pain in those undergoing bariatric surgery is that whilst weight loss reduces fat mass [241] and improves psychological health [242], this group often remains obese (BMI ≥ 30 kg / m^2) and will continue to be at risk of generalised musculoskeletal pain. Complete resolution of pain may be unlikely following bariatric surgery, however, it is clearly associated with a reduced severity of foot pain in the short-term for this cohort. Whether the relief of pain persists beyond this time is unknown, but data from a large cohort study investigating hip and knee pain suggests that the reduction in pain severity may be sustained [243].

Our study has some limitations. Firstly, the observational design means this was not a true waiting-list control trial, which would have made for a stronger study design and future trials may also focus on the change in foot pain by comparing bariatric procedures head-to-head. Secondly, our small sample size prohibited a large multivariable regression model, but the effect of bariatric surgery on foot pain is so large that the addition of the other variables is unlikely to change the statistical significance of this predictor. There may have been type II errors in the models e.g. FFMI, and a larger sample may have found a statistically significant association. Thirdly, given the sample size we were also not able to include the adipokines in the multivariable models. The partial correlation analysis, that found a significant inverse relationship between resistin and pain, suggests resistin may play a mediation role between body fat with pain. A previous study suggested that resistin

may have anti-inflammatory effects by activating transforming growth factor beta (TGF-β) [55], a molecule involved in tendon healing, but larger samples are required to sufficiently explore this relationship. Finally, the six-month follow up is a relatively short-term period and the results may not be representative of changes that occur over a longer period.

Our study has a number of strengths. It is the first study to examine if body composition predicts change in foot pain in bariatric participants, and the first to provide detailed, validated examination of foot pain, longitudinally in a bariatric cohort. The examination of FMI and FFMI and the inverse relationship they have with foot pain is novel and does question the usefulness of BMI in predicting a change in foot pain in bariatric populations. The analysis of serum adipokines in relation to foot pain is also novel.

5.7 Conclusion

Bariatric surgery is significantly associated with a reduction in foot pain. Body fat, but not body weight, is an independent predictor of increased foot pain at six-months follow up in a bariatric cohort. Serum adipokines are associated with foot pain, whereas BMI is not, thus the mechanisms underlying foot pain in bariatric cohorts may be more related to metabolic activity rather than mechanical overload.

6

Chapter 6: The effect of increasing body weight on plantar pressure and foot pain

6 WEIGHT GAIN AND PLANTAR PRESSURE

6.1 Introduction to publication

Walsh TP, Butterworth PA, Urquhart DM, Cicuttini FM, Landorf KB, Wluka AE, Shanahan EM, Menz HB. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. *J Foot Ankle Res.* 2017;10:31.

Purpose

The purpose of this study was to investigate if a change in body weight is associated with a change in plantar pressure and change in foot pain. Previous studies analysing the association between plantar pressure and foot pain have been cross-sectional, limiting conclusions that can be drawn about regional plantar pressures and the severity of foot pain. This study uses longitudinal data to explore temporal relationships between change in body weight and change in foot pain, and whether specific regions in the foot are associated with both change in pain and change in body weight.

Published in

Journal of Foot and Ankle Research

2016 Impact Factor: 1.405

5-year Impact Factor: 2.038

6 WEIGHT GAIN AND PLANTAR PRESSURE

Contribution from primary author

Primary Author – Tom Walsh

This study was performed using data collected at two-time points. The baseline data was not collected by the primary author, but it was made available by Monash University. The primary author collected all follow-up data.

The manuscript was written by the primary author, which followed consultation and review by the listed co-authors. The primary author conceived the research questions and completed the data analysis with guidance from the senior author.

6.2 Abstract

Background: There is a well-recognised relationship between body weight, plantar pressures and foot pain, but the temporal association between these factors is unknown. The aim of this study was to investigate the relationships between increasing weight, plantar pressures and foot pain over a two-year period.

Methods: Fifty-one participants (33 women and 18 men) completed the two-year longitudinal cohort study. The sample had a mean (standard deviation (SD)) age of 52.6 (8.5) years. At baseline and follow-up, participants completed the Manchester Foot Pain and Disability Index questionnaire, and underwent anthropometric measures, including body weight, body mass index, and dynamic plantar pressures. Within-group analyses examined differences in body weight, foot pain and plantar pressures between baseline and follow up, and multivariable regression analysis examined associations between change in body weight, foot pain and plantar pressure. Path analysis assessed the total impact of both the direct and indirect effects of change in body weight on plantar pressure and pain variables.

Results: Mean (SD) body weight increased from 80.3 (19.3), to 82.3 (20.6) kg, $p = 0.020$ from baseline to follow up. The change in body weight ranged from –16.1 to 12.7 kg. The heel was the only site to exhibit increased peak plantar pressures between baseline and follow up. After adjustment for age, gender and change in contact time (where appropriate), there were significant associations between: (i) change in body weight and changes in midfoot plantar pressure ($\beta = 4.6$, $p = 0.038$) and functional limitation ($\beta = 0.4$, $p = 0.010$) (ii) plantar pressure change in the heel and both functional limitation ($\beta = 4.1$, $p = 0.013$) and pain intensity ($\beta = 1.8$, $p = 0.006$), (iii) plantar pressure change in the midfoot and both functional limitation ($\beta = 4.5$, $p = 0.018$) and pain intensity ($\beta = 1.9$, $p = 0.015$).

Path analysis indicated that the effect increasing body weight has on foot-related functional limitation and foot pain intensity may be mediated by increased plantar pressure in the midfoot.

Conclusions: These findings suggest that as body weight and plantar pressure increase, foot pain increases, and that the midfoot may be the most vulnerable site for pressure-related pain.

6.3 Background

Foot pain is common in the community. Approximately one quarter of adults report frequent foot pain [21] and one in six adults aged greater than 50 years experience symptomatic foot osteoarthritis [19]. Foot pain is also associated with pain in other joints, reduced health-related quality of life and obesity [169]. A recent systematic review found that obesity, defined by elevated body mass index (BMI), was strongly associated with chronic plantar heel pain in a non-athletic population and with non-specific foot pain in the general population [86]. Elevated BMI has also been associated with worsening foot pain over a five-year period in women, even after adjusting for age, rheumatoid arthritis and diabetes [87].

One of the mechanisms that may link increased body weight and foot pain is mechanical loading. Increased body mass is known to contribute to elevated peak plantar pressures [98] and elevated peak plantar pressures are associated with foot pain [244]. A recent study of older people found higher midfoot peak pressures and overall foot pain with increased BMI [245]. It seems intuitive, then, that as body weight increases, plantar pressure increases, overloading plantar tissue and causing pain. Furthermore, a previous study has found that midfoot osteoarthritis is associated with higher midfoot pressures, suggestive of a mechanical relationship [246]. Other factors, however, linking foot pain and body mass, such as metabolic and psychological factors have been investigated [120], but whether there is mediation via mechanical mechanisms is not known

Indeed, despite the proposed relationship between body weight, plantar pressure and foot pain, previous studies have been cross-sectional and therefore have provided no information regarding the temporal relationship between these factors. This is important, as it is unknown if the foot can adapt to increased body weight over time. As such, the

effect of increased body weight on plantar pressures and foot pain may depend on the extent to which the foot can adapt to these changes. Prospective studies are needed to determine if a change in body weight is associated with pathological foot mechanics.

Therefore, the aims of this study were to: (i) examine if a change in body weight is associated with a change in plantar pressures, and to (ii) examine whether a change in body weight and plantar pressures are associated with a change in foot pain intensity or foot-related functional limitation over a two-year period.

6.4 Methods

6.4.1 Study participants

Participants from a previous study [98] that investigated obesity, foot posture, range of motion and plantar pressure characteristics were invited to participate in this two-year longitudinal cohort study. The aim of the previous (i.e. baseline) study was to evaluate plantar loading and foot structure patterns in obese and non-obese individuals, and to determine the influence of body weight and foot structure on plantar loading. The baseline and follow-up measures were taken in 2012 and 2014, respectively, at Epworth Hospital, Victoria, Australia. Of the original 68 participants, 51 were included in this study as 17 participants were unable to attend a scheduled follow-up session. The study was approved by the Alfred Human Research Ethics Committee (HREC) and Austin Health HREC, project number 121/11. All participants provided informed consent.

6.4.2 Demographic and anthropometric data

Age, gender, height and body mass were recorded at baseline and follow-up. Body weight was measured to the nearest 0.1 kg using electronic scales and height was measured to the nearest 0.1 cm using a stadiometer (with shoes, socks, and bulky clothing removed). From these data BMI was calculated in line with the baseline study [98].

6.4.3 Foot pain and disability

Foot pain and disability were measured with the Manchester Foot Pain and Disability Index (MFPDI), a valid and reliable measure of foot pain and disability [199,213]. The MFPDI consists of 19 items designed to assess four domains: functional limitation (10 items), pain intensity (5 items), personal appearance (2 items), and difficulties with work or leisure activities (2 items). Each item is preceded with the phrase, "because of pain in my feet," and is documented as being present 'none of the time' (0 points), 'on some days' (1 point), or 'on most/everyday' (2 points). All scores were summed and separated into the four domains, although only functional limitation and pain intensity were used in this study. The raw scores for these domains underwent a Rasch transformation as previously described by Gijon-Nogueron et al. [220], enabling the resultant values to be treated as continuous variables in the statistical analysis. Functional limitation is graded on a 0 – 20 scale, whereas pain intensity is graded on a 0 – 10 scale.

6.4.4 Plantar pressure

Dynamic plantar pressure data were collected with the MatScan® (Tekscan, USA) platform system. The platform consists of a 5 mm-thick floor mat (432 x 368 mm) incorporating 2288 resistive sensors (1.4 sensors / cm^2) with a sampling at a rate of 40 Hz. Step calibration was performed immediately prior to each participant's analysis. Following calibration, participants walked over the platform, which has been previously shown to have good accuracy [247] and moderate to good reliability for measuring plantar pressures in barefoot adults [248]. The MatScan® platform was positioned in the centre of a level walkway, where the participants were asked to walk barefoot in their normal gait pattern. A midgait protocol was used, whereby participants were instructed to take two steps and to then strike the platform on their third step, before continuing to walk for a further three steps. The midgait protocol has been found with few exceptions to have good to excellent

reliability [249]. Data from the right foot were collected from three valid trials. Individual "masks" were manually constructed to determine plantar pressures for the whole foot and under five regions; heel, midfoot, forefoot, hallux and lesser toes, using the Research Foot software (version 6.51) at baseline and follow-up (Figure 1). Measures of maximum force (kg), contact area (cm^2), peak pressure (kPa) and contact time (ms) were calculated for each of the trials and an average value obtained. Contact time was used as a proxy for walking speed [250]. Change in regional peak plantar pressure was used in this study given the known association of peak plantar pressure and foot pain [251]. Mean pressure or pressure-time integral, in addition, were not used in this study given the interdependence between these measures and peak plantar pressure [252,253].

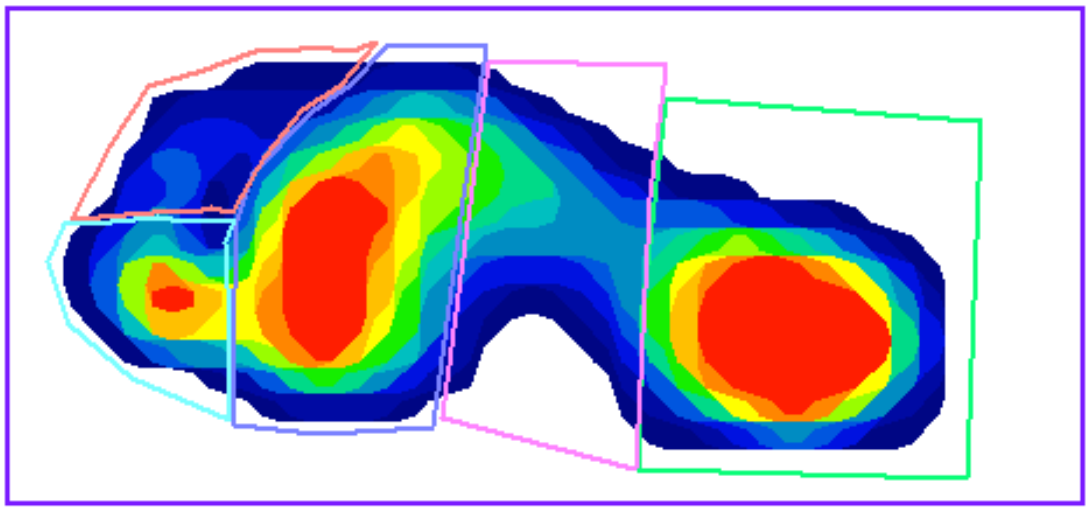


Figure 1. Example of individual 'masks', defining different regions of the foot

6.4.5 Data analysis

All data were checked for normality prior to inferential statistical analysis. The maximum force variables (hallux and forefoot) were logarithmically transformed because they were not normally distributed. Differences between baseline and follow-up measures for

anthropometry variables (height, body weight and BMI) and MFPDI subscale scores were analysed with paired-samples t-tests. The difference in the number of participants with foot pain at baseline and follow-up were analysed with the chi-squared test. Differences between baseline measures (age and BMI) of those who completed the study and those that failed to follow-up were analysed with Mann-Whitney *U* test, while differences in the prevalence of foot pain was analysed with the chi-squared test. Linear regression was used to test the differences between baseline and follow-up maximum force, contact area and peak pressure (adjusted for contact time). Correlations between change in body weight, change in regional peak pressure, change in foot pain intensity and functional limitation were assessed using multivariable linear regression, where unstandardized beta coefficients were generated, adjusting for age, gender and change in contact time (where appropriate), Multivariable linear regression, adjusting for age and gender, was also used for subgroup analyses of participants whom lost > 2 kg to provide clinical context for the association of weight loss and foot pain. Path analysis, a method used to detect hypothesised causal relationships between variables [254], was used to determine the total impact of both the direct and indirect effects of change in body weight on pressure and pain variables using standardised β weights. Only regions that showed significant association in the multivariable regressions were used in the path analysis. *P* values < 0.05 (2-tailed) were regarded as statistically significant. All analyses were performed using the SPSS statistical package (standard version 23.0, IBM Corp, NY, USA).

6.5 Results

6.5.1 Participant characteristics

Fifty-one of 68 participants (75%), completed the two-year study. The sample had a mean (standard deviation (SD)) age of 52.6 (8.5) years. Participant characteristics are shown in Table 1. The 17 participants (14 women, 3 men) who were lost to follow-up were not significantly older, with an age median (range) of 54.9 (40.9 – 65.0) years versus 53.8 (34.7 – 67.8) years, $p > 0.05$), but did have a significantly higher baseline BMI, median (range) of 33.0 (21.4 – 45.2) kg / m^2 versus 25.3 (17.6 – 48.1) kg / m^2, $p < 0.05$. Furthermore, the prevalence of baseline foot pain was higher (58.9% versus 47.1%, $p < 0.05$) in those lost to follow-up. There were significantly more women than men in this study, $\chi^2 = 4.412$, $p < 0.05$.

6.5.2 Change in body weight and BMI

Mean (SD) body weight increased from baseline to follow-up by 2.0 (5.9) kg from mean (SD) 80.3 (19.3), to 82.3 (20.6) kg, $p = 0.016$) as did BMI (28.2 kg / m^2 versus 28.9 kg / m^2, $p = 0.029$). The change in body weight ranged from -16.1 to 12.7 kg. Twenty-five participants gained more than 2 kg, with a mean (SD) of 6.6 (3.8) kg while 11 participants lost more than 2 kg, with a mean (SD) of 5.1 (4.3) kg.

Table 1. Participant characteristics (values are the means (SD)s unless otherwise indicated)

	Baseline	Follow-up	Mean difference	95% CI	*p* value
Age	52.6 (8.5)	54.8 (8.5)			
Gender, no. women (%)	33 (65)	33 (65)			
Height, m	1.69 (0.1)	1.69 (0.1)[a]	-0.0	-0.0 to 0.0	0.145
Body mass, kg	80.3 (19.3)	82.3 (20.6)[a]	2.0	0.4 to 3.6	0.016
BMI, kg/m^2	28.2 (6.9)	28.9 (6.9)[a]	0.6	0.1 to 1.2	0.029
MFPDI Functional limitation score	3.2 (4.5)	3.6 (5.1)[a]	0.4	-0.8 to 1.6	0.511
MFPDI Pain intensity score	1.9 (2.4)	1.9 (2.4)[a]	0.1	-0.5 to 0.6	0.784

[a] *p* calculated for differences between baseline and follow-up measures analysed with paired samples t-test

kg kilograms, *m* metres, *BMI* body mass index, *MFPDI* Manchester Foot Pain and Disability Index

6.5.3 Change in plantar pressure

The change in plantar pressure from baseline to follow-up is summarised in Table 2. The change in peak plantar pressure from baseline to follow-up ranged from -120.95 to 58.8 kPa. There were significant differences in all regions for contact area, and maximum force for whole foot, forefoot and heel before adjustment for differences in contact time. There were, however, only significant differences in the contact area of the hallux, mean (SD) 9.8 (1.7) cm^2 to 10.6 (1.6) cm^2, $p < 0.05$ and lesser toe regions, mean (SD) 9.5 (2.9) cm^2 to 11.0 (2.4) cm^2, $p < 0.05$ after adjusting for differences in contact time. The heel was the only specific region of the foot to demonstrate a significant increase in peak pressure from baseline to follow-up, mean (SD) 197 (45) to 222 (39) kPa, $p < 0.05$ after adjusting for differences in contact time.

6.5.4 Change in foot pain

Change in foot pain scores are detailed in Table 1. Current foot pain was reported by 24 (48%) and 28 (55%) participants at baseline and follow-up respectively. Mean (SD) functional limitation scores increased from baseline to follow-up 3.2 (4.5) points to 3.6 (5.1) points, $p = 0.511$, the change in scores ranged from -9.7 to 20.0. Mean (SD) foot pain intensity did not change between baseline and follow-up, but the change in scores ranged from -4.4 to 6.3 points.

Table 2. Change in maximum force, contact area and peak plantar pressure between baseline and follow-up[a] (values are means (SD)s unless otherwise indicated)

	Baseline	Follow-up	Mean difference	95% CI
Maximum force (kg)				
Whole foot	64.6 (19.3)	71.1 (22.1)	6.5	3.2 to 9.7
Heel	36.4 (10.5)	41.9 (12.0)	5.5	3.5 to 7.4
Midfoot	13.8 (9.1)	13.4 (8.9)	-0.4	-1.9 to 1.2
Forefoot	47.8 (13.8)	51.6 (16.1)	3.8	1.5 to 6.1
Hallux	8.0 (2.9)	8.2 (2.7)	0.2	-0.4 to 0.7
Lesser toes	4.5 (1.9)	4.5 (1.9)	0	-0.5 to 0.5
Contact area (cm^2)				
Whole foot	109.1 (17.1)	112.7 (16.7)	3.6	2.2 to 4.9
Heel	31.0 (4.5)	32.6 (4.7)	1.6	0.9 to 2.4
Midfoot	25.6 (9.3)	23.2 (8.0)	-2.4	-3.8 to -1.1
Forefoot	47.8 (6.4)	49.2 (6.8)	1.4	0.6 to 2.3
Hallux	9.8 (1.7)	10.6 (1.6)	0.8	0.2 to 1.1*
Lesser toes	9.5 (2.9)	11.0 (2.4)	1.5	0.7 to 2.1*
Peak pressure (kPa)				
Whole foot	238 (37)	247 (42)	9	-1 to 18
Heel	197 (45)	222 (39)	25	14 to 37*
Midfoot	92 (44)	90 (45)	-2	-12 to 8
Forefoot	233 (40)	238 (46)	5	-4 to 16
Hallux	155 (42)	150 (40)	-5	-14 to 6
Lesser toes	77 (29)	74 (26)	-3	-10 to 4

[a] *p* calculated for differences between baseline and follow-up measures analysed with linear regression, adjusted for contact time

* $p < 0.05$

kg kilograms, cm^2 centimetres squared, *kPa* kilopascal, *CI* confidence interval

6.5.5 Associations between change in body weight, plantar pressure and foot pain

Multivariable associations between change in body weight, change peak pressure and change in foot pain, after adjusting for age and gender and change in contact time (where appropriate) are summarised in Table 3 and Table 4. As body weight increased, peak pressure increased in all regions, however the midfoot was the only region to show significant, positive correlation with body weight in multivariable regression ($\beta = 4.6$, $p = 0.038$). There was also significant, positive correlation between change in body weight and change in functional limitation ($\beta = 0.4$, $p = 0.010$), but not pain intensity ($\beta = 0.2$, $p = 0.601$).

