An assessment of selected sensorimotor parameters and muscle performance in hand osteoarthritis for the development of treatment.

Nicoló Edoardo Magni

A thesis submitted to AUT University in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD)

2018

School of Clinical Sciences

Supervisors: Professor Peter McNair

Dr David Rice

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the publications section), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signed

Dated 26/11/2018

Awards and Publications

Work from this thesis has led to the following publications and an award from the New Zealand Pain Society:

1. Magni N.E., McNair P.J. and Rice D.A. (2018). Blood flow restriction training to counter muscle weakness and atrophy associated with disuse and ageing: A systematic review and meta-analysis. Manuscript under review with Arthritis Research and Therapy.
2. Magni N.E., McNair P.J. and Rice D.A. (2018). Sensorimotor performance and function in people with osteoarthritis of the hand: A case-control comparison. Seminars in Arthritis and Rheumatism, 47(5): 676-682.
3. Magni N.E., McNair P.J. and Rice D.A. (2017). The effects of resistance training on muscle strength, joint pain, and hand function in individuals with hand osteoarthritis: A systematic review and meta-analysis. Arthritis Research & Therapy, 19: 1-11.
4. Best Oral Presentation New Zealand Pain Society, for the paper: Magni N.E., McNair P.J. and Rice D.A. Sensorimotor performance and hand function in people with osteoarthritis of the hand: A case-control comparison. Presented in New Plymouth, New Zealand, April 2016.

Acknowledgments

This thesis would have not been possible without the help and support of many people. Firstly, to Peter McNair, thank you for your support, through your expert guidance and patience you have helped me achieve what I thought was not possible. To David Rice, thank you for sharing your passion for research and the love for your work. Thanks to Grant Mawston and Jeff Kilby, your help with programming was fundamental during the first year of data collection. Thank you to all the participants who volunteered to take part in these studies, without your contribution this work would not exist. To my parents, Paola and Alessandro, your support has been essential in this journey. To my sister Alice and my brother-in-law Marcello and their two little girls Ginevra and Matilda, your skype calls brightened my days. To all my Italian and New Zealand friends who have been part of this journey, your support was incredible.

Finally, this thesis is dedicated to the memory of grandma Lina and uncle Enrico. You both have been an example, inspiration, and guide in my life.

Abstract

Symptomatic hand osteoarthritis (OA) affects twenty percent of people over the age of 70. Its socioeconomic burden is increasing and despite severe repercussions on people's quality of life, it has not received as much scientific attention as OA at other joints such as the knee and hip. The need for effective conservative interventions for hand OA has been suggested by several authors. Moreover, in light of recent research at other joints, it is important to assess sensorimotor and muscle impairments and their relation to function to determine the primary needs of a conservative program of rehabilitation.

The first study compared selected measures of sensorimotor and muscle performance between people with hand OA and healthy controls. Furthermore, the relationship between these measures and function was assessed. People with hand OA were slower and less accurate in a hand left/right discrimination task and experienced neglect-like symptoms more frequently, suggesting they had a disrupted working body schema. However, no association was found between left/right discrimination performance and measures of hand function. While grip endurance was not different between groups, a significant loss of grip strength and a moderate relationship with self-reported function was identified in people with hand OA. We therefore hypothesised that improving grip strength may have beneficial effects in people with hand OA.

To test this hypothesis, we completed a review and meta-analysis of research papers assessing the effectiveness of resistance training interventions on grip strength, pain and function in people with hand OA (Study two). Five studies with 350 participants were included. The findings showed no improvements in grip strength or function and limited effects on joint pain. However, it was apparent that most studies utilised exercise regimes considered inadequate to induce strength changes. In some studies, fear of pain

exacerbations or doing further damage to the affected joints led researchers to limit load during the prescribed exercise regimes. The findings suggested that a low intensity exercise alternative may be beneficial to improve muscle strength and function in people with hand OA, while reducing the risk of pain exacerbations and attenuating joint compressive forces.

After a subsequent search of the literature for low load strengthening programs, blood flow restriction training (BFR) appeared to be a viable treatment. This intervention has been shown to improve muscle strength and size in young, healthy people while utilising low exercise intensities. It was unclear however, if it was effective and safe in older people or individuals undergoing a period of disuse, as is common in OA. We therefore completed a systematic review and meta-analysis on this topic (Study three). Twenty-four studies, including a total of 485 individuals, were included. Findings suggested that BFR alone decreases the magnitude of strength loss associated with disuse. Furthermore, BFR training was found to be effective in improving strength and muscle size compared to matched low intensity exercise without BFR or a no intervention control. No difference was shown in treatment effects when comparing BFR to traditional high intensity strength training and there were few side effects associated with BFR.

Thus, study four assessed the feasibility of BFR training in people with hand OA and compared training effects to a traditional high intensity strength training program (HIT). A six-week intervention was trialled and feasibility issues regarding recruitment potential were identified. These included regional differences in recruitment as well as potential for greater involvement of surgeons in the recruitment process. In patients who joined the study, compliance with treatment was good in both groups and after six weeks of training, pre-exercise joint pain reduced significantly. Both BFR and HIT

rarely led to acute exacerbations in joint pain. Pinch strength improved significantly in both groups, while grip strength improved significantly in the BFR group only.

The findings from this thesis suggest that people with hand OA present with both sensorimotor and muscle impairments but only grip strength was moderately associated with self-reported function. Both BFR and HIT appear effective in improving muscle strength and do not result in frequent pain exacerbations, with an overall decrease in pre-exercise joint pain intensity over the six-week training period, despite a progressive increase in training volume. Thus, in the future, an appropriately powered randomised controlled trial appears indicated and feasible, although additional strategies may be required to facilitate recruitment. Finally, although not explored in depth in this thesis, findings from study one suggest it is possible that interventions aiming at improving sensorimotor function may reduce symptoms and/or improve functional performance in people with hand OA. However, further research is required to explore these alternative treatment options.

Chapter One: Introduction

The Problem

Osteoarthritis (OA) is one of the most commonly encountered pathologies in clinical practice (Gore, Tai, Sadosky, Leslie, & Stacey, 2012). With an estimated 27 million adults suffering from OA in the United States alone (Lawrence et al., 2008), the joints most commonly affected include the hip, knee and hand (K. D. Allen, Coffman, Golightly, Stechuchak, & Keefe, 2009). Twenty percent of adults over the age of 71 present with symptoms and have evidence of OA affecting one or more joints in the hand on plain x-ray (Y. Zhang et al., 2002). In New Zealand, 134,000 people are affected by this condition and its economic burden is increasing, with two million dollars spent every year on non-steroidal anti-inflammatories (NSAIDs) alone (New Zealand Health Information Service) (Altman, 2010). The hallmarks of hand OA are articular cartilage damage leading to inflammation, which in turn induces pain and sensitisation of nociceptive pathways. Pain is the primary symptom for which patients seek treatment for OA. The combination of joint structural changes, pain and disuse leads to impairment in range of movement, muscle strength and proprioception (Altman et al., 1990). These subsequently lead to dysfunction and reduced ability to perform daily activities requiring both low and high muscle forces (Poole, Santhanam, & Latham, 2013). Despite its negative impact on society, hand OA has received very little attention in the scientific literature compared to OA in other joints such as the knee and hip. Currently, treatments are largely limited to pharmacological and surgical management without addressing other important causes of disability, nor assessing the efficacy of exercise (Brewer & Storey, 2016). The need for stronger evidence supporting safe and effective conservative treatments for hand OA has been highlighted

by several authors (Moe, Kjeken, Uhlig, & Hagen, 2009; W. Zhang et al., 2007). For conservative treatments to be most efficacious, the rationale for their prescription needs to be addressed. This requires a thorough examination of how sensorimotor and peripheral muscular factors contribute to pain, impaired hand function and disability.

As previously mentioned, hand OA is often associated with chronic pain, which can continue for many years. In other persistent pain conditions such as low back pain (LBP), complex regional pain syndrome (CRPS) and chronic upper limb pain of various aetiologies, researchers (H. Cohen et al., 2013; Kolb, Lang, Seifert, & Maihöfner, 2012; Moseley, 2006; Reinersmann et al., 2010; Schmid & Coppieters, 2012; Stanton et al., 2012) have reported altered function in sensory and motor areas of the brain involved in the planning and execution of movement. Furthermore, somatospatial inattention, which consists in a bias in attentional processing of sensory inputs away from the (most) painful area of the body (Reid et al., 2016), has been commonly reported in the scientific literature. Evidence of this has been shown by longer reaction time and accuracy deficit in motor imagery tasks across multiple conditions including CRPS and LBP (Moseley, 2004; Stanton et al., 2012). Furthermore, LBP (Luomajoki & Moseley, 2011) and knee OA (Stanton et al., 2013) are associated with tactile acuity impairments, which cannot be explained by peripheral tissue or neurological deficits. Additional evidence is provided by Galer and Jensen (1999), who showed patients with CRPS reporting their painful limb feeling as if it is not part of their body or having significant difficulties in moving it the way the want it to. Very limited research has assessed these impairments in people with hand OA. A study by Gilpin, Moseley, Stanton, and Newport (2015) showed that people with hand OA present with a distorted mental representation of their painful limb. When asked to estimate the size of their hand, people with hand OA reported it being significantly smaller compared to healthy controls. Interestingly, in a paper by Preston and Newport (2011), visuotactile

stimulation through illusionary resizing and manual traction of the fingers, provided significant analgesia in people with hand OA. Further understanding of sensorimotor impairments and their relation to function may provide alternative conservative treatment options for people with hand OA.

In addition, impairments in muscle performance have commonly been reported in people with hand osteoarthritis. Most often, grip strength has been shown to be significantly lower compared to healthy controls (Bagis, Sahin, Yapici, Cimen, & Erdogan, 2003; Kjeken et al., 2005; Y. Zhang et al., 2002). Neumann and Bielefeld (2003) and Valdes and von der Heyde (2012) have suggested that this deficit has notable repercussions for performance of daily life activities requiring even moderate intensity grip strength. Opening jars, using scissors and heavy manual labour often require grip strength beyond what some people with hand OA can generate on a maximum voluntary contraction. Whether muscle endurance is also impaired in hand OA has not been assessed in previous research studies. However, several activities involving object manipulation require submaximal grip strength for prolonged periods of time. In this regard, carrying objects, food preparation, and many recreational activities require a grip strength of at least 10 kg (Neumann & Bielefeld, 2003) for extensive periods of time. If impairments in muscle strength and endurance are apparent in hand OA, it seems logical that interventions aimed at improving the performance of muscles working during hand movements would help to reduce functional disability. However, despite their place as one of the mainstream conservative treatments for knee and hip OA (Hochberg et al., 2012), resistance training exercises have not yet found their place in the management guidelines for hand OA (W. Zhang et al., 2007) due to a lack of research evidence supporting their use. In contrast, at the knee, several papers (Bennell & Hinman, 2011; Golightly, Allen, & Caine, 2012; Li et al., 2015) have reported the benefits of resistance training for both pain relief and functional

improvements in OA. When compared to the amount of research on resistance training for knee OA, a very limited number of studies have assessed the effectiveness of this intervention for people with hand OA. When the effectiveness of exercises for hand OA was assessed in a recent review (Bertozzi et al., 2015) the results showed no effect on pain and function and mixed results for grip strength improvements. Methodological as well as exercise prescription limitations negatively affected the quality of the recommendations provided in this review. A lack of assessor blinding, small sample sizes and a lack of randomisation reduced the quality of studies. Furthermore, when resistance exercises were prescribed, the intensity, frequency and progression utilised did not follow international guidelines for such training. Recently, additional studies on strength training for hand OA have been published and a further review of the literature would be useful to clarify its role in clinical practice.

A common concern among clinicians and researchers when applying strength training in hand OA is the use of high intensity exercises. Thus, many hand therapists rarely prescribe any form of strengthening exercise for people with hand OA because they believe it exacerbates patients' symptoms, perhaps by subjecting the arthritic joint(s) to high loads. This view is reflected in several papers and hand therapy books (Cooper, 2014; Lefler & Armstrong, 2004; Rogers & Wilder, 2007), which suggest adapting exercises to avoid pain flares in hand OA patients. Even though pain levels should not necessarily guide exercise prescription in chronic musculoskeletal rehabilitation (Gardner et al., 2017; Rossettini, Carlino, & Testa, 2018), it would be useful to identify an alternative form of resistance training which did not utilise high intensities. Thus, if the load (i.e. force per unit of time) on the arthritic joints could be reduced while obtaining similar gains in strength to those of traditional resistance training, patients' satisfaction as well as exercise adherence may be higher.

Blood flow restriction (BFR) training is an alternative form of resistance training which utilises much lower loads compared to traditional high intensity training (HIT) while obtaining similar muscle hypertrophy and strength gains (Loenneke, Abe, et al., 2012). Exercise intensity is reduced to 30-40% of maximum voluntary contraction (MVC) and the blood flow to the exercising muscles is restricted by a pressure cuff positioned proximally on the limb. The inflated cuff reduces venous return, leading to muscle ischemia and a build-up of metabolites, which are thought to be strong stimuli for hypertrophy and strength gains (Jessee et al., 2018). BFR has been shown to increase intracellular swelling (Downs et al., 2014) and the recruitment of type II muscle fibres (Scott, Slattery, Sculley, & Dascombe, 2014), which lead to an increase in protein synthesis. Furthermore, there is evidence that BFR may increase corticospinal excitability (Brandner, Warmington, & Kidgell, 2015), thereby enhancing neural drive to the muscle. This form of resistance training has been utilised in young, healthy participants with good results (Scott, Loenneke, Slattery, & Dascombe, 2016). However, it is less clear whether the use of BFR training is warranted in other populations, including in those more relevant to hand OA, such as older adults and individuals who have undergone a period of disuse due to injury or pain and therefore may be less able or inclined to engage in traditional HIT regimes. The risks associated with BFR training in clinical populations are poorly described, although several papers have raised concerns about its safety (Spranger, Krishnan, Levy, O'Leary, & Smith, 2015). A review of the literature on this topic would extend our understanding of the feasibility of BFR training for people in a musculoskeletal rehabilitation setting.

If deemed safe and effective in these populations, BFR could be explored as an alternative intervention in people with hand OA and it could perhaps be compared to traditional HIT. Before a randomised controlled trial (RCT) is implemented, the feasibility of such training needs to be assessed. Of potential interest would be the

strength gains associated with each exercise regime, the number of pain exacerbations experienced after each training session, treatment adherence and acceptability, and recruitment potential for the Auckland area. The results of the study could lead to a larger scale RCT and potentially provide clinicians with a novel treatment approach for this condition.

Statement of the Problem

Hand OA is a severely disabling condition and the most utilised treatments are limited to splinting, medication, and surgery (W. Zhang et al., 2007). The contributing factors to pain and disability are currently incompletely understood and there is lack of evidence regarding effective conservative interventions to help clinicians treat their patients. The aim of the present study was therefore to examine selected sensorimotor and muscle performance related factors that may contribute to pain and disability in hand OA and explore the feasibility of a novel conservative treatment option for people affected by this condition.

To address this aim, the following questions were addressed:

Study 1 Are sensorimotor, grip strength and endurance impairments different between individuals with hand osteoarthritis and healthy controls, and are these measures associated with pain and functional performance in people with osteoarthritis of the hand? (Chapter three), (Design: Case-control study)

Study 2 Can resistance training improve muscle strength, joint pain, and hand function in individuals with hand osteoarthritis? (Chapter four), (Design: Systematic review and meta-analysis).

Study 3 Can blood flow restriction training improve muscle weakness and atrophy associated with disuse and ageing? (Chapter five), (Design: Systematic review and meta-analysis).

Study 4 Are blood flow restriction training and traditional high intensity strength training feasible interventions for people with hand osteoarthritis? (Chapter six), (Design: Intervention study)

Significance of the Research

The findings from this study have significance for health professionals involved in the rehabilitation of people affected by symptomatic hand OA. The study findings will strengthen our understanding of the sensorimotor and muscle performance related impairments associated with hand OA and their relationship to hand function. These results may help clinicians to design appropriate interventions to address impairments observed in people with hand OA and subsequently decrease the disability associated with this condition. A new conservative intervention, aiming at improving muscle strength, function and pain has been proposed and initial feasibility issues examined. Future research may assess its effectiveness through a full scale randomised controlled trial.

Chapter Two: Literature Review

Introduction

This literature review is divided into five sections. The first section will describe the search strategy adopted. A review of the changes in the nervous system due to chronic pain will follow. In this section, the peripheral and central mechanisms thought to underlie these changes will be explored with specific reference given to those studies that have focused on OA, particularly OA of the hand. The third section will focus on the measurement tools chosen to assess sensorimotor changes in people with hand OA. Impairments and physical function in people with hand OA will then be reviewed. Finally, considerations related to the measures of hand function will be presented.

Literature Search

An initial literature search was conducted on hand OA. From this initial search a keywords list which included terms that related to pain and function was created (See Table 1). These included: hand(s), osteo(arthritis)(arthrosis), OA, “degenerative arthritis”, “degenerative joint(s) disease”, pain(inful), “chronic pain”, neuromatrix, function(s), impairment(s), disab(le)(ility)(ilities). The key words were combined for the search on EBSCO health databases (Biomedical Reference Collection: Basic, Clinical Pharmacology, Clinical Reference Systems, CINAHL, Pre-CINAHL, Dentistry & Oral Sciences Source, Health Business FullTEXT Elite, Health Source: Consumer Edition, Health Source: Nursing/Academic Edition, MEDLINE, Psychology and Behavioural Sciences Collection, Stedman's Medical Dictionary) and Scopus. Search results were increased by citation reference searches of previous review articles. Review

articles were identified by combining the keywords list with additional keywords. These included: systematic, critical, review(s), meta.

Table 1. Final search strategy

Search 1	hand*
Search 2	osteo* OR OA OR "degenerative arthritis" OR "degenerative joint* disease"
Search 3	pain* OR "chronic pain" OR neuromatrix OR function* OR impairment* OR disab*
Search 4	Combine searches 1 AND 2 AND 3

Changes in the Nervous System due to Hand OA

The search strategy and databases used for this section were described in the “Literature Search” section. The key words included: hand(s), osteo(arthritis)(arthrosis), OA, “degenerative arthritis”, “degenerative joint(s) disease”, pain(ful), “chronic pain”, neuromatrix. As of June 2018, 4992 references were identified. The title screening of the 4992 studies, resulted in 147 articles suitable for abstract review. Fifty articles were deemed appropriate for full text review.

Pain in osteoarthritis is multifactorial and the underlying causes remain only partly understood (Dimitroulas, Duarte, Behura, Kitas, & Raphael, 2014). Several genetic, structural, metabolic, cardiovascular and neurophysiological factors appear to predispose patients to the increased perception of pain (Aslam et al., 2014; Courties et al., 2017; Damman et al., 2017; De Kruijf et al., 2014; Droz-Bartholet, Verhoeven, Prati, & Wendling, 2016; Hämäläinen et al., 2014; Haugen, Slatkowsky-Christensen, Bøyesen, van der Heijde, & Kvien, 2013; Marshall et al., 2013). Among these, neurophysiological factors have been the focus of several studies as they appear to strongly contribute to the overall pain experience (Dimitroulas et al., 2014). The

neurophysiological changes encountered in chronic pain are commonly described as peripheral sensitisation and central sensitisation according to the level of the nervous system involved (Wajed et al., 2012). Peripheral sensitisation refers to the alterations in nociceptor sensitivity taking place at the joint and associated peripheral tissues while central sensitisation specifically involves sensitisation of nociceptive pathways in the spinal cord, subcortical and cortical structures (Wajed et al., 2012). These phenomena are common in many, if not all, chronic pain conditions with variations related to the initiating pathology or trauma, duration of pain and as yet poorly understood individual factors (e.g. genetic polymorphisms) (Baliki et al., 2008).

Peripheral nervous system changes

Osteoarthritis pain is at least partly associated with anatomical and physiological modifications at the joint. Dimitroulas et al. (2014) reported that inflammation, neoinnervation of the articular cartilage and endochondral ossifications are amongst the peripheral factors contributing to joint pain. In particular, local inflammatory mediators sensitise peripheral nociceptors, which then release substance P and calcitonin gene related peptide upon activation, inducing further inflammation (Dimitroulas et al., 2014; Schaible, Ebersberger, & Natura, 2011). The result is peripheral sensitisation, which can include decreased nociceptor thresholds, increased resting discharge rates and the recruitment of additional so called “silent” nociceptors, leading to allodynia and/or primary hyperalgesia (Schaible et al., 2011). In addition, neoinnervation of the articular cartilage and endochondral ossifications may increase the likelihood of nociceptor discharge due to the presence of exposed free nerve endings in mechanically loaded tissues (Dimitroulas et al., 2014).

Central nervous system changes

OA may also be associated with a number of structural and functional changes in the central nervous system. Lee, Nassikas, and Clauw (2011) have suggested that central sensitisation of nociceptive pathways can take place at several levels of the central nervous system in OA. At the dorsal horn, as a consequence of persistent noxious peripheral inputs, the N-methyl-D-aspartate receptor channels are activated, enlarging the dorsal horn neurons receptive fields. In addition, a recent review by O'Leary, Smart, Moloney, and Doody (2017) has reported that the balance between endogenous descending inhibitory and descending pain facilitatory pathways, originating from cortical areas and key subcortical regions such as the hypothalamus and brainstem, are often impaired, favouring increased transmission of nociceptive stimuli from the dorsal horn to the brain. Furthermore, changes in cortical and subcortical excitability and functional connectivity can modify the way nociceptive inputs are processed and interpreted at a supraspinal level (O'Leary et al., 2017; Teunis, Bot, Thornton, & Ring, 2015). Together, these alterations may enhance OA pain by allowing non-nociceptive sensory inputs to activate nociceptive pathways, enhancing nociceptive transmission from the spinal cord to the brain and altering the processing of nociceptive input once it reaches subcortical and cortical levels (Skou et al., 2013).

Peripheral and central sensitisation of nociceptive pathways have been measured through several means (instruments) in patients with OA (Lee et al., 2011). Studies adopting quantitative sensory testing reported decreased pressure pain thresholds at the joint and in distant, non-painful body sites, suggesting a widespread increase in pain sensitivity at a central level (Bajaj, Bajaj, Graven-Nielsen, & Arendt-Nielsen, 2001; Imamura et al., 2008; Kosek & Ordeberg, 2000; O'Driscoll & Jayson, 1974). Additional evidence showed deficits in conditioned pain modulation, a measure of the balance between descending pain inhibitory and facilitatory pathways, which may be reversed

after the removal of peripheral nociceptive input (Arendt-Nielsen et al., 2010; Kosek & Ordeberg, 2000). Nevertheless, recent studies have shown a continued impairment in descending pain inhibition in some patients, even after joint replacement (Skou et al., 2013; Wylde, Palmer, Learmonth, & Dieppe, 2013) and persistence of pain in subgroups of people undergoing joint arthroplasty or denervation in the hand (Delclaux et al., 2017; Fuchsberger et al., 2018). Several neuroimaging studies reported alterations in cortical and subcortical nociceptive processing of patients with OA (Howard et al., 2012). Limbic areas of the brain such as the cingulate cortex, thalamus and amygdala were found to be significantly more active in people with OA than in controls (Baliki et al., 2008; Gwilym, Filippini, Douaud, Carr, & Tracey, 2010; Gwilym et al., 2009; Kulkarni et al., 2007; Parks et al., 2011), both at rest and in response to nociceptive input. In addition, gray matter volume reduction has been shown in many different areas of the brain involved in nociceptive processing, including the nucleus accumbens, amygdala, anterior cingulate cortex, insular cortex and operculum, dorsolateral prefrontal cortex, orbitofrontal cortex, primary somatosensory cortex and thalamus (Gwilym et al., 2010; Lewis, Parker, Sharma, Rice, & McNair, 2018; Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2013). Finally, white matter tract integrity may be reduced in areas such as the corpus callosum and brainstem (Lewis et al., 2018). These brain changes appeared to be partially reversible after joint arthroplasty (Gwilym et al., 2010; Lewis et al., 2018; Rodriguez-Raecke et al., 2013).

Changes are also apparent in sensorimotor regions of the brain. Disinhibition in the primary motor cortex (Parker, Lewis, Rice, & McNair, 2017) and reorganisation of both the primary somatosensory cortex (Stanton et al., 2012) and primary motor cortex (Shanahan, Hodges, Wrigley, Bennell, & Farrell, 2015) have been identified in patients with OA, who were also less accurate in performing motor imagery and force matching tasks (Shanahan et al., 2015; Stanton et al., 2012). Interestingly, in people with constant

pain associated with hand OA it has been shown that on different assessment days, the resting activation of the primary somatosensory cortex, is negatively correlated to changes on perceived pain while no changes are noticed in pain free controls (Howard et al., 2012). When people with hand OA are asked to move their fingers, the total area of the somatosensory cortex activated is significantly greater than in controls and the level of perceived pain increases (Sofat et al., 2013). Further evidence of functional alterations in sensorimotor areas of the brain is shown by increased mechanical detection thresholds in hands of participants with hand OA (Westermann et al., 2011) as well as widespread tactile hypoaesthesia to touch (Wylde, Palmer, Learmonth, & Dieppe, 2012) and reduced tactile acuity and impaired implicit motor imagery (Stanton et al., 2012) in people with knee OA. People with symptomatic hand OA have also been shown to present with body perceptual abnormalities (Gilpin et al., 2015), some of which may be similar to those encountered in hemi-neglect due to parietal cortex lesions (Kolb et al., 2012). These deficits appear to reflect impairments in the working body schema in the apparent absence of neurological lesions (Simons, Elman, & Borsook, 2014).

It has been suggested that sensorimotor reorganisation may be associated with and contribute to chronic pain (Moseley & Flor, 2012). For example, there is evidence that cortical reorganisation in phantom limb pain and complex regional pain syndrome (CRPS) may perpetuate chronic pain (Flor, Nikolajsen, & Staehelin Jensen, 2006; Lotze & Moseley, 2007). Several interventions aiming at normalising sensory and motor representations have also been shown to decrease pain in people with chronic pain (Moseley & Flor, 2012; Moseley, Gallace, & Spence, 2012). For example, in phantom limb pain and CRPS, tactile discrimination training has been shown to reduce pain (Flor, Denke, Schaefer, & Grüsser, 2001; Moseley & Wiech, 2009; Moseley, Zalucki, & Wiech, 2008). Improvements in tactile acuity and pain have further been shown to

correlate with a reversal in primary somatosensory cortex reorganisation (Flor et al., 2001; Moseley & Flor, 2012). Interestingly, other interventions aiming at normalising sensory representations in people with chronic or experimental pain have shown that illusory "minifying" of the painful limb reduces pain and, conversely, "magnification" may increase pain (Mancini, Longo, Kammers, & Haggard, 2011; Moseley, Parsons, & Spence, 2008). Together, all these results are suggestive of distorted mental representation of the symptomatic limb in people with chronic pain, including preliminary evidence in people with hand OA (Gilpin et al., 2015). Further evidence to confirm the presence and clinical importance of these impairments in hand OA is warranted.

Measures of Sensorimotor Function

Sensorimotor function can be assessed through several different measures in individuals with hand OA. We were particularly interested in the hand left/right discrimination test, two-point discrimination threshold and neglect-like symptoms. The choice of these measures is based on previous literature in other chronic pain conditions, the potential of the deficits identified in these tests to be modified by targeted interventions (graded motor imagery, tactile discrimination training) that may improve pain and function (Moseley & Flor, 2012) and the limited evidence to date regarding perceptual disturbances (neglect-like symptoms) in people with hand OA. In the following section, each of the measures will be discussed.

The hand left/right discrimination test (egocentric task)

In the hand left/right discrimination test (egocentric task), people are shown pictures of a hand in various degrees of rotation and asked to determine as quickly and as

accurately as possible whether the hand in each picture belongs to the left or right side of the body. The variables of interest in the test are the time taken (i.e. mean reaction time) to determine whether the hand is from the left or right side of the body and the accuracy of that choice (i.e. % correct responses). From a cognitive point of view the spatial transformation needed to complete this task is rather complex, with evidence that it requires the participant to imagine moving their own hand to match the position shown in the picture through a body-centred reference frame (Parsons, 2001; Zacks, 2008). As people are typically consciously unaware of this mental rotation, it can be considered a form of implicit motor imagery (Parsons, 2001). The hand left/right discrimination task is more complex than a simple object rotation as it is influenced by biomechanical constraints and the awkwardness of movement specific to the limb being visualised (Hoyek, Di Rienzo, Collet, Creveaux, & Guillot, 2014; Parsons, 2001). Specifically, palm up clockwise and counter clockwise rotated pictures (225°, 270°, and 315°) of the left and right hands respectively are the most difficult to recognise (Coslett, Medina, Kliot, & Burkey, 2010; Hoyek et al., 2014). Additionally, this task is influenced by current proprioceptive information (Hoyek et al., 2014; S. Silva et al., 2011). Thus, when the hand presented in the picture is in a different position compared to the participant's own hand position (e.g. palm/dorsal view) (Ionta, Fourkas, Fiorio, & Aglioti, 2007) or when the upper limb is under anaesthesia (S. Silva et al., 2011), participants are slower and less accurate in the task. From a neurophysiological perspective, the hand left/right discrimination task activates a number of brain areas. Specifically, functional MRI studies have shown that the prefrontal cortex, supplementary motor areas, inferior premotor cortex, superior frontal premotor cortex, and the contralateral cerebellum appear to be active during the task (Parsons, 2001; Zacks, 2008). These brain areas are similar to the ones activated during the preparation, action copying, sensory acquisition, control, and execution of movements (Kosslyn,

1998; Parsons, 2001). The importance of these areas of the brain for motor imagery, movement planning and execution is confirmed by neurological (Sirigu et al., 1995) and neurosurgical (Tomasino, Skrap, & Rumiati, 2011) studies on people with cortical lesions affecting these regions, which results in impaired left/right discrimination and motor execution. People with phantom limb pain, chronic low back pain, and CRPS have often shown impairments in left/right discrimination task accuracy and/or reaction times (Moseley, Gallace, et al., 2012). These impairments appear to be due to alterations of body-related representations in the brain (Moseley, Gallace, et al., 2012). Thus, people with chronic pain often present with cortical reorganisation in many sensorimotor regions, many of which are fundamental brain areas for the execution of hand left/right discrimination task (Lotze & Moseley, 2007).