There were positive, significant correlations between changes in heel ($\beta = 1.8$, $p = 0.006$) and midfoot ($\beta = 1.9$, $p = 0.015$) peak pressure and change in foot pain intensity, and a significant, positive correlation between changes in heel ($\beta = 4.1$, $p = 0.013$) and midfoot ($\beta = 4.5$, $p = 0.018$) peak pressure and change in functional limitation. Of the 11 participants that lost more than 2 kg, there was a significant positive correlation between change in weight and change in functional limitation ($\beta = 0.7$, $p = 0.015$), and there was a non-significant positive correlation between change in weight and change in pain intensity, ($\beta = 0.3$, $p = 0.056$)

Table 3. Multivariable linear regression between change in body weight with change in regional peak plantar pressure and change in foot pain

	β-coefficients (95% CI)	*p* value
i) Plantar pressures[a]		
Whole foot	2.2 (-2.3 to 7.2)	0.302
Heel	2.9 (-0.9 to 6.8)	0.135
Midfoot	4.6 (0.3 to 9.0)	0.038
Forefoot	2.2 (-2.2 to 6.7)	0.319
Hallux	1.4 (-3.0 to 5.9)	0.521
Lesser toes	4.3 (-1.0 to 9.6)	0.111
ii) Manchester Foot Pain and Disability Index[b]		
Pain intensity subscale	0.2 (-0.6 to 1.0)	0.601
Functional limitation subscale	0.4 (0.1 to 0.7)	0.010

[a] Adjusted for age, gender and change in contact time

[b] Adjusted for age and gender

Each region and pain subscale was analysed independently. The change in foot pain intensity and functional limitation units are Manchester Foot and Disability Index Rasch transformed scores (pain intensity and functional limitation domains)

CI confidence interval

Table 4. Multivariable linear regression between change in peak plantar pressure and change in foot pain[a]

	Pain intensity	*p* value	Functional limitation	*p* value
Region				
Whole foot	1.4 (-0.2 to 3.0)	0.092	3.4 (-0.5 to 7.4)	0.086
Heel	1.8 (0.5 to 3.1)	0.006	4.1 (0.9 to 7.2)	0.013
Midfoot	1.9 (0.4 to 3.4)	0.015	4.5 (0.8 to 8.2)	0.018
Forefoot	1.5 (-0.1 to 3.0)	0.064	3.2 (-0.5 to 7.0)	0.093
Hallux	-0.4 (-1.9 to 1.2)	0.672	1.1 (-2.7 to 5.0)	0.560
Lesser toes	0.6 (-1.3 to 2.6)	0.520	2.5 (-2.1 to 7.2)	0.276

[a] Adjusted for age, gender and change in contact time

Each region and pain subscale was analysed independently. Change in foot pain intensity and functional limitation units are Manchester Foot and Disability Index Rasch transformed scores (pain intensity and functional limitation domains)

Values are unstandardised β-coefficients (95% confidence intervals)

6.5.6 Path analysis

Results of the path analysis are shown in Figures 1 and 2. For pain intensity, there was a small (β = 0.078) direct effect of change in body weight, but a larger indirect effect with change in midfoot pressure as a mediator variable (β = 0.107). For functional limitation, change in body weight had a larger direct (β = 0.374) than indirect (β = 0.102) effect with change in midfoot pressure as a mediator variable. The total effect of change in body weight (i.e. the combined direct and indirect effects) was smaller for pain intensity (β = 0.185) than functional limitation (β = 0.476).

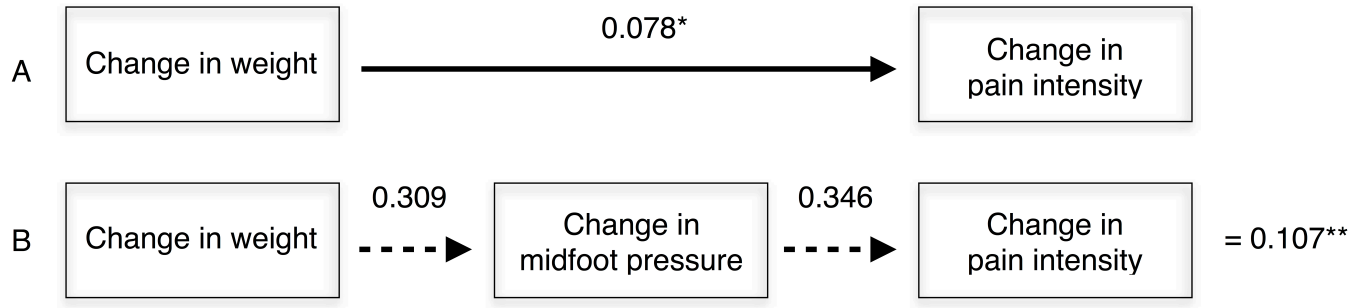


Figure 2. Calculation of direct and indirect effects of change in body weight on change in pain intensity

Values are standardised β-coefficients: (A) direct effect of change in body weight on foot pain intensity, (B) indirect effect of change in body weight, mediated by change in midfoot pressure. (*) Direct effect, (**) indirect effect. The total effect of change in body weight on foot pain intensity is therefore the sum of the direct and indirect effects, i.e. total impact is 0.078 + 0.107 = 0.185

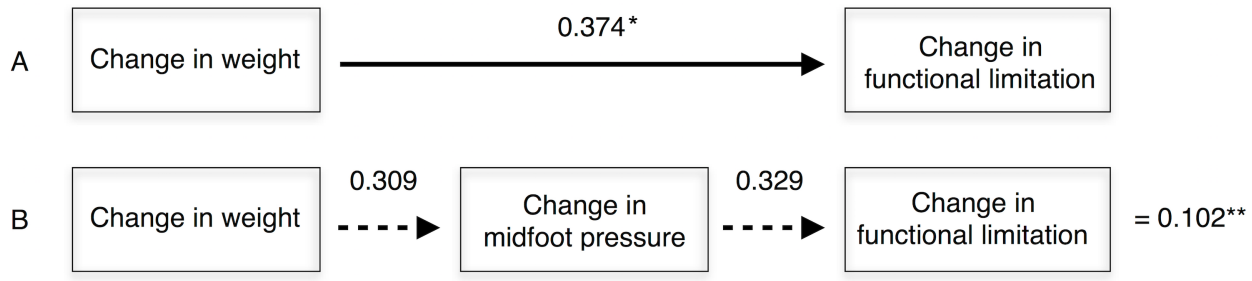


Figure 3. Calculation of direct and indirect effects of change in body weight on change in functional limitation

Values are standardised β-coefficients: (A) direct effect of change in body weight on functional limitation, (B) indirect effect of change in body weight, mediated by change in midfoot functional limitation is therefore the sum of the direct and indirect effects, i.e. total impact is 0.374 + 0.102 = 0.476

6.6 Discussion

This study is the first to examine the effect of increasing body weight on plantar pressures and foot pain using a prospective study design. Such a design allows for temporal inferences to be made. There were significant associations between change in body weight, change in midfoot plantar pressure and change in functional limitation. Change in heel plantar pressure was significantly associated with a change in functional limitation, but not a change in body weight. Path analysis indicated that the effect increasing body weight has on foot related functional limitation may be mediated by increased plantar pressure in the midfoot, supporting a significant biomechanical effect. These findings suggest that as body weight increases, foot pain increases, and that the midfoot may be the most vulnerable site for pressure-related pain.

6 WEIGHT GAIN AND PLANTAR PRESSURE

Change in body mass was not significantly associated with change in foot pain intensity, but there were significant, positive correlations between change in foot pain intensity and change in both heel and midfoot peak pressure. While there were statistically significant increases in contact area of the hallux and lesser toes from baseline to follow-up, following adjustment for differences in contact time, these are likely to be of questionable clinical significance given the lack of significant increases in peak pressures in these regions. The heel was the only site to increase in peak pressures following adjustment for differences in contact time. This implies that the foot is largely able to modulate force and contact area to reduce peak pressure, however given the heel is usually the first region to strike the ground in normal gait, [10] this region may be less efficient in increasing contact area. Previous studies investigating the effect of increasing body weight on plantar pressure have traditionally used weighted backpacks or vests [255-257], and therefore, have measured the instantaneous effects of increased body weight, and not weight that is physiologically gained over time. Previous studies have also used asymptomatic volunteers, which may not reflect how plantar pressures change with not only body mass gain, but also with foot pain. In contrast, our study examined the effect of increasing body weight on plantar pressures over time and measured this in the context of foot pain intensity and functional limitation.

The results of this study provide evidence to support the assertion that increases in peak plantar pressure are associated with foot pain and disability. Given that pain intensity and functional limitation increased as peak pressure under the midfoot and heel regions increased, these regions may be most at risk from increasing body weight. Furthermore, the significant positive correlation with body weight and peak pressure under the midfoot, but not other regions, is suggestive that the mechanical link between increased body

weight, increased plantar pressure and pain is focused in this region in particular. The positive association with plantar pressure and pain in this study are inconsistent with a recent study that found people with prolonged plantar heel pain paradoxically had reduced peak pressure in this region [103]. The authors suggested that this may be an offloading mechanism, which could be initiated as pain increases beyond tolerable levels. That is, people with plantar heel pain essentially limp to reduce resultant pressure from the ground being applied to the painful heel when walking. The association between increases in plantar pressure and foot pain observed in our study may reflect less disabling foot pain not yet requiring gait alterations to offload the painful region.

While a change in foot pain intensity was not significantly associated with a change in body weight, studies have found body composition, as opposed to body weight alone, may be more strongly associated with pain. An increase in fat mass, rather than fat-free mass, is the main component of body mass that contributes to foot pain [34,120] and likely does so via metabolic as opposed to mechanical mechanisms. The association between body weight and functional limitation may indicate that increasing body weight affects the ability to undertake daily activities more so than increasing the intensity of pain.

This study should be considered in light of some limitations. The site of foot pain was not recorded and we cannot, therefore, draw conclusions as to whether the region of increased plantar pressure corresponded to the region of pain. Differences in pressure between those with bilateral or unilateral foot pain was also not explored. There was a relatively small sample size, and the modest increase in body mass over the two-year period may also limit extrapolations for larger gains in body weight. A change in body weight of greater than 5% is considered clinically relevant, whereas our cohort increased by only 2.5% [258]. Those who took part in this study tended be younger and have a lower

BMI than those that failed to follow-up. Thus, our results are generalisable to this population only, which may also reduce the power of the study since the spectrum of obesity and foot pain will have been reduced. Minimal important differences for the MFPDI domains scores are not available [259] and therefore the clinical importance of changes in these scores cannot be reported.

The main clinical implication of this study is that higher peak pressures in the heel and midfoot are most strongly related to pain intensity and functional limitation as body weight increases. The midfoot may, therefore, be the most susceptible region to developing pain following weight gain and interventions that reduce pressure in this region may reduce foot pain. Moreover, the 11 participants that lost more than 2 kg had a significant correlation between change in functional limitation and change in weight, this provides temporal evidence that weight loss is associated with reduced foot pain, but studies involving larger samples and clinical trials with directed weight loss interventions are needed. Indeed, future research is also required to determine whether interventions designed to normalise or decrease plantar pressures can reduce foot symptoms over time.

6.7 Conclusion

Increasing body weight is associated with increasing midfoot plantar pressure and foot-related functional limitation over a two-year period, while changes in midfoot and heel plantar pressures are associated with changes in foot pain intensity. These findings suggest that as body weight and plantar pressure increase, foot pain increases, and that the midfoot may be the most vulnerable site for pressure-related pain.

7

Chapter 7: The effect of a change in weight on foot posture, plantar pressure and foot pain

7 FOOT POSTURE, PLANTAR PRESSURE & FOOT PAIN

7.1 Introduction to publication

Walsh TP, Gill TK, Evans AM, Yaxley A, Chisholm JA, Kow L, Arnold JB, Shanahan EM. Changes in foot pain, structure and function following bariatric surgery. *J Foot Ankle Res*. [In press].

Purpose

The primary purpose of this study was to investigate if foot pain before bariatric surgery is associated with mechanical or non-mechanical factors. The secondary purpose was to determine if the change in foot pain following bariatric surgery is associated with a change in plantar pressures and if there are specific regions where pressure changes. The study combines measures of non-mechanical factors (depression) with mechanical factors (foot posture, foot function, bodyweight) with a view to elucidate which features are related to foot pain. The participants used in this chapter are also used in chapter 5.

Accepted in

Journal of Foot and Ankle Research

2016 Impact Factor: 1.405

5-year Impact Factor: 2.038

7 FOOT POSTURE, PLANTAR PRESSURE & FOOT PAIN

Contribution from primary author

Primary Author – Tom Walsh

Arthritis Australia provided a research grant for this study. The successful grant application was led by the primary author, but included consultation with the listed co-authors.

The manuscript was written by the primary author, which followed consultation and review by the listed co-authors. The primary author conceived the research questions and completed the initial data analysis, the final analyses reported in the chapter were conducted by the study statistician.

7.2 Abstract

Background: Bariatric surgery candidates have a high prevalence of foot pain, depression and elevated plantar pressures. There is, however, limited research into how these factors interact pre- and post-surgery. The aims of this study were therefore to investigate the mechanical and non-mechanical factors associated with foot pain severity before, and the change after, surgery.

Methods: Bariatric surgery candidates underwent baseline and six-month follow-up measures. Foot pain was measured with the Manchester-Oxford Foot Questionnaire. Mechanical measures included body mass index (BMI), dynamic plantar pressures, radiographic foot posture, and hindfoot range of motion. Depressive symptoms, the non-mechanical measure, were assessed by questionnaire. Multivariable linear regression was used to determine which variables were associated with foot pain at baseline and at follow-up. Multilevel repeated models assessed the associations between foot pain and plantar pressure, adjusting for the interaction between group and follow-up time.

Results: Forty-five participants (84% female), with mean (SD) age of 45.7 (9.4) years were recruited. Twenty-nine participants had bariatric surgery and 16 participants remained on the waiting list (controls). Following bariatric surgery, foot pain reduced significantly by -35.7 points (95% CI -42.2 to -28.8), while depressive symptoms and whole foot peak pressures had a significant mean change of -5.9 points (95% CI -10.3 to -1.5) and -36 kPa (95% CI -50 to -22), respectively. In multivariable analysis, depressive symptoms were associated with foot pain at baseline $\beta = 0.7$ (95% CI 0.2 to 1.2) after controlling for age, gender, BMI, foot posture and plantar pressure. Depressive symptoms were also associated with foot pain at follow-up in those undergoing bariatric surgery, $\beta = 1.2$ (95% CI 0.8 to 1.7). Foot posture and hindfoot range of motion did not change

following surgery and a change in plantar pressures was not associated with a change in foot pain over time.

Conclusions: Foot pain severity in bariatric surgery candidates was associated with depressive symptoms at baseline. Reduced foot pain following bariatric surgery was associated with an improvement in depressive symptoms, without a significant change in foot posture or foot function. Foot pain severity in bariatric candidates may be mediated by non-mechanical or non-local factors before and following surgery.

7.3 Introduction

Foot pain is a common complaint, affecting almost one in four adults aged over 45 years [21]. Obesity is a risk factor for the development of foot pain [240], and an elevated body mass index (BMI) is strongly associated with both chronic plantar heel pain and non-specific foot pain [86]. Moreover, the feet of people with obesity are structurally and functionally different to their non-obese counterparts, manifesting as thicker, wider and larger, along with flatter-foot postures, reduced joint range of motion and increased peak plantar pressures [98,245]. It is therefore conceivable that foot pain in people with obesity is related to these mechanical adaptations, particularly the flattening of the foot arches and the increase in plantar pressures.

Studies have found that people with obesity display increases in plantar pressures that are not uniform, with the areas of highest pressure being the midfoot and forefoot, when compared to non-obese people [98,100,101]. Given that obesity is strongly associated with plantar heel pain [88,102], increased plantar pressure elsewhere is discordant if pain was strongly related to excessive pressure. Paradoxically, people with chronic plantar heel pain display *reduced* loading under the heel when compared to controls [103]. Indeed, pain may persist even when gait patterns change to offload a painful region of the foot. Thus, chronic foot pain in people with obesity may be more than mechanical overload, involving a complex interplay between mechanical, metabolic and psychological factors.

Musculoskeletal pain has a bidirectional relationship with both obesity [73] and depression [72], while depression and obesity also amplify each other [71]. These relationships, however, are not limited to weight-bearing joints with a known association between elevated BMI and symptomatic hand osteoarthritis [1], suggesting that metabolic mechanisms, including systemic inflammation [260], may underpin the relationship

between obesity and joint pain [230]. Whilst these relationships exist in the general population, it is particularly pertinent in bariatric surgery candidates, who are over-represented amongst those complaining of musculoskeletal pain [261]; with foot and ankle pain prevalence cited as 34-50% [91,92]. There is evidence that spatiotemporal gait patterns, such as increased limb swing and decreased double-limb support time [262] improve following bariatric surgery, but currently only limited investigations regarding associations between weight loss in a bariatric cohort and changes in foot pain, foot function and foot posture. In order to effectively develop and understand treatment methods, it is important to determine whether weight loss has a direct influence on foot structure and function that could be linked with pain, given the high prevalence of obesity across the community [23].

Despite a high prevalence of foot pain, depression and elevated plantar pressures, there is little evidence that mechanical and non-mechanical factors that may relate to foot pain before and after bariatric surgery. Therefore, the aims of this study were to investigate changes in foot pain, posture and function after bariatric surgery compared to a group remaining on the waiting-list, acting as controls, and to determine the factors related to changes in foot pain post-surgery.

7.4 Methods

7.4.1 Study participants

This study recruited a convenience sample of people with foot pain from bariatric surgery waiting lists at two tertiary hospitals in Adelaide, South Australia between January 2015 and June 2017. All patients on the lists were invited to participate in this study. Participants were recruited either immediately before surgery (treatment group) or when they were added to the waiting list (control group). All participants underwent baseline measures and

were reassessed at six-month follow-up. Baseline measures for participants in the treatment group were recorded 2-3 weeks prior to surgery, designed to reduce the impact of non-surgical weight loss that occurs with meal replacements prior to surgery. Bariatric surgery procedures (sleeve gastrectomy, laparoscopic adjustable gastric band or Roux-en-Y gastric bypass) were based on the clinical requirements of each patient, and not directed by this study. The study received ethical approval before commencement by the Southern Adelaide Clinical Human Research Ethics Committee (Project ID 211.14).

7.4.2 Inclusion and exclusion criteria

People aged ≥ 18 years were recruited if they reported current foot pain of ≥ 30 mm on a visual analogue scale [234], indicating moderate pain (at least), which had to have been present for ≥ 3 months. Participants were excluded if: pregnant, history of previous bariatric or foot surgery, systemic inflammatory disease, loss of peripheral sensation in the feet, known infectious disease, cancer, non-ambulatory.

7.4.3 Demographic and anthropometric data

Self-reported age and gender were recorded at baseline. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively using an electronic stadiometer (with shoes, socks, and bulky clothing removed) (Seca 284, Germany). From these data, BMI (weight (kg) / height (m^2)) was calculated [24].

7.4.4 Foot pain

Foot pain and disability were assessed using the Manchester-Oxford Foot and Ankle Questionnaire (MOXFQ). The MOXFQ is a reliable and valid 16-item questionnaire that comprises three separate underlying dimensions: walking/standing problems (seven items), foot pain (five items), and social interaction (four items). Item responses are each scored from 0 to 4, with 4 representing the most severe state [235]. The MOXFQ-index is

a summary score that incorporates all three domains and was used for this study as it investigates overall foot pain and disability and is graded on a 0 to 100 scale, with 100 being the most severe state.

7.4.5 Depressive symptoms

The Center for Epidemiologic Studies Depression scale (CES-D) consists of 20-items that assess depressive symptoms [186]. All items are graded via a four-point (0 to 3) Likert scale, giving a possible range of 0-60. The sum score was used as a continuous variable to assess depressive symptoms at baseline and follow-up.

7.4.6 Plantar pressure

Dynamic plantar pressure data were collected with the MatScan® (Tekscan, USA) platform system at baseline and follow-up. The platform is a 5 mm-thick floor mat (432 x 368 mm) incorporating 2288 resistive sensors (sensor size = 0.7 cm^2, sensors / cm^2) with data sampled at a rate of 40 Hz. Analyses conducted using the MatScan® platform have been previously shown to have good accuracy [247] and moderate to good inter-session reliability in adults, for total peak pressure and maximum force ICC (95% CI) of 0.58 (0.28 to 0.75) and 0.92 (0.84 to 0.96), respectively [248]. The MatScan® platform was positioned in a level walkway. Following individual step calibration, which involved entering the participant's body weight followed by a period of standing on the MatScan® platform, balancing on one foot. The participants were then asked to walk barefoot with their usual gait pattern across the MatScan® platform. Data were collected using a midgait protocol, whereby participants were instructed to take two steps, striking the platform on their third step, before continuing to walk for a further three steps. The midgait protocol has been found to have moderate to excellent reliability, for total peak pressure and maximum force ICC of 0.52 to 0.97 and 0.36 to 0.73, respectively [249]. Data were collected from three

complete, valid trials of the right foot. A valid trial was determined when participants' gait pattern was not perturbed and when no 'targeting' of the plantar pressure platform occurred. Individual "masks" were manually constructed to determine plantar pressures for the whole foot and also five regions of the foot; heel, midfoot, forefoot, hallux and lesser toes, using the Research Foot software (version 6.51). Measures of regional contact area (cm^2), maximum force (kgf), peak plantar pressure (kPa) and contact time (ms) were calculated for all trials to obtain a mean value. The right foot was chosen to ensure that the assumption of independence of data was met [263] and additional measures such as mean pressure or pressure-time integral were not collected given the interdependence between these measures and peak pressure [252,253]. Contact time was used as a proxy for walking speed [250].

7.4.7 Radiographic measures

Weight-bearing dorsoplantar and lateral radiographs were taken at baseline and follow-up using a standardised technique on a digital radiograph unit (Ysio, Siemens Healthcare, Germany). Dorsoplantar views were taken with the participant standing above the image receptor on both feet, the central beam was angled at 15 degrees towards the calcaneus and the centering point was aimed at the base of the third metatarsal. Lateral radiographs were taken with the participant standing on a platform, the image receptor was positioned on the medial aspect of the foot and the centering point was at the base of the metatarsals from a lateral to medial direction.