To date, only one study (Stanton et al., 2012) has utilised the left/right discrimination task in people with OA. Stanton et al. (2012) compared participants with knee OA to participants with arm pain and healthy pain-free controls. Two left/right discrimination tasks, one involving pictures of the hands and one involving pictures of the feet were used. Each task involved a practice and a trial set, each of which included 10 pictures. Only the trial data were analysed. The results of the study showed no significant differences in reaction times across groups. However, the healthy controls were more accurate in the feet and hand left/right discrimination when compared to both the knee OA and arm pain groups. No accuracy differences were shown between the knee OA and arm pain group. Stanton et al. (2012) suggested that the presence of pain rather than its location was the cause of the deficit in accuracy in both tasks.

There is some evidence that impaired left/right discrimination may lead to deficits in function. Two studies (Elsig et al., 2014; Pelletier, Higgins, & Bourbonnais, 2018) assessed the correlation between the hand left/right discrimination task and function in

people with musculoskeletal disorders. Elsig et al. (2014) found a correlation between the hand left/right discrimination task accuracy and the Neck Disability Index in the group of participants with recurrent neck pain while Pelletier et al. (2018) found no association between the hand left/right discrimination task reaction time and motor performance in people with hand/wrist pain. Further studies are required to clarify the correlation between this sensorimotor task and function.

Longer reaction times and decreased accuracy in the left/right discrimination task among people with chronic pain have been suggested to be due to specific sensorimotor alterations that lead to an impairment in the normal working body schema (Moseley, Butler, Beames, & Giles, 2012). Nevertheless, an alternative explanation to the findings is that chronic pain leads to a general impairment in cognitive function (Moriarty, McGuire, & Finn, 2011) and/or a decrease in processing speeds (i.e. increased reaction time) of the central nervous system due to increases in computational and attentional demands (Seminowicz & Davis, 2007). Furthermore, inability to properly discriminate between left and right (i.e. people confuse the right with the left and vice versa) could be a confounding factor (Coslett et al., 2010). For these reasons we consider it important to include a task that controls for some of these factors when assessing implicit motor imagery.

The control left/right discrimination test (allocentric task)

In the control left/right discrimination test (allocentric task), people are shown the same pictures of a hand in various degrees of rotation and asked to decide as quickly and accurately as possible whether a red marker is located on the left or right side of the hand (See Figure 1) (De Simone, Tomasino, Marusic, Eleopra, & Rumiati, 2013). Similar to the egocentric task, the variables of interest are the time taken (reaction time) to determine whether the marker is located on the left or right side of the hand and the

accuracy of that choice. From a cognitive point of view, this task is similar to spatial transformation of an object, which requires participants to mentally rotate a picture in an object-centred reference frame (Parsons, 2001; Zacks, 2008). This cognitive task is a form of visual imagery (Sirigu & Duhamel, 2001; Tomasino et al., 2011). Visual imagery does not present biomechanical constraints and the time required to accomplish the task is an approximately linear function of the picture rotation (Hoyek et al., 2014; Parsons, 2001). Visual imagery does not appear to be influenced by hand posture (Hoyek et al., 2014). From a neurophysiological perspective, the control left/right discrimination task appears to activate mainly the right cerebellum and right cerebral hemisphere (Parsons, 2001), including the posterior parietal, temporal, and occipital cortices (Wraga, Shephard, Church, Inati, & Kosslyn, 2005; Zacks, 2008). Additional evidence of the importance of these brain areas for the object-centred transformation is reported in a neuropsychological study by Sirigu and Duhamel (2001) in which a lesion of the infero-temporal cortex lead to impairments in the object-centred transformation but not in a motor imagery task. Further evidence of neurophysiological dissociation between the object-centred and motor imagery task is provided by Pelgrims, Andres, and Olivier (2009). Pelgrims et al. (2009) found that virtual lesions of the superior parietal cortex and the supramarginal gyrus, induced through repetitive transcranial magnetic stimulation, selectively altered object rotation and motor imagery respectively. Moreover, Tomasino, Budai, Mondani, Skrap, and Rumiati (2005) showed that electrical stimulation of the motor cortex did not affect an allocentric, visual imagery task but did impair an egocentric, motor imagery task. For these reasons, the allocentric left/right discrimination task could be included with the egocentric left/right discrimination task to test for selective impairments in the working body schema, while controlling for general cognitive impairments such as delays in the processing speed of

choice reaction time tasks, general impairments in tasks requiring mental rotation and/or a general inability to accurately discriminate between left and right.

Figure 1. Picture rotation for the allocentric task.

Two-point discrimination (TPD)

Our body is able to detect several forms of touch, which is necessary to protect us, as well as perceive, interpret, and interact with the environment around us. The TPD test assesses one aspect of touch called tactile acuity (Catley, Tabor, Wand, & Moseley, 2013). Tactile acuity is defined as the ability to discriminate between one or two points applied to the skin, with greater acuity reflected by the continued ability to perceive two points of touch applied closer together on the skin (Park & Kwon, 2012). Tactile acuity is often measured through sliding callipers, which are applied with a pressure sufficient to first blanch the skin (Catley et al., 2013). Assessment starts with zero mm between the two-points and it is gradually increased until the person reports feeling two-points.

The distance is then gradually decreased until the subject fails to report two points. Catch trials of one point only are used to ensure the subject is relying on sensory input, rather than guessing. Typically, the average of five ascending and five descending runs is used to determine TPD threshold, defined as the minimum distance (mm) that the subject can consistently perceive two points of touch (Moberg, 1990). The neurophysiological mechanisms behind two-point discrimination are extremely complex and incompletely understood. Mechanoreceptors, which are sensory neurons innervating the dermis and epidermis, are stimulated by mechanical deformation of the skin (Schepeler, Page, & Jensen, 2014). Most likely the mechanoreceptors stimulated during the TPD test are the Merkel cells (usually responsive to skin indentation), which are low-threshold receptors innervated by fast conducting Aβ fibres. The stimuli travel along the afferent axons until they reach the deep dorsal horn lamina (III-IV), where the axons synapse with second order neurons (Abraira & Ginty, 2013). The afferent input that reaches the spinal cord is regulated by a series of interneurons and descending projections (e.g. corticospinal and rubrospinal systems) that influence both ascending sensory signals and cutaneous-motor reflexes (Braz, Solorzano, Wang, & Basbaum, 2014; Panek, Bui, Wright, & Brownstone, 2014). The final output from the dorsal horn is then transmitted through the postsynaptic dorsal column (DC) of the spinal cord, which is responsible for the delivery of sensory input to the brain for the purposes of tactile discrimination (Abraira & Ginty, 2013). Sensory input from the DC reaches the thalamus, before projecting to the primary somatosensory cortex (Abraira & Ginty, 2013). The cerebellum is also extremely active during tactile discrimination tasks in the absence of movement (Parsons, 2001), with tactile information being relayed through the spino-cerebellar, reticulo-cerebellar, spino-olivo-cerebellar tracts and cerebro-cerebellar projections (Bushara et al., 2001). The sensory integration of tactile stimuli contributes to the creation of an internal body model, which serves to plan movements,

and adapt motor outputs to unsuccessful or unplanned experiences (Panek et al., 2014). In people with non-neuropathic chronic pain, tactile acuity is generally worse when compared to healthy controls. In a recent meta-analysis, Catley, O'Connell, Berryman, Ayhan, and Moseley (2014) examined TPD in people with chronic pain showing that in CRPS and low back pain, TPD thresholds, are larger when compared to healthy controls, particularly when measured at the site of pain. The same authors showed that with a few exceptions, TPD thresholds are generally not impaired in remote, pain free areas of the body. This suggests that TPD thresholds are specifically impaired at the site of pain rather than being altered across multiple body regions.

There could be several reasons for impaired TPD in populations with chronic pain. For example, deficits in peripheral nerve conduction (e.g. neuropathy) have been shown to impair tactile acuity (Johansson & Westling, 1984; Moberg, 1990). In the absence of peripheral deficits, alterations of the central nervous system are thought to contribute to higher TPD thresholds. At the spinal cord level, alterations of interneuron excitability may influence tactile stimuli reaching higher centres, impairing tactile acuity (Abraira & Ginty, 2013). Additionally, alterations of the descending pathways, which facilitate the transmission of mechanical tactile stimuli might impair the amount of tactile information processed by the brain and consequently TPD thresholds (Braz et al., 2014). Finally, reorganization of the primary somatosensory cortex appears to play an important role in tactile acuity impairments. In this regard, measures of primary somatosensory cortex reorganisation obtained through fMRI, are strongly correlated (ranging between $r = 0.77$ and $r = 0.82$) to TPD thresholds in people with CRPS type I (Pleger et al., 2006) It is not yet clear if nociception has a primary role in cortical reorganisation, or whether other factors such as disuse of the painful limb are more important. For example, Lissek et al. (2009) has shown that upper limb immobilisation for two weeks impairs tactile perception of the index finger while increased use of the

upper limb resulted in tactile acuity improvements. Furthermore, a decrease and increase in the activation of the primary somatosensory cortex has been shown for the former and latter conditions respectively.

To date, only two studies have assessed TPD in people with OA (Ayhan, Gül, Uyar, Erdem, & Borman, 2011; Stanton et al., 2013). TPD thresholds were higher in the affected and unaffected knee of people with knee OA when compared to arm pain and pain-free control groups (Stanton et al., 2013). Similarly, in people with hand OA, TPD thresholds were reported to be higher compared to healthy controls, although these findings have only been reported in abstract form (Ayhan et al., 2011). Further research is required to establish whether tactile acuity is indeed impaired in hand OA, the mechanisms responsible for any loss of tactile acuity and the relationship between tactile acuity and hand function.

Neglect-like symptoms

Attention is a cognitive ability that allows us to focus on specific information among the many that our sensory systems provide us with (Reid et al., 2016). Attention is fundamental to protect us from danger, interact with the environment, and achieve our goals. According to Charles and Jon (1994), the attentional shift towards specific stimuli is constantly modulated by exogenous and endogenous systems. These authors suggested that exogenous (involuntary) systems shift attention to unexpected but important events (e.g. an insect bite), while endogenous systems are utilized when attention is voluntarily directed to a specific spatial location or event (e.g. looking for cars before crossing the road). Several brain areas are involved in this cognitive process and it appears that the parietal, basal ganglia, and prefrontal cortex are the most active in the selection and processing of multisensory information arising from the body (Petkova et al., 2011). Lesions to these areas of the brain (e.g. after a stroke) often

causes hemispatial attentional and motor deficits, which can be classified according to the clinical presentation as unilateral neglect, anosognosia, asomatognosia and several other clinical subsets (Vallar & Ronchi, 2009). Perceptual and hemispatial attentional deficits have also been found in people with musculoskeletal pain, in the apparent absence of brain lesions (Birklein & Maihöfner, 2012; Kolb et al., 2012). These deficits are not comparable, in terms of severity, to those observed after stroke (Punt, Cooper, Hey, & Johnson, 2013). For instance, when patients with CRPS are assessed clinically through the line bisection test, clock drawing and reading tests that assess the mid line perception of the body, they are not impaired or only minimally impaired in comparison to healthy controls (Förderreuther, Sailer, & Straube, 2004; Kolb et al., 2012; Reinersmann et al., 2012). Nevertheless, people with chronic pain appear to share some neglect-like impairments when assessed under controlled conditions such as laboratory testing (Punt et al., 2013). For example, the phenomenon of extinction, which is an attentional deficit away from the affected side, commonly encountered in post stroke patients, is found, albeit to a lesser degree and to proprioceptive but not visual stimuli, in people with unilateral chronic low back pain (LBP) (Moseley, Gallagher, & Gallace, 2012) and CRPS (Moseley, Gallace, & Spence, 2009; Reid et al., 2016). To clinically assess "neglect-like" symptoms in chronic pain populations, the "Neurobehavioral Questionnaire" by Galer and Jensen (1999) can be used (See Appendix A). This questionnaire was developed after these authors identified the presence of feelings of "foreignness" and "motor neglect" impairments in limbs of some people affected by CRPS. The questionnaire includes five statements related to motor and cognitive neglect that patients can rate in terms of frequency (1 = "never", 6 = "always") on a five-points Likert scale (Frettlöh, Hüppe, & Maier, 2006). After the first publication by Galer, Butler, and Jensen (1995) additional studies utilising the Neurobehavioral questionnaire showed the presence of neglect-like symptoms not only in people with

CRPS but also in people with other upper and lower limb chronic pain conditions of various aetiologies (Frettlöh et al., 2006). The extent of these symptoms in people with other chronic pain conditions is typically lower when compared to people with CRPS but neglect like symptoms are still reported significantly more often than in healthy pain free controls (Kolb et al., 2012). To date, no studies have examined neglect like symptoms specifically in a hand OA population.

Impairments and Function in the OA Hand

The search strategy and databases used for this section were described in the "Literature Search" section on page 8. The key words included: hand(s), osteo(arthritis)(arthrosis), OA, "degenerative arthritis", "degenerative joint(s) disease", function(s)(al)(ality), impairment(s), disab(le)(ility). As of July 2018, 7138 references were identified. The title screening of the 7138 studies, resulted in 205 articles suitable for abstract review. Sixty-three articles were deemed appropriate for full text review.

Impairments

The most common impairments encountered in people with hand OA are pain, decreased muscle strength, range of motion limitations, and motor control deficits.

Pain

Pain is a cardinal complaint in patients with hand OA (K. D. Allen, 2007). W. Zhang et al. (2009) showed that it most frequently occurs in the distal interphalangeal, proximal interphalangeal, and carpometacarpal joint and it affects both hands in 7% and 16% of men and women respectively. Pain intensity varies according to the different subsets (e.g. erosive/non-erosive) of hand OA (Bijsterbosch et al., 2010). In erosive hand OA, which is rare (8.5% of people with hand OA), pain can be 10% higher than in non-

erosive hand OA (Bijsterbosch et al., 2010). Over a period of two years, pain intensity with hand OA can show increases of 5% when measured through self-reported pain ratings (AUSCAN) and pain sensitivity may increase 6.5% when assessed using pressure pain scores obtained through manual pressure applied to the hand joints (Botha-Scheepers et al., 2009; Doyle, Dieppe, Scott, & Huskisson, 1981). K. D. Allen et al. (2009) reported that pain intensities in hand OA may be lower when compared to OA of the hip and knee. These authors suggested that this is probably due to the weight bearing roles of lower limb joints in primary aspects of function such as gait, which can be difficult to avoid. Bellamy, Sothern, Campbell, and Buchanan (2002) have reported that pain intensity varies in a circadian rhythm in hand OA. The highest pain ratings (VAS) were usually experienced in the morning and before going to bed. At around four in the afternoon the pain appeared to be at its lowest. However, individual variations apply to this pain pattern (K. D. Allen et al., 2009). The presence of musculoskeletal and non-musculoskeletal comorbidities has been shown to affect pain perception with a higher count of lung and cardiovascular diseases associated with higher intensity hand OA pain (Damman et al., 2017). It has also been shown that people with hand OA can be subgrouped according to the pain intensity and level of functional impairments reported (K. D. Allen, Golightly, & Olsen, 2006; Green, Jordan, Protheroe, Windt, & van der Windt, 2016). Green et al. (2016) found that people with hand OA can present with high levels of pain and low functional deficits, high functional deficits and low pain or a combination of both high pain and functional impairments. Interestingly, these authors observed that more than 40% of people with high levels of pain and no functional deficits reported a significant reduction in pain at three and six years after baseline measurements. However, people with functional deficits appeared to be less likely to improve over time. There is limited information regarding the quality of pain in hand OA. In this regard, only one study by Stamm et al. (2009) reported patients'

descriptions of pain. The most common descriptions used were “pain like a knife”, “pain like a fever”, “itching”, “ache”, “tenderness” and “killing pain”. The frequency of each pain descriptor and their behaviour during the day is unknown and further research in this field would be helpful in identifying common daily patterns and/or different subsets of pain.

Muscle performance

Muscle strength deficits in people with hand OA appear to involve many of the muscles in the distal upper limb, including the extensors and flexors of the wrist and fingers, and the intrinsic hand muscles (MacIntyre, Wessel, MacDermid, & Galea, 2010). In healthy people, the radial fingers (II and III) usually contribute significantly more to overall grip strength than the ulnar fingers (IV and V). This relationship is maintained in people with hand OA even though radial digits are usually more affected by OA (MacIntyre et al., 2010). This suggests a global loss of grip strength, rather than local changes in grip strength affecting only the painful digit(s). On average, grip strength in people with hand OA is reduced by approximately 10-40% when compared to healthy controls (Bagis et al., 2003; Kalichman & Hernández-Molina, 2010; Kjeken et al., 2005; Nunes, de Oliveira, Aruin, & Dos Santos, 2012; Y. Zhang et al., 2002). No difference in terms of grip strength was identified between people with erosive and non-erosive hand OA (Bijsterbosch et al., 2010). It should be noted that comparison of grip strength deficits across studies are difficult because of different equipment and protocols utilised during testing (H. C. Roberts et al., 2011). In addition to deficits in the flexors muscles, hand OA induces weakness of the extensors muscles (Brorsson, Nilsdotter, Thorstensson, & Bremander, 2014). In people with hand OA, thumb abduction may be up to 67% weaker when compared to healthy controls (Villafañe & Valdes, 2013). Conflicting findings have been found in the literature in regard to the relation between muscle weakness and the degree of joint degeneration assessed through x-rays (Dahaghin et al., 2005;

Dominick, Jordan, Renner, & Kraus, 2005; G. Jones, Cooley, & Bellamy, 2001; Kalichman & Hernández-Molina, 2010). Some evidence suggests that greater joint degeneration is associated with more weakness (Ceceli, Gül, Borman, Uysal, & Okumuş, 2012; Dominick et al., 2005), while others report an absence of any correlation (Botha-Scheepers et al., 2009; Dahaghin et al., 2005; G. Jones et al., 2001). Some authors (Ding, Leino-Arjas, Murtomaa, Takala, & Solovieva, 2013; G. Jones et al., 2001) have commented that grip strength deficits appear to be mediated by pain intensity rather than joint damage. However, it is also possible that learned disuse or treatment modalities focusing on immobilisation (e.g. splinting) may perpetuate a vicious cycle of muscle weakness (Miles et al., 1994). Of interest is the relationship that exists between grip strength and hand function, for it has been shown that lower levels of muscle strength are associated with reduced self-reported function (Cantero-Téllez, Martín-Valero, & Cuesta-Vargas, 2015; G. Jones et al., 2001; Kjeken et al., 2005; MacIntyre & Wessel, 2009).

Previous studies have assessed grip endurance in elderly people (Desrosiers, Bravo, & Hébert, 1997), however, to our knowledge, no study has explored muscle endurance in people with hand OA. Similarly, very few studies have assessed muscle endurance in other forms of OA (Dos Santos, Rodrigues, & Mainenti, 2014; Elboim-Gabyzon, Rozen, & Laufer, 2013; Mau-Moeller et al., 2017; McNair & Molloy, 2016). In those that have, results are conflicting, with some research showing muscle endurance preservation (Elboim-Gabyzon et al., 2013; McNair & Molloy, 2016) and other authors reporting increased quadriceps' fatigue in patients with knee OA compared to healthy controls (Mau-Moeller et al., 2017). These results may partly be explained by different stages of the disease, with more advanced OA characterised by an increase in muscle oxidative muscle metabolism associated with a greater proportion of type I muscle fibre due to greater type II muscle fibre atrophy (Fink et al., 2007; Stockmar, Lill, Trapp,

Josten, & Punkt, 2006). In contrast there is some evidence that earlier stages of OA present with a decrease in type I muscle fibres and, given the same CSA, a higher proportion of extracellular matrix and collagen content (Noehren et al., 2018). Furthermore, many of these studies compared muscle endurance by contracting at a relative load (i.e. 50% of maximum voluntary contraction) to exhaustion. As maximal strength is often markedly lower in people with OA, the absolute load used to assess muscle endurance was likely much lower in the OA group, obscuring potential differences in muscle endurance that may be apparent when using the same load for both groups. Of note, while several activities of daily living including carrying objects, food preparation, and recreational activities require holding a grip strength of at least 10 kg (Neumann & Bielefeld, 2003) for prolonged periods of time, for some people with hand OA, a 10 kg grip strength level would be beyond 50% of maximum voluntary contraction (MVC), making the execution of these tasks more of a strength performance rather than endurance activity.

Range of motion

Range of motion restrictions of the fingers have also been shown in hand OA (Kjeken et al., 2005). In particular, fingers II-V usually present with limitations in extension and flexion while finger I is limited in several directions (Gehrmann et al., 2010; Kjeken et al., 2005). Finger II presents with a total range of motion deficit of approximately 10%, finger IV 20%, and finger III 17% (Kjeken et al., 2005). Finger I presents with limitations in abduction/adduction, flexion/extension, and opposition of 41%, 24%, and 21% respectively compared to healthy controls (Gehrmann et al., 2010; Villafañe & Valdes, 2013). The significant limitation in finger I abduction, which is very common in late stages of trapeziometacarpal OA, might be due to a deepening of the dorso-volar groove, lengthening of radial and ulnar horns of the trapezium, and inversion of the curvature in the dorso-volar axis of the first metacarpal (D'Agostino et al., 2017). These

important articular changes at finger I result in the transformation from a saddle to a condyle shaped joint, which significantly impairs the normal biomechanics of opposition and prehension in people with advance finger I OA (D'Agostino et al., 2017). The mobility of finger V appears to be preserved in people with hand OA (Kjeken et al., 2005).

Motor control

People with hand OA also present with motor control deficits when compared to healthy participants, including increased muscle activation levels and impairments in grip force timing and control. In this regard, Brorsson et al. (2014) showed that the extensor digitorum communis and the flexor carpi radialis were more active during the same tasks in subjects with hand OA when compared to healthy controls. The most significant difference is found in cutting tasks where people with hand OA demonstrate on average a 65% and 48% increase in muscle activation in the flexor carpi radialis and extensor digitorum communis respectively. In addition to activation changes, de Oliveira, Nunes, Aruin, and Dos Santos (2011) have shown that participants with hand OA present with alterations in grip strength control. During the same functional activities, participants with hand OA have higher grip forces when compared to healthy controls. Furthermore, the latency of the activity, defined as the time between grip force onset and object movement, is longer in people with hand OA. These alterations of grip force control are also associated with measures of hand function and dexterity (Nunes et al., 2012). Nunes et al. (2012) showed that the grip force at lift off and the latency were moderately (r = 0.71) to strongly (r = 0.85) correlated with the Moberg Pickup Test and the disabilities of the arm, shoulder, and hand questionnaire (DASH). The deficits in grip force regulation and their relation to function might be due to altered sensorimotor function in patients with hand OA. Ultimately, such changes may increase total load and

loading time in damaged joints, reduce hand function/dexterity, and perhaps increase the progression of joint degeneration (de Oliveira et al., 2011; Nunes et al., 2012)

Function

Hand function has been defined as the ability of a person to use their hands effectively in daily activities (N. Jones & Adams, 2003). It is recognized that hand OA causes a decrease in hand function (Bagis et al., 2003; Chen & Giustino, 2007; Stamm et al., 2011). The level of joint degeneration is not associated with disability and it has been shown that the presence of depression and upper limb comorbidities explain up to 35% of functional deficits on self-reported functional outcomes in people with hand OA (Calfee, Chu, Sorensen, Martens, & Elfar, 2015). Bukhave and Huniche (2014) and Stamm et al. (2014) have investigated common activity limitations in hand OA, which typically involve self-care, work and leisure activities. Self-care limitations include difficulties in personal hygiene, eating, cooking, getting dressed, buttoning, and lacing up shoes. Work is affected as well with handling small objects, typing on a computer, performing repetitive hand movements, and using tools such as paint rollers reported as being impaired. Leisure activities are often limited and people with hand OA report reducing or stopping leisure time activities such as golfing, canoeing, fishing, bicycling, gardening, knitting, sewing, and even reading. Other activities that are often difficult to perform include operating mobile phones, hand writing, shaking hands, playing the piano, playing cards, washing floors, vacuuming and wringing out washcloths, opening jars, opening bottles, and carrying heavy objects (Kjeken et al., 2005; Stamm et al., 2014; Stamm et al., 2009).

Self-reported function

The questionnaires most commonly utilised include the DASH questionnaire (Ceceli et al., 2012), which assess the overall function of the upper limb, the AUSCAN and the

Functional Index of Hand OA (FIHOA) (Stamm et al., 2009). When compared to healthy controls, people with hand OA, present with an overall score on the DASH that is approximately 32-52% higher (Davenport, Jansen, & Yeandle, 2012; MacDermid, Wessel, Humphrey, Ross, & Roth, 2007; Nunes et al., 2012). Note that higher scores represent increased loss of function. When measured by the AUSCAN, people with hand OA usually present with a deficit in function of approximately 40-45% (Bellamy, Campbell, et al., 2002; MacDermid et al., 2007; Moe et al., 2010; Wittoek, Vander Cruyssen, Maheu, & Verbruggen, 2009). Compared to healthy controls, people with hand OA present with functional deficits ranging from 31% to 36% when they are assessed on the FIHOA (Bellamy, Campbell, et al., 2002; Haugen et al., 2012; Moe et al., 2010; Wittoek et al., 2009).

Performance based functional measures

The dexterity performance tests utilised in assessing hand function include the bead intubation coordinometer, which is a timed task where patients have to insert beads into a small diameter hollow tube (Bellamy, Sothern, et al., 2002). Other tests utilised are the Nine Holes Peg Test (Kitisomprayoonkul, Promsopa, & Chaiwanichsiri, 2010; Poole et al., 2013) and Purdue Pegboard Test (Desrosiers, Hébert, Bravo, & Dutil, 1995a), which are timed dexterity tasks. The Moberg Pickup Test (Stamm et al., 2007) is a timed test in which participants are required to pick up small objects and drop them in a box next to their hand. When in pain, people with hand OA require twice the time to complete the bead intubation coordinometer test compared to when pain free (Bellamy, Sothern, et al., 2002). When measured through the Nine Hole Peg Test people with hand OA present a dexterity deficit of approximately 33% (Poole et al., 2013). On the Purdue Pegboard test, people with hand OA present with an average 20% deficit in dexterity compared to controls (Ceceli et al., 2012). When assessed with the Moberg Pickup Test,

participants with hand OA have a 28% deficit in hand dexterity compared to healthy participants (Nunes et al., 2012).

Pain, range of motion limitations, grip strength deficits, and joint stiffness all appear to reduce hand function (Ye, Kalichman, Spittle, Dobson, & Bennell, 2011). In a study that sought to identify how much function was associated with impairment deficits, hand impairments explained 37% of functional deficit (Kjeken et al., 2005) and they may explain even higher percentages in the case of finger I involvement (Dickson & Morrison, 1979; Kjeken et al., 2005). Grip strength and pain were the most important variables related to hand function (Kjeken et al., 2005). In particular, grip strength has been correlated with self-reported measures of hand function (r = -0.62) (G. Jones et al., 2001; MacIntyre et al., 2010). Other factors such as radiographic severity of hand OA and joint deformities have been suggested (Dahaghin, Bierma-Zeinstra, Hazes, & Koes, 2006) as variables influencing hand function. However, the majority of evidence shows no correlation between radiographic severity of joint degeneration and the ability to perform daily activities (Botha-Scheepers et al., 2009; Dahaghin et al., 2005; G. Jones et al., 2001; Leeb, Sautner, Andel, & Rintelen, 2003; Poiraudeau et al., 2001). Additionally, elderly people with asymptomatic Heberden and Bouchard nodes do not present with functional deficits when compared to healthy controls (Kitisomprayoonkul et al., 2010). Furthermore, function in people with hand OA varies across time without a predictable pattern (K. D. Allen et al., 2009; K. D. Allen et al., 2006; Gignac, Cao, Tang, & Beaton, 2011). These variations appear to be related to fluctuations in symptoms (Bellamy, Sothern, et al., 2002), suggesting that joint degeneration plays a lesser role in overall hand function. The only condition in which joint deformities and radiographic severity predict hand performance is erosive hand OA (Addimanda et al., 2012; Bijsterbosch et al., 2010; Kwok et al., 2013). This association might be due to the

severe erosive characteristics of the pathology, which can significantly limit hand mobility (Punzi, Ramonda, & Sfriso, 2004).

Validity and reliability of hand function measures utilised in the thesis

Among several measures available to assess functional limitations in individuals with hand OA we choose to focus on the DASH questionnaire, the upper extremity test for the elderly (TEMPA), and the Purdue Pegboard test.