Foot posture was assessed using four radiographic angles described by Murley et al [109]. The calcaneal inclination angle is the angle between the inferior aspect of the calcaneus and the supporting surface, while the calcaneal-first metatarsal angle is the angle on the dorsum of the foot taken between the inferior calcaneal angle and a line parallel to the

midshaft of the first metatarsal. Both of these angles were measured from the lateral view. The calcaneal-first metatarsal angle was used as a measure of foot posture in the regression analyses, having been shown to strongly correlate with clinical measures [109].

Two further angles were taken from the dorso-plantar radiograph: the talo-navicular and talo-second metatarsal angle. The anteromedial and anterolateral extremes of the talar head and the bisection of the proximal articular surface of the navicular formed the talo-navicular angle. The talo-second metatarsal angle is formed between the bisection of the shaft of the second metatarsal and the line perpendicular to the anteromedial and anterolateral extremes of the head of the talus.

7.4.8 Hindfoot range of motion

Ankle joint dorsiflexion was measured using the technique described by Munteanu et al [264], which has very good intra- and inter-rater reliability (ICC (95% CI) 0.88 (0.75-0.94) and 0.92 (0.86-0.96)) when taken in a weight-bearing position with the knee in full extension. A digital protractor (Gain Express, USA) was placed on the anterior aspect of the tibia and the angle between the ground and the leg was recorded. The measure was repeated in duplicate and a mean was obtained.

Frontal plane range of motion of the hindfoot (ankle and subtalar joints) was measured using the technique described by Menadue et al [265]. Participants are seated in an upright position with the foot positioned overhanging the examination table. The foot was moved from maximal abduction to maximal adduction with the total range of motion recorded with a goniometer (Physio-Med, AUS), this measure was repeated in duplicate and a mean was obtained.

7.4.9 Data analysis

Descriptive statistics (frequencies and means) were obtained. All data distributions were checked for normality via the inspection of histograms and the Shapiro-Wilks test prior to inferential statistical analysis. Differences between the treatment and control groups at baseline were assessed using chi-squared tests for categorical data and t-tests or Mann-Whitney *U* tests for continuous data that was normally or non-normally distributed, respectively. Multivariable linear regression was used to analyse the association between foot pain severity and mechanical (foot posture, plantar pressure, BMI) and non-mechanical (depressive symptoms) variables, along with age and gender at baseline and follow-up. Within group differences in contact area, force and peak plantar pressure between baseline and follow-up were analysed with either the paired-samples t-test or the Wilcoxon signed-rank test. As repeated measures were taken over six-months, a multilevel repeated model using the xtmixed command in STATA was used to assess the associations between MOXFQ-index and peak plantar pressure and other covariates (ankle joint range of motion [264], contact time [265], age and gender [266]) for both groups over six-months while adjusting for the interaction between group and follow-up time. This type of regression model allows for the correlations of observations within subjects. In all analyses, *p* values (two-sided) less than 0.05 were deemed to be statistically significant. All data analyses were performed with SPSS V25 (IBM SPSS Statistics, Armonk, NY, USA) and STATA V15 (StataCorp College Station, TX, USA).

7.5 Results

7.5.1 Participant characteristics

This study recruited 45 participants (38 women), with a mean (standard deviation) (SD) age of 45.7 (9.4) years. Twenty-nine participants had bariatric surgery, undergoing a

Roux-en-Y gastric bypass (n = 13), sleeve gastrectomy (n = 11), or laparoscopic adjustable gastric band (n = 5). Sixteen participants remained on the waiting-list and were used as controls. There were no significant differences in the characteristics between those undergoing bariatric surgery and those in the control group (Table 1). All participants underwent baseline measures, one participant who underwent bariatric surgery was lost to follow-up as they were uncontactable. Two additional participants from the treatment group were unavailable for follow-up plantar pressure data collection and four participants from the control group were unavailable for follow-up plantar pressure and foot posture data collection.

7.5.2 Baseline and follow-up foot pain

In multivariable regression analysis, only depressive symptoms were significantly associated with foot pain severity measured by MOXFQ at baseline (β = 0.7, 95% CI 0.2 to 1.2, $p = 0.008$). Age, gender, BMI, foot posture and whole-foot plantar pressure were included in the model, but these were not significantly related to foot pain severity, although age and BMI were trending towards statistical significance (Table 2). Multivariable regression analysis of the treatment group at follow-up found foot pain severity was also associated with depressive symptoms (β = 1.2, 95% CI 0.8 to 1.7, $p < 0.001$), while age, gender, foot posture and whole foot plantar pressure were not significantly associated with foot pain. There were no significant associations between foot pain severity and any of the listed variables in the control group (Table 3). The treatment group had a significant reduction in foot pain of 35.7 points (95% CI -42.2 to -28.8, $p < 0.001$), while the control group had a small non-significant reduction of 4.0 points (95% CI -15.2 to 7.1, $p = 0.454$) (Table 4). Nine people (one-third) in the treatment group had complete resolution of their foot pain at six-months follow-up.

Table 1: Baseline characteristics of the treatment and control groups[^a]

	Treatment group (n = 27)	Control group (n = 16)	*p* value
Age, years	45.1 (9.0)	45.3 (10.4)	0.958
Gender, women, n (%)[b]	25 (86.2)	13 (81.3)	0.661
Height, m	1.7 (0.1)	1.7 (0.1)	0.906
Weight, kg	123.9 (19.4)	132.4 (15.5)	0.140
Body mass index, kg / m^2	44.8 (7.0)	47.9 (5.2)	0.120
MOXFQ-index, points	49.7 (18.5)	61.0 (23.0)	0.081
Sum CES-D score	16.9 (11.6)	22.3 (12.0)	0.151
Plantar pressures			
Contact area (cm^2)			
Whole foot	181.2 (26.7)	185.2 (23.2)	0.625
Forefoot[c]	62.3 (9.3)	63.5 (8.6)	0.910
Hallux[c]	34.0 (6.9)	35.9 (13.3)	0.940
Heel	54.0 (8.6)	55.1 (5.0)	0.659
Lesser toes	31.8 (5.6)	31.7 (6.9)	0.952
Midfoot	45.8 (10.6)	46.9 (6.1)	0.658
Force (kgf)			
Whole foot	149.5 (31.5)	155.7 (17.5)	0.479
Forefoot	97.3 (20.6)	99.8 (14.4)	0.669
Hallux[c]	33.9 (7.2)	36.1 (13.1)	0.950
Heel	80.7 (19.6)	85.8 (10.8)	0.284
Lesser toes	31.2 (7.5)	30.8 (9.1)	0.870
Midfoot	41.4 (11.3)	41.6 (8.9)	0.953

	Treatment group (n = 27)	Control group (n = 16)	*p* value
Plantar pressure (kPa)			
Whole foot[c]	386 (50)	393 (34)	0.920
Forefoot	366 (56)	370 (41)	0.785
Hallux	170 (43)	186 (74)	0.437
Heel	354 (61)	365 (56)	0.561
Lesser toes	54 (20)	60 (22)	0.375
Midfoot	181 (77)	197 (55)	0.472
Contact time (seconds)	0.9 (0.1)	0.9 (0.1)	0.745
Hindfoot ROM (degrees)			
Frontal plane[c]	40.9 (6.3)	38.3 (4.7)	0.094
Dorsiflexion	61.2 (5.0)	62.4 (6.4)	0.492
Foot posture (degrees)			
Talo-second metatarsal angle	12.0 (8.4)	8.8 (10.1)	0.265
Talo-navicular angle	15.3 (6.9)	11.4 (7.6)	0.092
Calcaneal inclination angle[c]	20.6 (4.9)	22.1 (3.6)	0.445
Calcaneal-first metatarsal angle	133.1 (6.3)	131.6 (6.0)	0.420

^ values are mean (SD) unless otherwise stated

[a] *p* calculated for differences between the treatment and control groups analysed with the independent samples t-test

[b] *p* calculated for differences between the treatment and control groups analysed with the chi-squared test

[c] *p* calculated for differences between the treatment and control groups analysed with the Mann-Whitney *U* test

SD standard deviation, *m* metres, *kg* kilograms, m^2 metres squared, cm^2 centimetres squared, *CES-D* Center for Epidemiological Studies-Depression scale, *MOXFQ* Manchester-Oxford Foot Questionnaire, *kPa* kilopascal, *ROM* range of motion

Table 2: Multivariable relationships with MOXFQ-index at baseline for all participants (n = 43)

	β-coefficients (95% CI)	*p* value
Age	0.6 (-0.1 to 1.4)	0.095
Gender (female)	-0.5 (-17.2 to 16.3)	0.954
Body mass index	1.0 (-0.0 to 2.0)	0.052
Depressive symptoms‡	0.7 (0.2 to 1.2)	0.008
Foot posture^	-0.6 (-1.5 to 0.3)	0.206
Plantar pressure#	-0.1 (-0.2 to 0.1)	0.424

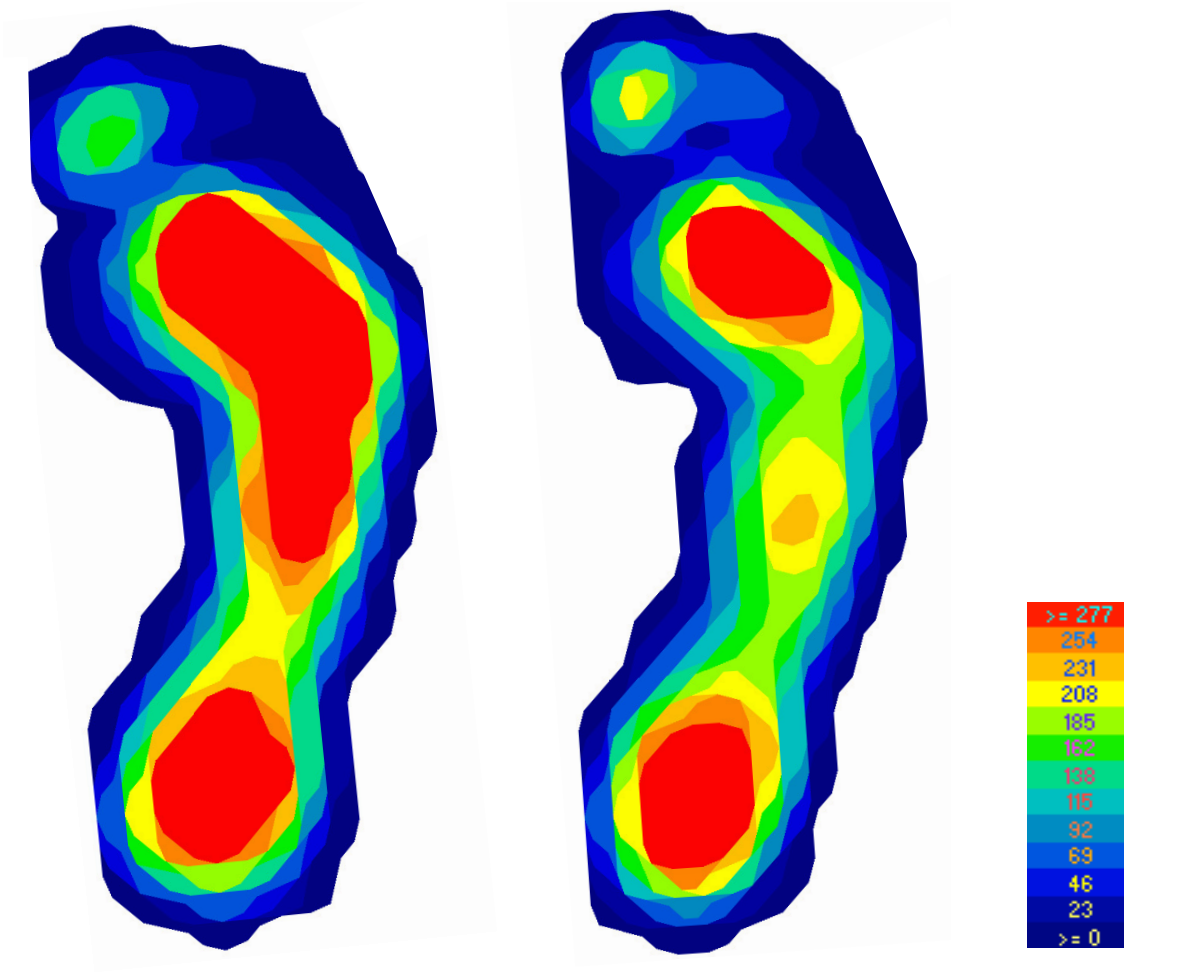
MOXFQ Manchester-Oxford Foot Questionnaire, *CI* confidence interval, ‡ sum Center for Epidemiological Studies-Depression scale score, ^ calcaneal-first metatarsal angle, # whole foot peak pressure

7.5.3 Change in mechanical and non-mechanical variables following bariatric surgery

The 29 participants who underwent bariatric surgery had a mean reduction in weight of 24.3 kg (95% CI -27.5 to -21.1, $p < 0.001$), representing a mean per cent change in body weight of 19.9 % (range 0.9 % to 31.8 %). The 16 participants who did not have bariatric surgery had a mean weight gain of 1.2 kg (95% CI -2.5 to 4.9, $p = 0.877$). In the treatment group, there were significant reductions in force and peak pressure in multiple regions, although the midfoot was the only site to exhibit a statistically significant mean reduction in contact area of 2.1 cm^2 (95% CI -3.9 to -0.3, $p = 0.022$). Representative peak plantar pressures of participants before and after bariatric surgery are depicted in Figure 1. In the control group, the only region to demonstrate a statistically significant change in plantar pressure was the whole foot variable, which increased by a mean 13 kPa (95% CI 0 to 25, $p = 0.046$). Depressive symptoms reduced in both groups, although only the treatment group had a significant mean reduction of 5.9 points (95% CI -10.3 to -1.5, $p = 0.007$).

7 FOOT POSTURE, PLANTAR PRESSURE & FOOT PAIN

There was no significant change in the ankle joint range of motion or foot posture in either the treatment group or the control group between baseline and follow-up. The crude changes between baseline and follow-up are detailed in Table 4.



Before bariatric surgery (135.7 kg)

After bariatric surgery (96.2 kg)

Calibrated pressure (kPa)

Figure 1. Representative peak plantar pressures during walking before and six-months following bariatric surgery

7.5.4 Repeated measures analysis for change in MOXFQ-index and plantar pressure

The change in foot pain severity between baseline and follow-up was not associated with peak pressure when adjusted for other covariates. Both group (β = -11.2, 95% CI -23.8 to 1.4, $p = 0.081$) and follow-up time (β = -7.7, 95% CI -18.5 to 3.2, $p = 0.168$) variables were associated with a reduction in foot pain, but only the group*time (six-months) interaction was statistically significant (β = -21.1, 95% CI -40.8 to -13.5, $p < 0.001$) (Table 5).

Table 3: Multivariable relationships with MOXFQ-index at follow-up for the treatment group and the control group

	Treatment group (n = 26)		Control groups (n = 12)	
	β-coefficients (95% CI)	*p* value	β-coefficients (95% CI)	*p* value
Age	0.2 (-0.3 to 0.8)	0.434	0.7 (-2.2 to 3.6)	0.582
Gender (female)	-1.1 (-14.3 to 12.0)	0.858	19.1 (-56.5 to 94.6)	0.545
Body mass index	0.4 (-0.3 to 1.1)	0.280	1.3 (-4.8 to 7.4)	0.609
Depressive symptoms‡	1.2 (0.8 to 1.7)	< 0.001	1.3 (-1.1 to 3.7)	0.229
Foot posture^	-0.2 (-0.8 to 0.4)	0.515	0.3 (-5.9 to 6.5)	0.915
Plantar pressure#	0.1 (-0.0 to 0.1)	0.291	-0.0 (-1.2 to 1.2)	0.959

MOXFQ Manchester-Oxford Foot Questionnaire, *CI* confidence interval, ‡ sum Center for Epidemiological Studies-Depression scale score, ^ calcaneal-first metatarsal angle, # whole foot peak pressure

Table 4: Comparison between baseline and six-month follow-up measures of body weight, foot pain, depressive symptoms, plantar pressure, foot posture and ankle joint range of motion for treatment and control groups[a]

	Treatment group (n = 26)			Control group (n = 12)		
	Mean difference	95% CI	*p* value	Mean difference	95% CI	*p* value
Weight, kg	-24.3	-27.5 to -21.1	< 0.001	1.2	-2.5 to 4.9	0.877[b]
Body mass index, kg / m^2	-8.8	-10.0 to -7.6	< 0.001	0.5	-0.8 to 1.8	0.440
MOXFQ-index, points	-35.7	-42.7 to -28.8	< 0.001	-4.0	-15.2 to 7.1	0.454
Sum CES-D score	-5.9	-10.3 to -1.5	0.007[b]	-4.6	-9.6 to 0.3	0.061[b]
Contact area (cm^2)						
Whole foot	-3.4	-8.7 to 2.0	0.210	-3.8	-6.7 to -0.9	0.014
Forefoot	-0.1	-2.1 to 1.9	0.427[b]	0.7	-0.6 to 2.1	0.239[b]
Hallux	1.0	-0.7 to 2.8	0.232	1.8	-3.3 to 6.9	0.844[b]
Heel	-1.4	-3.4 to 0.6	0.155	-0.4	-2.0 to 1.2	0.579
Lesser toes	-0.0	-1.8 to 1.7	0.960	1.2	-1.3 to 3.8	0.306
Midfoot	-2.1	-3.9 to -0.3	0.022	0.0	-1.5 to 1.6	0.946

	Treatment group (n = 26)			Control group (n = 12)		
	Mean difference	95% CI	*p* value	Mean difference	95% CI	*p* value
Force (kg)						
Whole foot	-30.2	-36.3 to -24.2	< 0.001	7.1	-2.4 to 16.6	0.126
Forefoot	-18.7	-24.4 to -13.0	< 0.001[b]	6.0	0.7 to 11.3	0.010[b]
Hallux	1.5	-0.9 to 3.9	0.215	-0.3	-2.7 to 2.1	0.724[b]
Heel	-13.9	-18.2 to -9.5	< 0.001	1.5	-3.0 to 6.1	0.477
Lesser toes	-0.0	-1.8 to 1.7	0.961	0.6	-1.6 to 2.7	0.581
Midfoot	-6.5	-9.2 to -3.9	< 0.001	0.1	-3.3 to 3.5	0.930
Plantar pressure (kPa)						
Whole foot	-36	-50 to -22	< 0.001	13	0 to 25	0.046
Forefoot	-40	-56 to -25	< 0.001	123	-3 to 28	0.098
Hallux	-16	-31 to -2	0.031	3	-15 to 21	0.705
Heel	-45	-65 to -25	< 0.001	10	-10 to 30	0.276
Lesser toes	-3	-9 to 3	0.366	3	-9 to 16	0.456[b]
Midfoot	-45	-63 to -26	< 0.001	3	-14 to 20	0.709

	Treatment group (n = 26)			Control group (n = 12)		
	Mean difference	95% CI	*p* value	Mean difference	95% CI	*p* value
Contact time (seconds)	-0.0	-0.0 to 0.0	0.617	0.0	-0.0 to 0.0	0.553
Hindfoot ROM (degrees)						
Frontal plane	-1.4	-4.2 to 1.4	0.410[b]	1.8	-0.3 to 3.8	0.090[b]
Dorsiflexion	0.5	-2.4 to 3.4	0.748	0.5	-2.0 to 3.0	0.643
Foot posture (degrees)						
Talus-second metatarsal angle	-0.2	-1.8 to 1.5	0.441[b]	1.3	-0.1 to 2.6	0.063
Talo-navicular angle	-1.4	-3.1 to 0.3	0.095[b]	1.0	-1.0 to 3.0	0.284
Calcaneal inclination angle	0.1	-0.3 to 0.6	0.623[b]	0.1	-0.7 to 0.9	0.665[b]
Calcaneal-first metatarsal angle	-0.4	-0.3 to 1.0	0.300	-0.4	-1.9 to 1.0	0.539

[a] *p* calculated for differences between baseline and follow-up measures analysed with the paired samples t-test unless otherwise stated

[b] *p* calculated for differences between baseline and follow-up measures analysed with the Wilcoxon signed-rank test

m metres, *kg* kilograms, m^2 metres squared, cm^2 centimetres squared, *MOXFQ* Manchester-Oxford Foot Questionnaire, *CES-D* Center for Epidemiologic Studies Depression, *kPa* kilopascal, *ROM* range of motion

Table 5: Repeated measures analysis of change in MOXFQ-index and plantar pressure

Variable	β-coefficients (95% CI)	*p* value
Age	0.5 (-0.1 to 1.2)	0.123
Gender	12.0 (-1.3 to 25.4)	0.077
Peak pressure[a]	0.0 (-0.1 to 0.1)	0.615
Ankle joint dorsiflexion	0.3 (-0.7 to 1.3)	0.541
Contact time	18.4 (-17.9 to 54.7)	0.320
Group (treatment)	-11.2 (-23.8 to 1.4)	0.081
Time (six-months)	-7.7 (-18.5 to 3.2)	0.168
Group*time	-27.1 (-40.8 to -13.5)	< 0.001

[a] Whole foot peak pressure

7.6 Discussion

This is the first study to comprehensively examine the effect of weight loss following bariatric surgery on foot pain, and to explore the mechanical and non-mechanical factors associated with foot pain severity. Depressive symptoms were associated with foot pain severity at baseline, after accounting for age, gender, BMI, foot posture and plantar pressure. At follow-up, foot pain severity was associated with depressive symptoms in those who had undergone bariatric surgery. The change in plantar pressure, walking speed or ankle joint dorsiflexion was not associated with a change in foot pain following bariatric surgery, but weight loss following bariatric surgery resulted in a significant reduction in foot pain severity at six-months. Therefore, in this cohort, both baseline foot

pain and change in foot pain appear more strongly related to non-mechanical or non-local factors.

Previous studies examining the association between the change in weight and change in plantar pressure have largely focused on the effect of weight gain. The effect of weight gain on plantar pressures has been frequently performed on asymptomatic participants, using weighted backpacks as a proxy for the increase in weight [102,257]. This method, while practical, measures the instantaneous effect of a change in weight and does so in asymptomatic feet, and therefore may not accurately reflect how pressures change over time in symptomatic feet. This method is also impractical in assessing weight loss. Investigations analysing the effects of weight loss are limited, although a randomised controlled trial investigated the effects of non-surgical weight loss on plantar pressures, albeit in asymptomatic participants, and found that even a small amount of weight loss can significantly reduce mean peak plantar pressure across multiple regions of the foot [266]. This study found that larger weight loss following bariatric surgery results in widespread reductions in plantar pressures in symptomatic feet, with the largest reduction in plantar pressure found in the midfoot.

Interestingly, the reduction in midfoot pressure in the treatment group occurred without a significant change in radiographic foot posture and may therefore be related to soft tissue changes. A previous cross-sectional study found that people with obesity have increased three-dimensional foot circumference at multiple sites when compared to people with a healthy weight [267], these differences are likely soft tissue related. Moreover, the change in BMI and midfoot pressure is concordant with a previous study investigating weight gain and plantar pressure [237], and suggests that the midfoot may be a region that is the most

responsive to a change in weight. The reduction of force in the midfoot in our study may have resulted in a larger reduction in peak pressure, if it were not for the significant simultaneous reduction in contact area of the midfoot. Furthermore, a study investigating contact area and body composition found a positive association between total body fat mass, but not fat-free mass, and the midfoot contact area only [268]. Together, these findings suggest that people with higher fat mass may deposit fat mass in the midfoot and, following bariatric surgery, there may be a loss of this fat mass that could appear to elevate the longitudinal arch of the foot. This may have implications for the fit of footwear or orthoses following soft tissue adaptations after bariatric surgery, and in patients with significant weight loss.

The association between foot pain severity and depressive symptoms has previously been established in a community cohort [15], suggesting that foot pain may be a manifestation of either widespread or reduced threshold for pain that extends beyond localised discomfort. The results of our study are concordant with this premise, although ours are unique given they are exclusively from a bariatric cohort and we were able to adjust for local foot measures, including foot posture and plantar pressure at baseline and follow-up. Given the high prevalence of depression in bariatric surgery candidates, and the improvement in depressive symptoms following surgery [269], it is possible that foot pain severity is mediated by depressive symptoms, rather than by body weight alone. There is evidence that while depressive symptoms improve in the short-term following bariatric surgery, there may be attenuation of this improvement in the longer term, and indeed some people have increased depressive symptoms following surgery, often with concomitant weight regain [270]. Whether this causes an exacerbation of musculoskeletal pain is not known, but this may be worth exploring.

This study should be considered in light of some limitations. Firstly, the small sample size limited the number of variables we could include in our models and may have may resulted in type II errors for the variables we did include. Secondly, the cohort was recruited via convenience sampling and consisted of mainly women which may limit the generalisability (and the ability to analyse between gender comparisons) of the findings, however, this is consistent with the demographics that present for bariatric surgery thus findings are applicable to that context [272]. Thirdly, the spatial resolution of the MatScan® plantar pressure system is relatively low and thus the sensitivity to detect all changes in plantar pressure may have been compromised. Furthermore, the importance of the size of the sensors used in plantar pressure systems has also been well described [271], and this may have impacted on measuring contact area, particularly for the lesser toe region, which is prone to measurement error [272]. Whilst there are limitations regarding sensor size and spatial resolution, the detection of subtle changes in plantar pressure was less important given the gross changes in body mass (and pressure) that occurs following bariatric surgery. Fourthly, the duration of foot pain was not recorded, so there may be variation of pain duration prior to participant enrolment. Finally, the change in foot pain and plantar pressure was measured over a six-months, and may not reflect changes seen over longer periods.

Nonetheless, this study has a number of strengths. It is the first to examine foot pain, foot posture and plantar pressures in bariatric candidates, reporting the effect of bariatric surgery on all variables. This study also considered relationships between mechanical and non-mechanical factors and foot pain severity at baseline and prospectively following bariatric surgery.

The results of this study provide proof of concept that weight loss improves foot pain, and future studies in this area, including non-surgical weight loss strategies and less obese cohorts, may be warranted. Deeper analysis of gait characteristics before and following weight loss in people with foot pain, may also determine if changes occurring beyond peak plantar pressures are important to consider in this cohort, and even footwear choices may be relevant.

7.7 Conclusion

Foot pain significantly improves following bariatric surgery instigated weight loss, but occurs without a change in foot structure. Dynamic peak plantar pressures reduce following bariatric surgery and weight loss, but these changes are not related to changes in pain. Depressive symptoms, however, are significantly related to foot pain both before and following bariatric surgery and associated weight loss. Thus, foot pain in bariatric candidates may be mediated by non-mechanical or non-local factors before and following surgery and resulting weight loss.

8

Chapter 8: Discussion; clinical implications, future research and conclusions

8 DISCUSSION

8.1 Introduction

Chapter 1 presented an overview of the current knowledge and principles of potential links between obesity and foot pain. Both mechanical and non-mechanical factors were presented to provide a framework of how obesity may interact with the foot and the experience of pain. The purpose of this chapter is summarise the key findings, identify the areas for future research and, importantly, the clinical implications presented in this thesis.

8.2 Key findings

Body composition is a more significant contributor to foot pain than body weight

In this thesis, all studies that investigated body composition found that body fat was positively associated with foot pain and lean mass was negatively associated with foot pain. There are clear clinical and research implications associated with these findings, which suggest that obesity should not be considered as just a mechanical factor, causing overload of tissues, as this premise does not explain why there is discordance between associations with different types of body tissue. Chapter 2 also found that widespread pain was associated with fat mass, suggesting that foot pain is not uniquely related to body fat and that musculoskeletal pain in general may be a manifestation of excessive adiposity.

The combination of body composition, body weight and adipokines in chapter 3, is novel in the area of foot pain research. Previous studies into foot pain and obesity found that FMI, but not FFMI was associated with pain, suggesting that there may be a metabolic relationship linking obesity and foot pain. The findings reported in chapter 3 suggest that FMI is independently associated with prevalent and future foot pain, after accounting for FFMI, BMI and adipokines / inflammatory markers. This work builds on previous studies that did not examine body composition concurrently with adipokines and BMI.

Furthermore, earlier studies that performed between group analyses, comparing a group of people with foot pain to an asymptomatic control, were often limited by their marked heterogeneity (particularly in BMI) between the groups. Not matching on BMI is a major limitation in these studies as bodyweight may confound the results. The results presented in chapter 4, demonstrate that the distribution of body fat between groups matched on BMI was different between those with and those without foot pain. A non-significant difference was found between groups, although this study may have been underpowered to detect overall differences in body fat, as the sample size was based on VAT / SAT ratio using a moderate effect size of 0.37. However, the group with foot pain had a significant positive relationship between both VAT / SAT and FMI, and foot pain severity, whereas FFMI was negatively associated.

Results presented in chapter 5 indicate that pre-operative body composition in bariatric surgery patients can predict changes in foot pain over time. This is a novel finding and it was also found that the use of BMI does not identify a meaningful level of risk given the divergence of FMI and FFMI in predicting the change in pain. The use of BMI likely underestimates the significance of obesity and, despite its ease of use, our results challenge the clinical relevance of this index with respect to risk of foot pain.

Psychological health is strongly associated with foot pain

The significance of psychological health on foot pain cannot be overlooked or understated. There were consistent, independent and significant relationships between pain and psychological health in all chapters that investigated psychological health measures. The interesting aspect of this thesis is that previous work had largely focussed on the

association of depression and pain, however our findings presented in chapter 4 also support associations with catastrophising and central sensitisation in those with chronic foot pain. Practitioners managing people with chronic foot pain, should be aware of these relationships as they may impact on prognosis and the response to treatment, particularly if they are overlooked.

Musculoskeletal research often focuses on the region of interest, exploring radiographic or histological changes in local tissues as a way of explaining and managing pain. Despite the known changes that occur with age, and the known associations with non-local factors, researchers and clinicians will often focus only on the region of complaint. This approach may be too simplistic particularly for non-traumatic, idiopathic complaints, principally because there are known external factors that contribute to the experience of pain. Many of the findings from this thesis reinforce this notion. Chapter's 6 and 7 were the only chapters to consider foot function in this thesis, and despite there being an association of foot pain to foot function in chapter 6, non-mechanical factors were unable to be considered because these data were not collected. The absence of a non-mechanical measure is certainly a limitation, however in chapter 7, which considered both mechanical and non-mechanical factors, there was no significant association between foot pain severity and foot posture or foot function. A limitation of the findings in chapter 7 is the small sample size that may have resulted in type II errors, particularly for BMI and possibly foot posture, although it is clear that depressive symptoms are related to foot pain severity. Studies with larger samples sizes are needed to provide robust evidence for the role of foot posture or function in foot pain severity in obese cohorts.

8 DISCUSSION

Bariatric surgery for proof-of-concept of weight loss for foot pain

The effect of weight loss on foot pain in bariatric surgery candidates was reported in chapter 5 and 7. As there had not been a study formally assessing the effectiveness of weight loss for foot pain severity, the decision to recruit bariatric surgery candidates with foot pain was due to the known high prevalence of foot pain and the strong likelihood that they would lose weight. The addition of a control group in this study also enabled the analysis to consider the effect of no treatment. The results of the study clearly demonstrate that weight loss following bariatric surgery is associated with a reduction in foot pain.

There are a number of limitations of our study which may limit its generalisability. The age of the participants, the high prevalence of depressive symptoms, the relatively short follow up time (six-months) and the over-representation of women in the study all may impact on its generalisability to the broader community. The participants were generally in their fifth decade and may be too young to have developed joint or soft tissue changes, such as osteoarthritis, that an older cohort may have developed. The high prevalence of depression may also have confounded the severity of pain and the reduction in pain following bariatric surgery. The absence of a diagnosis in this cohort limits specific conclusions that can be drawn about whether the change in pain is also dependant on the location or the underlying diagnosis i.e. pain associated with midfoot osteoarthritis or plantar heel pain may reduce more with weight loss than pain associated with hallux valgus. The positive results, however, suggest further studies using a community cohort is likely to be of value.

Mechanical factors may be associated with pain, but this message may need to be tempered

There were continued, non-significant associations between mechanical factors (BMI, plantar pressure and foot posture) and foot pain when psychological and body composition factors were considered. Nonetheless, there was an association between a change in foot pain and an increase in pressure in the midfoot in reported in chapters 6 and 7. The midfoot was the only region to change in contact area following weight loss. These results suggest that there may be mediation of pain via pressure in the midfoot, but using plantar pressures when analysing foot function in people with obesity may be a reflection of soft tissues around the foot (possibly fat), rather than a reflection of the underlying bones and joints. The absence of an association between foot posture or function and foot pain severity reported in in chapter 7, but a strong association with depression indicates that directing future studies at local foot mechanics only may be unwise.

Plantar pressure analysis has clear limitations in analysing and understanding foot function. These data cannot be used to interpolate total foot function, and there are indeed limitations to any extrapolation to gait. It does, however, provide at the very least practical data that demonstrates that it is unlikely that the association between foot pain and obesity has a direct, linear and mechanical relationship. These studies have shown that plantar pressures may provide some useful data with respect to change in foot pain, but the plantar pressure measures discussed in chapter's 6 and 7, in addition to the measures of foot posture, seem to have little effect on obesity and foot pain. The relationship between obesity and foot pain, as supported by the results of this thesis, appears to be largely mediated through non-mechanical factors.

8.3 Future research

Future research should focus on clinical trials that investigate how weight loss and a change in both body composition and psychological health impact foot pain. There is now a body of work that supports the premise that body composition, fat mass specifically, is likely the driver behind the association between pain and obesity. The continued use of BMI likely underestimates the significance of excessive adiposity.

Weight loss

The observational nature of the study reported in chapter's 5 and 7 means the results suggesting an improvement in foot pain following bariatric surgery should be interpreted cautiously. A randomised controlled trial would provide stronger evidence that this is an effective treatment for foot pain in people with obesity. There is certainly ample justification for a waiting-list controlled trial and such trials would provide further evidence. However, the focus of research in future should be to evaluate the effectiveness of *non*-surgical weight loss and in less obese cohorts. Non-surgical weight loss is undoubtedly more practical to implement on a wider scale and this may also provide people with incentives to minimise weight regain. In order to conduct a robust trial, a focus on pain in one region or a specific diagnosis should be considered. Given the strong association between plantar heel pain and obesity, this may be a condition that could be targeted. It is proposed that it is not the loss of weight that is most important, but rather *what* mass is lost and any study that assesses the impact of weight loss on foot pain should consider this. Reflecting on the results from chapter 5, the participants who underwent bariatric surgery had a marked loss of body weight, but weight is usually lost as fat [273] and therefore change in body

composition may be a better indication of an improvement in the metabolic or psychological profile.

Psychological health

In clinical practice, there is considerable focus on the joint or region that is symptomatic. The results discussed in chapter 5 suggest that weight loss may be beneficial, and indeed patients who present with obesity and foot pain can often understand the likely benefit of losing weight to improve pain. Interestingly the suggestion that psychological health may need to be assessed and concurrently managed is often met with hostility from patients , despite the known association between depression and musculoskeletal pain. Results reported in chapters 3, 4 and 7 provide some basis for further work in the area, particularly given the bidirectional relationship between depression and musculoskeletal pain. A trial that investigates the treatment of psychological health in those with chronic foot pain would be highly clinically relevant. Further work in this area may also help to explain the common clinical conundrum where medical imaging is unable to detect overt pathology, despite the complaint of sustained or disproportionate pain.

Body composition and adipokines / inflammatory markers

Further investigation into the differences in visceral and subcutaneous adipose tissue and musculoskeletal pain is warranted, particularly given that it was associated with foot pain severity as outlined in chapter 4. The known heterogeneity of adipose tissue between android and gynoid regions, as well as visceral and subcutaneous deposits does call for future work.

The adipokines and inflammatory mediators selected: leptin, resistin, adiponectin, TNF-α and IL-6 were chosen as these have been the focus of other studies investigating musculoskeletal pain and obesity, but there may be others that are more suitable. Visfatin is an adipokine that is primarily secreted from visceral fat and has been found to be associated with upper-limb pain. It may be worthy of future investigation, particularly in light of the associations between VAT / SAT ratio and foot pain severity discussed in chapter 4.

The lack of association between the adipokines and pain despite a negative association with change in resistin and change in foot pain may mean that there are other adipokines that are involved. It may also mean that there may be a threshold effect whereby once adiposity has reached a certain level, that there is a non-linear dose-response relationship. Future work may also extend into other proteins secreted by adipose tissue such as sex hormones.

Biomechanical analysis

Whilst the results of this thesis found that non-mechanical factors appear to be driving the relationship between obesity and foot pain, more detailed biomechanical analyses are required to determine if there are detrimental additive or symbiotic relationships between mechanical and non-mechanical factors. Given the accuracy and reliability of three-dimensional movement analysis is compromised by obesity, further work in modelling gait or improving data collection techniques is prudent to gain a deeper understanding of the mechanical relationship between obesity and foot pain. Given that the changes not only in peak plantar pressures, but also in the contact area of the foot on the ground, further work

assessing the impact of footwear on foot pain with obesity may also be prudent. The results of this thesis certainly do not discount mechanical factors altogether, but they do appear less important. The lack of significant associations between mechanical factors and foot pain may also be due to the measure of foot pain severity rather than the absence or pressure of foot pain, or the small samples sizes used in this thesis.

8.4 Clinical implications

The results of this thesis support the premise that there are non-mechanical factors that link obesity to foot pain. These factors may outweigh the impact of a mechanical relationship and this thesis provides preliminary data to clinicians managing foot pain that there must be consideration of these factors.

There remains the challenge for a clinician, faced with the responsibility of identifying, highlighting and explaining to a patient how their excessive adiposity may be associated with pain. The assessment and discussion about a patient's weight is often fraught with difficulty, it can be an emotive topic that traverses clinical and social domains. The practitioners usually involved in assessing and and managing musculoskeletal pain are Rheumatologists, Orthopaedic Surgeons, Podiatrists and Physiotherapists, professions that are not routinely well trained in counselling a patient about non-mechanical relationships between obesity and pain, or how to successfully overcome these factors. Often the prescribed treatments are locally based, focussed on shifting forces and pressures in the foot via a change in footwear design, foot orthoses, gait retraining, muscle strengthening, or other interventions such as injections and surgery. It is clear that people with obesity may have excessive fat mass, rather than excessive weight, but how this message is delivered does need careful thought. The integration of dieticians and

psychologists into multi-disciplinary teams managing musculoskeletal pain, with a view to helping patients reduce weight and improve their psychological health, could be considered for future research and models of care.

Indeed, whilst technically a patient may have excessive adipose tissue, in order to engage a reduction in adiposity, patients may need to be encouraged to improve their health, via non-commercial, non-stigmatising interventions that do not support fat or weight loss *per se*, but rather encourage a healthy lifestyle [274]. People can see obesity as a social identifier, rather than a clinical condition, and may consider targeted messaging as threatening, limiting the effectiveness [275]. People with obesity report that they are more responsive to a health practitioner whom avoids appearing insensitive, hostile or using language that is stigmatising [276]. Moreover, stigmatising health campaigns are not motivating for weight loss [277]. Health practitioners, however, tackling the problem of obesity and musculoskeletal pain may be misguided if the only focus is on moderating and shifting forces and pressure, and ignoring the metabolic and psychological aspects of obesity.

8.5 Conclusion

The interaction between obesity and pain is complex, it cannot be viewed as a linear, dose-dependent relationship between weight, pressure and pain. There are non-mechanical factors that should not be overlooked, and indeed these may be even more important than mechanical factors. Adipose tissue is not an inert, external structure, but rather a highly active endocrine organ that is *in* the body as opposed to *on* it. Thus, weight gain may be accompanied with metabolic and psychological disturbances, both of which may pilot and amplify foot pain. This thesis had a number of objectives to meet, as

reported in chapter 1 and a number of clinically relevant findings were made. Specifically, this thesis has determined that:

- Fat mass is associated with multi-site and single-site musculoskeletal pain.
- Fat mass is an independent risk factor in the general community for prevalent and future foot pain, independent of body weight.
- Psychological health is associated with chronic foot pain and it may be more related to foot pain than foot posture or foot function in the obese, but studies involving larger samples are required to confirm these findings.
- Weight loss following bariatric surgery is significantly associated with a reduction in foot pain and increased fat mass predicts increased foot pain following bariatric surgery, whereas increased fat-free mass predicts less foot pain following bariatric surgery.
- Bariatric surgery results in a significant reduction in plantar pressure, but the change in pressure is not associated with a change in foot pain

Health practitioners managing foot pain may need to reduce the temptation to focus solely on the foot in someone with obesity. It is clearly beyond the scope of this thesis to provide recommendations on how treatments should be implemented, but it does suggest that the line of future enquiry should not focus on just mechanical mechanisms. Non-mechanical factors may be driving the complaint of pain and these should be recognised and appreciated. In this thesis there were consistent associations between foot pain and both metabolic and psychological factors, whereas mechanical load appeared less important. In order to effectively manage musculoskeletal foot pain in a community where obesity is

increasing at an alarming rate, ensuring all of the pathways in which obesity may manifest as musculoskeletal foot pain is essential. Future prospective studies may continue to broadly explore the relationship between obesity and foot pain, but deep phenotyping may also provide further data to assist in understanding the relationship between obesity and pain, particularly the endocrine role of adipose tissue and the role of reduced psychological health.

A

Appendices

Appendix A Grant awards

Australian Podiatry Education and Research Foundation, Research grant 2016

Arthritis Australia, ARA Project grant, 2016

89 Nicholson Street
Brunswick East Vic 3057

T: +61 3 9416 3111
F: (03) 9416 3188
E: aperf@apodc.com.au
W: www.apodc.com.au

17 December, 2015

Mr Tom Walsh
Flinders University,
Department of Podiatry. Repatriation General Hospital
216 Daws Road,
Daw Park SA 5041

By Email: wals0169@uni.flinders.edu.au

Dear Mr Walsh,

Thank you very much for submitting an application to the Australian Podiatry and Education Research Foundation for a research grant. We are very pleased to advise that your application "Is chronic foot pain in middle-aged women associated with increased subcutaneous fat?" has been chosen for a grant.

Your project has been awarded the sum of $3580. This amount represents the grant request of $5000 less amounts not eligible for funding being $100 the external USB and $1320 for honorariums.

Note: the trustees chose not to fund the participant honorariums and the external hard drive for data storage is the responsibility of the host institution (i.e. the institution that the PhD student is enrolled in).

Additional recommendations from the trustees:

- The trustees had concerns about the limited data (i.e. other causes of foot pain) that will be entered into the statistical model, which may lead to limitations in the conclusions that can be drawn from the study (i.e. associations may be found, but other variables may have stronger associations)
- The trustees recommend alternative ways of advertising other than just newspapers because of declining readership (e.g. social and web-based media)

89 Nicholson Street
Brunswick East Vic 3057

T: +61 3 9416 3111
F: (03) 9416 3188
E: aperf@apodc.com.au
W: www.apodc.com.au

Payment will be available at the end of January, 2016, provided that you have sent evidence to this office of institutional ethics clearance for your project and an invoice for the abovementioned amount of $3580.00.