Disabilities of the arm, shoulder, and hand questionnaire (DASH)

The disabilities of the arm, shoulder, and hand questionnaire was first developed by Hudak et al. (1996) (See Appendix B). The DASH evaluates both impairments and symptoms and is designed to evaluate single or multiple disorders affecting the upper limb (Hoang-Kim, Pegreffi, Moroni, & Ladd, 2011). Participants answer 30 items by circling one of five options provided. The questionnaire is scored out of 100 and higher scores indicate greater levels of disability (Hoang-Kim et al., 2011). This questionnaire has high test-retest reliability with an ICC of 0.96 (Beaton et al., 2001). Convergent construct validity has been shown by Beaton et al. (2001) when comparing the DASH to the Brigham questionnaire, a hand specific questionnaire. The same authors showed high correlation between the two measures. The DASH is a responsive tool with a standardised response mean (SRM) of 2.01, which is similar to other more hand-specific function measures (e.g. Patient Rated Wrist Evaluation PRWE, SRM: 2.27) (MacDermid, Richards, Donner, Bellamy, & Roth, 2000). Interestingly, previous research in people with chronic arm pain reported a strong correlation ($r = 0.83$) between the DASH score and the Neurobehavioral Questionnaire score (Kolb et al.,

2012). Previous studies report that people with hand OA, and age matched controls scored on average 34-54 and 1.8 respectively on the DASH (Davenport et al., 2012; MacDermid et al., 2007; Nunes et al., 2012).

Upper extremity function test for the elderly (TEMPA)

The TEMPA test was developed by Desrosiers, Hébert, Dutil, and Bravo (1993) (See Appendix C). The test is designed to assess upper limb function, speed of movement execution, and sensorimotor skills of people older than 60 years old. Desrosiers et al. (1993) reported on the test-retest reliability of the TEMPA, with ICCs ranging from 0.77 to 1.00. These authors also showed convergent validity with the Action Research Arm Test ($r = 0.90$ to 0.95) and the Box and Block Test ($r = 0.73$ to 0.78). The TEMPA score was weakly to moderately associated with the Purdue pegboard test, with correlation coefficients ranging between $r = 0.26$ and $r = 0.59$ in healthy subjects (Desrosiers, Hébert, Bravo, & Dutil, 1995b). A significant correlation has been observed between the functional activities of the TEMPA and the two-point discrimination threshold at the hand (Desrosiers et al., 1995b). This correlation is probably explained by the importance of cutaneous afferents in the regulation of force and control of movement during different motor tasks (Panek et al., 2014). The close relation between hand function and tactile acuity has been shown previously (Moberg, 1958; Novak, Mackinnon, & Kelly, 1993; Periyasamy, Manivannan, & Narayanamurthy, 2008). Normative values for TEMPA scores in people with hand OA do not exist. Nevertheless, from the literature review, it seemed to be an appropriate test to use in these people considering that the TEMPA assesses many tasks in which people with hand OA are usually impaired. In healthy people between 70 and 79 years old, the total time required to complete all tasks is an average of 117.4 seconds (Desrosiers et al., 1995b).

Purdue pegboard test

The Purdue Pegboard Test is a measure of manipulative dexterity (Tiffin & Asher, 1948) (See Appendix D). It was initially designed to test dexterity in assembly line workers. It involves three different subtests in which the number of pins and assemblies placed on a board is counted. Participants completing the test are required to insert as many pins as possible on the board with the left, right hand, both hands in 30 seconds and creating as many assemblies of pins, washers, and collars in one minute. The assembly task has been suggested to assess finger coordination to a greater extent than the unilateral tasks (Gonzalez, Rowson, & Yoxall, 2017). The test-retest reliability for one trial has ICCs ranging between 0.85 and 0.9 (Gallus & Mathiowetz, 2003). Convergent validity for the Purdue pegboard test showed correlations between r = 0.92 and r = 0.95 with the Minnesota Manual Dexterity Test (Causby, Reed, McDonnell, & Hillier, 2014). People with hand OA have an average score of nine for the unilateral task and 16 for the assembly task (Ceceli et al., 2012). Healthy controls have scores of 11-13 and 23-25 in the unilateral and assembly Purdue pegboard tasks respectively (Desrosiers et al., 1995a). In healthy controls trained with repetitive sensory stimulation, the scores on a pegboard test have been shown to improve at the same time as two-point discrimination thresholds (Kowalewski, Kattenstroth, Kalisch, & Dinse, 2012).

Conclusion

Osteoarthritis has been associated with sensorimotor and musculoskeletal deficits, which may contribute to pain and disability. Limited evidence has assessed the presence of impairments on the hand left/right discrimination test, two-point discrimination threshold and neglect like symptoms in people with OA and an even smaller number of studies have focused on hand OA specifically. A larger number of studies has assessed

muscle weakness in hand OA, however, a gap in the literature was identified on impairments in muscle endurance in OA with no studies having yet assessed this muscle property in hand OA. Furthermore, the relation between both sensorimotor impairments and muscle performance and functional disability in hand OA requires further research. A deeper understanding of the sensorimotor and muscle impairments present in people with hand OA will provide a more rational basis for the development of effective conservative treatment options.

Chapter Three: Sensorimotor, strength, endurance and functional performance in people with osteoarthritis of the hand: A case-control comparison

Introduction

As discussed in the previous chapter, OA is associated with a range of changes in the nervous and musculoskeletal systems that may contribute to pain, motor and functional impairments (Cantero-Téllez, Martín-Valero, et al., 2015; Dimitroulas et al., 2014; Lee et al., 2011). Traditionally, research in hand OA has focused on the affected joint(s) and surrounding structures (e.g. muscles, ligaments) and pain has primarily been viewed as a symptom of joint degeneration and/or instability (Kloppenburg, 2014). With respect to grip strength, several studies (Bagis et al., 2003; Kalichman & Hernández-Molina, 2010; Kjeken et al., 2005; Nunes et al., 2012; Y. Zhang et al., 2002) have shown a 10-40% deficit in people with hand OA, which has been shown to be correlated with self-reported measures of hand function (Cantero-Téllez, Martín-Valero, et al., 2015; G. Jones et al., 2001; Kjeken et al., 2005; MacIntyre & Wessel, 2009). Interestingly, Cantero-Téllez, Martín-Valero, et al. (2015) and G. Jones et al. (2001) showed that grip strength deficits were mediated by pain intensity, with more pain associated with greater weakness. A factor that has not been assessed in hand OA is muscle endurance, which has been shown to be impaired in one (Mau-Moeller et al., 2017), but not other (Elboim-Gabyzon et al., 2013; McNair & Molloy, 2016) studies of OA at other joints. A number of functional tasks require sustained gripping (Neumann & Bielefeld, 2003;

Valdes & von der Heyde, 2012), thus if grip endurance were impaired, this may contribute to disability.

While joint related factors are likely important for both pain and disability, there is now extensive evidence that, similar to other chronic pain conditions, OA is associated with a range of neuroplastic changes in the central nervous system that may contribute to both pain and motor impairments (Dimitroulas et al., 2014; Lee et al., 2011). Notably, sensorimotor deficits have been implicated in OA of the hand and other joints, with observations of widespread tactile hypoesthesia (Wylde et al., 2012), reduced tactile acuity (Stanton et al., 2013), body size distortions (Gilpin et al., 2015) and both disinhibition (Parker, Lewis, Rice, & McNair, 2016) and reorganisation (Shanahan et al., 2015) of the primary motor cortex. Together, these findings suggest that a substantial amount of the variance in both OA related pain and disability may occur due to brain related, rather than simply joint related factors (Stanton et al., 2013).

Clinically, sensorimotor dysfunction can be assessed using a variety of tests including left/right discrimination tasks that assess implicit motor imagery performance (Moseley, Butler, et al., 2012), questionnaires assessing body perceptual disturbances or neglect like symptoms (Punt et al., 2013) and two-point discrimination (TPD) tests of tactile acuity (Catley et al., 2014). There is evidence (Luomajoki & Moseley, 2011; Stanton et al., 2013) that these elements of sensorimotor function are inter-related and are linked to the performance of an individual's working body schema. Working body schema is thought to be essential for the proper planning, coordination and execution of movement (Elsig et al., 2014). Given the extensive motor repertoire and fine motor control required at the hand during functional tasks (Ceceli et al., 2012; Gallus & Mathiowetz, 2003; Luomajoki & Moseley, 2011), it seems likely that if people with hand OA demonstrate a disrupted working body schema and/or impaired tactile acuity, these measures would

be related to hand dexterity and functional performance outcomes. Additionally, given that pain is a central feature in OA, and it has been shown to influence motor performance (Rice, McNair, Lewis, & Mannion, 2015), it seems likely that greater nociceptive input to the brain has the potential to disrupt the working body schema. Despite its importance, to date there has been little research that has investigated these sensorimotor issues in individuals with hand OA.

The aims of this study were to examine selected sensorimotor and muscle impairments and their association with different measures of hand function in people with hand OA. Furthermore, to better understand their underlying mechanisms and potential clinical consequences we examined the correlation between different measures of sensorimotor impairment and, in turn, their association with pain intensity. Our main hypotheses were that: 1) People with hand OA would be slower and less accurate when performing a hand left/right discrimination task but not a control left/right discrimination task; 2) People with hand OA would report more neglect-like symptoms; 3) Tactile acuity of the hand would be reduced in people with hand OA; 4) Hand left/right discrimination performance would be related to tactile acuity and pain intensity; 5) Both hand left/right discrimination performance and tactile acuity would be related to measures of hand function in people with hand OA; 6) Grip strength and endurance would be lower in people with hand OA; 7) Grip strength and endurance would be related to measures of hand function in people with hand OA and 8) Grip strength and endurance would be related to pain intensity in people with hand OA.

Methods

Participants

Two groups of participants were recruited. The first group included 20 participants with symptomatic hand OA. Hand OA was confirmed through radiographic evidence which involved scoring utilising the Kellgren-Lawrence scale (Schaefer et al., 2018) by an independent radiologist. The American College of Rheumatology (ACR) clinical criteria (Altman et al., 1990) were assessed by a musculoskeletal physiotherapist with postgraduate qualifications. See Table 2 for participants' eligibility criteria. The second group was composed of 20 age and gender matched participants without hand OA. A power calculation was performed to determine the sample size required to identify differences between groups on our primary outcome which was reaction time in the hand left/right discrimination task, while TPD threshold and grip strength were secondary outcomes. Based upon research by De Simone et al. (2013), Stanton et al. (2013) and Bagis et al. (2003), the sample size calculated was 36 participants in total. For these calculations, the alpha level was set at 0.05, with beta at 0.8 and the requirement for a medium effect size. All participants provided written informed consent for the experimental procedure. Ethical approval for the study was attained from the Auckland University of Technology Committee, in accordance with the principles set out in the declaration of Helsinki (See Appendix E).

Table 2. Eligibility criteria, recruitment method and flow of participants' recruitment

Study Information	Hand OA	Healthy pain-free controls
Eligibility criteria	Fulfils ACR criteria: Hand pain, aching, or stiffness and 3 or 4 of the following: - Hard tissue enlargement of 2 or more of 10 selected joints* - Hard tissue enlargement of 2 or more DIP joints - Fewer than 3 swollen MCP joints - Deformity of at least 1 of 10 selected joints* Radiographic evidence (Kellgren Lawrence > 1) No symptoms of upper limb radiculopathy No past or present Hx of neurological disease Hand pain for a least three months on consecutive days in the last year Hand pain in the week before testing scored at three or higher on an 11-point verbal NRS	Does not have: - Upper limb pain; - Cervical/Thoracic pain pathologies No symptoms of upper limb radiculopathy No past or present Hx of neurological disease
Source of participants	Hand clinics in Auckland, hand surgeons	Staff recruited from the Auckland University of Technology and volunteers recruited from the community
Method of recruitment	Advertisement	Snowball sampling

Note. * = second and third distal interphalangeal (DIP), the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands; MCP = Metacarpophalangeal; Hx = History; NRS = numeric rating pain scale (0-10, where 0 = "no pain" and 10 = "worst pain imaginable").

Procedures

Demographic information (age, gender, height, weight) was collected from all participants and pain location, duration and intensity were assessed. Participants were asked to rate their average pain intensity in the hand in the last week on an 11-point numeric rating pain scale (NRS) scale with anchors of 0 = no pain and 10 = worst pain

imaginable. The Edinburgh Handedness Inventory was used to assess handedness in all participants. Control participants were individually matched to hand OA participants according to age (± 5 years), gender and hand (dominant vs non-dominant). All testing procedures took place in a single session of approximately 2 hours. To minimise any effects of fatigue, rest periods (one minute) were given between tests and all tests were performed in a random order.

Hand left/right discrimination and control left/right discrimination tasks

Two left/right discrimination tasks were examined, a hand/left right judgement task and control left/right discrimination task. The hand left/right discrimination task provided a measure of implicit motor imagery performance and relies on an intact working body schema (Moseley, Butler, et al., 2012). The participants sat in a chair in front of a computer, approximately 60 cm from the screen. The palm of the participants' hands was comfortably placed on a table. A series of photographs of left and right hands were presented on the computer screen. These pictures showed either hand in differently rotated positions. See figure (See Figure 2).

Figure 2. A. Hand left/right discrimination (egocentric) pictures; B. Control left/right discrimination (allocentric) pictures

Upon viewing the picture, participants were asked to indicate "as quickly and as accurately as possible" whether they were viewing the left or right hand. Upon making their decision, they were instructed to speak the word "left" or "right" into a microphone positioned in front of them. The signal from the microphone was transmitted to a custom-made LabVIEW software program (LabVIEW software, Version: 2013, Austin, TX, USA), and the time (ms) from the presentation of the picture to the voice response was calculated. The accuracy of the response was also assessed. Each hand picture was shown for five seconds. Thereafter a blank screen with a black cross appeared on the screen for a two second interval before the next hand picture was shown. Based on previous experimental findings we examined four picture rotations (180°, 225°, 270°, 315°), which have previously been shown to be most difficult to discern as being left or right hands (De Simone et al., 2013). The validity of left/right discrimination tasks has been well established in both brain imaging and clinical studies (Catley et al., 2013; Coslett et al., 2010; Dagsdottir et al., 2015; Fiorio, Tinazzi, & Aglioti, 2006; Hudson, McCormick, Zalucki, & Moseley, 2006; Schwoebel, Friedman, Duda, & Coslett, 2001; Stanton et al., 2012). Reliability of this task has been established by pilot testing (ICC: 0.94; 95%CI: 0.82-0.98).

To control for a general decline in cognitive performance, or generally poorer performance of choice reaction time tasks (unrelated to working body schema), a control left/right discrimination task was performed. This provided an indirect measure of executive function. In this task, a red dot was placed on the right or left side of the hand being presented on the screen (De Simone et al., 2013). During this task, participants decided if the red dot was positioned on the right or left side of the hand as it would be seen with the hand orientated with the fingers pointing upward (See Figure 2). This task, although contextually very similar, involves mental rotation around an object centred frame of reference (allocentric), rather than mental rotation of one's own

hand to match the picture (egocentric) and thus, does not engage the working body schema (De Simone et al., 2013). The order of the hand left/right discrimination and the control left/right discrimination conditions and the rotation of the pictures was randomised. Two sets of control left/right discrimination and two sets of hand left/right discrimination were performed by each participant (practice and trial), from which only the trial set was analysed. Each set presented 48 pictures for a total of 192 pictures. The dependant variables from these tests were the reaction time (ms) of the left/right discrimination and the accuracy of the response (% correct). Only accurate left/right discrimination were used when calculating reaction time.

Neglect like symptoms

Symptoms of a body perceptual disturbances were assessed using a neglect-like symptoms questionnaire (5-30, with greater scores representing more neglect-like symptoms) (Frettlöh et al., 2006). This questionnaire investigates symptoms of cognitive neglect (e.g. “my painful limb feels like it is not part of the rest of my body”) and motor neglect (e.g. “I need to focus all my attention on my painful limb to make it move the way I want it to”) (Frettlöh et al., 2006; Kolb et al., 2012). The validity of the neglect-like questionnaire has been previously shown in participants with complex regional pain syndrome (CRPS), who showed increased signs of classic neglect as well as higher neglect-like questionnaire scores, indicative of a disrupted working body schema (Kolb et al., 2012).

Two-point discrimination

A digital sliding calliper (Craft Right, Digital Calliper) was utilised to measure two-point discrimination at the hand. The technique utilised was similar to previous studies (Catley et al., 2013). Specifically, two-point discrimination was defined as the smallest distance between two-points that could be identified as two-points rather than one.

Thirty measures were collected from the index, thenar and hypothenar sides of the hand. These were compared with the matched hand (dominant/non-dominant) of the control group. At each of the three locations, five ascending and five descending distances were assessed and the dependent variable was the mean of the smallest correct response. The sequence (index/thenar/hypothenar) of testing was randomised. The validity of two-point discrimination test has been previously shown through brain imaging studies (Akatsuka, Noguchi, Harada, Sadato, & Kakigi, 2008; Flor et al., 1995; Park & Kwon, 2012). In particular, the primary somatosensory cortex (S1) and the inferior parietal lobule are active during tactile discrimination tasks (Akatsuka et al., 2008; Park & Kwon, 2012) and the extent of S1 representation of a specific body part is correlated with its tactile acuity in both healthy (Duncan & Boynton, 2007) and chronic pain subjects (Catley et al., 2014; Flor et al., 1995; Moseley & Wiech, 2009). Reliability of this test has been established by Catley et al. (2013) and by pilot testing (ICC: 0.84; 95%CI: 0.6-0.94)

Strength and endurance of forearm flexors

Grip strength and endurance was assessed with a hydraulic Jamar hand dynamometer in the second handle position (Trampisch, Franke, Jedamzik, Hinrichs, & Platen, 2012). For grip strength, three measurements were obtained and their average was calculated (Ceceli et al., 2012). Grip endurance was assessed by asking participants to hold 50% of their age and gender matched normal grip strength until failure, defined as the inability to maintain the target level of force for three consecutive seconds. The target force (kg of grip strength) was calculated from normative values by Bohannon, Peolsson, Massy-Westropp, Desrosiers, and Bear-Lehman (2006). Reliability of these muscle performance measures has been established by Villafañe, Valdes, Vanti, Pillastrini, and Borboni (2015) and Gerodimos, Karatrantou, Psychou, Vasilopoulou, and Zafeiridis (2017)

Measures of hand function

Hand function was assessed using both a self-reported measure and measures of functional performance assessing elements of manual dexterity, strength, endurance and speed of motor execution. Self-reported function was assessed using the Disabilities of the Arm, Shoulder and Hand questionnaire (DASH) (0-100, with higher scores representing greater disability) (Beaton et al., 2001). Hand functional performance was assessed in two tests. The TEMPA (Desrosiers et al., 1993) comprises nine tasks and each one was practiced once by all participants. These tasks included picking up and moving small objects, opening jars, pouring water from a jug, opening a lock with a key and completing other common daily activities involving the hand. A stop watch was used to assess performance speed for each task and the total time across all tasks was the dependent variable. The validity and reliability of the TEMPA has been shown previously (Feys, Duportail, Kos, Van Asch, & Ketelaer, 2002). The Purdue Pegboard test involved placement of metal pins in holes on a standardised board as quickly as possible, and an assembly task in which participants combined a pin, washers and a collar in a predefined order. The dependant variables were the number of pins and assemblies that participants correctly inserted in 30 seconds and one minute respectively.

Data processing and analysis

Data were statistically analysed using SPSS software version 22 (SPSS, Chicago, IL, USA). Prior to inferential analyses, data were screened for normality (Shapiro-Wilk test) and the presence of outliers. Non-normality was observed in some instances (Reaction times and accuracy for the hand left/right discrimination task, DASH, Purdue Pegboard, and Neglect-like scores). Reciprocal transformations were used to normalise reaction times of the control and hand left/right discrimination tasks while logarithmic

transformations were used for the DASH, and Purdue Pegboard scores. Following successful transformation of the data, two separate two-way mixed ANOVAs were used to compare the reaction time between groups for the hand left/right discrimination and control left/right discrimination tasks. Any significant interaction effect between picture rotation and group was investigated using independent samples t-tests. Mann-Whitney U tests were used to analyse accuracy differences in the hand left/right discrimination and control tasks. A Pearson chi-square test was used to examine differences in the frequency of neglect-like symptoms between groups. Independent t-tests and Wilcoxon signed-rank tests were used to assess differences between hand OA participants and healthy matched controls on single variables including TPD, hand function, grip strength and endurance. Pearson product-moment correlation coefficients or Kendall's tau coefficients were used to calculate the strength of correlations between variables in the hand OA group. Based on our a priori hypotheses, informed by previous experimental findings, one-tailed tests with an alpha-level of 0.05 were used throughout the analysis. In respect to multiple comparisons, percentage error rates were calculated to assess the probability of incurring in type I error (Ottenbacher, 1991).

Results

All results are presented as mean (SD). Table 3 presents participants characteristics. Handedness level measured through the Edinburgh Handedness Inventory was not different between the two groups ($p = 0.82$). In total, 40 participants were tested. Upon further examination, one participant in the control group revealed symptoms consistent with early hand OA and we therefore excluded them from the final analysis.

Table 3. Participants' characteristics

	Hand OA (*n* = 20)	Control (*n* = 19)
Age (years)	71.7(6.9)	70.5(7.7)
Females, *n*	15	14
Right hand dominant, *n*	18	18
Height (m)	1.64(0.1)	1.66(0.1)
Mass (kg)	69.1(12.5)	68.8(10.9)
BMI (kg/m^2)	25.7(3.6)	24.9(2.8)
Right hand most painful	11	-
Bilateral hand pain	15	-
Average number of painful joints	7.4(7.2)	-
Average hand pain in the last week (NRS)*	4.6(2)	-
Duration of pain (years)	14.7(13)	-
Kellgren-Lawrence score of 2	1	-
Kellgren-Lawrence score of 3	3	-
Kellgren-Lawrence score of 4	16	-

Note. All values are mean (SD) unless otherwise specified. n = number of participants; BMI = body mass index; NRS = numerical pain rating scale (0-10, where 0 = no pain and 10 = worst pain you can imagine); * = in most painful hand.

Hand left/right discrimination task

Participants with hand OA were slower in performing the hand left/right discrimination task when compared to controls. Specifically, there was a statistically significant main effect for group ($F_{1,33} = 3.261$, $p < 0.05$). There was also a significant interaction between rotation and group factors ($F_{3,99} = 3.002$, $p < 0.05$). Planned contrasts revealed the hand OA group was significantly slower ($d = 0.5$) compared to the control in the 225°, 270° and 315° hand rotation images (See Figure 3). The hand OA group (*Mdn* = 91.7, *IQR* = 77.1, 100) was also less accurate ($\eta^2 = 0.09$) in identifying the pictures correctly during the hand left/right discrimination task compared to the control group (*Mdn* = 100, *IQR* = 91.7, 100), ($U = 129.5$, $p < 0.05$). The percentage error rate

calculation showed that 6.25% of the significant results obtained from the planned comparisons might be the result of chance.

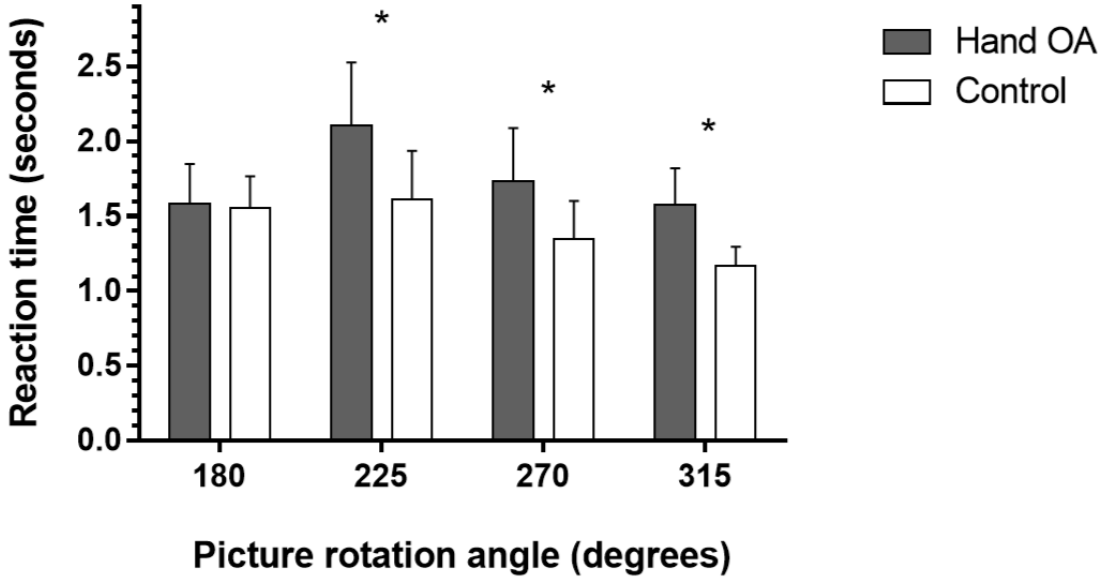


Figure 3. Reaction time during the hand left/right discrimination (egocentric) task for the most difficult picture rotations. Means and 95% CI are shown.

Control left/right discrimination task

As predicted there was no group difference ($F_{1,36} = 0.85$, $p = 0.18$) or interaction effect between picture rotation and group ($F_{3,108} = 0.184$, $p = 0.45$) for the control left/right discrimination task. Participants with hand OA did not differ in accuracy of the response when compared to controls (*Mdn* = 100, *IQR* = 100) ($U = 189.5$, $p = 0.58$).

Neglect-like symptoms

The hand OA group reported neglect-like symptoms significantly more often than the control group ($\chi^2(1) = 12.78$, $p < 0.001$, Cramer's V = 0.6). Individual scores for the hand OA and control groups are illustrated in Figure 4.

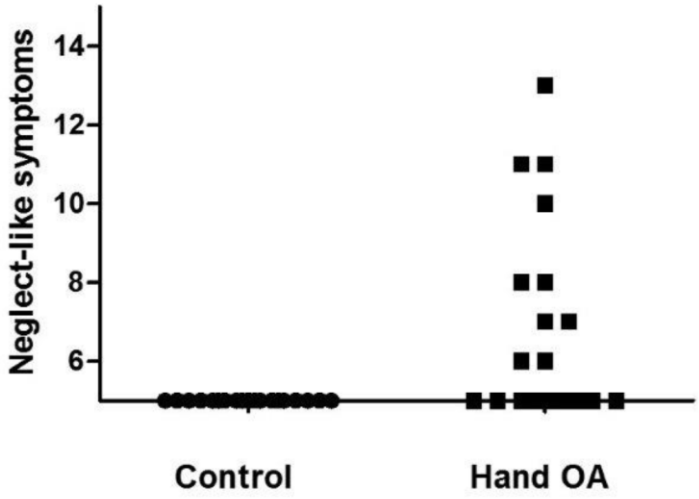


Figure 4. Neglect-like symptom scores for the control and hand OA groups.

Two-point discrimination

There was no significant difference in two-point discrimination threshold between the control group (M = 9.48, *95% CI* = 8.66, 10.45) and the hand OA group (M = 10.31, *95% CI* = 8.75, 12.44), (t_{37} = 0.9, p = 0.19).

Relationship between sensorimotor tests and their relation to pain

There was no correlation between the hand left/right discrimination reaction time or accuracy and TPD thresholds (reaction time, τ_b = 0.04, p = 0.4; accuracy, τ_b = 0.006, p = 0.5). However, there was a correlation between pain intensity and both reaction time and accuracy (reaction time, r = 0.44, $p < 0.05$; accuracy, τ_b = -0.4, $p < 0.05$). No correlation was identified between pain intensity and TPD threshold (τ_b = 0.00, p = 0.5).

Measures of hand function

Participants with hand OA scored significantly higher on the DASH (t_{37} = -9.63, $p < 0.001$) and lower on the Purdue assembly tasks (t_{37} = 2.196, $p < 0.05$) compared to

the controls. Additionally, the hand OA group was significantly slower at completing functional tasks in the TEMPA compared to controls (t_{37} = -3.28, p < 0.05). No significant differences were found between groups for the Purdue unilateral test (t_{37} = 1.57, p = 0.063).

Relationship between sensorimotor tests and hand function

There was no correlation between the hand left/right discrimination reaction time or accuracy and DASH (reaction time, r = 0.210, p = 0.19; accuracy, r = 0.23, p = 0.08), TEMPA (reaction time, r = 0.18, p = 0.23; accuracy, r = -0.15, p = 0.2), Purdue unilateral (reaction time, r = -0.1, p = 0.34; accuracy, r = 0.12, p = 0.25), or Purdue assembly (reaction time, r = -0.093, p = 0.35, accuracy, r = 0.17, p = 0.17) measures. However, two-point discrimination threshold at the hand was significantly correlated with the TEMPA total time (r = 0.65, p < 0.05). Two-point discrimination threshold was also negatively correlated with the Purdue unilateral (r = -0.6, p < 0.05), and the Purdue assembly scores (r = -0.52, p < 0.05) (See Figure 5). No significant correlation was found between the two-point discrimination threshold and the DASH total score (r = 0.24, p = 0.16).

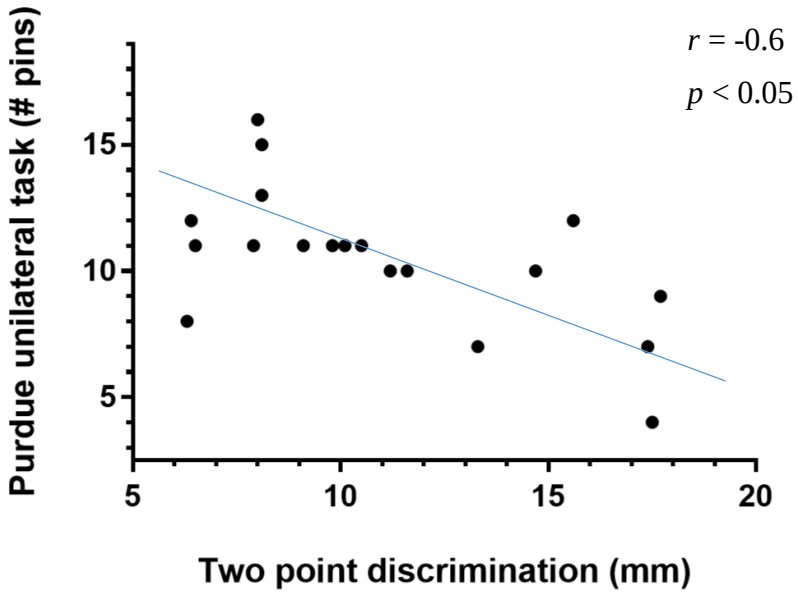


Figure 5. The relationship between TPD thresholds and the Purdue unilateral score for the hand OA group. TPD = two-point discrimination at the hand. # = number.

Grip strength and endurance

There was a significant difference in grip strength (d = 0.45) between the control group (M = 24.8, *95% CI* = 21, 28.7) and the hand OA group (M = 21.2, *95% CI* = 17.3, 25.2), (t_{18} = -2.5, $p < 0.05$). No difference was shown when comparing grip endurance between the control group (*Mdn* = 74, *IQR* = 45, 96) and the hand OA group (*Mdn* = 42, *IQR* = 23, 94), (T = 66, p = 0.24). The percentage error rate calculation showed that 10% of the significant results obtained from the planned comparisons might be the result of chance.

Relationship between muscle impairments and pain

There was no correlation between grip strength or endurance and pain intensity (grip strength, r = -0.35, p = 0.07; endurance, τ_b = 0.1, p = 0.29).

Relationship between muscle impairments and hand function

There was a correlation between grip strength and DASH (r = -0.63, $p < 0.05$) (See Figure 6). There was no correlation between grip strength and TEMPA (τ_b = -0.24, p = 0.075), Purdue unilateral (r = 0.26, p = 0.14) or Purdue assembly (r = 0.24, p = 0.16) measures.

There was no correlation between grip endurance and DASH (τ_b = -0.07, p = 0.35), TEMPA (τ_b = -0.12, p = 0.24), Purdue unilateral (τ_b = 0.11, p = 0.27) or Purdue assembly (τ_b = -0.16, p = 0.17).

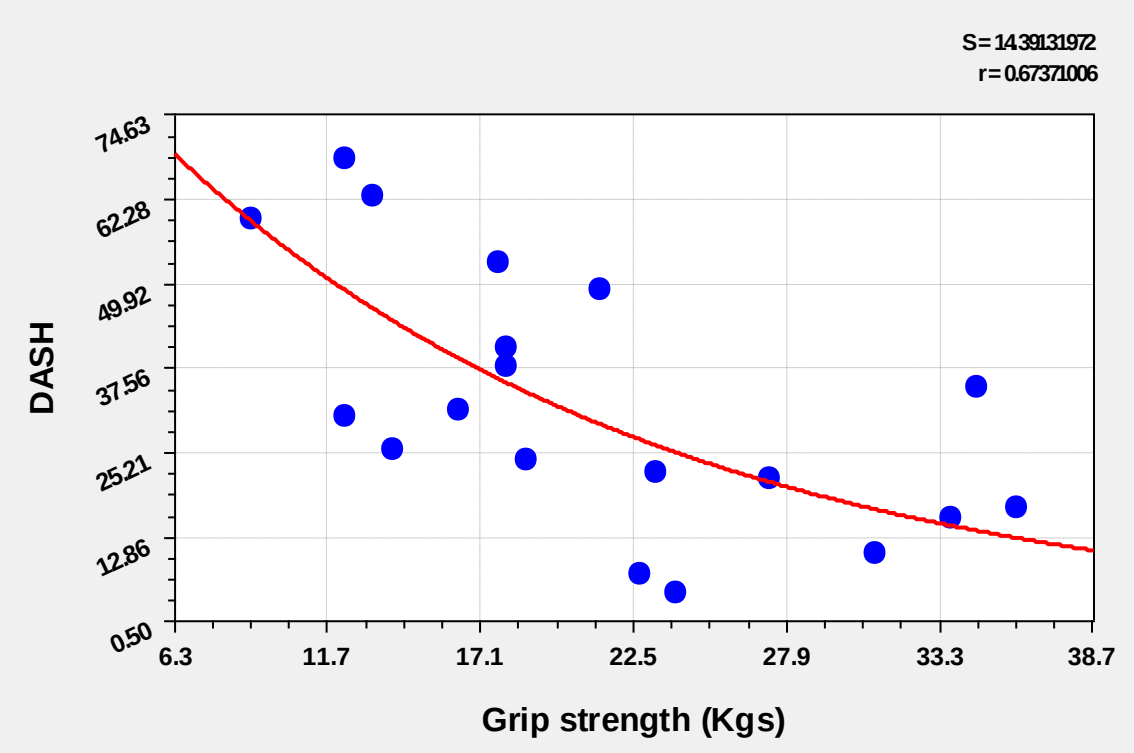


Figure 6. Relationship between grip strength (kg) and DASH scores.

Discussion

Sensorimotor measures and their relation to pain and hand function

This study provides evidence of a disrupted working body schema in people with painful hand OA. Compared to matched control participants, people with hand OA were slower and less accurate in performing a hand left/right discrimination task and reported more frequently neglect-like symptoms. However, we were unable to demonstrate a significant between group difference in tactile acuity, as measured by TPD.

Previous research has observed similar deficits in the performance of left/right discrimination tasks and neglect like symptoms in participants with other chronic pain conditions including CRPS (Moseley, 2004), chronic neck pain (Elsig et al., 2014), and chronic upper or lower limb pain of various aetiologies (Coslett et al., 2010; Fiorio et al., 2006; Schwoebel et al., 2001). Similarly, Stanton et al. (2012) reported impaired accuracy of a foot left/right discrimination task in people with knee OA but, in contrast to our findings, reaction time was unaffected. The difference may be explained by the nature of the left/right discrimination tasks utilised. While mental rotation of the foot likely necessitates rotation of the whole lower limb, including the painful knee, it may be that relatively preserved proprioceptive input from the rest of the lower limb led to less disruption in left/right discrimination of the foot in people with knee OA. Furthermore, Stanton et al. (2012) were not able to account for rotation positions which have been defined as the most difficult during left/right discrimination tasks (De Simone et al., 2013) as their task involved only 10 pictures drawn randomly from a pool of 20. In contrast, we presented the same 48 pictures to all participants (in a random order) and were therefore able to assess the most difficult rotation positions for comparison between groups.

It is possible that other factors such as cognitive decline, or generally slower performance in choice reaction time tasks could account for impaired left/right discrimination, unrelated to a disrupted working body schema. As such, we included a control left/right discrimination task that, although contextually similar, involved mental rotation around an object centred frame of reference (allocentric), rather than mental rotation of one's own hand to match the picture (egocentric). That only the egocentric task was affected suggests a specific deficit of the working body schema in people with hand OA.

Possible mechanisms of disrupted working body schema

This is the first study to explore the relationship between left/right discrimination performance and TPD in hand OA. Similar to our findings, Stanton et al. (2013) failed to demonstrate a correlation between left/right discrimination accuracy and TPD in people with knee OA. In contrast, healthy controls and people with chronic low back pain showed a significant positive relationship between left/right discrimination accuracy and tactile acuity (Stanton et al., 2013). Experimental studies have shown that body perceptual disturbances and deficits in left/right discrimination can be induced by both altered proprioceptive input (Dagsdottir et al., 2015; Hudson et al., 2006; McCormick, Zalucki, Hudson, & Moseley, 2007; S. Silva et al., 2011; Türker, Yeo, & Gandevia, 2005) and an increase in nociceptive input (Dagsdottir et al., 2015; Hudson et al., 2006). Thus, it could be that even with relatively preserved tactile acuity, nociceptive input from the arthritic joint(s) is sufficient to disrupt the working body schema in people with OA. Moreover, it has been suggested that a bias in attentional processing of sensory inputs away from the (most) painful limb or side of space may at least partially explain impaired left/right discrimination performance, especially with respect to reaction time (Moseley et al., 2009; Moseley, Gallagher, et al., 2012; Reid et al., 2016). Our findings of an increased frequency of neglect like symptoms in our study

population provides support for such an attentional bias existing in people with hand OA.

Relationships between working body schema, tactile acuity and measures of hand function

Somewhat surprisingly, we could find no relationship between hand left/right discrimination reaction time or accuracy and measures of hand function. This may relate to the nature of the functional tasks we assessed, which were largely quantified by the speed, rather than the quality of performance. It is possible that a disrupted working body schema impairs quality of movement more than speed of execution (Luomajoki & Moseley, 2011). Nevertheless, we found that tactile acuity was associated with several measures of function and dexterity in people with hand OA. Previous studies across a range of different pathologies have shown a correlation between tactile acuity and hand function (Guclu-Gunduz, Citaker, Nazliel, & Irkec, 2012; Kaluga, Kostiukow, Samborski, & Rostkowska, 2014; Melchior, Vatine, & Weiss, 2007; Meyer, Karttunen, Thijs, Feys, & Verheyden, 2014; Novak et al., 1993). This relationship may be explained by the fine regulation of descending motor commands at the spinal level by interneurons that receive cutaneous inputs (Pierrot-Deseilligny & Burke, 2005). Interestingly, tactile acuity can be improved by interventions such as tactile discrimination training, even in chronic pain populations (Flor et al., 2001; Moseley & Wiech, 2009; Moseley, Zalucki, et al., 2008). It is therefore possible that tactile discrimination training may prove a useful adjunct to rehabilitation in people with hand OA, leading to improvements in hand function and dexterity.

Measures of muscle performance and their relation to pain and hand function

Previous studies have assessed grip endurance in elderly people (Desrosiers et al., 1997), however, this is the first study assessing muscle endurance in people with hand

OA. In contrast to our hypothesis, no difference in grip endurance was found between the hand OA group and healthy controls and grip endurance was not correlated with any measures of hand function. This is similar to some findings in OA of other joints such as the knee. McNair and Molloy (2016) and Elboim-Gabyzon et al. (2013) showed that people with knee OA present with quadriceps weakness, yet muscle endurance was preserved and even higher in subjects with knee OA compared to healthy controls. In contrast, Mau-Moeller et al. (2017) found significant impairments in both knee extensor strength and endurance compared to healthy controls. It is also important to note that several methods have been utilised to assess muscle endurance (McCarthy, Callaghan, & Oldham, 2008; Swallow et al., 2007; White, Dixon, Samuel, & Stokes, 2013). Most commonly, participants have been asked to maintain isometric muscle contractions at a percentage of their maximum voluntary contraction (MVC) until failure (Desrosiers et al., 1997; Mau-Moeller et al., 2017), or repeatedly perform/maintain maximal contractions from which a fatigue index representing the decrease in torque over time was calculated (Elboim-Gabyzon et al., 2013; Fisher, White, Yack, Smolinski, & Pendergast, 1997). These protocols have shown moderate to high reliability for both grip (Gerodimos et al., 2017; Reuter, Massy-Westropp, & Evans, 2011) and quadricep endurance in healthy subjects (Bouzubar, Kelley Fitzgerald, Sparto, & Irrgang, 2015). We chose to measure grip endurance during a sustained isometric contraction. Furthermore, given the notable grip strength deficits among hand OA participants observed in this and other studies (Bagis et al., 2003; Kjeken et al., 2005; Y. Zhang et al., 2002), a relative grip force target (i.e. a % of each individual's MVC) may have obscured any true differences in muscle endurance between the two groups, as the absolute load would have been significantly less in the hand OA group. Furthermore, several activities of daily living including carrying objects, food preparation, and recreational activities require holding a sustained grip force at an absolute load (e.g. 10

kg) for prolonged periods of time (Neumann & Bielefeld, 2003). Thus, instead of assessing relative grip endurance, we elected to test participants by quantifying their time to fatigue based on an absolute force target (50% of their age and gender normative values) (Bohannon et al., 2006). Despite this, we could not demonstrate any difference in muscle endurance between the hand OA and control groups. This may be due to morphological changes in the forearm muscles of our hand OA group which may have developed a higher proportion of type I muscle fibres due to preferential atrophy of type II fibres, as has been seen in chronic knee OA (Fink et al., 2007) and after knee joint injury (Stockmar et al., 2006).

In line with previous evidence (Bagis et al., 2003; Y. Zhang et al., 2002), there was a 15% deficit in grip strength in people with hand OA compared to healthy participants. It seems likely that grip strength deficits are at least partly driven by muscle atrophy in hand OA. Forearm muscle atrophy has never been assessed in hand OA, however, previous research showed that 33% and 46% of grip strength was explained by forearm cross sectional area in rheumatoid arthritis subjects and healthy controls respectively (Helliwell & Jackson, 1994), suggesting that deficits in muscle activation due to neural inhibition may be another factor interfering with maximal force production in hand OA. In this regard, knee OA is typically associated with neural activation deficits due to factors such as joint swelling and pain (Becker, Berth, Nehring, & Awiszus, 2004; Hart, Pietrosimone, Hertel, & Ingersoll, 2010; Pietrosimone, Hertel, Ingersoll, Hart, & Saliba, 2011). Previous research has shown that grip strength in people with symptomatic hand OA is moderately correlated (r = -0.45) with joint pain (G. Jones et al., 2001). However, in the current study, we could not replicate this finding. Future research may wish to explore this further, perhaps by comparing the ratio between grip strength and muscle size in people with hand OA and in healthy controls (Konishi et al., 2007).

Our results showed that grip strength was associated with the DASH score in people with hand OA (r = -0.63) and from the data presented in Figure 6, it appears that less than 20 kg of grip strength is particularly associated with higher levels of disability as measured on the DASH. It has been suggested that during daily grasping activities, gripping forces of 20-25 kg are required for tasks such as opening a bottle/jar, turning a key in a lock and cutting with scissors (Cooney & Chao, 1977; Neumann & Bielefeld, 2003; Valdes & von der Heyde, 2012). Grip strength of at least 10 kg has been suggested to be sufficient for other less exerting daily tasks (Neumann & Bielefeld, 2003). Similarly, the combination of grip, key, tip to tip and three point pinch has been shown to explain 79% of the variance in the DASH score in people with first carpometacarpal OA (Cantero-Téllez, Medina-Porqueres, Such-Sanz, Garcia-Orza, & Martin-Valero, 2015). Furthermore, when hand exercises were performed for twelve weeks in a group of people with RA, increases in grip strength were accompanied by improvements in self-reported function, as measured on the DASH (Brorsson, Hilliges, Sollerman, & Nilsdotter, 2009).

This study is not without its limitations. Our hand OA sample was relatively small and heterogeneous in nature, including patients with carpometacarpal (CMC) OA, interphalangeal (IP) OA, or a mixture of both. This may have led to a type II error, affecting our ability to detect significant between group differences in the dependent variables and to observe significant relationships between measures of hand function and certain sensorimotor and muscle performance parameters. Furthermore, tactile acuity was assessed as the mean TPD distance across 3 sites on the hand (thenar, hypothenar, index finger), as pilot work (n = 19 healthy controls) showed this measure was more reliable than TPD distance taken from any one of these sites alone (Magni et al, unpublished observations). However, given the detailed representation of the hand in the primary somatosensory cortex (Hlustik, Solodkin, Gullapalli, Noll, & Small, 2001)

and the specificity of impaired tactile acuity observed in other chronic pain conditions (Moseley, 2008), it is possible we would have observed a difference in TPD thresholds had we assessed this at the most painful site for each person with hand OA and the matched site in the control group. Unfortunately, this was not possible as, although we counted the number of painful joints, pain intensity was measured as the average pain intensity of the whole hand in the last week, rather than at each specific joint(s). Future research should aim to assess sensorimotor impairments according to pain location or in subgroups of people affected by CMC OA and IP OA. Furthermore, although we observed a significant association between pain intensity and left/right discrimination performance, the cross-sectional nature of our study makes it difficult to determine the direction of this relationship. It is possible that higher pain intensity at least partially reflects greater nociceptive input to the brain, which in turn disrupts the working body schema. Alternatively, previous studies have suggested that a disrupted working body schema could in fact lead to an increase in pain (Harris, 1999; McCabe, Haigh, Halligan, & Blake, 2005). In support of such a top down mechanism, it has been shown that illusory resizing of the OA hand can produce immediate and, in many cases, substantial pain relief (Preston & Newport, 2011) and that this intervention can partially correct distorted perceptions of the size of the painful hand (Gilpin et al., 2015). Similarly, while the relationship observed between grip strength and self-reported disability suggests that interventions targeting muscle strength may improve hand function, it is not possible to identify causal relationships between variables with a cross-sectional study like the present one. Thus, the aim of the next chapter was to provide a review of existing studies that assessed the effectiveness of strength training interventions on muscle strength, pain and function in people with hand OA.

Conclusions

This study identified differences between groups in sensorimotor performance, yet muscle strength was the only outcome which was significantly impaired in people with hand OA and at the same time associated with worst self-reported measures of hand function. Specifically, lower levels of grip strength were correlated with worse function as measured by the DASH questionnaire. This finding is supported by previous evidence, which highlighted the importance of moderate grip strength levels for important daily life activities. It is therefore possible that resistance training interventions may improve muscle strength as well as function in people with hand OA, providing clinicians with an additional conservative treatment approach for patients with this condition.

Chapter Four: The effects of resistance training on muscle strength, joint pain, and hand function in individuals with hand osteoarthritis: A systematic review and meta-analysis.

Introduction

Resistance training is often utilised to decrease symptoms, and improve both muscle strength and function in individuals with OA at the knee and hip (Li et al., 2015; van Baar, Assendelft, Dekker, Oostendorp, & Bijlsma, 1999). Several studies have demonstrated its effectiveness and this treatment modality is included in the American College of Rheumatology 2012 treatment guidelines for knee and hip OA, but not for hand OA (Hochberg et al., 2012). The EULAR 2007 recommendations for the management of hand OA suggested the use of education plus exercise for the treatment of this pathology (W. Zhang et al., 2007). However, it is not clear whether a specific type of exercise is more suitable for people with hand OA.

In the previous chapter, we found evidence of grip strength deficits and a moderate correlation with self-reported disability on the disability of the arm, shoulder and hand questionnaire (DASH) in people with hand OA. Grip strength deficits have been previously reported by several authors in hand OA populations (Bagis et al., 2003; Kjeken et al., 2005; Y. Zhang et al., 2002) and there is evidence suggesting that at least 20-25 kg of grip strength are required to perform some important daily tasks (Neumann & Bielefeld, 2003; Valdes & von der Heyde, 2012). Nevertheless, a paucity of studies

have attempted implementing exercises in people with hand OA and an even smaller number of studies have assessed the efficacy of resistance training exercises in this population (Bertozzi et al., 2015; Kjeken et al., 2011; Mahendira & Towheed, 2009; Ye et al., 2011).

To date, no reviews have focused specifically on the efficacy of resistance training exercises for hand OA and examined the training regimes adopted in the intervention studies. Thus, the aim of the current study was to perform a systematic review and meta-analysis of the effect of resistance training on grip strength, joint pain, and hand function in people with hand OA.

Methods

Design and search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). The search strategy was based on the PICO (Population, Intervention, Comparison and Outcome) format. The electronic databases EBSCO host (CINAHL, MEDLINE, SPORTDiscus), Allied and Complementary Medicine Database (AMED) via OVID, Cochrane Central Register of Controlled Trials via Wiley, Web of Science, and Scopus were searched between 1975 and July 2016. The search was limited to published studies, including human participants older than 18 years and published in English, Italian or Spanish. The keywords utilised for the search included: hand(s), thumb(s), carpometacarpal(s), trapeziometacarpal(s), wrist(s), osteoarthr(itis)(osis)(itic), OA, train(ining)(ed), strength(ening)(ened), exercis(e)(ed)(es)(ing), physiotherap(y)(ist), physical therap(y)(ist), rehab(ilitation)(ilitative), manual

therap(y)(ies), RCT(s), random(ly)(ised), trial(s)(led), experiment(s)(al). Each database was searched by two people.

Eligibility criteria

To be included in this review, studies must have been investigating the effects of resistance training in adults with hand OA. Eligible papers were published randomised controlled trials (RCT). Studies were considered if they included a between-group comparison after treatment in people with hand OA. As this review was focused on the effect of resistance training, studies had to compare resistance training interventions to a non-exercising control intervention, to be eligible for inclusion. Studies including multimodal intervention (e.g. splinting, manual therapy, ultrasound, yoga) were excluded. Studies including exercise without reference to resistance/strength training were not suitable for inclusion. The primary variables of interest were grip strength, joint pain, and hand function. Systematic, narrative reviews, and experimental studies were identified and manual searches of their reference lists were undertaken to identify additional studies. Forward searches of included studies were completed in Google Scholar and Scopus.

Study inclusion

All the studies identified were collected in bibliographic software (Endnote X7, Thomson Reuters), where the inclusion and exclusion criteria were applied by two individuals. All duplicated studies were eliminated before title and abstract screening. The retained articles were retrieved in full text and assessed for inclusion. Disagreement on study inclusion was first discussed and if consensus was not reached, the opinion of a third person was sought. A search of the reference lists of the included studies was undertaken to identify further articles.

Risk of bias and Overall quality of evidence

Using the risk of bias table suggested by the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group (Higgins & Green, 2011), a critical appraisal of each study was performed by two researchers. Its seven items assessed the internal validity of the studies. Each item was scored as low risk, high risk or unclear risk.

To evaluate the overall quality of the evidence the GRADE system was utilised (Grade Working Group, 2004). The quality of evidence was downgraded by one point from high quality for each factor that we encountered: (1) risk of bias (if it was deemed that the bias may affect trial outcomes), (2) inconsistency of results (wide variance of effect sizes or significant or large heterogeneity between trials: $p < 0.05$, $I^2 > 50\%$), (3) indirectness (application of intervention, intervention or outcomes that differed from what we indicated in our PICO research question), (4) imprecision (optimal information size not met). A GRADE profile was completed for each pooled estimate. Two reviewers judged whether these factors were present for each outcome and in cases of disagreement a third reviewer was involved. The quality of evidence was defined as (1) high (the authors are confident that the true effect is close to the one estimated); (2) moderate (the authors are moderately confident in the effect estimate); (3) low (the true effect may be significantly different from the estimated); (4) very low (the true effect is most likely different from the estimated) (Schünemann, Brozek, Guyatt, & Oxman, 2009).

Data extraction

Descriptive statistics (means, standard deviations) for demographic and pre-post outcome dependent variables were extracted and cross-checked. When appropriate, the post-intervention values for the exercise and control groups were used to calculate the

mean difference (MD) or the standardised mean difference (SMD), which was the difference between groups values, divided by the pooled SD, with adjustment for small sample sizes (Hedges g: SMD). If more information was required for the quantitative analysis, authors were contacted to obtain further data.

Data synthesis and analysis

Meta-analysis was performed in Review Manager (RevMan) software (version 5.3, Cochrane Collaboration) using the inverse variance method. We assumed that the studies' variability, beyond subject-level sampling error, was random and consequently we adopted a random-effect model (Liberati et al., 2009; Lipsey & Wilson, 2001). Effect sizes of 0.2, 0.5, 0.8 were considered small, medium, and large, respectively (Guyatt et al., 2012). Publication bias was assessed by visually inspecting funnel plots (Schünemann et al., 2009). Statistical heterogeneity was assessed using the chi-square tests and the I^2 statistics, the latter providing a measure of the proportion of the observed variance that would remain if sampling error was eliminated (Borenstein, Higgins, Hedges, & Rothstein, 2017). Where this proportion is of further interest, Borenstein et al. (2017) have suggested that 95% prediction intervals be calculated to appreciate the variability of the true effect size within the population under study.

Results

The initial search identified 2072 papers. After duplicate elimination, 1470 studies underwent title and abstract screening, resulting in 42 studies considered suitable for inclusion. Following full paper review, five articles met the criteria for inclusion. Figure 7 outlines the RCT selection through the review. No additional papers were retrieved from previous reviews, reference searches or forward searches of included studies.

Table 4 presents a comprehensive description of each trial included in the paper.

Summary of findings and GRADE quality ratings are reported in Table 5.

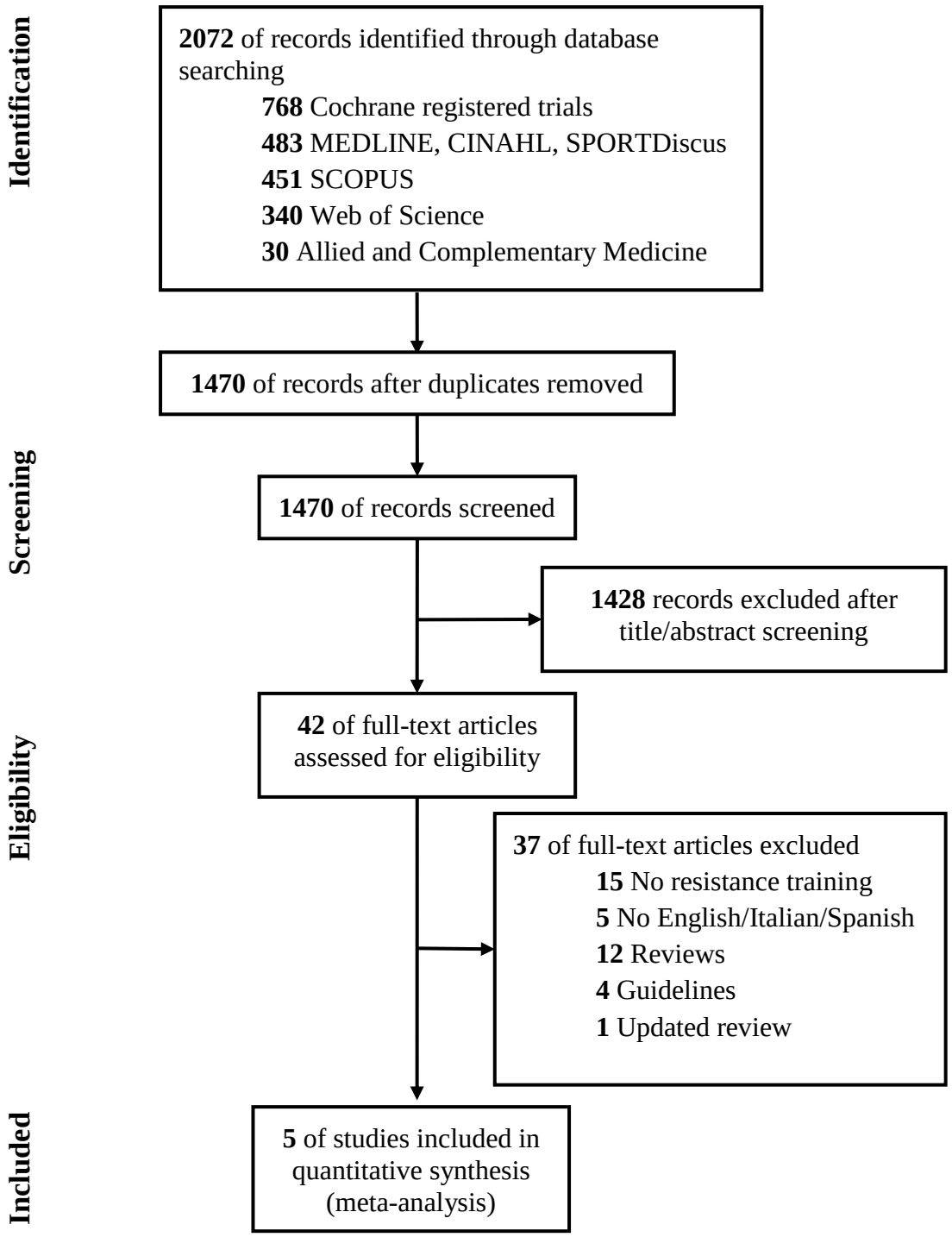


Figure 7. Flow chart of study selection

Table 4. Characteristics of included studies and intervention

Study	Participants	Interventions	Outcome (Follow-up time): statistical significance	Baseline differences
Dziedzic et al (2015)	RGb = 65 CGb = 65 N = 104 66% F 66(9.1)yrs	RG (n = 55): supervision = 1 group session/wk (For 4 wks). exercise = elastic bands fingers e/f, Play-Doh finger e/f (? % MVC), 0.5-0.75 kg wrist e/f dosage = 3 reps/day, everyday progression = up to 10 reps/day. CG (n = 49): Leaflet and advice (extensive information)	Grip strength (24 wks): NS AUSCAN pain (12 wks): NS AUSCAN function (12 wks): NS	STRENGTH (p =?) PAIN (p = 0.6) FUNCTION (p = 0.5)
Hennig et al (2015)	RGb = 40 CGb = 40 N = 71 100% F 60.8(7)yrs	RG (n = 37): supervision = 1 individual session with 8 follow-up calls exercise = elastic bands e/a thumb, rubber ball for grip strength (100% MVC) dosage = 10 reps (wks 1 & 2); 3 days/wk progression = 12 reps (wks 3 & 4); 15 reps, (wks 5-12); 3 days/wk CG (n = 34): Leaflet and advice (limited information)	Grip Strength (12 wks): S NRS pain (12 wks): S FIHOA (12 wks): S	STRENGTH (p = 0.4) PAIN (p =?) FUNCTION (p =?)
Lefler et al (2004)	RGb = ? CGb = ? N = 19 90% F 81(9)yrs	RG (n = 9): supervised = every session (For 6 wks) exercise = pinch grip lifting (isometric, 6 sec holds), wrist rolls (isotonic) (MVC = 40%) dosage = 10 reps; 3 days/wk progression = up to 15 reps, 60% MVC isometric; 6-8 reps more than 60% MVC isotonic CG (n = 10): No intervention	Grip Strength (6 wks): S Likert pain scale (6 wks): NS	STRENGTH (p = 0.08) PAIN (p = 0.53)

Østeras et al (2014)	RGb = 65 CGb = 65 N = 120 90% F 66(9)yrs	RG (n = 57): supervised = 4 group sessions (wk 1-3 & 8) exercise = shoulder e/f, biceps curl, elastic band e/a thumb, pipe squeeze (100% MVC) dosage = 10 reps, moderate/vigorous intensity (wk 1 & 2); 3 days/wk progression = 15 reps (wk 3-12) CG (n = 63): Usual care (GP visit)	Grip strength (12 wks): NS NRS pain (12 wks): S FIHOA (12 wks): NS	STRENGTH (p = 0.3) PAIN (p = 0.4) FUNCTION (p = 0.26)
Rogers et al (2009)ǂ	RGb = 76 CGb = 76 N = 46 87% F 75(6.7)yrs	RG (n = 46): supervised = 1 individual session exercise = gripping (16-19% MVC), key pinch, fingertip pinch all with rubber ball dosage = 10 reps (wk 1, 2, 3 & 4), everyday progression = 12 reps, 15 reps, 20 reps all increased every fourth wk CG (n = 46): Sham hand moisturiser	Grip strength (16 wks): NS AUSCAN pain (16 wks): NS AUSCAN function (16 wks): NS	STRENGTH (p = 0.96) PAIN (p = 0.84) FUNCTION (p = 0.87)

Note. RGb = participants allocated to the resistance training group; CGb = participants allocated to the control group; N = participants retained at follow-up; F = female; yrs = years old; RG = resistance training group; *n* = group sample size retained at follow-up; wk = weeks; e/f = extension/flexion; MVC = maximum voluntary contraction; ? = unable to calculate, unknown; reps = repetitions; CG = control group; AUSCAN = Australian Canadian Osteoarthritis Hand Index; NS = non-significant; e/a = extension/abduction; NRS = Numeric Rating Scale; FIHOA = Functional Index of Hand Osteoarthritis; S = significant; sec = seconds; ǂ = cross-over study design.