Your research office is asked to invoice the Australian Podiatry Education and Research Fund ABN: 47 055 668 959 and forward the invoice to finance@apodc.com.au for the amount of $3,580. An invoice for payment of your grant may be included with your ethics clearance, or sent immediately following. Please note, the grant will be made at the outset of your research. $3,580 is the total amount payable and is inclusive of GST, if applicable to your institution. Please ensure details of the bank account into which the sum is to be paid is included

Finally, as we communicate only with the chief investigator or nominated research officer, may I ask that the news of your success and the congratulations from the Trustees is passed on to other researchers in your team as soon as possible? Good wishes for your success.

Kind regards

Pauline Taylor
On behalf of the APERF Trustees

Donations of $2.00 or more to the Australian Podiatry Education and Research Foundation are an allowable deduction under Section 78 (1) (a) of the Income Tax Assessment Act 1936. (Reference VJ80/7).

Arthritis Foundation of Australia
Level 2, 255 Broadway, Glebe NSW 2037
PO Box 550, Broadway NSW 2007
Phone: +61 2 9518 4441 Fax: +61 2 9518 4011
info@arthritisaustralia.com.au
www.arthritisaustralia.com.au

9 November 2015

Mr Tom Walsh
School of Medicine
Faculty of Medicine
Nursing and Health Sciences
Flinders University
BEDFORD PARK SA 5042

Dear Mr Walsh

Application from: Rheumatology, School of Medicine, Flinders University for a **2016 Arthritis Australia Project Grant**
Subject: ***Is a change in body composition and adipokines associated with foot pain?***
Awarded: The ARA Project Grant & Arthritis Australia and State/Territory Affiliate Grant
funded by Australian Rheumatology Association & Arthritis South Australia
Amount Awarded: $ 15,000

We have pleasure in advising that your 2016 Arthritis Australia National Research Program application has been successful and that you are the recipient of the **ARA Project Grant & Arthritis Australia and State/Territory Affiliate Grant.**

Please note that this grant is to support research during the 2016 calendar year only and you must re-apply by the application closing date in July 2016 for further funding.

By June 2017, you will be required to submit the following written reports on the outcomes of your completed grant:

- A scientific report that describes the achievements of the grant and includes references for original papers that have been published or accepted for publication, as well as information about meetings at which you may have presented the research. We also require copies of any publications resulting from this work.

- A 'plain language' report that not only outlines the achievements of the grant, but places the objectives of the research in a wider disease context and explains the importance of your findings to people with musculoskeletal disease.

The plain language report is of particular importance. It will be published and used to advise the principal donor(s) of the outcomes of the grant, as well as to communicate your research to a broader non-scientific readership. It must be written in 'everyday' language, and scientific terminology should be avoided. More detailed guidance for the writing of both reports will be sent to you in May 2017.

As research impacts continue to develop long after a grant has completed, it is also important that you keep us informed of any further outcomes of the research that may occur after you have submitted your final reports. This includes publications of any kind, meetings at which you have presented this research, media coverage of the research and any other impacts of the research that you consider to be worthy of reporting to us. This information is very important as it keeps us up-to-date of your achievements and helps promote our fundraising efforts.

In the interest of transparency, it is vital that you acknowledge the support of the donor(s) and Arthritis Australia on all publications, meeting presentations (oral and poster) and in any other ways that you disseminate the research directly arising out of the funding.

Your acceptance of the funding automatically indicates that you agree with the reporting requirements.

In order to finalise arrangements promptly, we would appreciate your acceptance in writing (email or post), by no later than Friday 4 December 2015. If you have any questions, please contact Dora Stavrakis on (02) 9518 4441 or email: dstavrakis@arthritisaustralia.com.au

Your **first quarterly instalment** is due to be paid in March 2016. We will require you to submit a tax invoice, with or without GST, on company letterhead by email or post from your intended institution to Dora Stavrakis at email: dstavrakis@arthritisaustralia.com.au or Arthritis Australia, PO Box 550, BROADWAY NSW 2007.

To read about the variety of activities undertaken by Arthritis Australia during 2014-2015, please download ***'A year in review'*** from our website www.arthritisaustralia.com.au

In anticipation of your acceptance of this award, we convey to you our best wishes and congratulations. Thank you for your ongoing commitment to arthritis.

Yours sincerely

Dora Stavrakis
Projects Coordinator/National Research Program

Appendix B Ethics approvals

Office for Research

Flinders Medical Centre / The Flats F6/F8
Flinders Drive, Bedford Park SA 5042
Tel: (08) 8204 6453
E: Health.SALHNOfficeforResearch@sa.gov.au

Government of South Australia
SA Health
Southern Adelaide Local Health Network

Final approval for ethics application

You are reminded that this letter constitutes **ethical** approval only. **Ethics approval is one aspect of the research governance process**.
You must not commence this research project at any SA Health sites listed in the application until a Site Specific Assessment (SSA), or Access Request for data or tissue form has been authorised by the Chief Executive or delegate of each site.

02 December 2015

Dear A/Professor Shanahan

This is a formal correspondence from the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188). This committee operates in accordance with the "National Statement on Ethical Conduct in Human Research (2007)." No hard copy correspondence will be issued.

Application Number: 431.15 - HREC/15/SAC/396

Title: Chronic foot pain in middle aged women – an exploration into the effect of fat mass distribution on pain

Chief investigator: A/Professor Michael Shanahan

The Issue: The Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC) have reviewed and provided ethical approval for the above application. The approval extends to the following documents/changes:

- Cover Letter dated 06 October 2015
- NEAF AU/1/BAC1214
- SAC HREC General Research Application Form v2 dated 10 November 2015 (tracked)
- Head of Department Support Letter – A/Professor Michael Shanahan
- Flinders University Indemnity email dated 19 November 2015
- Participant Information Sheet/Consent Form v2.0 dated 13 October 2015 (tracked)
- MFPDI – Questionnaire – Screening Tool
- CES-D Scale – Questionnaire
- CSI – Part A – Questionnaire
- PainDETECT – Questionnaire – modified
- PCS – Questionnaire
- Radiation Safety Report dated 19 November 2015
- Advertisement – Foot Pain – GP Rooms, Noticeboards
- Advertisement – No Foot Pain – GP Rooms, Noticeboards
- Newspaper Advertisements
- Advertisement – Foot Pain - Social Media – Gumtree
- Advertisement – No Foot Pain - Social Media - Gumtree
- Foot Pain Chart – Diagram
- Full Body Pain Chart – Diagram
- EPA Notification Form v2
- Minute addressing specific committee concerns dated 19 November 2015

Approval Period: 02 December 2015 to 02 December 2019

Southern Adelaide Clinical Human Research Ethics Committee

Government of South Australia
Southern Adelaide Health Service

Ethics application approval

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a SA Health site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

08 July 2014

Dear Dr Shanahan

This is a formal correspondence from the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188). This committee operates in accordance with the "National Statement on Ethical Conduct in Human Research (2007)." No hard copy correspondence will be issued.

Application Number: 211.14 - HREC/14/SAC/208

Title: The effect of weight loss on foot pain, structure and function

Chief investigator: Dr Michael Shanahan

Public health sites approved:

- Repatriation General Hospital
- Royal Adelaide Hospital

The Issue: The Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC) have reviewed and approved the above application. The approval extends to the following documents/changes:

- Cover letter dated 02 May 2014
- SA Health indemnity approval dated 02 May 2014
- Letter of support from A/Professor Andrew Chew, Divisional Director PARS, RGH dated 01 April 2014
- Letter of support from Professor David Watson, Head, Flinders University Dept of
- Surgery Head, Oesophago---Gastric Surgery Unit FMC dated 01 April 2014
- Letter of support from Professor Peter Devitt, Department of Surgery RAH dated 03 April 2014
- Letter of support from Dolores Pilkington, Director Podiatry RGH dated 01 April 2014
- Letter of support from University of Manchester dated 28 March 2014
- Data collection forms: visit 1, FFQ, FPI-6
- Letter of support from Con Kapsis, Campus Operations Manager, RGH Radiology dated 22 March 2014
- Location of foot pain form
- Laval questionnaire
- Center for Epidemiologic Studies Depression Scale (CES-D Scale)
- Manchester-Oxford Foot Questionnaire (MOxFQ)

Your response to committee concerns received via email containing the following:

- Minute addressing specific committee concerns dated 04 July 2014
- SAC HREC general research application form dated 18 June 2014
- Participant information sheet and consent form v3 dated 07 July 2014
- Letters to patients on waiting list – RAH and RGH dated 04 July 2014

Approval Period: 08 July 2014 to 07 July 2017

Flinders Medical Centre

The Flats G5 – Rooms 3 and 4

Flinders Drive, Bedford Park SA 5042

T: 08 8204 6453

F: 08 8204 4586

E:Research.ethics @health.sa.gov.au

Ethics Committee

Certificate of Approval of Amendments

This is to certify that amendments to

Project: **121/11 Is the structure of the lumbar spine important in low back pain?**

Principal Researchers: **Dr Donna Urquhart, Prof Flavia Cicuttini, A/Prof Anita Wluka and Dr Richard O'Sullivan**

Amendment:
Change to research personnel –
Addition of Mr Tom Walsh (student researcher)

Attachment:
Participant Information & Consent Form version **8** dated **8-May-2014**

have been approved in accordance with your amendment application dated **8-May-2014** on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.

Chair, Ethics Committee (or delegate) Date: **9-May-2014**

R Frew
Secretary, Ethics Committee

All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).

Appendix C **Ethics approved Participant Information Sheet and Consent Forms (chapters 4, 5-7)**

Government of South Australia
SA Health

Participant Information Sheet/Consent Form

Non-Interventional Study - *Adult providing own consent*

Title	Chronic foot pain in middle aged women – an exploration into the effect of fat mass distribution on pain
Short Title	Foot pain in women
Protocol Number	431.15
Project Sponsor	
Coordinating Principal Investigator/ Principal Investigator	A/Prof E Michael Shanahan
Associate Investigator(s)	Mr Tom Walsh, Dr John Arnold, Dr Alison Yaxley, Dr Angela Evans, A/Prof Catherine Hill,
Location	Adelaide Bodyscan, Rose Park

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in a research study because you have foot pain or have qualified as a control participant and we believe you may be suitable for the study. The research project is investigating whether there is a difference in body composition between women with and without chronic foot pain.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests involved. Knowing what is involved will help you decide if you want to take part in the research.

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

Participation in this research is voluntary. If you don't wish to take part, you don't have to. Please note there is no treatment offered as part of this study.

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

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

2 What is the purpose of this research?

The purpose of this research is to examine the differences in body composition in women with and without foot pain. Our specific investigation is to see if there are differences between where fat is stored around the abdomen in women with and without foot pain. Mr. Tom Walsh (a student at Flinders University) will be using this project for the purposes of his PhD under the supervision of Associate Professor Michael Shanahan, from the School of Medicine at Flinders University.

3 What does participation in this research involve?

Participation in this study involved one visit to Adelaide Bodyscan (24 Kensington Road, Rose Park). You will have a full-body scan to determine your body composition (amount of lean tissue and fat) and complete up to five short questionnaires about your pain and general health (depending on whether you have foot pain or not). It is estimated the questionnaires and scan will take no longer than 45 minutes to complete.

4 What do I have to do?

You will first be asked to fill out questionnaires about your foot pain and general health.
Whilst most of the measures taken are quite straight forward, you may not see the relevance for some of the questions asked in the questionnaires. The reason for these questionnaires is that pain can be affected not only by local factors (within the foot), other joint pain and by other factors of health – for example; how you feel about yourself, if you have depression or anxiety or what your menopause status is.

After this, your height and weight will be measured. You will then be required to have your body composition assessed using a dual x-ray absorptiometry scanner (iDXA). This is a non-invasive procedure, which involves lying on a flat scanning plinth while the scanner moves over your body. The scan is painless and takes approximately 10 minutes

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.
The conduct of the research will be monitored by progress reports to the institutional ethics committee to ensure all conduct is in accordance with the granted ethical approval. There are no additional costs associated with participating in this research project, nor will you be paid.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

5 Other relevant information about the research project

There will be 88 people taking part in this project, which is being conducted in collaboration between researchers and clinicians from Flinders University.

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

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

7 What are the alternatives to participation?

Participation in this study is entirely voluntary. If you do not wish to take part, you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage without providing a reason.

8 What are the possible benefits of taking part?

We will provide you with $20 to assist in travelling to Adelaide Bodyscan. We expect this study to benefit the community by providing details on what impact body composition has on foot pain. This will assist in determining how much foot pain can be attributed to the type of body composition someone has and it may help guide future treatment options.

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

Medical tests often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study investigator. Your study investigator will also be looking out for side effects. There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell the investigator immediately about any new or unusual symptoms that you get.

There is a small chance that you may experience some discomfort whilst lying on the scanning plinth during your body composition assessment. However, the scanning process is very short. If you feel discomfort, you are free to reposition yourself or indicate you would like to sit in a chair. The scan would then need to be repeated if it is safe to do so.

This research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this research project is about 0.002 mSv. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. This risk is believed to be minimal.

10 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

11 What happens when the research project ends?

Once you complete the visit, your involvement in the study will end. If you are a participant with foot pain, documentation will be provided regarding booking an appointment at the University of South Australia Podiatry Clinic (Adelaide CBD), where low-cost Podiatry services are available for you to seek an opinion on management as soon as possible. After the research project is completed, a summary of the results will be mailed by post to your residential address at your request.

Part 2 How is the research project being conducted?

12 What will happen to information about me?

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

The information collected from you will be stored in a locked filing cabinet, password protected computer within the office of one of the study investigators (Tom Walsh) and on a password protected computer database at Flinders University. Once you agree to take part you will be allocated a participant code number and all of your information is associated with that number. This makes your information re-identifiable. By law we need to keep your information for 15 years after the study has finished. If you consent to participating, your data will be used for this project only. It is possible that your data may be used for future studies; however ethics approval will be sought separately. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Information will only be published about the results for the entire group and not for participants individually.

The data collected for this research project may also be used in future in studies that are closely aligned to this one. Further ethical approval will be sought before this may occur. In accordance with relevant Australian and/or South Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project and for the future research described in Section 16 that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

13 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate care.

14 Who is organising and funding the research?

This research project is being conducted by researchers from the School of Medicine at Flinders University. No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

15 Who has reviewed the research project?

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

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

16 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study investigator on (08) 8275 1662 or any of the following people:

Clinical contact person

Name	Tom Walsh
Position	Project co-ordinator/PhD candidate
Telephone	(08) 8275 1662
Email	wals0169@uni.flinders.edu.au

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

Complaints contact person

Name	Tom Walsh
Position	Project co-ordinator/PhD candidate
Telephone	(08) 8275 1662
Email	wals0169@uni.flinders.edu.au

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

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Southern Adelaide Clinical Human Research Ethics Committee
HREC Executive Officer	Petrina Kasperski
Telephone	(08) 8204 6453
Email	Health.SALHNOfficeforResearch@sa.gov.au

Consent Form - *Adult providing own consent*

Title	Chronic foot pain in middle aged women – an exploration into the effect of fat mass distribution on pain
Short Title	Foot pain in women
Protocol Number	431.15
Coordinating Principal Investigator/ Principal Investigator	A/Prof E Michael Shanahan
Associate Investigator(s)	Mr Tom Walsh, Dr John Arnold, Dr Alison Yaxley, Dr Angela Evans, A/Prof Catherine Hill,
Location	Adelaide Bodyscan, Rose Park

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

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

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

Signature _____ Date _____

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

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

Government of South Australia
SA Health

Flinders UNIVERSITY

PARTICIPANT INFORMATION SHEET

Study title: The effect of weight loss on foot pain, structure and function

You are being invited to take part in a research study because you have foot pain and are either waiting for weight loss surgery or are in a weight management clinic. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If you want to ask any questions that are not dealt with on this form please feel free to contact the investigators. Their details can be found at the end of the document. Take time to decide whether or not you wish to take part.

Invitation to participate and selection process
You are invited to participate in this research project but you do not have to be involved, whether you wish to or not is entirely up to you. Whether you take part or not, your medical care/relationship with the university/the services which you receive will not be affected in any way.

What is the purpose of the study?
The purpose of this research is to examine if weight loss surgery has an impact on foot pain.. Our specific investigation is to see if weight loss reduces foot pain and also how your foot function and body composition changes before and after your surgery. Assoc. Professor Michael Shanahan, from the School of Medicine at Flinders University and the Repatriation General Hospital (RGH), is conducting this project. Mr. Tom Walsh (a student at Flinders University) will be using this project for the purposes of his PhD and will be actively involved with participants throughout.

What is involved in the study and what commitments are required?
The study will examine people with foot pain once, and again 6 months later. We will ask people on the waiting list to have testing done over a 6 month period while they are waiting and those undergoing surgery will have the testing done before and 6 months after surgery. The commitments we will want you to make regarding this study is to undergo

- basic measurements to define the size of your body,
- measures of your foot posture
- a scan of your foot to determine how it functions,
- seven questionnaires
    - 1 regarding your general health,
    - 1 regarding your mental health,
    - 1 regarding your knee health,
    - 2 regarding your back health,
    - 1 regarding your foot health and
    - 1 regarding your food intake
- an xray of your feet,
- an xray of your whole body (DEXA),
- venipuncture (blood sample)
- Use of a pedometer for 1 week

These measures can all be performed on the same day. Most measures can be performed in the podiatry department at the RGH. Foot xrays will be performed in radiology department at RGH.

It is estimated the clinical measures will take 20 minutes. The questionnaires should take no longer than 60 minutes to complete. The foot xray and DEXA can be done directly after the clinical measures. We would ask you allow 130 minutes for the entire process.

Whilst most of the measures taken are quite straight forward, you may not see the relevance for some of the questions asked in the questionnaires. The reason for these questionnaires is that pain can be affected not only by local factors (within the foot), other joint pains and by other factors of health – for example; How you feel about yourself? and What do you eat and how often?

All questionnaires have been used in other projects and have been developed to make sure both psychological and physical health are considered.

We kindly ask you complete all questions in the questionnaires and please understand that the rationale for the questions is for thoroughness and are not designed to upset anyone. If you feel uncomfortable answering any of the questions, you do not have to answer them.

What are the risks of taking part in this study?
We do not foresee significant risks to you if you decide to take part in this study. There is one invasive procedure, which involves taking a blood sample from a vein in the arm. There are also two procedures which will expose you to ionizing radiation (xrays). One is a whole body scan (DEXA) and the other is an xray of both feet. We will ask to take a sample of your blood, initially and again 6 months later you may experience some pain during this process. We will ask to take a DEXA and foot xrays initially and again 6 months later – you will be exposed to a very small dose of radiation. Participation in this study does not affect on your basic legal right to seek compensation; however, if you do suffer harm, you may receive compensation without litigation.

What are the possible benefits of taking part in the study?
We expect this study to benefit the community by providing details on what impact weight loss has on foot, knee and low back pain and foot osteoarthritis, along with foot structure and function. This will assist in determining how much foot, knee and low back pain can be attributed to weight (and to weight loss) and whether the structure and function of the feet changes after weight loss surgery. Whilst we are unable to pay you for your time, we will provide you with $40 to assist in travelling to and from the hospital at each visit.

Will my taking part in this study be kept confidential?
All records containing personal information will remain confidential and no information which could lead to your identification will be released, except as required by law. To ensure your confidentiality, access to the data will be limited to the members of the research team. All data collected will be stored in password protected secure computer drives at the Repatriation General Hospital. The data will be kept until it has been analysed.

Will I receive a copy of the results?
The results of this study will be shared with others through peer reviewed publications and conference presentations. If you would like to receive notification regarding the results of the research please contact Tom Walsh. If you have any other questions relating to the study please contact Tom on wals0169@uni.flinders.edu.au or on 0402 304 343

How can I make a complaint about this study?
This study has been reviewed by the Southern Adelaide Clinical Human Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Executive Officer, SAC HREC at the Flinders Medical Centre (8204 6453) or email research.ethics@health.sa.gov.au

All information received is confidential and will be handled as soon as possible. By completing the consent form, this indicates that you understand the above conditions of participation in this study and that you have had the opportunity to have your questions answered by the researchers.

Chief Investigator:
Associate Professor Michael Shanahan
School of Medicine, Flinders University
Department of Rheumatology, Repatriation General Hospital
Tel. 8275 1316
Email: Michael.Shanahan@health.sa.gov.au

Associate Investigators:
Mr Tom Walsh
School of Medicine
Flinders University
Tel: 0402 304 343
Email: wals0169@uni.flinders.edu.au

Dr Angela Evans
Department of Podiatry
La Trobe University
Tel: 8298 1133
Email: angela.evans@latrobe.edu.au

Dr Alison Yaxley
School of Health Science
Flinders University
Tel. 8204 4645
Email: Alison.yaxley@flinders.edu.au

Please retain a copy of this letter for your reference

Government of South Australia
SA Health

Flinders UNIVERSITY

CONSENT FORM

I, ... (first or given names) ..... (last name)

give consent to my involvement in the research project:

The effect of weight loss on foot pain, structure and function

- I acknowledge the nature, purpose and contemplated effects of the research project, especially as far as they affect me, have been fully explained to my satisfaction by **Mr. Tom Walsh** and my consent is given voluntarily.
- I acknowledge that the detail(s) of the following has/have been explained to me, including indications of risks; any discomfort involved; anticipation of length of time; and the frequency with which they will be performed:
    1. basic measurements to define the size of your body,
    2. measures of your foot posture
    3. a scan of your foot to determine how it functions,
    4. seven questionnaires,
    5. an xray of your feet,
    6. an xray of your whole body (DEXA),
    7. venipuncture (blood sample)
    8. Use of a pedometer for 1 week
- I have understood and am satisfied with the explanations that I have been given.
- I have been provided with a written information sheet.
- I understand that my involvement in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.
- I declare that I am over the age of 18 years.
- I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

Signature of Research Participant: .....