Table 5. Summary of findings (GRADE).

Resistance training compared to no exercise for hand osteoarthritis

Patient or population: Hand osteoarthritis; Setting: General practice, community, retirement villages; Intervention: Resistance training; Comparison: No exercise

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no exercise	Risk with Resistance training			
Grip strength (at study completion) assessed with: Hand dynamometer. Follow up: range 6 to 24 weeks	The mean grip strength (at study completion) in the control group was 17.7 kg	The mean grip strength (at study completion) in the intervention group was 1.35 kg higher (0.84 lower to 3.54 higher)	350 (5 RCT)	⊕⊕⊕◯ MODERATE [a]	MD 1.35 kg (95% CI -0.84 to 3.54). Relative increase 8% with resistance exercise (95% CI -5% weaker to 20% stronger).
Hand pain (at study completion) assessed with: AUSCAN pain, 11-point NRS, Likert scale. Lower scores mean less pain. Follow up: range 6 to 16 weeks	The pain score in the resistance training groups was on average -0.23 SDs (-0.42 lower to -0.04 lower) lower than in the control groups.		379 (5 RCT)	⊕⊕◯◯ LOW [a,b]	These results can be interpreted as an improvement of 0.46 (95% CI 0.08 to 0.84) points on a 11-point NRS scale.[c] The MCID for pain is 2 points (Farrar, Young, LaMoreaux, Werth, & Poole, 2001).
Hand function (at study completion) assessed with: AUSCAN function, FIHOA Lower scores mean better function. Follow up: range 6 to 16 weeks	The hand function score in the resistance training groups was on average -0.10 SDs (-0.33 lower to 0.13 higher) lower than in the control groups.		363 (4 RCT)	⊕⊕◯◯ LOW [a,b]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; MD: Mean difference; SD: Standard deviation; SMD: Standardised mean difference; MCID: Minimal clinically important difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Downgraded because few participants, wide confidence intervals (Imprecision).
b. Downgraded because participants were not blinded to intervention (Risk of bias).
c. The control group pain mean(SD) 4.6(2) was calculated by averaging the 11-point NRS scores of Dziedzic et al. (2015), Hennig et al. (2015) and Østerås et al. (2014).

Study characteristics

The participants' count was based on the participants retained at the follow-up period (see Table 4). Out of the 350 participants, 305 (87%) were female. Mean age ranged from 61 to 81 years old. The primary outcome measures were grouped into grip strength, joint pain, and self-reported hand function. Grip strength was assessed through a dynamometer (Dziedzic et al., 2015; Hennig et al., 2015; Lefler & Armstrong, 2004; Østerås et al., 2014; Rogers & Wilder, 2009). Joint pain measurements included the Australian Canadian osteoarthritis hand index (AUSCAN) pain subscale (Rogers & Wilder, 2009), the numeric rating pain scale (NRS) (Dziedzic et al., 2015; Hennig et al., 2015; Østerås et al., 2014), and a six-point Likert scale (Lefler & Armstrong, 2004). Self-reported measures of hand function included the AUSCAN function subscale (Dziedzic et al., 2015; Rogers & Wilder, 2009) and the Functional Index of Hand Osteoarthritis (FIHOA) (Hennig et al., 2015; Østerås et al., 2014).

Experimental intervention

Duration and supervision

Dziedzic et al. (2015) had an ongoing exercise program with no set ending date. The remaining studies adopted training programs of 6 – 16 weeks (Lefler & Armstrong, 2004; Østerås et al., 2014; Rogers & Wilder, 2009). Outcome measures were assessed at the end of the exercise period except Dziedzic et al. (2015), who measured grip strength at 24 weeks after participants' inclusion in the trial. Two studies supervised participants individually over one session, followed by a home exercise program (Hennig et al., 2015; Rogers & Wilder, 2009). Two studies supervised participants over four group sessions (Dziedzic et al., 2015; Østerås et al., 2014). Østerås et al. (2014) provided group sessions over the first three weeks and towards the end of the trial (week eight). The timing of participant attendance in the group sessions of the study by Dziedzic et al.

(2015) was not clear. Lefler and Armstrong (2004) reported that participants were supervised over 6 weeks, three times a week (18 sessions). However, it is not clear if the sessions were individual or group sessions.

Training modality and frequency

Gripping and forearm flexor exercises were performed in all studies through different exercises (See Table 4). Three studies included specific exercises to improve thumb extension and abduction strength (Dziedzic et al., 2015; Hennig et al., 2015; Østerås et al., 2014). Finger and wrist extensor strengthening exercises were performed by two studies (Dziedzic et al., 2015; Lefler & Armstrong, 2004). Shoulder strengthening exercises were performed in only one study (Østerås et al., 2014). Two studies required participants to exercise every day (Dziedzic et al., 2015; Rogers & Wilder, 2009) and three studies to exercise three times per week (Hennig et al., 2015; Lefler & Armstrong, 2004; Østerås et al., 2014). Repetitions at the beginning of training for each exercise ranged from three (Dziedzic et al., 2015) to 10 (Hennig et al., 2015; Lefler & Armstrong, 2004; Østerås et al., 2014; Rogers & Wilder, 2009).

Exercise intensity and progression

Only one study reported the percent of maximum voluntary contraction (40% of MVC) at which participants exercised (Lefler & Armstrong, 2004). Three other studies (Hennig et al., 2015; Østerås et al., 2014; Rogers & Wilder, 2009) presented enough data to infer an exercise load. Hennig et al. (2015) and Østerås et al. (2014) reported that participants were asked to 'squeeze as hard as possible' (100% of MVC) while performing gripping exercises. Rogers and Wilder (2009) had participants perform exercises between 16-19% of MVC. We were unable to calculate exercise intensity for Dziedzic et al. (2015) as there was not enough information available. All studies progressed the exercises by increasing the number of repetitions up to a maximum of

20. Only one study (Lefler & Armstrong, 2004), included a progressive increase in exercise load (up to 60% of MVC).

Control intervention

Two studies provided the control group with a leaflet and advice over one session (Dziedzic et al., 2015; Hennig et al., 2015). Two studies did not provide any intervention to the control group (Lefler & Armstrong, 2004; Østerås et al., 2014). Østerås et al. (2014) control group was allowed to receive usual care, which in Norway consisted of general practitioner visits only. Rogers and Wilder (2009) crossed over the same participants from a placebo hand moisturiser to the resistance training group and vice versa, with a 16 weeks washout period.

Risk of bias

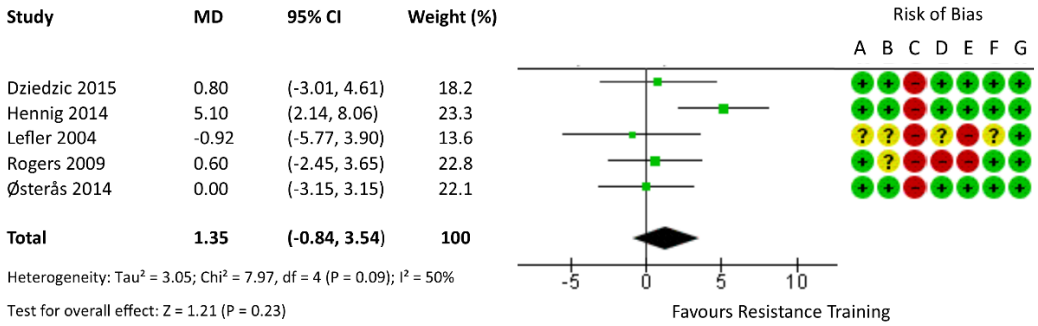
The risk of bias across the studies varied substantially (See Figure 8). All the studies failed to blind the treatment providers and participants due to the nature of the intervention. Dziedzic et al. (2015), Hennig et al. (2015), and Østerås et al. (2014) presented the lowest risk of bias. Rogers and Wilder (2009) and Lefler and Armstrong (2004) presented the highest risk of bias.

Figure 8. Risk of bias summary for the studies included.

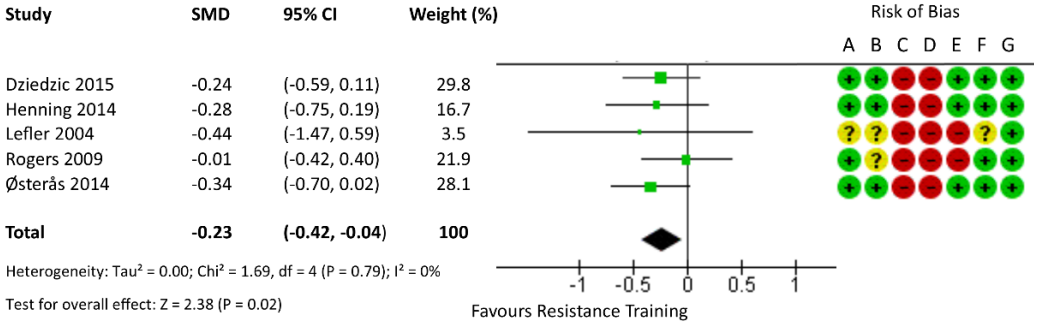
Overall quality of evidence and Meta-analyses

The results from the meta-analyses for grip strength, joint pain, and hand function are presented as forest plots in Figure 9. Funnel plots for each outcome are provided in Figure 10. Visual inspection did not reveal publication bias.

Grip strength



Joint pain



Hand Function

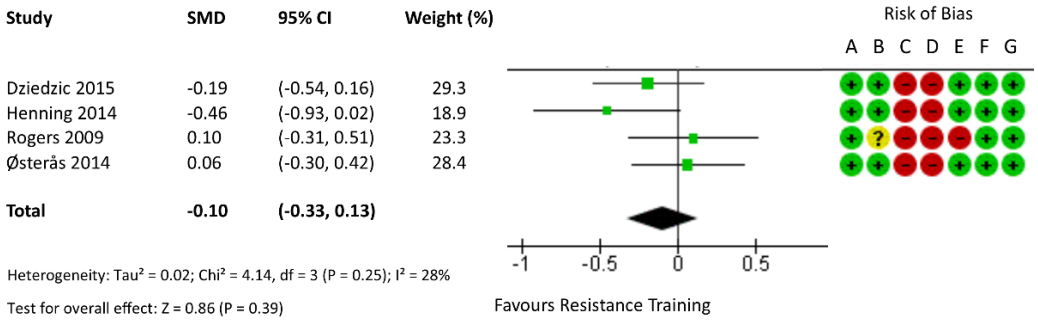
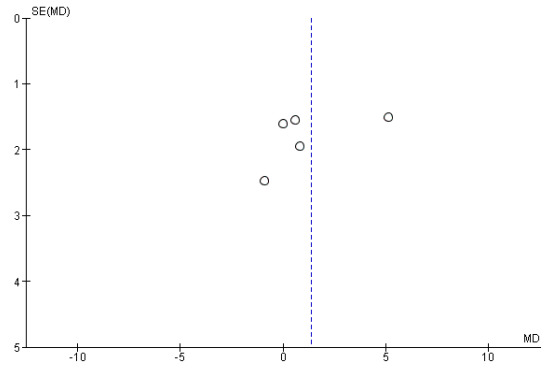
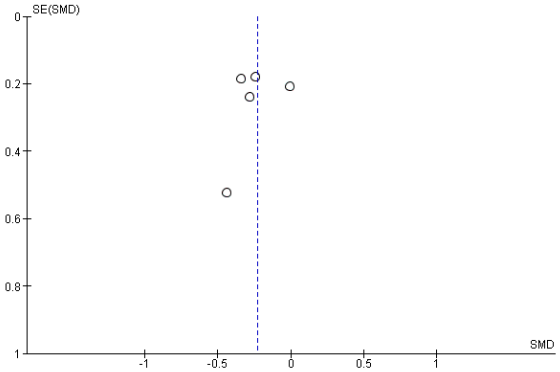


Figure 9. Forest plot showing the effect of resistance training on grip strength, pain, and function in people with hand OA.

Grip strength



Joint pain



Hand Function

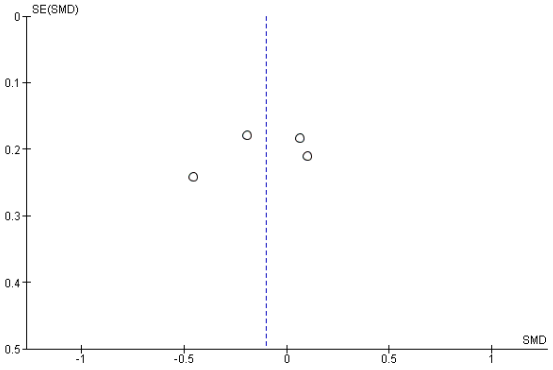


Figure 10. Funnel plot for grip strength, pain and function in people with hand OA.

Grip strength

Out of the five studies included, only two studies showed a significant change in grip strength after resistance training compared to the control group (Hennig et al., 2015; Lefler & Armstrong, 2004). The pooled results provide moderate quality evidence that

resistance exercises, as performed by these combined interventions, do not improve grip strength (MD 1.35 [95% CI -0.84, 3.54], $p = 0.23$). The I^2 was 50% ($X^2 = 7.97$, $p = 0.09$). The prediction interval indicated that 95% of the effect of resistance training would lie between -5.2 to 7.9 kg.

Joint pain

Most of the studies included in the present review showed a trend toward improvement in pain intensity for the resistance training group. However, only two studies reported statistically significant changes in pain (Hennig et al., 2015; Østerås et al., 2014) compared to the control group. The pooled results provide low quality evidence that resistance exercises provide pain relief (SMD -0.23 [95% CI -0.42, -0.04], $p = 0.02$). The I^2 was 0% ($X^2 = 1.69$, $p = 0.79$). The prediction interval indicated that 95% of effect sizes would lie between -0.54 to 0.08.

Hand function

Only one study reported significant differences in self-reported hand function after resistance training compared to the control group (Hennig et al., 2015). The pooled results provide low quality evidence that resistance exercises do not improve hand function (SMD -0.1 [95% CI -0.33, 0.13], $p = 0.39$). The I^2 was 28% ($X^2 = 4.14$, $p = 0.25$). The prediction interval indicated that 95% of effect sizes would lie between -0.9 to 0.7.

Discussion

This meta-analysis assessed the effect of resistance training on grip strength, joint pain, and hand function in participants with hand OA. It was clear that there are very few

experimental studies that have specifically addressed the effects of resistance training in this population. Previous reviews have highlighted this problem, and also emphasised the general scarcity of research involving conservative interventions for hand OA (Bertozzi et al., 2015; Kjeken et al., 2011; Kloppenburg, 2014; Østerås et al., 2014; Valdes & von der Heyde, 2012; Ye et al., 2011). These findings are surprising considering that resistance training has been used in other forms of OA with positive effects on pain, function and patients' quality of life (Nguyen, Lefèvre-Colau, Poiraudeau, & Rannou, 2016). The five studies included had small sample sizes and the outcome data was not available for participants lost at follow-up.

There was 'moderate quality evidence' that the resistance training utilised in the included studies did not improve grip strength. Of note, our overall finding concerning grip strength is in contrast to a recent review by Østerås et al. (2017). These authors noted that there was a strong trend for an improvement following training. This discrepancy most likely is related to the data analysed in the meta-analysis. That is, Østerås et al. (2017) included findings from an abstract in their analysis, and furthermore, they were not able to include additional data concerning the findings of Rogers and Wilder (2009) work, (which we were able to include after personal communication).

Nevertheless, our findings are surprising as all studies included in our analysis included gripping or forearm flexor exercises against resistance. The absence of grip strength improvement in the majority of the studies raises some questions regarding the appropriateness of the resistance training programs utilised. In addition, the technique used in the measurement of grip strength may not be congruent with the types of exercise undertaken in the intervention (Pelland et al., 2004). For instance, in the current review only two papers identified the hand position utilised for grip strength testing

(Østerås et al., 2014; Rogers & Wilder, 2009), and in both instances, the same position was utilised for all participants. This would limit the observation of strength gains if individuals trained at hand positions notably shorter or longer than the testing position (training specificity principle) (Wilson, 1994).

Additionally, a key point in resistance training guidelines concerns the volume of exercise required. The majority of the studies adopted exercise frequency, intensity, sets, repetitions and progression which are not sufficient to induce strength gains in older adults (Garber et al., 2011). For instance, it was apparent that four studies progressed participants by increasing the number of repetitions rather than the exercise intensity (Dziedzic et al., 2015; Hennig et al., 2015; Østerås et al., 2014; Rogers & Wilder, 2009), and were therefore pursuing an approach that is more efficacious for enhancing muscle endurance as compared to strength (Garber et al., 2011). In regard to absolute exercise intensity, it has been recommended that loads of at least 60% of MVC are utilised with intensity increasing as training progresses to levels approaching 80% of MVC (Garber et al., 2011). Only two studies (Hennig et al., 2015; Østerås et al., 2014) reported resistance training loads sufficient to induce increases in muscle strength (100% of MVC). Of these, Hennig et al. (2015) reported significant changes in grip strength while Østerås et al. (2014) reported only limited changes. In both cases, participants were instructed to squeeze an object as hard as possible. As grip forces are unable to be measured using such a protocol, there is no way of being sure that participants were indeed working at 100% of MVC, as compared to exercising at resistance levels that can be quantified more accurately (e.g. on a hand-held dynamometer or weights).

Pain during exercise may have influenced load and intensity performed. In this regard, Hennig et al. (2015) reported that participants' joint pain intensity immediately post

exercise was high (NRS: 5.6±2.2) while no data was available for the study by Østerås et al. (2014). It is possible that in the study by Østerås et al. (2014), in which strength changes were small, participants self-limited the exercise intensity to avoid increases in joint pain. Similarly, the low exercise load utilised by the other included studies (Lefler & Armstrong, 2004; Rogers & Wilder, 2009) may reflect the intention to avoid high joint compressive forces and further damage to the articular cartilage. However, there is a growing body of evidence suggesting that high levels of pain during or immediately after resistance training sessions (up to 6 on a NRS scale) do not negatively affect outcomes, but rather, improve overall levels of pain for the duration of the training program in people with hand and knee OA (Bryk et al., 2016; Hennig et al., 2015; Jorge et al., 2015). Such pain intensities have been previously considered acceptable in people with OA, on the condition that pain intensity returns to baseline values within 24 hours of the previous session (Hennig et al., 2015; Kjeken, Grotle, Hagen, & Østerås, 2015). Considering that exercise induced pain or clinical concerns of protecting the affected joints from high compressive forces may be significant problems when implementing traditional resistance training, alternative exercise modalities could be considered.

In the current study, there was low quality evidence suggesting that resistance training reduces joint pain. Additionally, when the standardised mean difference calculated in the current study was transformed into absolute values on a 11-point NRS scale (See Table 5), the difference between groups was 0.46 points (95% CI 0.08, 0.84), which does not reach the minimal clinically important difference of two points commonly used in OA trials (Farrar et al., 2001). At the knee joint, findings are more encouraging, with a randomised control trial (Jorge et al., 2015) reporting a mean reduction in pain of 2.3 points following high intensity resistance exercises and additional studies showing a correlation between knee extensors strength gains and improvement in pain (Bartholdy et al., 2017; Hall et al., 2018). There is no reason to suspect that such findings might not

be possible at the hand given the mechanisms advanced for its success. These include muscle strengthening altering alignment and hence loading on damaged structures within a joint, reducing the potential for inflammation and hence pain. Other authors (Runhaar, Luijsterburg, Dekker, & Bierma-Zeinstra, 2015) have suggested that increased proprioceptive awareness leads to improved placement of joints during motion, reducing load. There is also a strong potential for an antinociceptive effect of resistance training through modulation of endogenous analgesia (Daenen, Varkey, Kellmann, & Nijs, 2015; Galdino et al., 2014; Nijs, Kosek, Van Oosterwijck, & Meeus, 2012) and/or anti-inflammatory effects that may reduce peripheral and central sensitisation (Lundberg & Nader, 2008).

Low quality evidence demonstrated that hand function was not improved following resistance training. Similar results were obtained by a recent review by Bertozzi et al. (2015) which showed no significant effects of exercise interventions on hand function in people with thumb carpo-metacarpal joint OA. In contrast, Østerås et al. (2017) found a trend ($p = 0.07$) toward exercise being beneficial for function. A number of factors may be associated with these findings. These include the assessment of function by questionnaires that do not include tasks that the participants find difficult to perform, questionnaires that focus primarily on tasks requiring fine motor control tasks, rather than strength tasks, and/or resistance training programs not targeting appropriate muscle groups. As suggested by van Baar et al. (1999) and adopted by Hoeksma et al. (2004), it may be that targeting the individual's specific needs is a solution. However, where researchers take this pathway, it is important that they provide descriptions of the criteria that led them to focus on a specific type of exercise, and also provide the training parameters and improvements that occurred for those participants. Without such information, readers have no way of discerning how to prioritise types of exercise that would be most valuable for their patients.

It may be viewed as a limitation of the current study that we chose to focus on studies utilising resistance training exercises only. We are aware that in clinical practice multimodal therapies are often utilised and a combination of conservative and pharmacological interventions are adopted. However, to optimise both the efficiency and cost effectiveness of OA treatment it is important to understand which component(s) of an intervention offer the most benefit (or otherwise). In addition, the selection of resistance training studies was justified by the fact that we found evidence of muscle strength deficits and a relation to function in our previous study (Chapter three). Our focus on resistance training is also justified by the established effectiveness of this intervention in other joints such as knee OA (Li et al., 2015). Furthermore, a number of functional tasks at the hand require notable muscle forces to be generated and it has been suggested that 20-25 kg of grip strength is required for several important daily life activities (Valdes & von der Heyde, 2012). Another limitation of the present study is the small number of participants included in the meta-analysis. This was acknowledged, and the overall quality of evidence was downgraded (See Table 5). Nevertheless, all the studies except Lefler and Armstrong (2004) performed power calculations, suggesting that the optimal information size was probably met. A per-protocol analysis was performed on the post intervention data reported in each study. Data for participants who dropped out were not available. Formal statistical analyses to assess publication bias were not performed due to the limited number of studies available. However, visual inspection of funnel plots did not identify any clear indication of publication bias. In addition, the absence of clinically significant improvements in the main outcome variables makes the effects of any publication bias unlikely to change the main conclusions of our review. Finally, we need to acknowledge as a limitation the inclusion of studies published only in English, Spanish or Italian.

Conclusions

There is no evidence indicating that resistance training increases grip strength or has a clinically significant benefit on hand OA pain and function. However, this may be related to the paucity of studies and low-quality study designs. In addition, the lack of appropriate exercise intensities and frequency might have contributed to the limited effectiveness of the intervention. It is not entirely clear why some of the studies utilised suboptimal exercise intensities, however, some authors indicated that fear of exercise induced exacerbations in pain and a desire to protect the affected joints contributed to the choice of low loads in the exercise programs. Alternative exercise interventions may be more suitable for people with hand OA.

Chapter Five: Blood flow restriction training to counter muscle weakness and atrophy associated with disuse and ageing: A systematic review and meta-analysis.

Introduction

Resistance training interventions are known to be effective in improving muscle size and strength. According to the American College of Sports Medicine, exercise intensities greater than 60% of maximum voluntary contractions (MVC) should be used when aiming to increase muscle strength (Garber et al., 2011). However, it is not always possible to perform high intensity exercise in rehabilitation settings, for a variety of reasons. These may include the presence of comorbidities, the risk of symptom exacerbation (e.g. flares in pain) and a desire to protect damaged tissues (e.g. ligaments, cartilage) from detrimental levels of loading. As a result, clinicians are often inclined to utilise lower intensity resistance training in people undergoing rehabilitation. Unfortunately, this approach can compromise treatment efficacy as lower intensity training may not provide a sufficient physiological stimulus to maintain or improve muscle mass and strength (Watanabe, Madarame, Ogasawara, Nakazato, & Ishii, 2014). The results of inadequate exercise prescription have been shown in our systematic review and meta-analysis on resistance training for hand OA, which showed no overall change in grip strength after six to 16 weeks of training with the regimes utilised in the included studies, only two of which used exercise intensities considered sufficient to stimulate strength gains (Chapter four). A key reason for the low exercise intensities used in these studies appears to be the fear of eliciting exercise induced flares in joint

pain or further damaging the joints due to the joint compressive forces associated with high intensity training (HIT) (Lefler & Armstrong, 2004; Rogers & Wilder, 2009). In support of this, a recent systematic review reports that exercise in hand OA is associated with a 4.55 times increased relative risk of increasing adverse events such as joint inflammation and hand pain and a 2.88 times increased relative risk of withdrawing from treatment due to adverse events (Østerås et al., 2017). Thus, there may be a need to develop novel resistance training interventions that, while still effective, minimise the loads placed on arthritic joints.

Recent evidence has shown that in healthy, young participants, exercise intensities as low as 20%-30% of MVC can induce strength gains and hypertrophy when they are performed with a partial vascular occlusion of the exercising muscles – a paradigm known as blood flow restriction (BFR) training (Loenneke, Abe, et al., 2012). BFR training is performed by inflating a pressure cuff proximally to the exercising muscles, which reduces arterial blood flow to the muscle and induces venous pooling, resulting in a hypoxic muscular environment (Mouser et al., 2017). In turn, muscle hypoxia is thought to augment the metabolic drivers of muscle hypertrophy, leading to gains in both muscle mass and strength (Scott, Slattery, & Dascombe, 2015). Training with low levels of resistance, as BFR allows, reduces the mechanical loads placed on joints and soft tissue structures and may provide a suitable alternative to HIT in those groups of patients who cannot undergo high intensity exercise.

Several small studies or case series have highlighted the potential usefulness of BFR exercise in a rehabilitation setting (Gualano et al., 2010; Loenneke, Young, Wilson, & Andersen, 2013). In a recent systematic review, Hughes, Paton, Rosenblatt, Gissane, and Patterson (2017) demonstrated that low intensity BFR training is more effective than a low intensity training alone and that BFR training is almost as effective as HIT in

maintaining muscle strength in populations relevant to musculoskeletal rehabilitation. Further questions however, are still unanswered. Specifically, it is unclear if BFR alone (i.e. without exercise) can prevent muscle atrophy and strength deficits associated with disuse. In addition, Hughes et al. (2017) only examined the effects of BFR training on muscle strength and they did not report the effect of BFR training on muscle size. Finally, a concern raised about the application of BFR training in clinical populations is its safety, in part due to the publication of case studies reporting adverse events. However, the nature and seriousness of these events has not been systematically evaluated and compared to adverse events arising from traditional HIT. Thus, at present such information may raise false alarms regarding this new and potentially clinically useful intervention (Higgins & Green, 2011). Therefore, the aims of the current study were to perform a systematic review and meta-analysis on the effectiveness of BFR alone and BFR training on both muscle strength and muscle size in populations relevant to the rehabilitation musculoskeletal conditions, including hand OA. Specific populations included were those undergoing a period of disuse, immobilisation due to surgery and ageing adults over the age of 50. In addition, a systematic search of the literature was undertaken to compare case reports of adverse events following BFR training and traditional HIT. In addressing these aims, this review attempts to draw on the available literature to assess the likely efficacy, safety and feasibility of applying BFR training in people with hand OA.