Date: .....

I, ... have described to .....

the research project and nature and effects of procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: .....

Date: .....

Status in Project: .....

Appendix D Permissions for inclusion of material from published papers in thesis

Professor Michael Shanahan

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, Arnold JB, Evans AM, Yaxley A, Damarell RA, **Shanahan EM**. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. [In press].
- Walsh TP, Quinn SJ, Evans AM, Yaxley A, Chisholm JA, Kow L, **Shanahan EM**. Fat mass, but not fat-free mass, predicts increased foot pain with morbid obesity, independent of bariatric surgery. *Surg Obes Relat Dis*. [In press].
- Walsh TP, Gill TK, Evans AM, Yaxley A, Chisholm JA, Kow L, Arnold JB, **Shanahan EM**. Changes in foot pain, structure and function following bariatric surgery. *J Foot Ankle Res.* [In press].
- Walsh TP, Butterworth PA, Urquhart DM, Cicuttini FM, Landorf KB, Wluka AE, **Shanahan EM**, Menz HB. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. *J Foot Ankle Res*. 2017;10:31.
- Walsh TP, Arnold JB, Gill TK, Evans AM, Yaxley A, Hill CL, **Shanahan EM**. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *Rheum Int*. 2017;37(7):1175-1182.
- Walsh TP, Gill TK, Evans AM, Yaxley A, **Shanahan EM**, Hill CL. Association of Fat Mass and Adipokines With Foot Pain in a Community Cohort. *Arthritis Care Res (Hoboken)*. 2016;68(4):526-533.

Professor Michael Shanahan

Dr Angela Evans

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, Arnold JB, **Evans AM**, Yaxley A, Damarell RA, Shanahan EM. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. [In press]
- Walsh TP, Quinn SJ, **Evans AM**, Yaxley A, Chisholm JA, Kow L, Shanahan EM. Fat mass, but not fat-free mass, predicts increased foot pain with morbid obesity, independent of bariatric surgery. *Surg Obes Relat Dis*. [In press]
- Walsh TP, Gill TK, **Evans AM**, Yaxley A, Chisholm JA, Kow L, Arnold JB, Shanahan EM. Changes in foot pain, structure and function following bariatric surgery. *J Foot Ankle Res.* [In press].
- Walsh TP, Arnold JB, Gill TK, **Evans AM**, Yaxley A, Hill CL, Shanahan EM. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *Rheum Int*. 2017;37(7):1175-1182.
- Walsh TP, Gill TK, **Evans AM**, Yaxley A, Shanahan EM, Hill CL. Association of Fat Mass and Adipokines With Foot Pain in a Community Cohort. *Arthritis Care Res (Hoboken)*. 2016;68(4):526-533.

Dr Angela Evans

Dr Alison Yaxley

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, Arnold JB, Evans AM, **Yaxley A**, Damarell RA, Shanahan EM. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. [In press].
- Walsh TP, Quinn SJ, Evans AM, **Yaxley A**, Chisholm JA, Kow L, Shanahan EM. Fat mass, but not fat-free mass, predicts increased foot pain with morbid obesity, independent of bariatric surgery. *Surg Obes Relat Dis*. [In press].
- Walsh TP, Gill TK, Evans AM, **Yaxley A**, Chisholm JA, Kow L, Arnold JB, Shanahan EM. Changes in foot pain, structure and function following bariatric surgery. *J Foot Ankle Res.* [In press].
- Walsh TP, Arnold JB, Gill TK, Evans AM, **Yaxley A**, Hill CL, Shanahan EM. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *Rheum Int*. 2017;37(7):1175-1182.
- Walsh TP, Gill TK, Evans AM, **Yaxley A**, Shanahan EM, Hill CL. Association of Fat Mass and Adipokines With Foot Pain in a Community Cohort. *Arthritis Care Res (Hoboken)*. 2016;68(4):526-533.

Dr Alison Yaxley

Dr Tiffany Gill

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, **Gill TK**, Evans AM, Yaxley A, Chisholm JA, Kow L, Arnold JB, Shanahan EM. Changes in foot pain, structure and function following bariatric surgery. *J Foot Ankle Res.* [In press].
- Walsh TP, Arnold JB, **Gill TK**, Evans AM, Yaxley A, Hill CL, Shanahan EM. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *Rheum Int*. 2017;37(7):1175-1182.
- Walsh TP, **Gill TK**, Evans AM, Yaxley A, Shanahan EM, Hill CL. Association of Fat Mass and Adipokines With Foot Pain in a Community Cohort. *Arthritis Care Res (Hoboken)*. 2016;68(4):526-533.

Dr Tiffany Gill

Dr John Arnold

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, **Arnold JB**, Evans AM, Yaxley A, Damarell RA, Shanahan EM. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. [In press].
- Walsh TP, Gill TK, Evans AM, Yaxley A, Chisholm JA, Kow L, **Arnold JB**, Shanahan EM. Changes in foot pain, structure and function following bariatric surgery. *J Foot Ankle Res.* [In press].
- Walsh TP, **Arnold JB**, Gill TK, Evans AM, Yaxley A, Hill CL, Shanahan EM. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *Rheum Int*. 2017;37(7):1175-1182.

Dr John Arnold

Professor Catherine Hill

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, Arnold JB, Gill TK, Evans AM, Yaxley A, **Hill CL**, Shanahan EM. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *Rheum Int*. 2017;37(7):1175-1182.
- Walsh TP, Gill TK, Evans AM, Yaxley A, Shanahan EM, **Hill CL**. Association of Fat Mass and Adipokines With Foot Pain in a Community Cohort. *Arthritis Care Res (Hoboken)*. 2016;68(4):526-533.

Professor Catherine Hill

Mr Jacob Chisholm

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, Quinn SJ, Evans AM, Yaxley A, **Chisholm JA**, Kow L, Shanahan EM. Fat mass, but not fat-free mass, predicts increased foot pain with morbid obesity, independent of bariatric surgery. *Surg Obes Relat Dis*. [In press].
- Walsh TP, Gill TK, Evans AM, Yaxley A, **Chisholm JA**, Kow L, Arnold JB, Shanahan EM. Changes in foot pain, structure and function following bariatric surgery. *J Foot Ankle Res.* [In press].

Mr Jacob Chisholm

Associate Professor Lilian Kow

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, Quinn SJ, Evans AM, Yaxley A, Chisholm JA, **Kow L**, Shanahan EM. Fat mass, but not fat-free mass, predicts increased foot pain with morbid obesity, independent of bariatric surgery. *Surg Obes Relat Dis*. [In press].
- Walsh TP, Gill TK, Evans AM, Yaxley A, Chisholm JA, **Kow L**, Arnold JB, Shanahan EM. Changes in foot pain, structure and function following bariatric surgery. *J Foot Ankle Res.* [In press].

Associate Professor Lilian Kow

Dr Paul Butterworth

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, **Butterworth PA**, Urquhart DM, Cicuttini FM, Landorf KB, Wluka AE, Shanahan EM, Menz HB. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. *J Foot Ankle Res*. 2017;10:31.

Dr Paul Butterworth

Dr Donna Urquhart

I have given permission for the work undertaken and published as part of the co-authored publication listed below to be included in the candidate's thesis:

- Walsh TP, Butterworth PA, **Urquhart DM**, Cicuttini FM, Landorf KB, Wluka AE, Shanahan EM, Menz HB. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. *J Foot Ankle Res*. 2017;10:31.

Dr Donna Urquhart

Professor Flavia Cicuttini

I have given permission for the work undertaken and published as part of the co-authored publication listed below to be included in the candidate's thesis:

- Walsh TP, Butterworth PA, Urquhart DM, **Cicuttini FM**, Landorf KB, Wluka AE, Shanahan EM, Menz HB. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. *J Foot Ankle Res*. 2017;10:31.

Professor Flavia Cicuttini

Associate Professor Karl Landorf

I have given permission for the work undertaken and published as part of the co-authored publication listed below to be included in the candidate's thesis:

- Walsh TP, Butterworth PA, Urquhart DM, Cicuttini FM, **Landorf KB**, Wluka AE, Shanahan EM, Menz HB. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. *J Foot Ankle Res*. 2017;10:31.

Associate Professor Karl Landorf

Associate Professor Anita Wluka

I have given permission for the work undertaken and published as part of the co-authored publication listed below to be included in the candidate's thesis:

- Walsh TP, Butterworth PA, Urquhart DM, Cicuttini FM, Landorf KB, **Wluka AE,** Shanahan EM, Menz HB. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. *J Foot Ankle Res*. 2017;10:31.

Associate Professor Anita Wluka

Professor Hylton Menz

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, Butterworth PA, Urquhart DM, Cicuttini FM, Landorf KB, Wluka AE, Shanahan EM, **Menz HB**. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. *J Foot Ankle Res*. 2017;10:31.

Professor Hylton Menz

Dr Stephen Quinn

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, **Quinn SJ**, Evans AM, Yaxley A, Chisholm JA, Kow L, Shanahan EM. Fat mass, but not fat-free mass, predicts increased foot pain with morbid obesity, independent of bariatric surgery. *Surg Obes Relat Dis*. [In press].

Dr Stephen Quinn

Ms Raechel Damarell

I have given permission for the work undertaken and published as part of co-authored publications listed below to be included in the candidate's thesis:

- Walsh TP, Arnold JB, Evans AM, Yaxley A, **Damarell RA**, Shanahan EM. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. [In press].

Ms Raechel Damarell

Appendix E Summary notes on primary author contribution

Proposal development

The candidate was responsible for the development of project proposals and the methodologies undertaken for the studies in this thesis. Professor E Michael Shanahan, Dr Angela Evans and Dr Alison Yaxley provided supervision and guidance throughout.

Ethics approval

Ethics applications for chapters 4, 5 and 7 were written and submitted by the candidate. For the purpose of the longitudinal plantar pressure study (chapter 6), the candidate was responsible for writing and submitting an ethics amendment to collect follow-up data.

Literature review

The candidate conducted the systematic review for chapter 2 and all relevant reviews of the literature for the other studies in this thesis.

Data collection

The candidate collected all clinical and questionnaire data for chapters 4, 5 and 7 and he collected follow-up data for chapter 6. The APERF research grant funding contributed to the cost of a DXA technician to measure body composition for chapter 5. The Arthritis Australia grant funding contributed to participant honorariums and the adipokine analysis of blood samples for chapter 5.

Data analysis

Statisticians were consulted during the development stage of chapters 4, 5 and 7 to ensure studies were appropriately powered, and they provided advice regarding the appropriateness of statistical tests used by the candidate. A statistical consultant at Flinders University assisted the candidate perform the meta-analysis for chapter 2.

Preparation and writing of manuscripts for submission

The candidate was the primary author on all published manuscripts. The candidate prepared the first draft for all publications, following comments from other co-authors, the candidate finalised and submitted all manuscripts for publication.

Appendix F Publications (print copy)

Walsh TP, Butterworth PA, Urquhart DM, Cicuttini FM, Landorf KB, Wluka AE, Shanahan EM, Menz HB. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. *J Foot Ankle Res*. 2017;10:31

Walsh TP, Arnold JB, Evans AM, Yaxley A, Hill CL, Shanahan EM. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat mass index and depression. *Rheum Int*. 2017;37(7):1175-1182.

Walsh TP, Gill TK, Evans AM, Yaxley A, Shanahan EM, Hill CL. Association of Fat Mass and Adipokines With Foot Pain in a Community Cohort. *Arthritis Care Res (Hoboken)*. 2016;68(4):526-533.

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

This page has been removed due to copyright restrictions

R

Reference list

1. Jiang L, Xie X, Wang Y, Wang Y, Wang Y, Lu Y, et al. Body mass index and hand osteoarthritis susceptibility: an updated meta-analysis. Int J Rheum Dis. 2016;19:1244–54.

2. Scott A, Zwerver J, Grewal N, de Sa A, Alktebi T, Granville DJ, et al. Lipids, adiposity and tendinopathy: is there a mechanistic link? Critical review. Br J Sports Med. 2014;49:984-8

3. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons - a scoping review. Obes Rev. 2014;15:578–86.

4. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord. 2008;9:116.

5. Gill TK, Shanahan EM, Allison D, Alcorn D, Hill CL. Prevalence of abnormalities on shoulder MRI in symptomatic and asymptomatic older adults. Int J Rheum Dis. 2014;17:863–71.

6. Vellucci R. Heterogeneity of chronic pain. Clin Drug Investig. 2012;32 Suppl 1:3–10.

7. Tashani OA, Astita R, Sharp D, Johnson MI. Body mass index and distribution of body fat can influence sensory detection and pain sensitivity. Eur J Pain. 2017;21:1186-96.

8. Windham BG, Lirette ST, Fornage M, Benjamin EJ, Parker KG, Turner ST, et al. Associations of Brain Structure With Adiposity and Changes in Adiposity in a Middle-Aged and Older Biracial Population. J Gerontol A Biol Sci Med Sci. 2017;72:825–31.

9. Ridola CG, Cappello F, Marcianò V, Francavilla C, Montalbano A, Farina-Lipari E, et al. The synovial joints of the human foot. Ital J Anat Embryol. 2007;112:61–80.

10. Perry J. Gait Analysis: Normal and Pathological Function, McGraw-Hill, New York, USA; 1992.

11. Kirby KA. Longitudinal arch load-sharing system of the foot. Rev Esp Podol. 2017;28:e18–e26.

12. Symeonidis PD, Iselin LD, Simmons N, Fowler S, Dracopoulos G, Stavrou P. Prevalence of interdigital nerve enlargements in an asymptomatic population. Foot Ankle Int. 2012;33:543–7.

13. Gregg J, Silberstein M, Schneider T, Marks P. Sonographic and MRI evaluation of the plantar plate: a prospective study. Eur Radiol 2006;16:2661–9.

14. Menz HB, Roddy E, Thomas E, Croft PR. Impact of hallux valgus severity on general and foot-specific health-related quality of life. Arthritis Care Res (Hoboken). 2011;63:396–404.

15. Awale A, Dufour AB, Katz P, Menz HB, Hannan MT. Link Between Foot Pain Severity and Prevalence of Depressive Symptoms. Arthritis Care Res (Hoboken). 2016;68:871–6.

16. Irving DB, Cook JL, Young MA, Menz HB. Impact of chronic plantar heel pain on health-related quality of life. J Am Podiatr Med Assoc. 2008;98:283–9.

17. Menz HB, Morris ME, Lord SR. Foot and ankle risk factors for falls in older people: a prospective study. J Gerontol A Biol Sci Med Sci. 2006;61:866–70.

18. Awale A, Hagedorn TJ, Dufour AB, Menz HB, Casey VA, Hannan MT. Foot Function, Foot Pain, and Falls in Older Adults: The Framingham Foot Study. Gerontology. 2017;63:318–24.

19. Roddy E, Thomas MJ, Marshall M, Rathod T, Myers H, Menz HB, et al. The population

prevalence of symptomatic radiographic foot osteoarthritis in community-dwelling older adults: cross-sectional findings from the clinical assessment study of the foot. Ann Rheum Dis. 2015;74:156–63.

20. Glazebrook M, Daniels T, Younger A, Foote CJ, Penner M, Wing K, et al. Comparison of health-related quality of life between patients with end-stage ankle and hip arthrosis. J Bone Joint Surg Am. 2008;90:499–505.

21. Thomas MJ, Roddy E, Zhang W, Menz HB, Hannan MT, Peat GM. The population prevalence of foot and ankle pain in middle and old age: a systematic review. Pain. 2011;152:2870–80.

22. Australian Institute of Health and Welfare 2017. A picture of overweight and obesity in Australia 2017. Cat. no.PHE 216. Canberra: AIHW

23. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:766–81.

24. Nuttall FQ. Body Mass Index: Obesity, BMI, and Health: A Critical Review. Nutr Today. 2015;50:117–28.

25. Roth J, Qiang X, Marbán SL, Redelt H, Lowell BC. The Obesity Pandemic: Where Have We Been and Where Are We Going? Obes Res. 2004;12:88S–101S.

26. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88.

27. Specchia ML, Veneziano MA, Cadeddu C, Ferriero AM, Mancuso A, Ianuale C, et al. Economic impact of adult obesity on health systems: a systematic review. Eur J Public Health. 2015;25:255–62.

28. Tremmel M, Gerdtham U-G, Nilsson PM, Saha S. Economic Burden of Obesity: A Systematic Literature Review. Int J Environ Res Public Health. 2017;14:E435.

29. World Health Organisation. Mean Body Mass Index (kg/m2), ages 18+, 2016 (age standardized estimate) Female http://gamapserver.who.int/mapLibrary/Files/Maps/Global_BMI_2016_Female.png [accessed 26th March 2018]

30. World Health Organisation. Mean Body Mass Index (kg/m2), ages 18+, 2016 (age standardized estimate) Male http://gamapserver.who.int/mapLibrary/Files/Maps/Global_BMI_2016_Male.png [accessed 26th March 2018]

31. Rothman KJ. BMI-related errors in the measurement of obesity. Int J Obes (Lond). 2008;32 Suppl 3:S56–9.

32. Thomas D, Apovian C. Macrophage functions in lean and obese adipose tissue. Metabolism. 2017;72:120–43.

33. Pasco JA, Nicholson GC, Brennan SL, Kotowicz MA. Prevalence of obesity and the relationship between the body mass index and body fat: cross-sectional, population-based data. PLoS One. 2012;7:e29580.

34. Butterworth PA, Urquhart DM, Cicuttini FM, Menz HB, Strauss BJ, Proietto J, et al. Fat mass is a predictor of incident foot pain. Obesity (Silver Spring). 2013;21:E495–9.

35. Urquhart DM, Berry P, Wluka AE, Strauss BJ, Wang Y, Proietto J, et al. 2011 Young Investigator Award winner: Increased fat mass is associated with high levels of low back pain intensity and disability. Spine (Phila Pa 1976). 2011;36:1320–5.

36. Mellis MG, Oldroyd B, Hind K. In vivo precision of the GE Lunar iDXA for the measurement of visceral adipose tissue in adults: the influence of body mass index. Eur J Clin Nutr. 2014;68:1365–7.

37. Guo SS, Zeller C, Chumlea WC, Siervogel RM. Aging, body composition, and lifestyle: the Fels Longitudinal Study. Am J Clin Nutr. 1999;70:405–11.

38. Gray DS, Bray GA, Bauer M, Kaplan K, Gemayel N, Wood R, et al. Skinfold thickness measurements in obese subjects. Am J Clin Nutr. 1990;51:571–7.

39. Yap MD, Deurenberg P. Bioelectrical impedance: from theories to applications. Malays J Nutr. 2001;7:67–74.

40. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol. 2005;115:911–9.

41. Kershaw EE, Flier JS. Adipose Tissue as an Endocrine Organ. J Clin Endocrinol Metab. 2004;89:2548–56.

42. Castro AM, Macedo-de la Concha, LE, Pantoja-Meléndez CA. Low-grade inflammation and its relation to obesity and chronic degenerative diseases. Rev Med Hosp Gen Méx. 2017;80:101-5.

43. Okosun IS, Seale JP, Lyn R. Commingling effect of gynoid and android fat patterns on cardiometabolic dysregulation in normal weight American adults. Nutr Diabetes. 2015;5:e155.

44. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues - the biology of pear shape. Biol Sex Differ. 2012;3:13.

45. Marliss E. Obesity. http://mmiweb.mmi.mcgill.ca/Dev/Unit4/Marliss/marobe.htm [accessed 26th March 2018]

46. Chau YY, Bandiera R, Serrels A, Martínez-Estrada OM, Qing W, Lee M, et al. Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source. Nat Cell Biol. 2014;16:367–75.

47. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev. 2010;11:11–8.

48. Seidell JC, Pérusse L, Després JP, Bouchard C. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. Am J Clin Nutr. 2001;74:315–21.

49. de Boer TN, van Spil WE, Huisman AM, Polak AA, Bijlsma JW, Lafeber FP, et al. Serum adipokines in osteoarthritis; comparison with controls and relationship with local parameters of synovial inflammation and cartilage damage. Osteoarthritis Cartilage. 2012;20:846–53.

50. Yusuf E, Ioan-Facsinay A, Bijsterbosch J, Klein-Wieringa I, Kwekkeboom J, Slagboom PE, et al. Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. Ann Rheum Dis. 2011;70:1282–4.

51. Thomas T. Leptin: a potential mediator for protective effects of fat mass on bone tissue. Joint Bone Spine. 2003;70:18–21.

52. Minocci A, Savia G, Lucantoni R, Berselli ME, Tagliaferri M, Calò G, et al. Leptin plasma concentrations are dependent on body fat distribution in obese patients. Int J Obes Relat Metab Disord. 2000;24:1139–44.

53. Figenschau Y, Knutsen G, Shahazeydi S, Johansen O, Sveinbjörnsson B. Human articular chondrocytes express functional leptin receptors. Biochem Biophys Res Commun. 2001;287:190–7.

54. Yasukawa H, Sasaki A, Yoshimura A. Negative regulation of cytokine signaling pathways. Annu Rev Immunol. 2000;18:143–64.

55. Rechardt M, Viikari-Juntura E, Shiri R. Adipokines as predictors of recovery from upper extremity soft tissue disorders. Rheumatology (Oxford). 2014;53:2238–42.

56. Younger J, Kapphahn K, Brennan K, Sullivan SD, Stefanick ML. Association of Leptin with Body Pain in Women. J Womens Health (Larchmt). 2016;25:752–60.