Methods

Design and search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al.,

2009). The search strategy was based on the PICO (Population, Intervention, Comparison and Outcome) format. The electronic databases CINAHL, MEDLINE, SPORTDiscus, Allied and Complementary Medicine Database (AMED), Cochrane Central Register of Controlled Trials, Web of Science, and Scopus were searched between 1975 and October 2016. The search was limited to published studies, including participants older than 18 years and published in English, Italian or Spanish. The keywords utilised for the search included: limb(s) suspension, ULLS, unweighting, bed rest, immobi(lisation)(lization)(le)(lised)(lized)(lity), disuse(d), elderl(y)(ies), sarcopeni(a)(c), arthros(is)(copy)(copic), surg(ery)(ical), ischaemic training, occlusion training, vascular restriction, restriction of blood flow, blood flow-restrict(ion)(ions)(ed), blood flow restrict(ion)(ions)(ed), BFR, kaatsu. Each database was searched by two people.

In addition, published case studies on adverse events in both BFR and traditional high resistance training were searched in CINAHL, MEDLINE, SPORTDiscus, Allied and Complementary Medicine Database (AMED), Web of Science, and Scopus between 2002 and March 2017. The search was limited to published studies, in English, Italian or Spanish. The keywords utilised for the search included: ischemic training, occlusion training, vascular restrict(ed)(ion)(ions), restriction of blood flow, blood flow-restrict(ion)(ions)(ed), blood flow restrict(ion)(ions)(ed), BFR, kaatsu, resistance training, strength training, high intensity training, weight training, crossFit, adverse event(s), side effect(s), injur(y)(ies)(ed), trauma(tic)(s), rhabdomyolysis, case stud(y)(ies), case report(s), case series. Each database was searched by two people.

Eligibility criteria

To be included in this review, studies must have been investigating the effects of BFR training in adults over 50 years old or younger adults undergoing either an

immobilisation period or peripheral joint surgery. Eligible papers were published randomised/non-randomised controlled trials. Studies were considered if they included a between-group comparison after treatment. The intervention group had to consist of BFR in isolation or combined with low intensity resistance training (BFR training) and the control group had to undergo either no exercise, the same low intensity resistance training with no BFR, or HIT. The primary variables of interest were muscle strength and size. Studies reporting adverse events following BFR training or HIT were included in the present study if they were case studies or case series. Systematic and narrative reviews were identified and manual searches of their reference lists were undertaken to identify additional studies.

Study inclusion

All the studies identified were collected in bibliographic software (Endnote X7, Thomson Reuters), where the inclusion and exclusion criteria were applied by two individuals. All duplicated studies were eliminated before title and abstract screening. The retained articles were retrieved in full text and assessed for inclusion. Disagreement on study inclusion was first discussed and if consensus was not reached, the opinion of a third person was sought. A search of the reference lists of the included studies was undertaken to identify further articles.

Risk of bias and overall quality of evidence

Only the studies included in the meta-analysis were assessed for Risk of Bias and overall quality. Using the risk of bias table suggested by the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group (Higgins & Green, 2011), a critical appraisal of each study was performed by two researchers. Its seven items

assessed the internal validity of the studies. Each item was scored as low risk, high risk or unclear risk.

To evaluate the overall quality of the evidence the GRADE system was utilised (Grade Working Group, 2004). The quality of evidence was downgraded by one point from high quality for each factor that we encountered: (1) risk of bias (if it was deemed that the bias may affect trial outcomes), (2) inconsistency of results (wide variance of effect sizes and significant large heterogeneity between trials: $p < 0.05$, $I^2 > 50\%$), (3) indirectness (application of intervention, intervention or outcomes that differed from what we indicated in our PICO research question), (4) imprecision (optimal information size not met). A GRADE profile was completed for each pooled estimate. Two reviewers judged whether these factors were present for each outcome and in case of disagreement a third reviewer was involved. The quality of evidence was defined as (1) high (the authors are confident that the true effect is close to the one estimated); (2) moderate (the authors are moderately confident in the effect estimate); (3) low (the true effect may be significantly different from the estimated); (4) very low (the true effect is most likely different from the estimated) (Schünemann et al., 2009).

Data extraction

Descriptive statistics (means, standard deviations) for demographic and pre-post outcome dependent variables were extracted and cross-checked. The post-intervention values for the BFR and control groups were used to calculate the standardised mean difference (SMD), which was the difference between groups values, divided by the pooled SD, with adjustment for small sample sizes (Hedges g: SMD). The number of adverse events in each group was also extracted. Drop-outs without specific reasons, were classified as an adverse event. If more information was required for the quantitative analysis, authors were contacted to obtain further data.

Data synthesis and analysis

Meta-analysis was performed in Review Manager (RevMan) software (version 5.3, Cochrane Collaboration) using the inverse variance method. We assumed that beyond subject-level sampling error, the studies' variability was random and thus adopted a random-effect model (Liberati et al., 2009; Lipsey & Wilson, 2001). Effect sizes of 0.2, 0.5, 0.8 were considered small, medium, and large, respectively (Guyatt et al., 2012). Publication bias was assessed by visually inspecting funnel plots when the number of studies per outcome was less than 10 (Schünemann et al., 2009). When more than 10 studies per outcome were available, Egger's test (Egger, Davey Smith, Schneider, & Minder, 1997) was performed in R 3.3.3 (R Core Team, 2017) using the METAFOR package (Viechtbauer, 2010). Statistical heterogeneity was assessed using the chi-square tests and the I^2 statistic, the latter providing a measure of the proportion of the observed variance that would remain if sampling error was eliminated (Borenstein et al., 2017).

Results

The initial search identified 505 papers. After duplicate elimination, 270 studies underwent title and abstract screening, resulting in 33 studies considered suitable for inclusion. Following full paper review, 24 articles met the criteria for inclusion. An outline of study selection throughout the review is presented in Figure 11. No additional papers were retrieved from study bibliographies. Table 6 presents a comprehensive description of each trial included in the paper.

The search for reports of adverse events resulted in 447 papers. After duplicate elimination, 233 studies underwent title and abstract screening, with 32 papers

considered suitable for inclusion. Following full paper review, 32 papers were included in the present review.

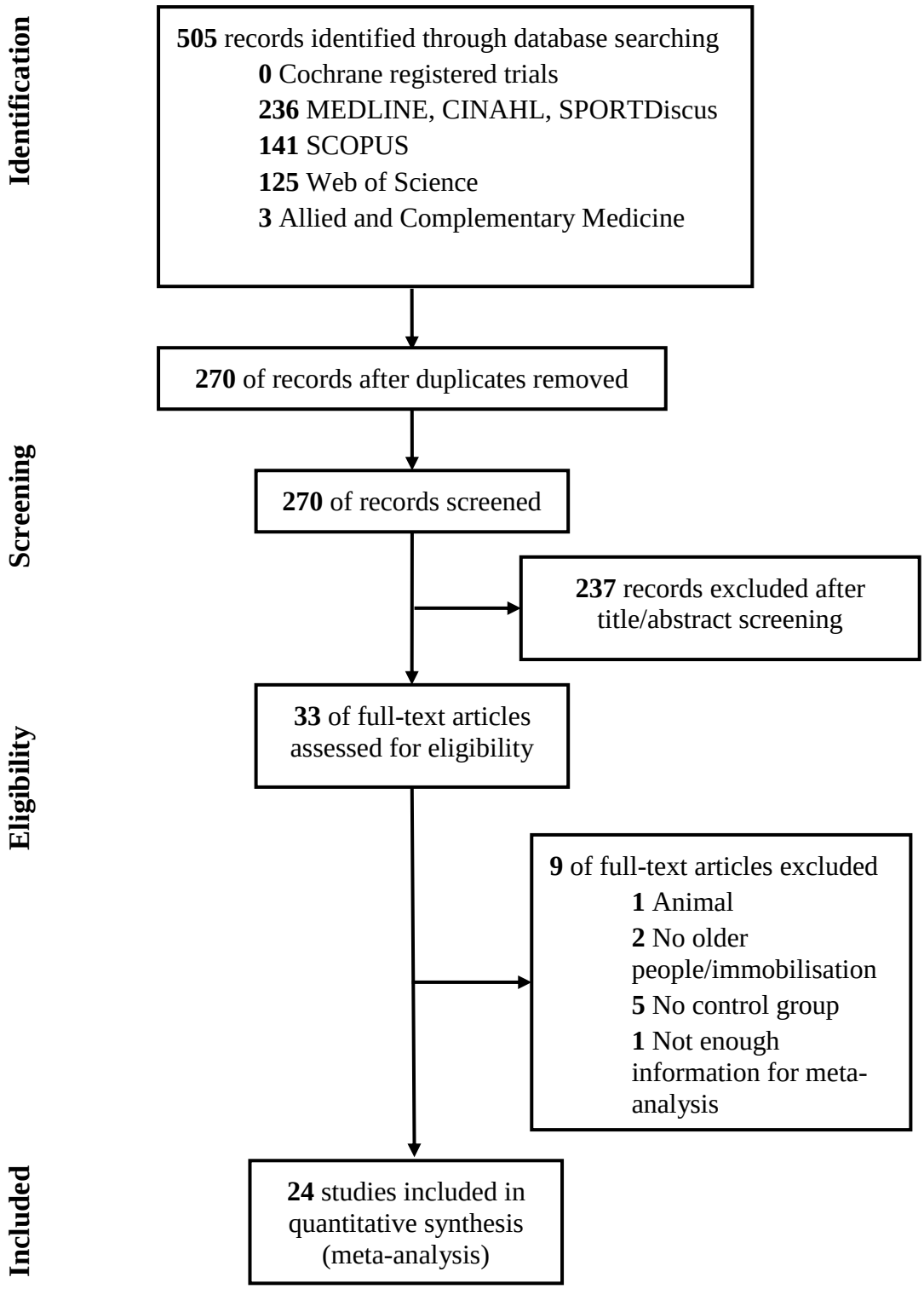


Figure 11. Flow chart of study selection

Table 6. Summary of the participants and intervention characteristics of the studies included in the blood flow restriction review meta-analysis

Study	Participants	Design	Model	Interventions	Cuff	Outcomes	Notes
Abe (2010)	*N* = 19 79% F 60 to 78 yrs	E	S	BFR (*n* = 11): exercise = walking w/ BFR dosage = 20 minutes, ? % MVC, 5/week pressure = 100mmHg, progressed during exercise up to 200mmHg, 30 sec on and 10 sec off. CG (*n* = 8): No intervention	Kaatsu-master	KE -MVIC (6 wks): S -CSA (Ultrasound MTH) (6 wks): S	Baseline: STRENGTH ($p = 0.04$)[C] CSA ($p = 0.84$) A: 72 hours
Araújo (2015)	*N* = 18 100% F 54(4) yrs	E	S	BFR (*n* = 10): exercise = water exercise w/ BFR dosage = 1 set, 30 reps, 3 sets 15 reps, Borg 9-11 (6-20) ? % MVC, 3/week, 1 min rest pressure = 80% of occlusion pressure, ? brake CG (*n* = 8): water exercise	18*80cm	KE -1-RM (8 wks): S	Baseline: STRENGTH ($p = 0.4$) A: 48-72 hours
Bryk (2016)	*N* = 34 100% F BFR: 62(7) yrs CG: 60(7) yrs	E	OA	BFR (*n* = 17): exercise = lower limb strengthening + knee extension w/ BFR dosage = 3 sets, 30 reps, 30% MVC, 3/week pressure = 200mmHg HIT (*n* = 17): exercise = lower limb strengthening + knee extension w/out BFR, 70% MVC	Thigh pressure cuff	KE - MVIC (6 wks): NS	Baseline STRENGTH ($p = 0.8$) A: ?

Clark (2006)	*N* = 12 67% F BFR: 20(1) yrs CG: 21(1) yrs	QE	ULLS	BFR only (*n* = 6): dosage = 3 sets, 5 mins BFR, 3/week, 3 mins rest between sets w/out pressure pressure = 220mmHg CG(*n* = 6): No intervention	?	PF -MIVC (4 wks): NS - CSA (MRI) (4 wks): NS	Baseline: STRENGTH ($p = 0.07$)[B] CSA ($p = 0.36$)
Cook (2010)	*N* = 16 44% F BFR: 26(10) yrs CG: 19(1) yrs	QE	ULLS	BFR (*n* = 8): exercise = knee extensors w/ BFR dosage =3 sets, to failure, 20% MVC, 3/week, 1.5 min rest between sets pressure = 1.3 systolic pressure, whole session CG (*n* = 8): No intervention	6*83 cm	KE -1-RM knee extension (4 wks): S -CSA (MRI) (4 wks): S	Baseline: STRENGTH ($p = 0.24$) CSA ($p = 0.7$) A: 24-48 hours

Hackney (2016)	*N* = 13 62% F BFR: 34(14) yrs CG: 30(12) yrs	QE	ULLS	BFR (*n* = 7): exercise = leg press and plantar flexion w/ BFR dosage = 3 sets, to failure, 20-30% MVC, 3/week, 1.5 min rest between sets pressure = 1.3 systolic pressure, maintained between sets. No pressure between exercises. HIT (*n* = 6): leg press and plantar flexion, 3 sets to failure, 70-80% MVC, 3/week	6*83 cm	PF -1-RM plantar flexion (25 days): S favouring HIT -CSA (MRI) (25 days): S favouring HIT	Baseline: STRENGTH (p = 0.13) CSA (p = 0.9) A: ?
Iversen (2016)	*N* = 24 42% F BFR: 25(7) yrs CG: 30(9) yrs	E	ACL	BFR (*n* = 12): exercise = ACL rehab w/ BFR dosage = 5 sets, 20reps each, ? % MVC, 5 mins each, 2/day, 3 min rest pressure = 130-180mmHg, 3 mins rest between sets w/out pressure CG (*n* = 12): ACL rehab	14 cm width	KE -CSA (MRI) (2 wks): NS	Baseline: CSA (p = 0.09)[B] A: 48 hours

Karabulut (2010)	*N* = 24 0% F BFR: 56(1) yrs CG: 58(1) yrs	QE	S	BFR (*n* = 13): exercise = leg press, leg extension w/ BFR dosage = 1 set, 30 reps, 2 sets, 15 reps, 20% MVC, 3/week, 1 min rest between sets, 5-10 mins brake between exercises pressure = 160-240mmHg, maintained between sets. No pressure between exercises CG (*n* = 11): No intervention HIT (*n* = 13): leg press, leg extension, 3 sets, 8 reps, 80% MVC, 3/week	Kaatsu Master	KE BFRvsCG: -1-RM leg ext (8 wks): S BFRvsHIT: -1-RM leg ext (8 wks): S favours HIT	Baseline: BFRvsCG: STRENGTH (p = 0.64) BFRvsHIT: STRENGTH (p = 0.04)[B] 6 weeks training
Karabulut (2013)	-	-	-	Same participants (only males) and protocol to Karabulut (2010)	5 cm Kaatsu Master	KE - CSA (CT) (6 wks): NS	Baseline: CSA (p = 0.05) A: ?
Kubota (2008)	*N* = 11 0% F BFR: 23(1) yrs CG: 23(2) yrs	E	CIA	BFR only (*n* = 5): dosage = 5 sets, 5 mins BFR, 2/day, 3 mins rest between sets w/out pressure pressure = 200mmHg CG (*n* = 6): No intervention	8*80cm tourniquet	KE -MVIC (2 wks): S	Baseline STRENGHT (p = 0.9)

Kubota (2011)	*N* = 11 0% F BFR: 23(1) yrs CG: 23(1) yrs	E	CIA	BFR only (*n* = 5): dosage = 5 sets, 5 mins BFR, 2/day, 3 mins rest between sets w/out pressure pressure = 50mmHg CG (*n* = 6): No intervention	8*80cm tournique t	KE -MIVC (2 wks): NS	Baseline STRENGTH ($p = 0.01$)[B]
Libardi (2015)	*N* = 25 ?% F BFR: 64(4) yrs CG: 65(5) yrs HIT: 65(4) yrs	E	S	BFR (*n* = 10): exercise = endurance training (walking/running 40-50 mins) + leg press w/ BFR dosage = 1 set, 30 reps, 3 set, 15 reps, 20-30% MVC, 4/week, 1 min rest between sets pressure = 50% occlusion pressure CG (*n* = 7): no exercise HIT (*n* = 8): exercise = same endurance training as BFR + 70-80% MVC leg press, 4/week	18*92 cm	KE BFRvsCG: - 1-RM leg press (12 wks): S - CSA (MRI) (12 wks): S BFRvsHIT: - 1-RM leg press (12 wks): NS - CSA (MRI) (12 wks): NS	Baseline: BFRvsCG: STRENGTH ($p = 0.23$) CSA ($p = 1$) BFRvsHIT: STRENGTH ($p = 1$) CSA ($p = 0.96$) A: ?

Ohta (2003)	*N* = 44 43% F BFR: 28(10) yrs CG: 30(10) yrs	QE	ACL	BFR (*n* = 22): exercise = ACL rehab w/ BFR dosage = 2-3 sets, 20 reps, ? % MVC, 2/day, 6/week pressure = 180mmHg, maintained for 15 mins max, 15-20 mins brake before resuming exercises. CG (*n* = 22): ACL rehab	?	KE -MVIC (16 wks): S -CSA (MRI) (16 wks): S	Baseline: STRENGTH (*p* = 0.7) CSA (*p* = ?) A: ?
Ozaki (2011)	*N* = 23 78% F BFR: 66(1) yrs CG: 68(1) yrs	QE	S	BFR (*n* = 13): exercise = Walk training w/ BFR dosage = 20 min treadmill, 45% HRR, 4/week pressure = 120-200mmHg CG (*n* = 10): Walk training	5 cm Kaatsu Master	KE - Isokinetic (10 Wks): S - CSA (MRI) (10 Wks): S	Baseline: STRENGTH (*p* = 0.7) CSA (*p* = 0.15) A: ?
Shimizu (2016)	*N* = 40 18% F BFR: 72(4) yrs CG: 70(4) yrs	E	S	BFR (*n* = 20): exercise = leg extension, leg press, rowing and chest press w/ BFR dosage = 3 sets, 20 reps, 20% MVC, 3/week pressure = 100% systolic pressure CG (*n* = 20): resistance training w/out BFR	10 cm wide	KE -1-RM leg ext (4 wks): S	Baseline: STRENGTH (*p* = 0.27) A: 24hrs

Silva (2015)	*N* = 10 100% F BFR: 63(4) yrs CG: 62(4) yrs	E	S	BFR (*n* = 5): exercise = Knee extension w/ BFR dosage = 4 sets, to failure, 30% MVC, 2/week, 0.5 min rest between sets pressure = 80% of occlusion pressure, ? brake CG (*n* = 5): No intervention HIT (*n* = 5): 4 sets, to failure, 80% MVC, 2/week, 2 min rest between sets	18*80 cm	KE BFRvsCG: -1-RM leg ext (6 wks): S BFRvsHIT: -1-RM leg ext (6 wks): NS	Baseline: BFRvsCG: STRENGTH ($p = 0.05$)[B] BFRvsHIT: STRENGTH ($p = 0.04$)[B] A: ?
Takarada (2000)	*N* = 19 100% F BFR: 58(2) yrs CG: 57(2) yrs	QE	S	BFR (*n* = 11): exercise = single arm elbow flexion w/ BFR + High intensity contralateral limb dosage = 3 sets, to failure, ≈50% MVC,2/week, 1 min rest between sets pressure = 110(±23)mmHg, whole session CG (*n* = 8): single arm elbow flexion (one limb only)	3*80 cm MPS-700 Sato	EF -MVIC (16wks): S -CSA (MRI) (16wks): S	Baseline: STRENGTH ($p = 1$) CSA ($p = 1$) A: ?
Takarada (2000)	*N* = 16 50% F BFR: 23(1) yrs CG: 23(1) yrs	QE	ACL	BFR only (*n* = 8): dosage = 5 sets, 5 mins BFR, 2/day, 3 mins rest between sets w/out pressure pressure = 180-260mmHg CG (*n* = 8): No intervention	9*70 cm tourniquet	KE - CSA (MRI) (2 wks): S	Baseline: CSA ($p = 0.7$) A: 24 hrs

Tennent (2016)	*N* = 17 30% F BFR: 37(30-46) yrs CG: 37(32-47) yrs	E	ART	BFR (*n* = 10): exercise = rehab + leg press, extension, reverse press w/ BFR dosage = 1 set, 30 reps, 3 sets 15 reps, 30% MVC, 2/week, 0.5 min rest between sets, 1 min between exercises. pressure = 80% of occlusion pressure, whole session CG (*n* = 7): rehab	PTS ii, Delphi Medical	KE - Isokinetic (6 Wks): NS	Baseline: STRENGTH (*p* = 0.33)
Thiebaud (2013)	*N* = 14 100% F BFR: 59(2) yrs HIT: 62(2) yrs	QE	S	BFR (*n* = 6): exercise = chest press, row, shoulder press, lower limb exercises w/BFR dosage = 1 set, 30 reps, 2 sets 15 reps, 10%-30%MVC, 3/week, 0.5 min rest between sets, 0.5-2 mins between exercises pressure = 80-120mmHg, whole session HIT (*n* = 8): exercise = chest press, row, shoulder press, lower limb exercises dosage = 3 sets 10 reps, 70%-90% MVC, 3/week, 1-2 mins rest between sets, 0.5-2 mins between exercises	3.3*58 cm KAATS U Master	KE - 1-RM leg extension (8 wks): NS - CSA (Ultrasound MTH) (8 wks): NS	Baseline: STRENGTH (*p* = 0.8) CSA (*p* = 0.6) A: 72 hrs

Vechin (2015)	*N* = 15 40% F BFR: 65(2) yrs CG: 66(5) yrs	E	S	BFR (*n* = 8): exercise = Leg press w/BFR dosage = 1 set, 30 reps, 3 sets, 15 reps, 20-30% MVC, 2/week, 1 min rest between sets pressure = 50% of systolic pressure, whole session CG (*n* = 7): No intervention HIT (*n* = 8): exercise = leg press dosage = 4 sets, 10 reps, 70%-80% MVC, 1 min rest between sets	18cm	KE BFRvsCG: -1-RM leg press (12 wks): NS -CSA (MRI) (12 wks): S BFRvsHIT: -1-RM leg press (12 wks): ? -CSA (MRI) (12 wks): ?	Baseline: BFRvsCG: STRENGTH (*p* = 0.36) CSA (*p* = 0.2) BFRvsHIT: STRENGTH (*p* = 0.1) CSA (*p* = 0.3) A: 120 hrs
Yasuda (2014)	*N* = 19 76% F BFR: 71(7) yrs CG: 68(6) yrs	E	S	BFR (*n* = 9): exercise = Leg extension and leg press w/ BFR dosage = 4 sets of 30, 20, 15, 10 reps, 20-30% MVC, 2/week, 0.5 min rest between sets, 1.5 min rest between exercises pressure = 120-270mmHg, whole session CG (*n* = 10): No intervention	5cm KAATS U Master	KE -1-RM leg ext (12 wks): S -CSA (MRI) (12 wks): S	Baseline: STRENGTH (*p* = 0.9) CSA (*p* = 0.9) A: 72-120 hrs

Yasuda (2015)	*N* = 17 82% F BFR: 72(6) yrs CG: 68(5) yrs	QE	S	BFR (*n* = 9): exercise = arm curl, triceps press down w/ BFR dosage = 1 set, 30 reps, 3 sets, 15 reps, ? % MVC, 2/week, 0.5 min rest between sets, 1.5 min rest between exercises pressure = 120-270mmHg, whole session CG (*n* = 8): arm curl, triceps press down	3cm	EF -MVIC (12 wks): S -CSA (MRI) (12 wks): S	Baseline: STRENGTH ($p = 0.9$) CSA ($p = 0.3$) A: 72-120 hrs
Yasuda (2016)	*N* = 20 100% F BFR: 70(6) yrs CG: 68(6) yrs	E	S	BFR (*n* = 10): exercise = squat, knee extension w/ BFR dosage = 1 set, 30 reps, 3 sets, 15 reps, ? % MVC, 2/week, 30 sec between sets, 1.5 min rest between exercises. pressure = 120-200mmHg, whole session CG (*n* = 10): No intervention HIT (10): exercise = squat, knee extension w/out BFR dosage = ? sets, ? reps, 70-90% MVC	5cm KAATS U Master	KE BFRvsCG: -1-RM leg ext (12 wks): NS -CSA (MRI) (12 wks): S BFRvsHIT: -1-RM leg ext (12 wks): NS -CSA (MRI) (12 wks): S favouring BFR	Baseline: BFRvsCG: STRENGTH ($p = 0.5$) CSA ($p = 0.07$)[C] BFRvsHIT: STRENGTH ($p = 0.8$) CSA ($p = 0.9$) A: 72-168 hrs

Note. N = Sample; F = female; yrs = years old; E = experimental; S = adults over 50 years old (potential sarcopenia); BFR = blood flow restriction; ? = unable to calculate/unknown; MVC = maximum voluntary contraction; CG = control group; KE = knee extensors; MVIC = maximum voluntary isometric contraction; wks = weeks; S = significant; CSA = cross-sectional area; MTH = muscle thickness; A = assessment time; reps = repetitions; min = minute; cm = centimetres; 1-RM = one-repetition maximum; B = greater baseline value for the BFR group; OA = osteoarthritis; HIT = high intensity training; NS = non-significant; QE = quasi-experimental; ULLS = unilateral lower limb support; PF = plantar flexors; MRI

= magnetic resonance imaging; H = greater baseline value for the HIT group; ACL = post-surgical anterior cruciate ligament rehabilitation; S = sarcopenia; leg ext = leg extension; CIA = cast immobilisation of ankle; CT = Computer tomography; C = greater baseline value for the CG group; HRR = heart rate reserve; EF = elbow flexors; ART = arthroscopy.

Participants and outcomes

The participants' count was based on the participants retained at the follow-up period (See Table 6). In total, 485 participants were examined. Of the total sample, 324 (74%) participants were females. Mean age ranged from 19 to 72 years old.

The primary outcome measures varied between articles and were grouped into muscle strength and muscle size. Muscle strength was assessed by isotonic 1-Repetition Maximum (1-RM), hand held dynamometers or Isokinetic dynamometers. Multiple methods of strength measurements were considered acceptable when comparing BFR training to a matched or no exercise intervention because both groups were 'naïve' to the high intensity testing method (Buckner et al., 2017). When comparing BFR training to HIT, subgroups analyses to decrease outcome measures heterogeneity were performed.

Muscle size measurements involved MRI, CT scan and ultrasound muscle thickness assessment. Muscle anatomical cross-sectional area (ACSA) was calculated with MRI or CT scans. Subgroup analyses to decrease outcome measures heterogeneity were completed.

Experimental intervention

A variety of BFR training interventions were used. BFR was either utilised in isolation or in combination with low intensity resistance training. Four studies utilised BFR in isolation (Clark, Fernhall, & Ploutz-Snyder, 2006; Kubota et al., 2011; Kubota, Sakuraba, Sawaki, Sumide, & Tamura, 2008; Takarada, Takazawa, & Ishii, 2000). In these studies, three (Clark et al., 2006) to five (Kubota et al., 2011; Kubota et al., 2008; Takarada, Takazawa, & Ishii, 2000) sets of five minutes of BFR was implemented twice a day every day (Kubota et al., 2011; Kubota et al., 2008; Takarada, Takazawa, & Ishii,

2000) or three times a week (Clark et al., 2006). The pressure was maintained for three to five minutes at a range between 50 and 260 mm Hg. Three minutes' rest without pressure was provided between each set. All four studies applied BFR in one lower limb only.

Twenty studies implemented BFR with low intensity resistance training that ranged from 20% to 50% of MVC. The number of sets and repetitions varied greatly, with one set of 30 and three sets of 15 repetitions being the most frequently adopted. The pressures utilised ranged between 60 and 270 mm Hg. The pressure was usually maintained during the inter-sets rest period and released between different exercises. Inter-set rest periods most often lasted 30 seconds, while rest periods between exercises varied greatly. Commonly, BFR training was performed two to three times a week. Seventeen studies utilised BFR training in the lower limb, two (Takarada, Takazawa, Sato, et al., 2000; Yasuda et al., 2015) in the upper limb, and one (Thiebaud et al., 2013) trained both the upper and lower limbs. Leg presses were used across most studies, while in the upper limb arm curls were the exercise of choice.

Control and comparison intervention

Four studies compared BFR only (without the addition of exercise) to a no intervention control group (Clark et al., 2006; Kubota et al., 2011; Kubota et al., 2008; Takarada, Takazawa, & Ishii, 2000).