57. Fowler-Brown A, Kim DH, Shi L, Marcantonio E, Wee CC, Shmerling RH, et al. The mediating effect of leptin on the relationship between body weight and knee osteoarthritis in older adults. Arthritis Rheumatol. 2015;67:169–75.

58. De Rosa A, Monaco ML, Capasso M, Forestieri P, Pilone V, Nardelli C, et al. Adiponectin oligomers as potential indicators of adipose tissue improvement in obese subjects. Eur J Endocrinol. 2013;169:37–43.

59. Wang Q, Cai J, Wang J, Xiong C, Yan L, Zhang Z, et al. Down-regulation of adiponectin receptors in osteoarthritic chondrocytes. Cell Biochem Biophys. 2014;70:491–7.

60. Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human

resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. Biochem Biophys Res Commun. 2005;334:1092–101.

61. van Spil WE, Welsing PMJ, Kloppenburg M, Bierma-Zeinstra SM, Bijlsma JW, Mastbergen SC, et al. Cross-sectional and predictive associations between plasma adipokines and radiographic signs of early-stage knee osteoarthritis: data from CHECK. Osteoarthritis Cartilage. 2012;20:1278–85.

62. Aronson D, Bartha P, Zinder O, Kerner A, Markiewicz W, Avizohar O, et al. Obesity is the major determinant of elevated C-reactive protein in subjects with the metabolic syndrome. Int J Obes Relat Metab Disord. 2004;28:674–9.

63. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. Nat Rev Endocrinol. 2017;13:633–43.

64. Teng KT, Chang CY, Chang LF, Nesaretnam K. Modulation of obesity-induced inflammation by dietary fats: mechanisms and clinical evidence. Nutr J. 2014;13:12.

65. Parkitny L, McAuley JH, Di Pietro F, Stanton TR, O'Connell NE, Marinus J, et al. Inflammation in complex regional pain syndrome: a systematic review and meta-analysis. Neurology. 2013;80:106–17.

66. Shafer DM, Assael L, White LB, Rossomando EF. Tumor necrosis factor-alpha as a biochemical marker of pain and outcome in temporomandibular joints with internal derangements. J. Oral Maxillofac Surg. 1994;52:786–91; discussion791–2.

67. Lasselin J, Kemani MK, Kanstrup M, Olsson GL, Axelsson J, Andreasson A, et al. Low-grade inflammation may moderate the effect of behavioral treatment for chronic pain in adults. J Behav Med. 2016;39:916–24.

68. Wang H, Ahrens C, Rief W, Gantz S, Schiltenwolf M, Richter W. Influence of depression symptoms on serum tumor necrosis factor-α of patients with chronic low back pain. Arthritis Res Ther. 2010;12:R186.

69. Carvalho AF, Rocha DQ, McIntyre RS, Mesquita LM, Köhler CA, Hyphantis TN, et al. Adipokines as emerging depression biomarkers: a systematic review and meta-analysis. J Psychiatr Res. 2014;59:28–37.

70. Pan A, Sun Q, Czernichow S, Kivimaki M, Okereke OI, Lucas M, et al. Bidirectional association between depression and obesity in middle-aged and older women. Int J Obes (Lond). 2012;36:595–602.

71. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry. 2010;67:220–9.

72. Kroenke K, Wu J, Bair MJ, Krebs EE, Damush TM, Tu W. Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. J Pain. 2011;12:964–73.

73. Cameron AJ, Magliano DJ, Dunstan DW, Zimmet PZ, Hesketh K, Peeters A, et al. A bi-directional relationship between obesity and health-related quality of life: evidence from the longitudinal AusDiab study. Int J Obes (Lond). 2012;36:295–303.

74. Raison CL, Miller AH. Is depression an inflammatory disorder? Curr Psychiatry Rep. 2011;13:467–75.

75. Sullivan MJ, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychological Assessment. 1995;7:524–32.

76. Burns LC, Ritvo SE, Ferguson MK, Clarke H, Seltzer Z, Katz J. Pain catastrophizing as a risk factor for chronic pain after total knee arthroplasty: a systematic review. J Pain Res. 2015;8:21–32.

77. Bond DS, Buse DC, Lipton RB, Thomas JG, Rathier L, Roth J, et al. Clinical Pain Catastrophizing in Women With Migraine and Obesity. Headache. 2015;55:923–33.

78. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. J Behav Med. 2007;30:77–94.

79. Somers TJ, Keefe FJ, Carson JW, Pells JJ, Lacaille L. Pain catastrophizing in borderline morbidly obese and morbidly obese individuals with osteoarthritic knee pain. Pain Res Manag. 2008;13:401–6.

80. Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain. 2013;14:438–45.

81. Imamura M, Imamura ST, Kaziyama HH, Targino RA, Hsing WT, de Souza LP, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. Arthritis Rheum. 2008;59:1424–31.

82. Hozumi J, Sumitani M, Matsubayashi Y, Abe H, Oshima Y, Chikuda H, et al. Relationship between Neuropathic Pain and Obesity. Pain Res Manag. 2016;2016:2487924.

83. Buckwalter JA, Anderson DD, Brown TD, Tochigi Y, Martin JA. The Roles of Mechanical Stresses in the Pathogenesis of Osteoarthritis: Implications for Treatment of

Joint Injuries. Cartilage. 2013;4:286–94.

84. Galloway MT, Lalley AL, Shearn JT. The role of mechanical loading in tendon development, maintenance, injury, and repair. J Bone Joint Surg Am. 2013;95:1620–8.

85. Felson DT. Osteoarthritis as a disease of mechanics. Osteoarthritis Cartilage. 2013;21:10–5.

86. Butterworth PA, Landorf KB, Smith SE, Menz HB. The association between body mass index and musculoskeletal foot disorders: a systematic review. Obes Rev. 2012;13:630–42.

87. Gay A, Culliford D, Leyland K, Arden NK, Bowen CJ. Associations between body mass index and foot joint pain in middle-aged and older women: a longitudinal population-based cohort study. Arthritis Care Res (Hoboken). 2014;66:1873–9.

88. Irving DB, Cook JL, Young MA, Menz HB. Obesity and pronated foot type may increase the risk of chronic plantar heel pain: a matched case-control study. BMC Musculoskelet Disord. 2007;8:41.

89. Messier SP, Ettinger WH, Doyle TE, Morgan T, James MK, OToole ML, et al. Obesity: Effects On Gait In An Osteoarthritic Population. J Appl Biomech.1996;12:161–72.

90. Villarrasa-Sapiña I, Serra-Añó P, Pardo-Ibáñez A, Gonzalez LM, García-Massó X. Relationship between body composition and vertical ground reaction forces in obese children when walking. Clin Biomech (Bristol, Avon). 2017;41:77–81.

91. McGoey BV, Deitel M, Saplys RJ, Kliman ME. Effect of weight loss on musculoskeletal pain in the morbidly obese. J Bone Joint Surg Br. 1990;72:322–3.

92. Hooper MM, Stellato TA, Hallowell PT, Seitz BA, Moskowitz RW. Musculoskeletal

findings in obese subjects before and after weight loss following bariatric surgery. Int J Obes (Lond). 2007;31:114–20.

93. Menz HB, Dufour AB, Riskowski JL, Hillstrom HJ, Hannan MT. Association of planus foot posture and pronated foot function with foot pain: the Framingham foot study. Arthritis Care Res (Hoboken). 2013;65:1991–9.

94. Menz HB, Dufour AB, Riskowski JL, Hillstrom HJ, Hannan MT. Foot posture, foot function and low back pain: the Framingham Foot Study. Rheumatology (Oxford). 2013;52:2275–82.

95. Menz HB, Dufour AB, Katz P, Hannan MT. Foot Pain and Pronated Foot Type Are Associated with Self-Reported Mobility Limitations in Older Adults: The Framingham Foot Study. Gerontology. 2016;62:289–95.

96. Horsak B, Schwab C, Clemens C, Baca A, Greber-Platzer S, Kreissl A, et al. Is the reliability of 3D kinematics of young obese participants dependent on the hip joint center localization method used? Gait Posture. 2018;59:65–70.

97. Fernando ME, Crowther RG, Lazzarini PA, Yogakanthi S, Sangla KS, Buttner P, et al. Plantar pressures are elevated in people with longstanding diabetes-related foot ulcers during follow-up. PLoS One. 2017;12:e0181916.

98. Butterworth PA, Urquhart DM, Landorf KB, Wluka AE, Cicuttini FM, Menz HB. Foot posture, range of motion and plantar pressure characteristics in obese and non-obese individuals. Gait Posture. 2015;41:465–9.

99. Tekscan. Pressure mapping, force measurement & tactile sensors. https://www.tekscan.com/blog/medical/tekscan-medical-biomechanics-evolutionary-partnership
[accessed 26th March 2018]

100. Birtane M, Tuna H. The evaluation of plantar pressure distribution in obese and non-obese adults. Clin Biomech (Bristol, Avon). 2004;19:1055–9.

101. Fabris SM, Valezi AC, de Souza SAF, Faintuch J, Cecconello I, Junior MP. Computerized baropodometry in obese patients. Obes Surg. 2006;16:1574–8.

102. van Leeuwen KDB, Rogers J, Winzenberg T, van Middelkoop M. Higher body mass index is associated with plantar fasciopathy/"plantar fasciitis": systematic review and meta-analysis of various clinical and imaging risk factors. Br J Sports Med. 2016;50:972-81.

103. Sullivan J, Burns J, Adams R, Pappas E, Crosbie J. Plantar heel pain and foot loading during normal walking. Gait Posture. 2015;41:688–93.

104. Evans AM, Copper AW, Scharfbillig RW, Scutter SD, Williams MT. Reliability of the foot posture index and traditional measures of foot position. J Am Podiatr Med Assoc. 2003;93:203–13.

105. Jarvis HL, Nester CJ, Bowden PD, Jones RK. Challenging the foundations of the clinical model of foot function: further evidence that the root model assessments fail to appropriately classify foot function. J Foot Ankle Res. 2017;10:7.

106. Jarvis HL, Nester CJ, Jones RK, Williams A, Bowden PD. Inter-assessor reliability of practice based biomechanical assessment of the foot and ankle. J Foot Ankle Res. 2012;5:14.

107. Buldt AK, Murley GS, Levinger P, Menz HB, Nester CJ, Landorf KB. Are clinical measures of foot posture and mobility associated with foot kinematics when walking? J Foot Ankle Res. 2015;8:63.

108. Menz HB, Munteanu SE. Validity of 3 clinical techniques for the measurement of static foot posture in older people. J Orthop Sports Phys Ther. 2005;35:479–86.

109. Murley GS, Menz HB, Landorf KB. A protocol for classifying normal- and flat-arched foot posture for research studies using clinical and radiographic measurements. J Foot Ankle Res. 2009;2:22.

110. Storheim K, Zwart JA. Musculoskeletal disorders and the Global Burden of Disease study. Ann Rheum Dis. 2014;73:949–50.

111. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2197–223.

112. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000;85:317–32.

113. Ferguson S, Al-Rehany L, Tang C, Gougeon L, Warwick K, Madill J. Self-reported causes of weight gain: among prebariatric surgery patients. Can J Diet Pract Res. 2013;74:189–92.

114. Thorp LE, Sumner DR, Wimmer MA, Block JA. Relationship between pain and medial knee joint loading in mild radiographic knee osteoarthritis. Arthritis Rheum. 2007;57:1254–60.

115. Hurwitz DE, Ryals AR, Block JA, Sharma L, Schnitzer TJ, Andriacchi TP. Knee pain and joint loading in subjects with osteoarthritis of the knee. J Orthop Res. 2000;18:572–9.

116. Coenen P, Kingma I, Boot CRL, Bongers PM, van Dieën JH. Cumulative mechanical low-back load at work is a determinant of low-back pain. Occup Environ Med. 2014;71:332–7.

117. Bakker EW, Verhagen AP, Lucas C, Koning HJ, Koes BW. Spinal mechanical load: a predictor of persistent low back pain? A prospective cohort study. Eur Spine J. 2007;16:933–41.

118. Romero-Corral A, Somers VK, Sierra-Johnson J, Thomas RJ, Collazo-Clavell ML, Korinek J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. Int J Obes (Lond). 2008;32:959–66.

119. Zhou ZY, Liu YK, Chen HL, Liu F. Body mass index and knee osteoarthritis risk: a dose-response meta-analysis. Obesity (Silver Spring). 2014;22:2180–5.

120. Walsh TP, Gill TK, Evans AM, Yaxley A, Shanahan EM, Hill CL. Association of Fat Mass and Adipokines With Foot Pain in a Community Cohort. Arthritis Care Res (Hoboken). 2016;68:526–33.

121. Brady SR, Mamuaya BB, Cicuttini F, Wluka AE, Wang Y, Hussain SM, et al. Body Composition Is Associated With Multisite Lower Body Musculoskeletal Pain in a Community-Based Study. J Pain. 2015;16:700-6.

122. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr. 2006;83:461S–465S.

123. Gold MS, Flake NM. Inflammation-mediated hyperexcitability of sensory neurons.

Neurosignals. 2005;14:147–57.

124. Stannus O, Jones G, Cicuttini F, Parameswaran V, Quinn S, Burgess J, et al. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage. 2010;18:1441–7.

125. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009. 6:e1000097.

126. Genaidy AM, Lemasters GK, Lockey J, Succop P, Deddens J, Sobeih T, et al. An epidemiological appraisal instrument – a tool for evaluation of epidemiological studies. Ergonomics. 2007;50:920–60.

127. Crowe M, Sheppard L. A review of critical appraisal tools show they lack rigor: Alternative tool structure is proposed. J Clin Epidemiol. 2011;64:79–89.

128. Nix S, Smith M, Vicenzino B. Prevalence of hallux valgus in the general population: a systematic review and meta-analysis. J Foot Ankle Res. 2010;3:21.

129. Uden H, Scharfbillig R, Causby R. The typically developing paediatric foot: how flat should it be? A systematic review. J Foot Ankle Res. 2017;10:37.

130. Cohen J. A power primer. Psychol Bull. 1992;112:155-9

131. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990;33:160–72.

132. Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. Psychol

Bull. 1995;117:167-178.

133. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.

134. Pan F, Laslett L, Blizzard L, Cicuttini F, Winzenberg T, Ding C, et al. Associations Between Fat Mass and Multisite Pain: A Five-Year Longitudinal Study. Arthritis Care Res (Hoboken). 2017;69:509–16.

135. Yoo JJ, Cho NH, Lim SH, Kim HA. Relationships between body mass index, fat mass, muscle mass, and musculoskeletal pain in community residents. Arthritis Rheumatol. 2014;66:3511–20.

136. Iizuka Y, Iizuka H, Mieda T, Tajika T, Yamamoto A, Ohsawa T, et al. Association between neck and shoulder pain, back pain, low back pain and body composition parameters among the Japanese general population. BMC Musculoskelet Disord. 2015;16:333.

137. Chou L, Brady SR, Urquhart DM, Teichtahl AJ, Cicuttini FM, Pasco JA, et al. The Association Between Obesity and Low Back Pain and Disability Is Affected by Mood Disorders: A Population-Based, Cross-Sectional Study of Men. Medicine (Baltimore). 2016;95:e3367.

138. Scott D, Blizzard L, Fell J, Jones G. Prospective study of self-reported pain, radiographic osteoarthritis, sarcopenia progression, and falls risk in community-dwelling older adults. Arthritis Care Res (Hoboken). 2012;64:30–7.

139. Tanamas SK, Wluka AE, Berry P, Menz HB, Strauss BJ, Davies-Tuck M, et al. Relationship between obesity and foot pain and its association with fat mass, fat

distribution, and muscle mass. Arthritis Care Res (Hoboken). 2012;64:262–8.

140. Walsh TP, Arnold JB, Gill TK, Evans AM, Yaxley A, Hill CL, et al. Foot pain severity is associated with the ratio of visceral to subcutaneous fat mass, fat-mass index and depression in women. Rheumatol Int. 2017;37:1175-1182.

141. Butterworth PA, Menz HB, Urquhart DM, Cicuttini FM, Landorf KB, Pasco JA, et al. Fat Mass Is Associated with Foot Pain in Men: The Geelong Osteoporosis Study. J Rheumatol. 2016;43:138–43.

142. Sakai Y, Matsui H, Ito S, Hida T, Ito K, Koshimizu H, et al. Sarcopenia in elderly patients with chronic low back pain. Osteoporos Sarcopenia. 2017;3:195–200.

143. Jordani, PC, Campi LB, Circeli GZ, Visscher CM, Bigal ME, Gonçalves DA. Obesity as a risk factor for temporomandibular disorders. J Oral Rehabil. 2017;44:1–8.

144. Yalcinkaya H, Ucok K, Ulasli AM, Coban NF, Aydin S, Kaya I, et al. Do male and female patients with chronic neck pain really have different health-related physical fitness, depression, anxiety and quality of life parameters? Int J Rheum Dis. 2017;20:1079–87.

145. Celan D, Turk Z. The impact of anthropometric parameters on the incidence of low back pain. Coll Antropol. 2005;29:101–5.

146. Dario AB, Ferreira ML, Refshauge K, Sánchez-Romera JF, Luque-Suarez A, Hopper JL, et al. Are obesity and body fat distribution associated with low back pain in women? A population-based study of 1128 Spanish twins. Eur Spine J. 2016;25:1188–95.

147. Toda Y, Segal N, Toda T, Morimoto T, Ogawa R. Lean body mass and body fat distribution in participants with chronic low back pain. Arch Intern Med. 2000;160:3265–9.

148. Ozer Kaya D, Düzgün I, Baltaci G. Differences in body fat mass, muscular

endurance, coordination and proprioception in woman with and without knee pain: a cross-sectional study. Acta Orthop Traumatol Turc. 2014;48:43–9.

149. Sabeti V, Khoshraftar Yazdi N, Bizheh N. The relationship between Shin Splints with anthropometric characteristics and some indicators of body composition. J Sports Med Phys Fitness. 2014;[Epub ahead of print].

150. Hodselmans AP, Dijkstra PU, Geertzen JHB, van der Schans CP. Nonspecific chronic low back pain patients are deconditioned and have an increased body fat percentage. Int J Rehabil Res. 2010;33:268–70.

151. Spyropoulos P, Chronopoulos E, Papathanasiou G, Georgoudis G, Koutis H, Kompoti A. Chronic low back pain and function of Greek office workers. J Back Musculoskelet Rehabil. 2008;21:129–35.

152. Sutbeyaz ST, Sezer N, Koseoglu BF, Ibrahimoglu F, Tekin D. Influence of knee osteoarthritis on exercise capacity and quality of life in obese adults. Obesity (Silver Spring). 2007;15:2071–6.

153. Kodesh E, Shargal E, Kislev-Cohen R, Funk S, Dorfman L, Samuelly G, et al. Examination of the Effectiveness of Predictors for Musculoskeletal Injuries in Female Soldiers. J Sports Sci Med. 2015;14:515–21.

154. Jin X, Ding C, Wang X, Antony B, Laslett LL, Blizzard L, et al. Longitudinal associations between adiposity and change in knee pain: Tasmanian older adult cohort study. Semin Arthritis Rheum. 2016;45:564–9.

155. Hussain SM, Urquhart DM, Wang Y, Shaw JE, Magliano DJ, Wluka AE, et al. Fat mass and fat distribution are associated with low back pain intensity and disability: results

from a cohort study. Arthritis Res Ther. 2017;19:26.

156. Dario AB, Loureiro Ferreira M, Refshauge K, Luque-Suarez A, Ordoñana JR, Ferreira PH. Obesity does not increase the risk of chronic low back pain when genetics are considered. A prospective study of Spanish adult twins. Spine J. 2017;17:282–90.

157. Hashimoto Y, Matsudaira K, Sawada SS, Gando Y, Kawakami R, Kinugawa C, et al. Obesity and low back pain: a retrospective cohort study of Japanese males. J Phys Ther Sci. 2017;29:978–83.

158. Wright LJ, Schur E, Noonan C, Ahumada S, Buchwald D, Afari N. Chronic pain, overweight, and obesity: findings from a community-based twin registry. J Pain. 2010;11:628–35.

159. Shimizu H, Shimomura Y, Hayashi R, Ohtani K, Sato N, Futawatari T, et al. Serum leptin concentration is associated with total body fat mass, but not abdominal fat distribution. Int. J Obes Relat Metab Disord. 1997;21:536–41.

160. Zhang P, Zhong ZH, Yu HT, Liu B. Significance of increased leptin expression in osteoarthritis patients. PLoS One. 2015;10:e0123224.

161. Lübbeke A, Finckh A, Puskas GJ, Suva D, Lädermann A, Bas S, et al. Do synovial leptin levels correlate with pain in end stage arthritis? Int Orthop. 2013;37:2071–9.

162. Liu ZJ, Bian J, Liu J, Endoh A. Obesity reduced the gene expressions of leptin receptors in hypothalamus and liver. Horm Metab Res. 2007;39:489–94.

163. Ding C, Parameswaran V, Cicuttini F, Burgess J, Zhai G, Quinn S, et al. Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. Ann Rheum Dis. 2008;67:1256–61.

164. Festa A, D'Agostino R, Williams K, Karter AJ, Mayer-Davis EJ, Tracy RP, et al. The relation of body fat mass and distribution to markers of chronic inflammation. Int J Obes Relat Metab Disord. 2001;25:1407–15.

165. Sommer C, Kress M. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neurosci Lett. 2004;361:184–7.

166. Appleton CT, Hawker GA, Hill CL, Pope JE. Editorial: “Weighing in” on the Framingham Osteoarthritis Study: Measuring Biomechanical and Metabolic Contributions to Osteoarthritis. Arthritis Rheumatol. 2017;69:1127–30.