Seventeen studies compared BFR training to a no intervention control group (n = 9) (Abe et al., 2010; Cook, Brown, DeRuisseau, Kanaley, & Ploutz-Snyder, 2010; Karabulut, Abe, Sato, & Bemben, 2010; Karabulut, Sherk, Bemben, & Bemben, 2013; Libardi et al., 2015; J. Silva et al., 2015; Vechin et al., 2015; Yasuda et al., 2014; Yasuda, Fukumura, Tomaru, & Nakajima, 2016) or a matched low intensity training

group (n = 8) (Araújo et al., 2015; Iversen, Røstad, & Larmo, 2016; Ohta et al., 2003; Ozaki, Miyachi, Nakajima, & Abe, 2011; Shimizu et al., 2016; Takarada, Takazawa, Sato, et al., 2000; Tennent et al., 2016; Yasuda et al., 2015).

Eight studies compared BFR training to a HIT regime (Bryk et al., 2016; Hackney, Downs, & Ploutz-Snyder, 2016; Karabulut et al., 2010; Libardi et al., 2015; J. Silva et al., 2015; Thiebaud et al., 2013; Vechin et al., 2015; Yasuda et al., 2016). The HIT group performed exercises at intensities between 70% and 90% of MVC, two to four times a week.

Risk of bias

The risk of bias across the studies varied substantially (See Figure 12). All the studies failed to blind the treatment providers and participants due to the nature of the intervention. Tennent et al. (2016) presented the lowest risk of bias (6 out of 7 criteria were satisfied). Ohta et al. (2003) presented the highest risk of bias (2 out of 7 criteria were satisfied).

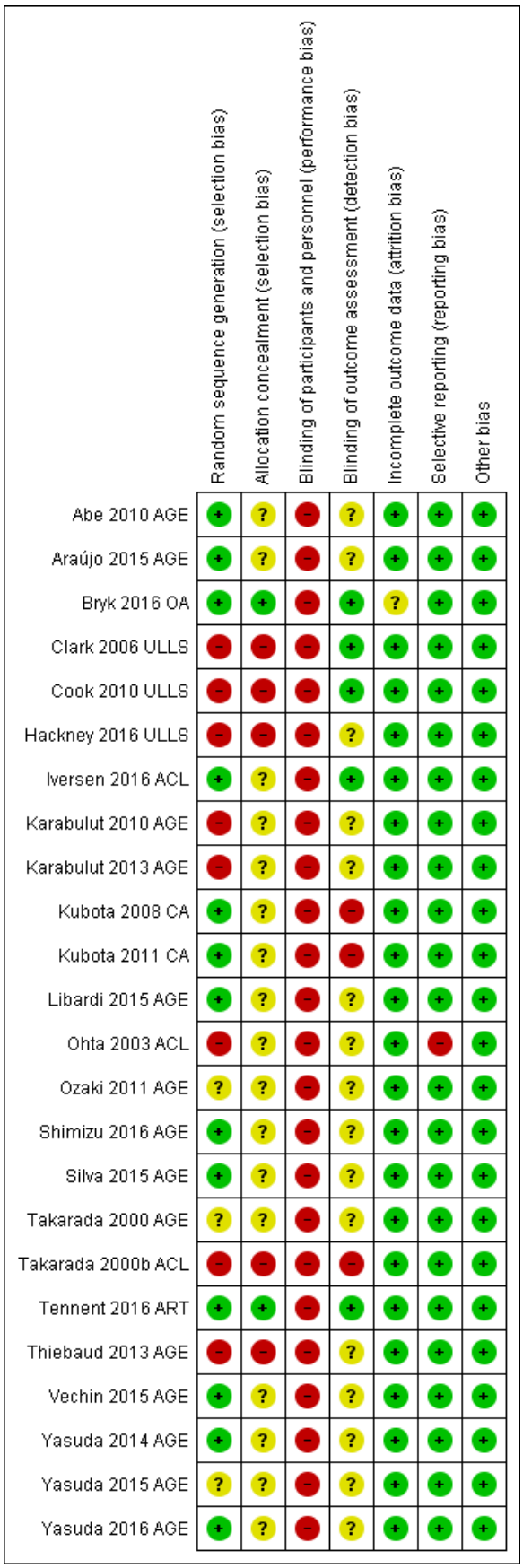
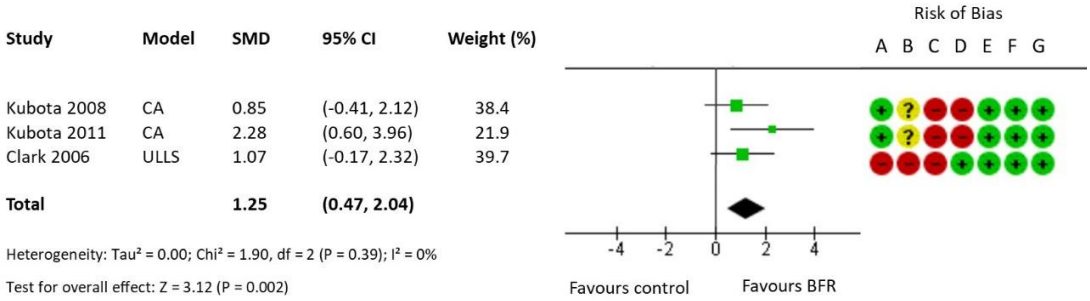


Figure 12. Risk of bias summary for the studies included

Blood flow restriction only (no exercise) vs no pressure control: meta-analysis

Forest plots of the results are presented in Figure 13. Summary of findings and GRADE quality ratings are reported in Table 7. Funnel plots for muscle strength and size are reported in Figure 14. Visual inspection did not identify any clear funnel plot asymmetry.

A



B

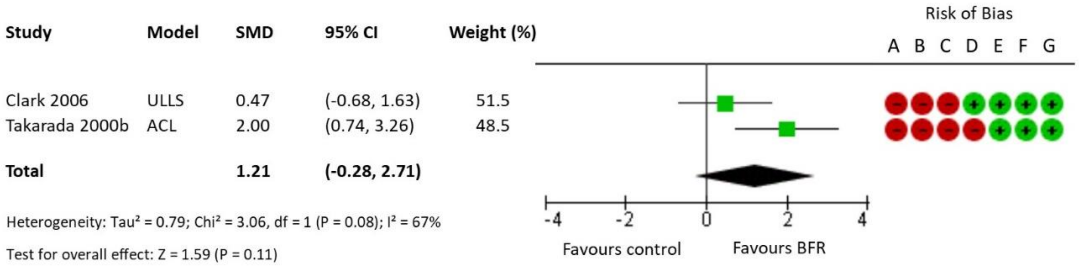


Figure 13. Forest plot of the standardised mean difference (SMD) between the effect of blood flow restriction (BFR) only vs. no pressure control on strength (A) and size (B) variables. CI confidence interval, CA cast immobilisation of the ankle, ULLS unilateral lower limb suspension, ACL post-surgical anterior cruciate ligament rehabilitation

Table 7. Summary of findings (GRADE)

BFR only compared to control for Disuse

Patient or population: Disuse, Setting: ULLS, CIA, ACL, Intervention: BFR only, Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
Strength - BFR only vs control assessed with: MVIC Follow up: range 2 to 4 weeks	Muscle strength in the BFR only group was 1.25 SDs (0.47 higher to 2.04 higher) higher than in the control group.	34 (2 RCT, 1 quasi-experimental study)	⨁⨁◯◯ LOW [a,b]	The results suggest that the BFR only group was 32.4 Nm stronger (95% CI 12.2 to 52.9 Nm stronger) than the control group following an immobilisation period. This would be equivalent to a 17.9% difference in strength with BFR (95% CI 6.7% to 29.1% stronger).[c]
Size - BFR only vs control assessed with: MRI Follow up: range 2 to 4 weeks	Muscle size in the BFR only group was 1.21 SDs (0.28 lower to 2.71 higher) higher than in the control group.	28 (2 quasi-experimental studies)	⨁⨁◯◯ LOW [a,b]	The results suggest that CSA in the BFR only groups was 4.1 cm2 larger (95% CI -0.95 cm2 smaller to 9.2 cm2 larger) than in the control group following a period of immobilisation. This would be equivalent to a 9.8% larger muscle size with BFR (95% CI -2.26% smaller to 21.9% larger).[d]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

BFR: Blood flow restriction training, ULLS: Unilateral lower limb support, CIA: Cast immobilisation of the ankle, ACL: anterior cruciate ligament surgery, MVIC: Maximum voluntarily isometric contraction, SD: Standard deviation, CI: Confidence interval, MRI: Magnetic resonance imaging

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Downgraded because of Risk of bias (Lack of randomisation, allocation concealment, and outcome assessor blinding).
b. Downgraded because of Imprecision (Optimal information size not met).
c. The control group strength mean(SD) 181.95(25.9) Nm was calculated by averaging the MVIC of Kubota et al. (2011) and Kubota et al. (2008).
d. The control group strength mean(SD) 42.1(3.4) cm2 was calculated by averaging the knee extensors' size of Takarada, Takazawa, and Ishii (2000).

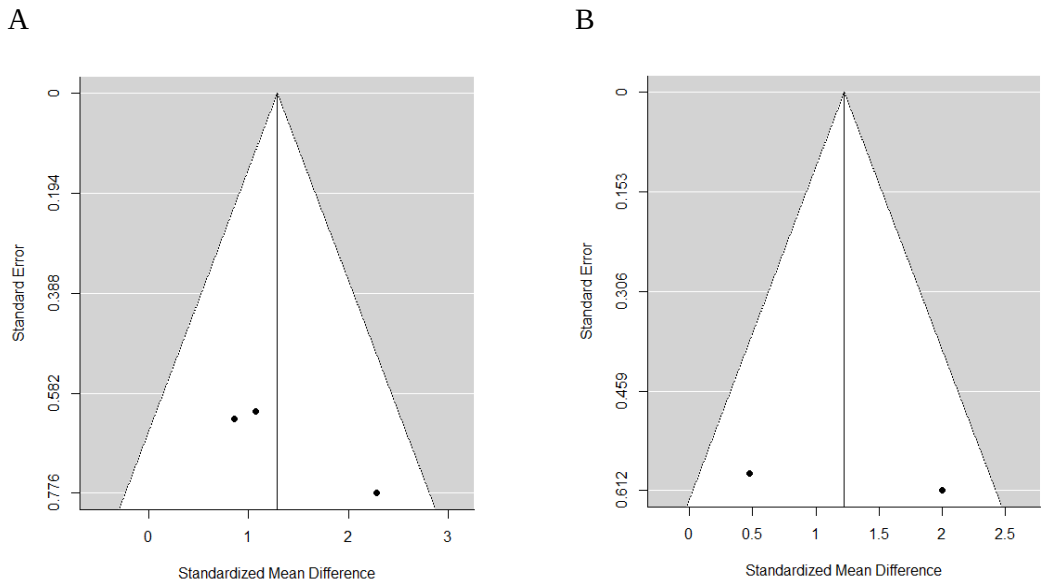


Figure 14. Funnel plot for blood flow restriction (BFR) only vs. no pressure control group for strength (A) and size (B) variables.

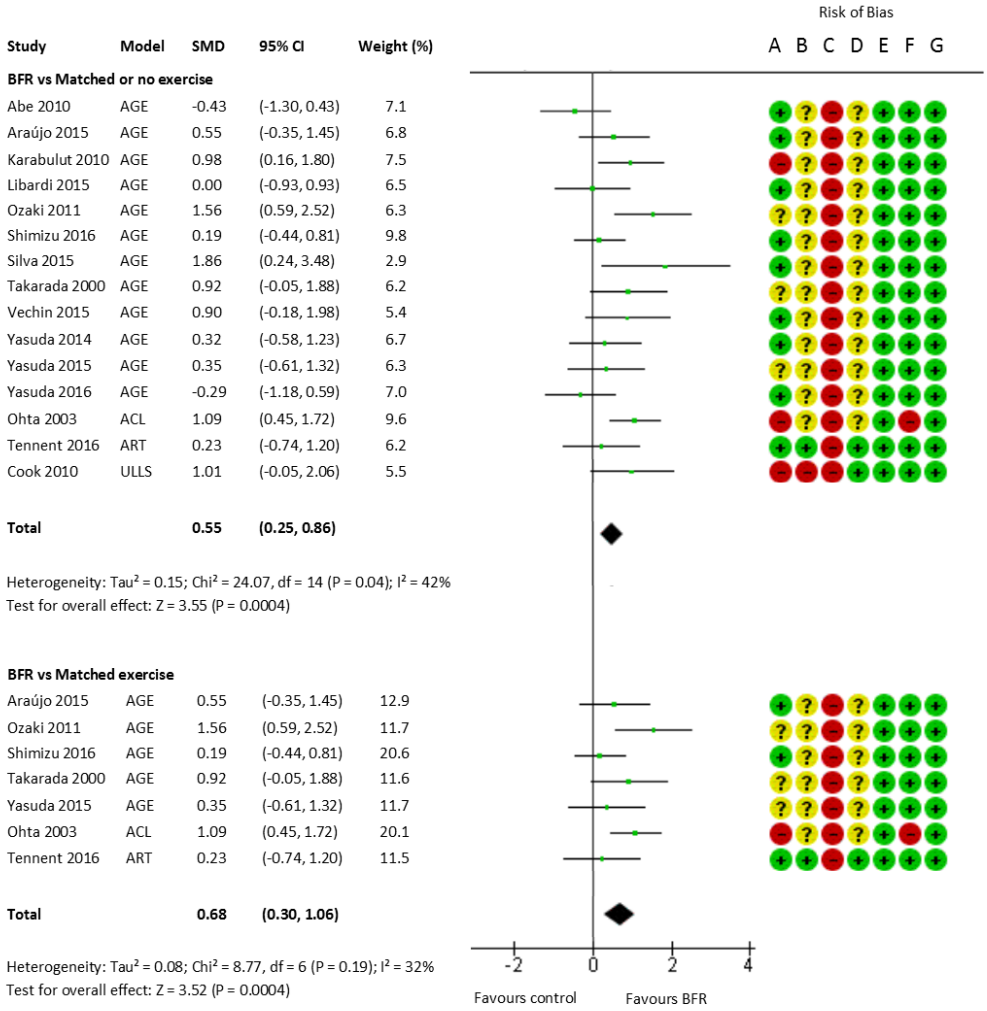
Of the three studies examining changes in muscle strength (Clark et al., 2006; Kubota et al., 2011; Kubota et al., 2008), only one showed a significant benefit after BFR alone compared to the control group. The pooled results provide low quality evidence that BFR alone reduces the decline in muscle strength observed after a period of disuse (SMD 1.25 [95% CI 0.47, 2.04], $p = 0.002$). The I^2 was 0% ($X^2 = 1.9$, $p = 0.39$).

One of two studies (Clark, Issac, Lane, Damron, & Hoffman, 2008; Takarada, Takazawa, & Ishii, 2000) examining changes in muscle size showed a significant improvement in favour of the BFR only group. The pooled results provide low quality evidence that BFR alone does not reduce the decline observed in muscle size after a period of disuse (SMD 1.21 [95% CI -0.28, 2.71], $p = 0.11$). The I^2 was 67% ($X^2 = 3.06$, $p = 0.08$).

Blood flow restriction training vs matched volume/no exercise

Forest plots of the results are presented in Figure 15. Summary of findings and GRADE quality ratings are reported in Table 8. Funnel plots for muscle strength and size are reported in Figure 16. Egger's test showed no statistically significant funnel plot asymmetry (Muscle strength: t = 1.26, p = 0.23; Muscle size: t = 0.82, p = 0.43).

A



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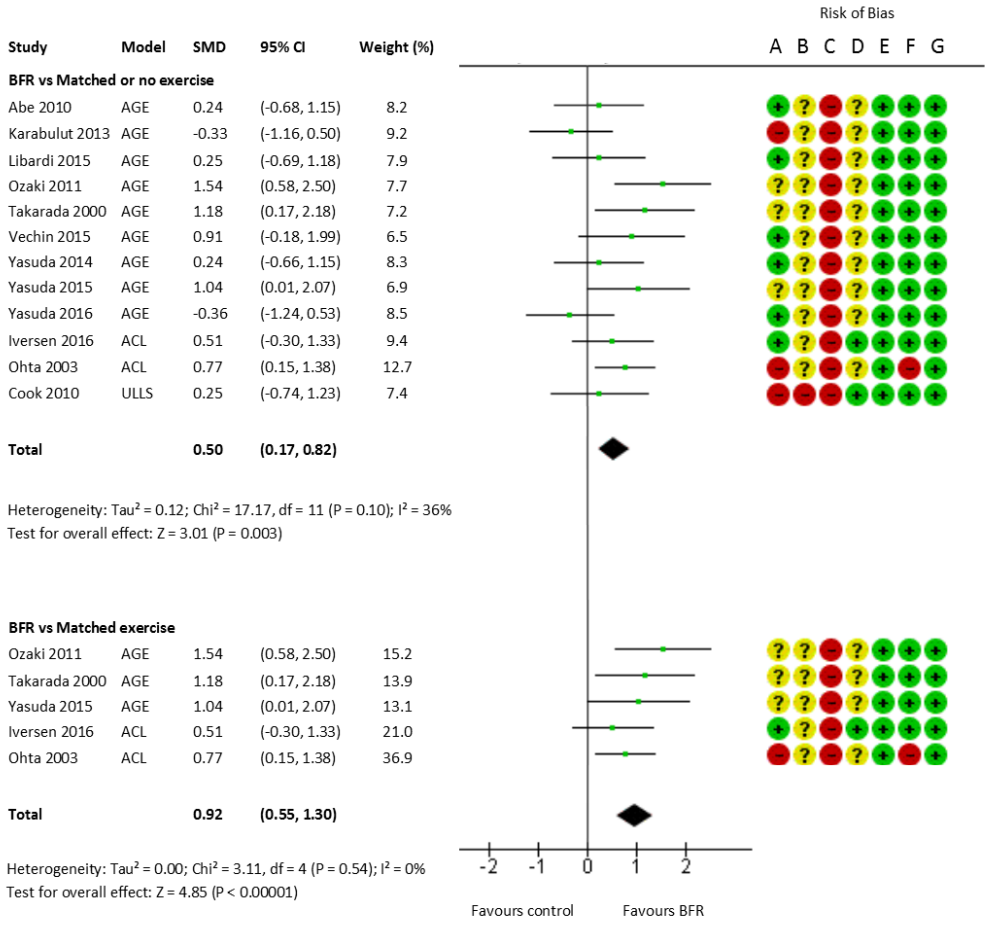


Figure 15. Forest plot of the standardised mean difference (SMD) between the effect of blood flow restriction (BFR) training vs. matched or no exercise on strength (A) and size (B) variables. CI confidence interval, AGE adults over 50 years old (potential sarcopenia), ACL post-surgical anterior cruciate ligament rehabilitation, ART arthroscopy, ULLS unilateral lower limb suspension.

Table 8. Summary of findings (GRADE)

BFR training compared to Matched volume/no intervention for Disuse

Patient or population: Disuse, Setting: Post-surgical, immobilisation, osteoarthritis, over 50 yrs old, Intervention: BFR training, Comparison: Matched volume exercise, no intervention.

Outcomes	Anticipated absolute effects* (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
Strength - BFR training vs Matched volume/no intervention assessed with: MVIC, Isokinetic testing, 1RM Follow up: range 4 to 16 weeks	Muscle strength in the BFR training group was 0.55 SDs (0.25 to 0.86 higher) higher than in the Matched volume/no intervention group.	325 (9 RCT, 6 quasi experimental studies)	⊕⊕⊕◯ MODERATE [a,b]	The results can be interpreted as an improvement of 7.8 kg (95% CI 3.5 to 12.1 kg stronger) in the BFR training group. This would be equivalent to a 16.3% increase in strength with BFR (95% CI 7.3% to 25.3% stronger).[d]
Strength – BFR training vs Matched volume assessed with: MVIC, Isokinetic testing, 1RM Follow up: range 4 to 16 weeks	Muscle strength in the BFR training group was 0.68 SDs (0.30 to 1.06 higher) higher than in the Matched volume group.	180 (3 RCT, 4 quasi experimental studies)	⊕⊕⊕◯ MODERATE [a,b]	The results can be interpreted as an improvement of 7.4 kg (95% CI 3.3 to 11.6 kg stronger) in the BFR training group. This would be equivalent to a 16.3% increase in strength with BFR (95% CI 7.3% to 25.6% stronger).[e]

Size - BFR training vs Matched volume/no intervention assessed with: MRI, CT, ultrasound. Follow up: range 2 to 16 weeks	Muscle size in the BFR training group was 0.50 SDs (0.17 to 0.82 higher) higher than in the Matched volume/no intervention group.	257 (6 RCT, 6 quasi experimental studies)	⊕⊕⊕◯ MODERATE [a,c]	The results can be interpreted as an improvement of 3.4 cm2 (95% CI 1.9 to 5.7 cm2 larger) in the BFR training group. This would be equivalent to a 5.6% hypertrophy with BFR (95% CI 3.1% to 9.4% larger).[f]
Size - BFR training vs Matched volume assessed with: MRI, ultrasound. Follow up: range 2 to 16 weeks	Muscle size in the BFR training group was 0.92 SDs (0.55 to 1.30 higher) higher Matched volume group	127 (1 RCT, 4 quasi experimental sudies)	⊕⊕⊕◯ MODERATE [a,c]	The results can be interpreted as an improvement of 7.4 cm2 (95% CI 4.4 to 10.4 cm2 larger) in the BFR training group. This would be equivalent to a 10.2% hypertrophy with BFR (95% CI 6.1% to 14.3% larger).[g]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

BFR: Blood flow restriction training, MVIC: Maximum voluntarily isometric contraction, 1-RM: One-repetition maximum, SD: Standard deviation, CI: Confidence interval, MRI: Magnetic resonance imaging, CT: Computer tomography

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Downgraded because of Risk of bias (Lack of allocation concealment and outcome assessor blinding)
b. Optimal information size based on Yasuda et al. (2015) mean(SD)
c. Optimal information size based on Iversen et al. (2016) mean(SD)

d. The control group strength mean(SD) 47.9(14.1) kg was calculated by averaging the knee extension 1-RM of Araújo et al. (2015), Cook et al. (2010), Karabulut et al. (2010), Shimizu et al. (2016), J. Silva et al. (2015), Yasuda et al. (2014), and Yasuda et al. (2016).
e. The control group strength mean(SD) 45.4(10.95) kg was calculated by averaging the knee extension 1-RM of Araújo et al. (2015), and Shimizu et al. (2016).
f. The control group muscle size mean(SD) 60.8(6.9) cm2 was calculated by averaging the thigh MRI findings of Cook et al. (2010), Iversen et al. (2016), Libardi et al. (2015), Ozaki et al. (2011), Vechin et al. (2015), Yasuda et al. (2014), and Yasuda et al. (2016).
g. The control group muscle size mean(SD) 72.6(8) cm2 was calculated by averaging the thigh MRI findings of Iversen et al. (2016), Ozaki et al. (2011), and Vechin et al. (2015).

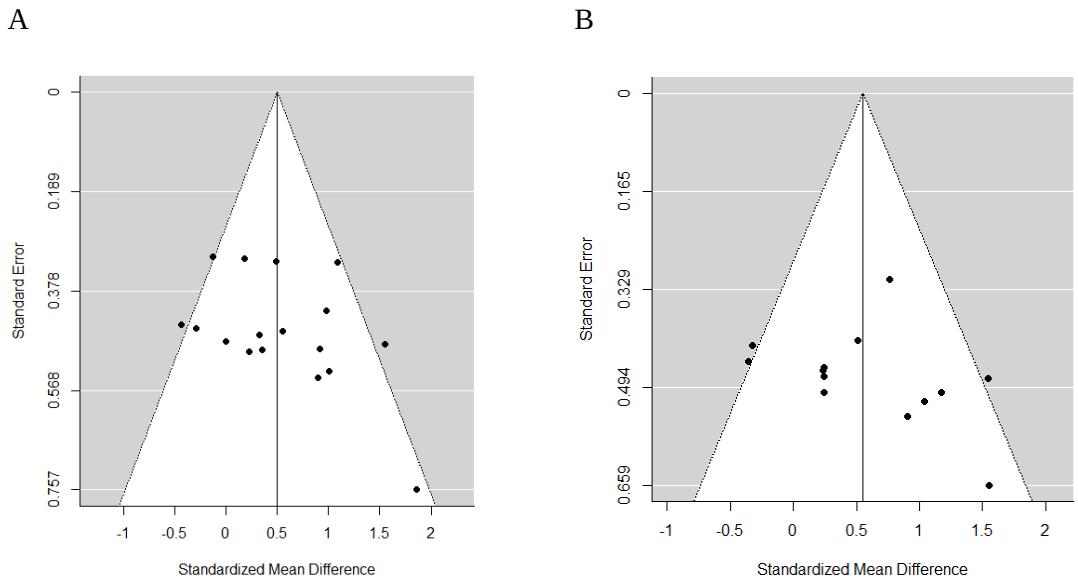


Figure 16. Funnel plot for blood flow restriction (BFR) training vs. a matched volume or no exercise control group for strength (A) and size (B) variables.

Of the 15 studies examining muscle strength, 12 showed a significant change in muscle strength after BFR training compared to the control groups. The pooled results provide moderate quality evidence that BFR training improves muscle strength compared to low intensity training without BFR or no intervention (SMD 0.55 [95% CI 0.25, 0.86], p = 0.0004). The I^2 was 42% (X^2 = 24.07, p = 0.04).

Ten of the 12 studies examining muscle size, showed significant improvements in the BFR training group compared to the control groups. All the studies except Abe et al. (2010) and Karabulut et al. (2013), which adopted ultrasound and CT scans respectively, assessed muscle size by MRI. The pooled results provide moderate quality evidence that BFR training increases muscle size compared to low intensity training without BFR or no intervention (SMD 0.50 [95% CI 0.17, 0.82], p = 0.003). The I^2 was 36% (X^2 = 17.17, p = 0.10). When the two studies utilising ultrasound (Abe et al., 2010) and CT scan (Karabulut et al., 2013) were excluded, the analysis did not lead to

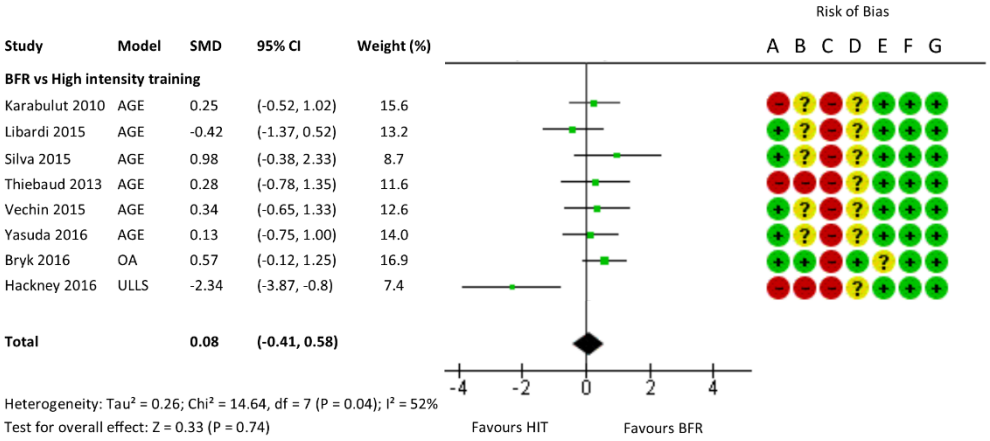
different results (SMD 0.61 [95% CI 0.28, 0.95], $p = 0.0003$; $I^2 = 28\%$; $X^2 = 12.44$, $p = 0.19$).

A subgroup analysis comparing BFR training to a matched volume intervention (n = 8 studies) was performed. The pooled results provide moderate quality evidence that BFR training improves muscle strength (SMD 0.68 [95% CI 0.30, 1.06], $p = 0.0004$) with an I^2 of 32% ($X^2 = 8.77$, $p = 0.19$), as well as muscle size (SMD 0.92 [95% CI 0.55, 1.33], $p < 0.00001$) with an I^2 of 0% ($X^2 = 3.11$, $p = 0.54$) compared to matched volume low intensity training without BFR.

Blood flow restriction training vs high intensity training

Forest plots of the results are presented in Figure 17. Summary of findings and GRADE quality ratings are reported in Table 9. Funnel plots for muscle strength and size are reported in Figure 18. Visual inspection did not identify any clear funnel plot asymmetry.

A



B

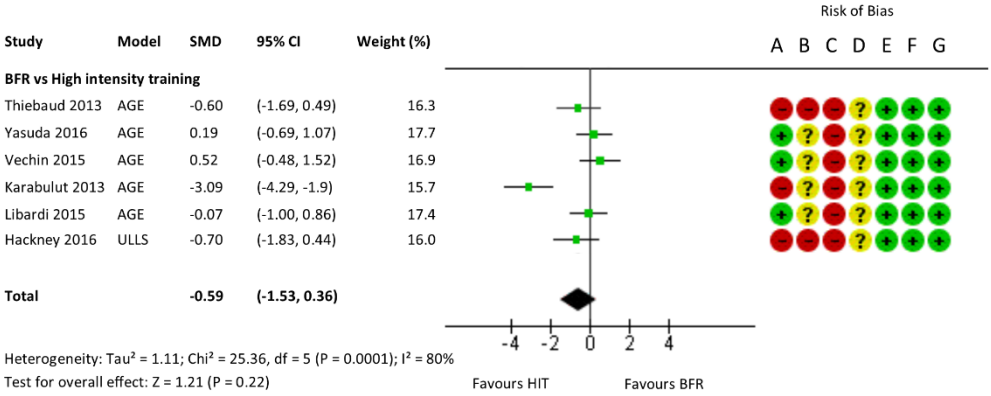


Figure 17. Forest plot of the standardised mean difference (SMD) between the effect of blood flow restriction (BFR) training vs. HIT on strength (A) and size (B) variables. CI confidence interval, AGE adults over 50 years old (potential sarcopenia), OA osteoarthritis, ULLS unilateral lower limb suspension.