167. Livshits G, Zhai G, Hart DJ, Kato BS, Wang H, Williams FM, et al. Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: The Chingford Study. Arthritis Rheum. 2009;60:2037–45.

168. Gaida JE, Ashe MC, Bass SL, Cook JL. Is adiposity an under-recognized risk factor for tendinopathy? A systematic review. Arthritis Rheum. 2009;61:840–9.

169. Hill CL, Gill TK, Menz HB, Taylor AW. Prevalence and correlates of foot pain in a population-based study: the North West Adelaide health study. J Foot Ankle Res. 2007;1:2.

170. Rolls ET. Understanding the mechanisms of food intake and obesity. Obes Rev. 2007;8 Suppl 1:67–72.

171. Pietiläinen KH, Kaprio J, Borg P, Plasqui G, Yki-Järvinen H, Kujala UM, et al. Physical inactivity and obesity: a vicious circle. Obesity (Silver Spring). 2008;16:409–14.

172. Bergman RN, Stefanovski D, Buchanan TA, Sumner AE, Reynolds JC, Sebring NG,

et al. A Better Index of Body Adiposity. Obesity (Silver Spring). 2011;19:1083–9.

173. Scotece M, Conde J, Gómez R, López V, Lago F, Gómez-Reino JJ, et al. Beyond fat mass: exploring the role of adipokines in rheumatic diseases. ScientificWorldJournal. 2011;11:1932–47.

174. Ackerman IN, Osborne RH. Obesity and increased burden of hip and knee joint disease in Australia: results from a national survey. BMC Musculoskelet Disord. 2012;13:254.

175. Richette P, Poitou C, Garnero P, Vicaut E, Bouillot JL, Lacorte JM, et al. Benefits of massive weight loss on symptoms, systemic inflammation and cartilage turnover in obese patients with knee osteoarthritis. Ann Rheum Dis. 2011;70:139–44.

176. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. BMC Musculoskelet Disord. 2008;9:132.

177. Rechardt M, Shiri R, Lindholm H, Karppinen J, Viikari-Juntura E. Associations of metabolic factors and adipokines with pain in incipient upper extremity soft tissue disorders: a cross-sectional study. BMJ Open. 2013;3:e003036.

178. Samartzis D, Karppinen J, Cheung JPY, Lotz J. Disk degeneration and low back pain: are they fat-related conditions? Global Spine J. 2013;3:133–44.

179. Grant JF, Chittleborough CR, Taylor AW, Dal Grande E, Wilson DH, Phillips PJ, et al. The North West Adelaide Health Study: detailed methods and baseline segmentation of a cohort for selected chronic diseases. Epidemiol Perspect Innov. 2006;3:4.

180. Grant JF, Martin SA, Taylor AW, Wilson DH, Araujo A, Adams RJT, et al. Cohort

profile: The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study. Int J Epidemiol. 2014;43:1040–53.

181. Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, et al. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care. 2013;36:2388–94.

182. Australian Bureau of Statistics. National Health Survey: users' guide. Canberra: ABS; 2003.

183. McCallum J. The SF-36 in an Australian sample: validating a new, generic health status measure. Aust J Public Health. 1995;19:160–6.

184. Gill TK, Broderick D, Avery JC, Dal Grande E, Taylor AW. Self reported overall health status: Implications for intervention strategies. AMJ. 2009;1:44–57.

185. National Heart Foundation. Australian Institute of Health and Welfare. Risk factor prevalence study: Survey no 3. Canberra: NHF; 1989

186. Radloff LS. The CES-D scale a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1:385–401.

187. World Health Organisation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. 2006. Available at: http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf. Accessed April 1, 2015.

188. Hosmer DW, Lemeshow S. Applied Logistic Regression, 2nd ed. New York: J Wiley and Sons; 2000

189. Stannus OP, Jones G, Blizzard L, Cicuttini FM, Ding C. Associations between serum

levels of inflammatory markers and change in knee pain over 5 years in older adults: a prospective cohort study. Ann Rheum Dis. 2013;72:535–40.

190. Magni G, Moreschi C, Rigatti-Luchini S, Merskey H. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. Pain. 1994;56:289–97.

191. Chumlea WC, Guo SS, Kuczmarski RJ, Flegal KM, Johnson CL, Heymsfield SB, et al. Body composition estimates from NHANES III bioelectrical impedance data. Int J Obes Relat Metab Disord. 2002;26:1596–609.

192. Krishnadas R, Cavanagh J. Depression: an inflammatory illness? J Neurol Neurosurg Psychiatr. 2012;83:495–502.

193. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A Meta-Analysis of Cytokines in Major Depression. Biol Psychiatry. 2010;67:446–57.

194. Karsenty G. Convergence between bone and energy homeostases: leptin regulation of bone mass. Cell Metab. 2006;4:341–8.

195. Simopoulou T, Malizos KN, Iliopoulos D, Stefanou N, Papatheodorou L, Ioannou M, et al. Differential expression of leptin and leptin's receptor isoform (Ob-Rb) mRNA between advanced and minimally affected osteoarthritic cartilage; effect on cartilage metabolism. Osteoarthritis Cartilage. 2007;15:872–83.

196. Karvonen-Gutierrez CA, Harlow SD, Mancuso P, Jacobson J, Mendes de Leon CF, Nan B. Association of leptin levels with radiographic knee osteoarthritis among a cohort of midlife women. Arthritis Care Res (Hoboken). 2013;65:936–44.

197. Laurberg TB, Frystyk J, Ellingsen T, Hansen IT, Jørgensen A, Tarp U, et al. Plasma

adiponectin in patients with active, early, and chronic rheumatoid arthritis who are steroid- and disease-modifying antirheumatic drug-naive compared with patients with osteoarthritis and controls. J Rheumatol. 2009;36:1885–91.

198. Gorter KJ, Kuyvenhoven MM, de Melker RA. Nontraumatic foot complaints in older people. A population-based survey of risk factors, mobility, and well-being. J Am Podiatr Med Assoc. 2000;90:397–402.

199. Menz HB, Tiedemann A, Kwan MM, Plumb K, Lord SR. Foot pain in community-dwelling older people: an evaluation of the Manchester Foot Pain and Disability Index. Rheumatology (Oxford). 2006;45:863–7.

200. Roddy E, Muller S, Thomas E. Onset and persistence of disabling foot pain in community-dwelling older adults over a 3-year period: a prospective cohort study. J Gerontol A Biol Sci Med Sci. 2011;66:474–80.

201. Wearing SC, Hennig EM, Byrne NM, Steele JR, Hills AP. Musculoskeletal disorders associated with obesity: a biomechanical perspective. Obes Rev. 2006;7:239–50.

202. Cotchett M, Munteanu SE, Landorf KB. Depression, Anxiety, and Stress in People With and Without Plantar Heel Pain. Foot Ankle Int. 2016;37:816–21.

203. Butterworth PA, Urquhart DM, Cicuttini FM, Menz HB, Strauss BJ, Proietto J, et al. Relationship between mental health and foot pain. Arthritis Care Res (Hoboken). 2014;66:1241–5.

204. Cotchett MP, Whittaker G, Erbas B. Psychological variables associated with foot function and foot pain in patients with plantar heel pain. Clin Rheumatol. 2015;34:957–64.

205. Schutz Y, Kyle UU, Pichard C. Fat-free mass index and fat mass index percentiles in

Caucasians aged 18-98 y. Int J Obes Relat Metab Disord. 2002;26:953–60.

206. Blaak E. Gender differences in fat metabolism. Curr Opin Clin Nutr Metab Care. 2001;4:499.

207. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Després JP. Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. Am J Clin Nutr. 1993;58:463–7.

208. Murabito JM, Massaro JM, Clifford B, Hoffmann U, Fox CS. Depressive symptoms are associated with visceral adiposity in a community-based sample of middle-aged women and men. Obesity (Silver Spring). 2013;21:1713–9.

209. Lee ES, Kim YH, Beck SH, Lee S, Oh SW. Depressive mood and abdominal fat distribution in overweight premenopausal women. Obes Res. 2005;13:320–5.

210. Dantzer R. Depression and inflammation: an intricate relationship. Biol Psychiatry. 2012;71:4–5.

211. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. J Clin Invest. 2003;112:1785-6

212. Capuron L, Lasselin J, Castanon N. Role of Adiposity-Driven Inflammation in Depressive Morbidity. Neuropsychopharmacology. 2017;42:115–28.

213. Garrow AP, Papageorgiou AC, Silman AJ, Thomas E, Jayson MI, Macfarlane GJ. Development and validation of a questionnaire to assess disabling foot pain. Pain. 2000;85:107–13.

214. Kaul S, Rothney MP, Peters DM, Wacker WK. Dual-energy X-ray absorptiometry for

quantification of visceral fat. Obesity (Silver Spring). 2012;20:1313-8.

215. Rothney MP, Martin FP, Xia Y, Beaumont M, Davis C, Ergun D, et al. Precision of GE Lunar iDXA for the measurement of total and regional body composition in nonobese adults. J Clin Densitom. 2012;15:399–404.

216. Weissman MM, Sholomskas D. Assessing depressive symptoms in five psychiatric populations: a validation study. Am J Epidemiol. 1977;106:203-14.

217. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, et al. The development and psychometric validation of the central sensitization inventory. Pain Pract. 2012;12:276–85.

218. Walton DM, Wideman TH, Sullivan MJ. A Rasch analysis of the pain catastrophizing scale supports its use as an interval-level measure. Clin J Pain. 2013;29:499–506.

219. Roddy E, Muller S, Thomas E. Defining disabling foot pain in older adults: further examination of the Manchester Foot Pain and Disability Index. Rheumatology (Oxford). 2009;48:992–6.

220. Gijon-Nogueron G, Ndosi M, Luque-Suarez A, Alcacer-Pitarch B, Munuera PV, Garrow A, et al. Cross-cultural adaptation and validation of the Manchester Foot Pain and Disability Index into Spanish. Qual Life Res. 2014;23:571–9.

221. Freynhagen R, Tölle TR, Gockel U, Baron R. The painDETECT project - far more than a screening tool on neuropathic pain. Curr Med Res Opin. 2016;32:1033–57.

222. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006;22:1911–20.

223. Kaess BM, Pedley A, Massaro JM, Murabito J, Hoffmann U, Fox CS. The ratio of visceral to subcutaneous fat, a metric of body fat distribution, is a unique correlate of cardiometabolic risk. Diabetologia. 2012;55:2622–30.

224. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med. 2003;163:2433–45.

225. Capuron L, Poitou C, Machaux-Tholliez D, Frochot V, Bouillot JL, Basdevant A, et al. Relationship between adiposity, emotional status and eating behaviour in obese women: role of inflammation. Psychol Med. 2011;41:1517–28.

226. Guneli E, Gumustekin M, Ates M. Possible involvement of ghrelin on pain threshold in obesity. Med Hypotheses. 2010;74:452–4.

227. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444:881–7.

228. Dugan SA, Powell LH, Kravitz HM, Everson Rose SA, Karavolos K, Luborsky J. Musculoskeletal pain and menopausal status. Clin J Pain. 2006;22:325–31.

229. Peltonen M, Lindroos AK, Torgerson JS. Musculoskeletal pain in the obese: a comparison with a general population and long-term changes after conventional and surgical obesity treatment. Pain. 2003;104:549–57.

230. Viester L, Verhagen EA, Oude Hengel KM, Koppes LL, van der Beek AJ, Bongers PM. The relation between body mass index and musculoskeletal symptoms in the working population. BMC Musculoskelet Disord. 2013;14:238.

231. Toda Y, Toda T, Takemura S, Wada T, Morimoto T, Ogawa R. Change in body fat, but not body weight or metabolic correlates of obesity, is related to symptomatic relief of

obese patients with knee osteoarthritis after a weight control program. J Rheumatol. 1998;25:2181–6.

232. Butterworth PA, Menz HB, Urquhart DM, Cicuttini FM, Landorf KB, Pasco JA, et al. Fat Mass Is Associated with Foot Pain in Men: The Geelong Osteoporosis Study. J Rheumatol. 2016;43:138-43

233. Visser A, Ioan-Facsinay A, de Mutsert R, Widya RL, Loef M, de Roos A, et al. Adiposity and hand osteoarthritis: the Netherlands Epidemiology of Obesity study. Arthritis Res Ther. 2014;16:R19.

234. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain. 1997;72:95–7.

235. Morley D, Jenkinson C, Doll H, Lavis G, Sharp R, Cooke P, et al. The Manchester-Oxford Foot Questionnaire (MOXFQ): Development and validation of a summary index score. Bone Joint Res. 2013;2:66–9.

236. Dawson J, Boller I, Doll H, Lavis G, Sharp R, Cooke P, et al. Minimally important change was estimated for the Manchester-Oxford Foot Questionnaire after foot/ankle surgery. J Clin Epidemiol. 2014;67:697–705.

237. Walsh TP, Butterworth PA, Urquhart DM, Cicuttini FM, Landorf KB, Wluka AE, et al. Increase in body weight over a two-year period is associated with an increase in midfoot pressure and foot pain. J Foot Ankle Res. 2017;10:31.

238. Downes TJ, Chesterton L, Whittle R, Roddy E, Menz HB, Marshall M, et al. The symptomatic course of foot osteoarthritis phenotypes: an 18-month prospective analysis of community-dwelling older adults. Arthritis Care Res (Hoboken). 2017;[Epub ahead of print]

239. Dawson J, Doll H, Coffey J, Jenkinson C. Responsiveness and minimally important change for the Manchester-Oxford foot questionnaire (MOXFQ) compared with AOFAS and SF-36 assessments following surgery for hallux valgus. Osteoarthritis Cartilage. 2007;15:918–31.

240. Gill TK, Menz HB, Landorf KB, Arnold JB, Taylor AW, Hill CL. Predictors of foot pain in the community: the North West Adelaide health study. J Foot Ankle Res. 2016;9:23.

241. de Aquino LA, Pereira SE, de Souza Silva J, Sobrinho CJ, Ramalho A. Bariatric surgery: impact on body composition after Roux-en-Y gastric bypass. Obes Surg. 2012;22:195–200.

242. Dawes AJ, Maggard-Gibbons M, Maher AR, Booth MJ, Miake-Lye I, Beroes JM, et al. Mental Health Conditions Among Patients Seeking and Undergoing Bariatric Surgery: A Meta-analysis. JAMA. 2016;315:150–63.

243. King WC, Chen J-Y, Belle SH, Courcoulas AP, Dakin GF, Elder KA, et al. Change in Pain and Physical Function Following Bariatric Surgery for Severe Obesity. JAMA. 2016;315:1362–71.

244. Menz HB, Fotoohabadi MR, Munteanu SE, Zammit GV, Gilheany MF. Plantar pressures and relative lesser metatarsal lengths in older people with and without forefoot pain. J Orthop Res. 2013;31:427–33.

245. Mickle KJ, Steele JR. Obese older adults suffer foot pain and foot-related functional limitation. Gait Posture. 2015;42:442–7.

246. Menz HB, Munteanu SE, Zammit GV, Landorf KB. Foot structure and function in older people with radiographic osteoarthritis of the medial midfoot. Osteoarthritis Cartilage.

2010;18:317–22.

247. Giacomozzi C. Appropriateness of plantar pressure measurement devices: a comparative technical assessment. Gait Posture. 2010;32:141–4.

248. Zammit GV, Menz HB, Munteanu SE. Reliability of the TekScan MatScan(R) system for the measurement of plantar forces and pressures during barefoot level walking in healthy adults. J Foot Ankle Res. 2010;3:11.

249. Bryant A, Singer K, Tinley P. Comparison of the reliability of plantar pressure measurements using the two-step and midgait methods of data collection. Foot Ankle Int. 1999;20:646–50.

250. Taylor AJ, Menz HB, Keenan AM. The influence of walking speed on plantar pressure measurements using the two-step gait initiation protocol. Foot (Edinb). 2004;14:49–55.

251. Menz HB, Zammit GV, Munteanu SE. Plantar pressures are higher under callused regions of the foot in older people. Clin Exp Dermatol. 2007;32:375–80.

252. Keijsers NL, Stolwijk NM, Pataky TC. Linear dependence of peak, mean, and pressure–time integral values in plantar pressure images. Gait Posture. 2010;31:140–2.

253. Waaijman R, Bus SA. The interdependency of peak pressure and pressure-time integral in pressure studies on diabetic footwear: no need to report both parameters. Gait Posture. 2012;35:1–5.

254. Stage FK, Carter HC, Nora A. Path Analysis: An Introduction and Analysis of a Decade of Research. J Educ Res. 2004;98:5–13.

255. Vela SA, Lavery LA, Armstrong DG, Anaim AA. The effect of increased weight on peak pressures: implications for obesity and diabetic foot pathology. J Foot Ankle Surg.

1998;37:416–20–discussion 448–9.

256. Pirozzi K, McGuire J, Meyr AJ. Effect of variable body mass on plantar foot pressure and off-loading device efficacy. J Foot Ankle Surg. 2014;53:588–97.

257. Arnold JB, Causby R, Pod GD, Jones S. The impact of increasing body mass on peak and mean plantar pressure in asymptomatic adult subjects during walking. Diabet Foot Ankle. 2010;1.

258. Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight maintenance. Int J Obes (Lond). 2006;30:391–9.

259. Riskowski JL, Hagedorn TJ, Hannan MT. Measures of foot function, foot health, and foot pain: American Academy of Orthopedic Surgeons Lower Limb Outcomes Assessment: Foot and Ankle Module (AAOS-FAM), Bristol Foot Score (BFS), Revised Foot Function Index (FFI-R), Foot Health Status Questionnaire. Arthritis Care Res (Hoboken). 2011;63:S229–39.

260. Cancello R, Clement K. Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue. BJOG. 2006;113:1141–7.

261. Speck RM, Bond DS, Sarwer DB, Farrar JT. A systematic review of musculoskeletal pain among bariatric surgery patients: implications for physical activity and exercise. Surg Obes Relat Dis. 2014;10:161–70.

262. Gill SV, Walsh MK, Pratt JA, Toosizadeh N, Najafi B, Travison TG. Changes in spatiotemporal gait patterns during flat ground walking and obstacle crossing 1 year after bariatric surgery. Surg Obes Relat Dis. 2016;12:1080–5.

263. Menz H. Two feet, or one person? Problems associated with statistical analysis of paired data in foot and ankle medicine. Foot (Edinb). 2004;14:2–5.

264. Munteanu SE, Strawhorn AB, Landorf KB, Bird AR, Murley GS. A weightbearing technique for the measurement of ankle joint dorsiflexion with the knee extended is reliable. J Sci Med Sport. 2009;12:54–9.

265. Menadue C, Raymond J, Kilbreath SL, Refshauge KM, Adams R. Reliability of two goniometric methods of measuring active inversion and eversion range of motion at the ankle. BMC Musculoskelet Disord. 2006;7:60.

266. Lavery LA, Armstrong DG, Boulton AJ: Diabetex Research Group. Ankle Equinus Deformity and Its Relationship to High Plantar Pressure in a Large Population with Diabetes Mellitus. J Am Podiatr Med Assoc. 2002;92:479–82.

267. Burnfield JM, Few CD, Mohamed OS, Perry J. The influence of walking speed and footwear on plantar pressures in older adults. Clin Biomech (Bristol, Avon). 2004;19:78–84.

268. Wandner LD, Scipio CD, Hirsh AT, Torres CA, Robinson ME. The perception of pain in others: how gender, race, and age influence pain expectations. J Pain. 2012;13:220–7.

269. Song J, Kane R, Tango DN, Veur SS, Furmato J, Komaroff E, et al. Effects of weight loss on foot structure and function in obese adults: a pilot randomized controlled trial. Gait Posture. 2015;41:86–92.

270. Price C, Nester C. Foot dimensions and morphology in healthy weight, overweight and obese males. Clin Biomech (Bristol, Avon). 2016;37:125–30.

271. Wearing SC, Hills AP, Byrne NM. The arch index: a measure of flat or fat feet? Foot

Ankle Int. 2004;25:575-81.

272. Dixon JB, Dixon ME, O'Brien PE. Depression in association with severe obesity: changes with weight loss. Arch Intern Med. 2003;163:2058–65.

273. Switzer NJ, Debru E, Church N, Mitchell P, Gill R. The Impact of Bariatric Surgery on Depression: a Review. Curr Cardiovasc Risk Rep. 2016;10:12.

274. Australian Institute of Health and Welfare 2017. Weight loss surgery in Australia 2014–15: Australian hospital statistics. Cat. no. HSE 186. Canberra: AIHW.

275. Carey DG, Pliego GJ, Raymond RL. Body composition and metabolic changes following bariatric surgery: effects on fat mass, lean mass and basal metabolic rate: six months to one-year follow-up. Obes Surg. 2006;16:1602–8.

276. Thomas SL, Lewis S, Hyde J, Castle D, Komesaroff P. “The solution needs to be complex.” Obese adults' attitudes about the effectiveness of individual and population based interventions for obesity. BMC Public Health. 2010;10:420.

277. Robinson B, Coveleski S. Don't Say That to ME: Opposition to Targeting in Weight-Centric Intervention Messages. Health Commun. 2018;33:139–147.

278. Puhl R, Peterson JL, Luedicke J. Motivating or stigmatizing? Public perceptions of weight-related language used by health providers. Int J Obes (Lond). 2013;37:612–9.

279. Puhl R, Luedicke J, Peterson JL. Public reactions to obesity-related health campaigns: a randomized controlled trial. Am J Prev Med. 2013;45:36–48.