Table 9. Summary of findings (GRADE)

BFR compared to High intensity training for Disuse

Patient or population: Disuse, Setting: Osteoarthritis, over 50 yrs old, Intervention: BFR training, Comparison: HIT.

Outcomes	Anticipated absolute effects* (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
Strength - BFR training vs High intensity training assessed with: 1-RM, MVIC Follow up: range 6 to 12 weeks	Muscle strength in the BFR training group was 0.08 SDs (-0.41 lower to 0.58 higher) higher than in the HIT group.	151 (5 RCT, 3 quasi experimental)	⊕⊕◯◯ LOW [a,b,c]	The results can be interpreted as an improvement of 0.94 kg (95% CI -4.8 weaker to 6.8 kg stronger) in the BFR training group. This would be equivalent to a 1.9% increase in strength with BFR (95% CI -10% weaker to 14.1% stronger).[d]
Size - BFR training vs High intensity training assessed with: MRI, ultrasound. Follow up: 6 to 12	Muscle size in the BFR training group was -0.57 SDs (-1.53 lower to 0.36 higher) lower than in the HIT group.	107 (3 RCT, 3 quasi experimental)	⊕⊕◯◯ LOW [a,b,c]	The results can be interpreted as an improvement of 6.1 cm2 (95% CI -3.7 smaller to 15.9 cm2 larger) in the HIT group. This would be equivalent to a 11.4% hypertrophy with HIT (95% CI -6.95% smaller to 29.5% larger).[e]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

BFR: Blood flow restriction training, HIT: High intensity training, 1-RM: One-repetition maximum, MVIC: Maximum voluntarily isometric contraction, SD: Standard deviation, CI: Confidence interval, MRI: Magnetic resonance imaging

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Downgraded because of Risk of bias (Lack of allocation concealment and outcome assessor blinding)
b. Downgraded because of Inconsistency (Wide variance, large and significant heterogeneity)
c. Optimal information size not calculated as we did not expect differences between groups
d. The control group strength mean(SD) 48.6(3.3) kg was calculated by averaging the knee extension 1-RM of Karabulut et al. (2010), J. Silva et al. (2015), Thiebaud et al. (2013), and Yasuda et al. (2016).
e. The control group muscle size mean(SD) 53.9(10.4) cm^2 was calculated by averaging the thigh MRI findings of Libardi et al. (2015), Vechin et al. (2015), and Yasuda et al. (2016)

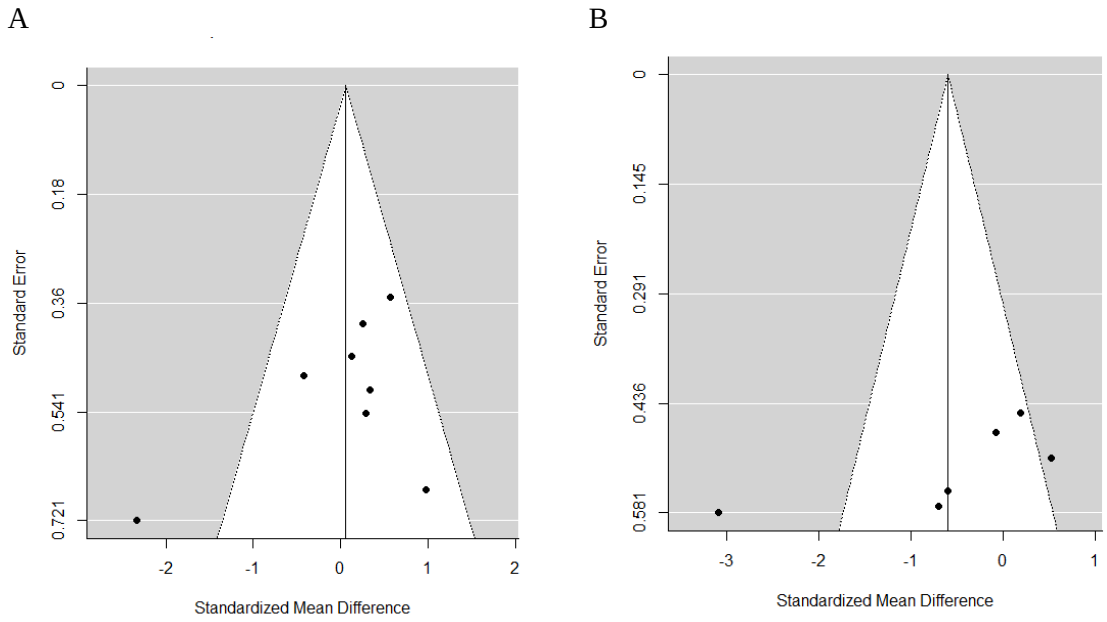


Figure 18. Funnel plot for blood flow restriction (BFR) training vs. a high intensity training (HIT) group for strength (A) and size (B) variables.

Six of the eight studies examining muscle strength showed that BFR training induced similar gains when compared to HIT. All the studies except Bryk et al. (2016), which adopted a maximum voluntary isometric contraction testing, utilised 1-RM as a strength outcome measure. The pooled results provide low quality evidence that BFR training does not induce greater strength improvements compared to HIT (SMD 0.08 [95% CI -0.41, 0.58], $p = 0.74$). The I^2 was 52% ($X^2 = 14.64$, $p = 0.04$). When the study by Bryk et al. (2016) was excluded, the pooled results showed a similar pattern, suggesting no difference between the two groups (SMD -0.02 [95% CI -0.59, 0.55], $p = 0.95$) with an I^2 of 53% ($X^2 = 12.88$, $p = 0.05$).

Only one study out of six showed a significantly greater improvement in muscle size for the BFR training group compared to HIT (Yasuda et al., 2016), with four studies showing similar gains (Karabulut et al., 2013; Libardi et al., 2015; Thiebaud et al.,

2013; Vechin et al., 2015) and one study showing a greater improvement in muscle size following HIT (Hackney et al., 2016). The pooled results provide low quality evidence that BFR training does not induce greater hypertrophy compared to HIT (SMD -0.59 [95% CI -1.53, 0.36], $p = 0.22$). The I^2 was 80% ($X^2 = 25.36$, $p = 0.0001$). Excluding the studies by Thiebaud et al. (2013) and Karabulut et al. (2013), which utilised ultrasound and CT scan assessments respectively, did not change the results (SMD 0.03 [95% CI -0.45, 0.52], $p = 0.89$) with an I^2 of 0% ($X^2 = 2.66$, $p = 0.45$).

Adverse events following blood flow restriction training or traditional resistance training

Amongst the studies included in this meta-analysis, three adverse events were reported after BFR interventions, one after a control intervention, and none after traditional HIT. The absolute risk of an adverse event following BFR was 1.1% versus 0.5% in the control intervention. In the subsequent literature review of published case studies concerning adverse events, 45 adverse events (32 case studies/series) were reported following HIT and BFR (Table 10). Of these, 16 events occurred in females. Age of the affected participants ranged from 19 to 73 years old. Of the 45 adverse events, four occurred following BFR training and 41 following traditional HIT. Following BFR training, three patients presented with exertional rhabdomyolysis while one had a central retinal vein occlusion. Of the 41 patients with adverse events following traditional HIT, 29 had rhabdomyolysis, 10 presented with a musculoskeletal injury, six presented with a vascular adverse event including strokes (n = 2), internal carotid artery dissection (n = 2), upper limb deep vein thrombosis (n = 1), and renal hematoma (n = 1), two with compartment syndrome and one with tetraplegia following C5/6 disk sequestration.

Table 10. Summary of case studies/series on adverse events following BFR and HIT

Study	BFR	HIT	Details	Adverse event
Alexandrino et al. (2014)		x	N = 2 41 and 32 yrs Female/Male Abdominal exercises/Crossfit	Stroke
Al-Kashmiri, Sun, and Delaney (2007)		x	N = 1 53 yrs Male Dumbbells lifting	Avulsion fracture anconeus
Auten, Schofer, Banks, and Rooney (2010)		x	N = 1 23 yrs Male Abdominal exercises	Rectus sheath hematomas
Avery, Carolan, and Festa (2014)		x	N = 1 49 yrs Female Bench press	Pectoralis major rupture
Busche, Knobloch, Rosenthal, and Vogt (2008)		x	N = 1 19 yrs Male Military style push-ups	Hamate body and fourth metacarpal stress fracture
Cheema, Lassere, Shnier, and Fiatarone Singh (2007)		x	N = 1 73 yrs Female Overhead press exercise	Rotator cuff tear
Chow, Dickson, and Khan (2013)		x	N = 1 21 yrs Male Isometric grip holds (40ks)	Flexor digitorum superficialis muscle belly rupture

Clark and Manini (2017)	x		N = 1 20 yrs Male Knee and elbow flexion w/ BFR	Exertional rhabdomyolysis
Clewer, Carmont, and Jaffray (2006)		x	N = 1 31 yrs Male Shoulder presses and shoulder shrugs	Tetraplegia secondary to C5/6 disc sequestration.
Do, Bellabarba, and Bhananker (2007)		x	N = 1 22 yrs Male Weight training	Exertional rhabdomyolysis
Felderman, Shih, and Maroun (2009)		x	N = 1 44 yrs Female Chin-up exercise	Bilateral anterior shoulder dislocation
Friedman, Stensby, Hillen, Demertzis, and Keener (2015)		x	N = 1 43 yrs Male Muscle up exercise – Crossfit	Latissimus dorsi myotendinous junction tear
Gill and Mbubaegbu (2004)		x	N = 1 28 yrs Male Bench press	Shaft of clavicle fracture
Goubier, Hoffman, and Oberlin (2002)		x	N = 1 30 yrs Male Upper limb HIT	Exertional rhabdomyolysis

Have and Drouet (2011)		x	N = 1 25 yrs Female Arm tractions	Exertional rhabdomyolysis
Hegedus, Cooper, and Cook (2006)		x	N = 1 21 yrs Female Upper and lower limb HIT	Upper extremity deep vein thrombosis
Hoppes, Ross, and Moore (2013)		x	N = 1 29 yrs Male Bench press	Pectoralis major tendon rupture
Huynh et al. (2016)		x	N = 10 19-36 yrs Males/females CrossFit/Weight training	Exertional rhabdomyolysis
Iversen and Røstad (2010)	x		N = 1 31 yrs Male Knee extension exercise with BFR	Exertional rhabdomyolysis
Kasikcioglu, Kaysrilioglu, and Kadioglu (2004)		x	N = 1 45 yrs Male Dumbbell lifting	Renal hematoma
Khalil and Saab (2016)		x	N = 2 19/20 yrs Male Upper limb HIT	Exertional rhabdomyolysis
Lozowska, Liewluck, Quan, and Ringel (2015)		x	N = 6 26-43 yrs Male/female CrossFit	Exertional rhabdomyolysis

Lu et al. (2015)		x	N = 2 NA yrs Male/female CrossFit	Internal carotid artery dissection
Martin (2016)		x	N = 1 High school student Male Dead lifts	Exertional rhabdomyolysis
Mattiassich et al. (2013)		x	N = 1 30 yrs Male Lumbar spine extensors HIT	Paravertebral compartment syndrome
Ozawa, Koto, Shinoda, and Tsubota (2015)	x		N = 1 45 yrs Male BFR training regime	Central retinal vein occlusion
Pearcey, Bradbury-Squires, Power, Behm, and Button (2013)		x	N = 1 31 yrs Male Pull-up and push-up	Exertional rhabdomyolysis
Rathi (2014)		x	N = 2 33/37 yrs Male CrossFit	Exertional rhabdomyolysis
Shinde (2014)		x	N = 1 20 yrs Male Upper and lower limbs HIT	Exertional rhabdomyolysis and renal failure

Springer and Clarkson (2003)		x	N = 2 22/37 yrs Male/female Upper and lower limb HIT	Exertional rhabdomyolysis
Tabata, Yukio, Koichiro, and Hideo (2016)	x		N = 1 30 yrs Male Squats w/ BFR	Exertional rhabdomyolysis
Willick, DeLuigi, Taskaynatan, Petron, and Coleman (2013)		x	N = 1 21 yrs Male Upper limb HIT	Chronic exertional compartment syndrome

Note. BFR = blood flow restriction training; HIT = high intensity training; N = sample; yrs = years old.

Discussion

In the last 20 years, interest in BFR interventions has steadily grown. While the research literature has primarily focused on utilising BFR in young, healthy athletes, this form of training may be a useful alternative for older people and those with musculoskeletal conditions who may be unable to perform HIT due to symptom exacerbation, a desire to avoid high levels of loading or comorbid conditions which limit their exercise capacity. The findings of this review highlight the potential effectiveness of BFR interventions in counteracting muscle strength loss and atrophy in people undergoing a period of disuse and in adults over the age of 50. Specifically, we found moderate quality evidence that BFR training improves both muscle strength and muscle size to a greater extent than matched low intensity resistance training program without BFR or no exercise. The size of the improvement in the BFR training group, over the control group (matched volume or no exercise), was 16% and 6% for muscle strength and muscle size respectively. The present review also found low quality evidence that BFR training produces similar

benefits in muscle strength and size compared to traditional HIT. Finally, there was also low quality evidence that BFR alone may help to prevent muscle weakness associated with disuse, even in the absence of resistance training. While these results suggest that BFR training may a promising intervention in populations with musculoskeletal conditions such as hand OA, the low to moderate quality evidence suggests that further high quality research is needed comparing BFR training to HIT and/or no exercise control groups.

Several potential mechanisms have been advanced to explain strength and hypertrophy gains with BFR training. Firstly, it is possible that neural adaptations contribute to muscle strength improvements after BFR training. In this regard, several studies (Moore et al., 2004; Takarada, Nakamura, et al., 2000; Yasuda et al., 2006) have shown increased electromyography amplitude of the active muscle(s) during BFR training compared to matched low intensity training without BFR. This is thought to reflect the accelerated fatigue of smaller type I motor units by BFR and subsequent recruitment of larger type II motor units in order to maintain adequate muscle force production (Scott et al., 2014). Furthermore, a recent study has shown that a single session of BFR training enhances corticomotor excitability compared to a matched volume exercise without BFR (Brandner et al., 2015). As disuse is associated with a reduction in corticomotor excitability (Clark et al., 2008; D. R. Roberts et al., 2010), this could partially explain the benefits of BFR on muscle strength. During traditional HIT, the mechanical tension produced by the active muscle fibres is thought to be a key driver of hypertrophy, activating chemical signals that in turn facilitate anabolic pathways. However, due to the low intensity of exercise performed during BFR training, it is unlikely that mechanical tension plays an important role in its efficacy (Ozaki, Loenneke, Buckner, & Abe, 2016). This is supported by the findings of our subgroup analysis (n = 8 studies), where BFR training was found to lead to significant gains in

both muscle hypertrophy and strength compared to matched volume low intensity exercise without BFR. Instead, a key difference with BFR training is that it induces a hypoxic environment in the exercised muscle(s), thus increasing metabolic stress, another critical driver of muscle hypertrophy (Pearson & Hussain, 2015). Muscle hypoxia may mediate hypertrophy via several interrelated mechanisms, including increased intracellular swelling, reduced myostatin expression and increased systemic hormone and nitric oxide production - ultimately leading to enhanced activation and proliferation of satellite cells and increased muscle protein synthesis (See Figure 19) (Scott et al., 2014).

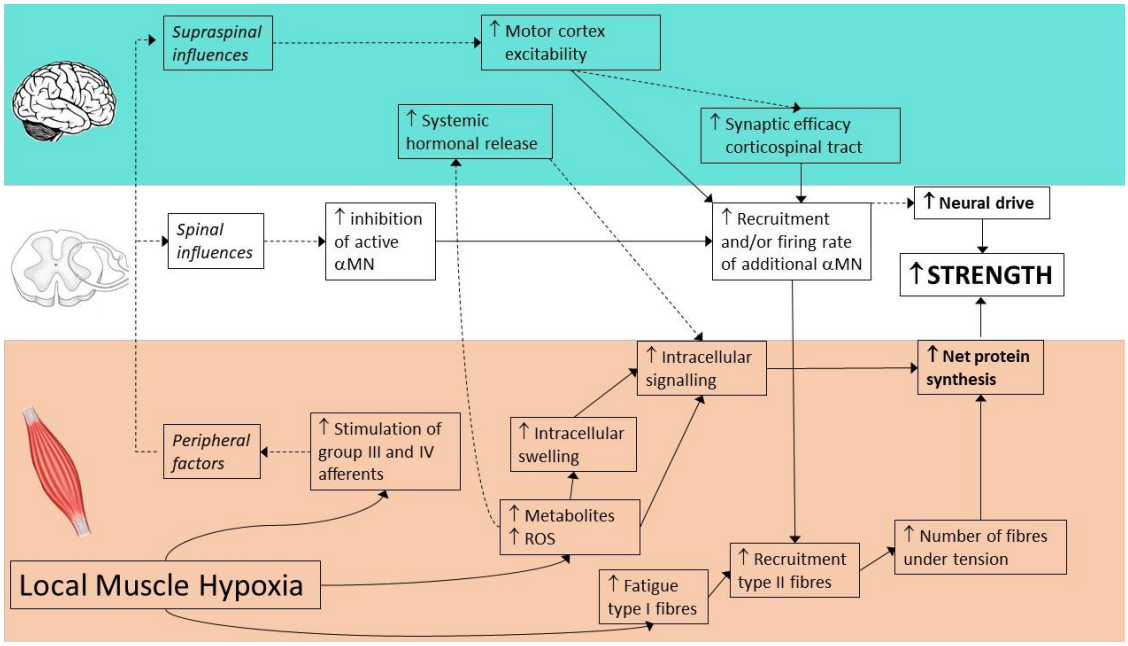


Figure 19. Possible BFR mechanisms leading to muscle strength increases.

In young healthy populations, traditional HIT appears to have superior efficacy compared to BFR training, especially when considering gains in muscle strength (Ogasawara, Loenneke, Thiebaud, & Abe, 2013). In contrast, we could provide no evidence of a difference in muscle strength and size gains when comparing BFR training to HIT in people undergoing a period of disuse and in adults 50 years of age

and above. These findings should be interpreted with caution due to the low-quality evidence supporting them. However, it is plausible that the relative efficacy of BFR training is enhanced in a rehabilitation setting. By reducing the load (i.e., the force acting upon a tissue per unit of time) on injured and/or peripherally sensitised tissues, BFR training may minimise exercise induced flares in pain and swelling compared to HIT. In turn, this may reduce or prevent adverse neuromuscular consequences such as arthrogenic muscle inhibition, which typically exacerbates atrophy and delays or prevents effective muscle strengthening (Rice & McNair, 2010). For example, Giles, Webster, McClelland, and Cook (2017) recently found that eight weeks of BFR training was significantly more effective at improving quadriceps strength than eight weeks of traditional HIT in patients with patellofemoral pain who experienced pain during active knee extension.

As indicated in our findings, another interesting alternative to HIT, is the application of BFR only, without any form of exercise. It has been suggested that BFR alone mediates hypertrophy by stimulating mTORC1 pathways, which are promoters of protein synthesis (Jessee et al., 2018). Although limited by low quality evidence, our findings suggest that BFR alone, without exercise, may be utilised in the very early stages after injury or surgery to minimise the loss of muscle strength associated with these conditions. Moreover, BFR training might be able to be implemented earlier in the rehabilitation program than traditional HIT after certain types of surgery (e.g. ACL reconstruction, microfracture or osteochondral grafts), where care must be taken to minimise the loads placed on healing tissues.

In addition, due to reduced mechanical tension within muscle compared to HIT, BFR training could be associated with reduced muscle fibre damage and inflammation, which might be particularly valuable when rehabilitating individuals with rheumatic conditions

involving specific muscle symptoms (e.g. myositis) (Loenneke, Thiebaud, & Abe, 2014). Reduced muscle fibre damage due to less mechanical tension may also mean that less recovery is needed after each session, allowing an increased frequency of training (Fujita, Brechue, Kurita, Sato, & Abe, 2008) and thereby expediting gains in muscle strength and hypertrophy. Thus, BFR has the potential to notably accelerate rehabilitation, allowing a faster return to function and sporting activities.

Several papers have questioned the safety of BFR training due to concerns about the potential of disturbed haemodynamics and reperfusion injury (Spranger et al., 2015). In this respect, three of the included studies reported adverse events with BFR training. Furthermore, a systematic literature search revealed only four case studies reporting adverse events associated with BFR training. Three case studies (Clark & Manini, 2017; Iversen & Røstad, 2010; Tabata et al., 2016) reported incidences of rhabdomyolysis, while a single case study (Ozawa et al., 2015) reported central retinal vein occlusion in a diabetic and previously undiagnosed hypertensive patient following BFR training. An accurate medical screening and exclusion of this person from BFR training may have avoided such an event.

In contrast, 41 studies were found reporting adverse events associated with traditional HIT. This could simply reflect HIT being practiced by a greater proportion of the population when compared to BFR. However, an epidemiological study of BFR training in Japan (Nakajima et al., 2006) reported a very low occurrence of all adverse events apart from skin bruising, with the incidence of rhabdomyolysis estimated at 0.008%. Furthermore, amongst the adverse events reported in the literature, several incidences of rhabdomyolysis also occurred after HIT, as well as more serious adverse events such as stroke, tetraplegia due to cervical disc sequestration and internal carotid artery dissection. Thus, at present, the available evidence does not support increased safety

concerns associated with BFR training when compared to HIT. Nevertheless, specific safety guidelines and screening tools have been developed for BFR training and should always be utilised when undertaking this intervention (Kacin, Rosenblatt, Žargi, & Biswas, 2015).

Of interest, the BFR occlusion pressures used in the included studies varied considerably ranging from 60mmHg (approximately 50% of systolic pressure) up to pressures of 270mmHg. Previous experimental studies (Counts et al., 2016) have suggested that a specific level of arterial occlusion is required to obtain the benefits of BFR training, beyond which further gains are either absent or minimal. Importantly, higher BFR pressures are associated with more discomfort during training (Counts et al., 2016). Furthermore, when BFR is applied directly to the exercising muscle, it has been shown that pressures can double during the concentric phase of the exercise (Kacin et al., 2015). This may raise the restriction pressures to levels close to or even beyond arterial occlusion, potentially increasing the risk of adverse events, including thromboembolism (Moore et al., 2004). As increased occlusion pressures do not appear to improve intervention efficacy it is recommended that future applications of BFR training use pressures up to a maximum of 50% of arterial occlusion as suggested by Loenneke, Kim, et al. (2015).

Limitations of the present study include the relatively small number of participants and heterogeneity of the populations included in the meta-analysis. This was acknowledged, and the overall quality of evidence was downgraded (See Table 7 and Table 9). In addition, a per-protocol analysis was performed on the post intervention data reported in each study and baseline differences were indicated, when available, in Table 6. Data for participants who dropped out were not available. Formal statistical analyses to assess publication bias were only performed when sufficient studies were available. Visual

inspection of funnel plots did not identify any clear indication of publication bias. Finally, we need to acknowledge as a limitation the inclusion of studies published only in English, Spanish or Italian.

Conclusion

There is moderate quality evidence that BFR training is an effective intervention to counter muscle atrophy and weakness associated with disuse and ageing compared to matched volume exercise or no exercise. By minimising the loads placed on healing or damaged tissue, BFR training may expedite rehabilitation, allowing earlier, and more effective muscle strengthening to occur after surgery or in those with arthritic conditions. It is possible that BFR training may also be more acceptable and allow more effective muscle strengthening in older adults or individuals with comorbidities who may otherwise not tolerate or be able to perform HIT. Further research is needed to support these claims in specific populations, such as hand OA.

Chapter Six: Blood flow restriction vs traditional strength training for hand osteoarthritis: a feasibility study

Introduction

In chapter three, we identified significant deficits in grip strength, which were moderately associated with self-reported hand function in people with hand OA. In people with knee OA, it has been shown that an increase in lower limb muscle strength is associated with improvements in pain and functional activities (Hall et al., 2018). It appeared logical to suggest that resistance training may lead to similar findings in people with hand OA. However, when the literature was systematically reviewed in Chapter four, only five studies had assessed resistance training in this population. The results across these studies were inconsistent and several methodological and exercise prescription limitations were identified. These included lack of randomisation, allocation concealment and outcome assessor blinding. Furthermore, not all the studies followed international guidelines when prescribing resistance training exercises. Overall improvements in strength were not significant when results were pooled in our meta-analysis and there was an increase of 8% in grip strength, with wide confidence intervals ranging from -5% to 20%. It is also not clear whether a properly designed strength training program could prove beneficial for people with hand OA. It is possible that a high intensity strength training regime may exacerbate pain in people with hand OA. Indeed, a recent systematic review reports that exercise in hand OA is associated with a 4.6 times increased relative risk of inducing adverse events such as joint inflammation and hand pain, and a 2.9 times increased relative risk of withdrawing from treatment due to adverse events (Østerås et al., 2017). Therefore, the efficacy of

alternative forms of exercise training such as blood flow restriction (BFR), which could provide similar benefits to traditional strength training while limiting the load on the affected joints and reducing the risk of symptom exacerbation were explored.

BFR has been utilised for at least two decades as an alternative to traditional high intensity training (HIT). Several reviews (Loenneke, Wilson, Marín, Zourdos, & Bemben, 2012; Scott et al., 2016) have shown its effectiveness in improving muscle strength and size in young, healthy participants. In Chapter five, our meta-analysis provided some evidence that BFR training is effective in improving muscle strength and size and produces similar gains to HIT in people over 50 years old and with muscle weakness due to disuse, which are characteristics commonly encountered in people with hand OA. Interestingly, no study has yet applied BFR training to people with hand OA. One study has utilised BFR in people with knee OA and showed that pain during exercise was significantly lower in the BFR compared to the HIT group (Bryk et al., 2016). Thus, it is possible that if BFR was applied in people with hand OA, the exercise induced pain might be lower compared to HIT, leading to a more acceptable, yet still effective, intervention for participants.

Apart from the intervention and improving upon methodological limitations of previous work, several important questions related to feasibility still needed to be answered before implementing in a full-scale randomised controlled trial (RCT) (Arain, Campbell, Cooper, & Lancaster, 2010). Specifically, participant's recruitment potential requires assessment to quantify the resources available for a larger trial and the most successful advertising strategies. In previous studies (Hennig et al., 2015; Østerås et al., 2014), 30% to 50% of potential participants met the inclusion criteria, 4% to 8% declined to participate for a wide range of reasons and 90% of the participants randomised were retained at follow-up. Low treatment adherence in OA has been

identified as a problem when implementing exercises interventions (Bennell, Dobson, & Hinman, 2014; Marks, 2012). Treatment adherence in OA has been shown to range between 50% to 95%, with longer program durations associated with lower compliance (Beckwée, Bautmans, Scheerlinck, & Vaes, 2015; Marks, 2012; McKnight et al., 2010). Pain exacerbations with strength training in knee OA appear to be relatively rare however, where this does occur, exercise adherence was notably reduced (Beckwée et al., 2015).

It was therefore the aim of this study to determine whether BFR and HIT are feasible interventions for people with hand OA. Specifically, we were interested in seeking the opinion of hand therapists regarding the use of strength training for hand OA. Furthermore, it was important to determine the ability of HIT and BFR to induce strength gains in grip and pinch strength after a short program of six weeks of training in people with hand OA. In addition, we were interested in assessing pre-exercise pain and exercise induced pain across six weeks of training. Finally, participants' completion rate, treatment adherence, pain exacerbations, training acceptability, and recruitment potential also needed assessment.

Methods

Consultation with hand therapists

Before identifying participants for the study, we met with several groups of hand therapists from private and public clinics to (1) seek their opinion regarding strength training for people with hand OA, (2) identify what exercises they most often prescribed, (3) seek their help for participants' recruitment.

Participants

Participants were recruited through advertisement in a national newspaper and three suburban newspapers in different regions of Auckland. These regions had quite different socioeconomic members of their communities. In addition, recruitment occurred at local gyms ("Never2old" at AUT gym, "Active Ageing Classes" at JustWorkout), local physiotherapy clinics, Waitemata District Health Board (WDHB), Counties Manukau District Health Board (CMDHB), and retirement villages. Hand OA was confirmed through radiographic evidence which involved scoring utilising the Kellgren-Lawrence scale (Schaefer et al., 2018) by an independent radiologist. The American College of Rheumatology (ACR) clinical criteria (Altman et al., 1990) were assessed by a musculoskeletal physiotherapist with postgraduate qualifications. See Table 11 for participants' eligibility criteria. An a priori sample size calculation was completed to determine the number of participants needed in each group to identify a significant change in grip strength from baseline to follow-up on a paired t-test. Based upon research by Hennig et al. (2015) and Bryk et al. (2016), the sample size calculated was 22 participants per group. Interested participants were mailed an information sheet. The information sheet explained the aims, rationale, methodology, potential risks and benefits of the study. If participants were happy to participate they were given the opportunity to ask questions, then screened according to the following criteria. Ethical approval for the study was attained from the Auckland University of Technology Committee, in accordance with the principles set out in the declaration of Helsinki (See Appendix F).

Table 11. Inclusion and exclusion criteria for participants' recruitment

Inclusion criteria	Exclusion criteria
Fulfils ACR criteria: Hand pain, aching, or stiffness and 3 or 4 of the following: - Hard tissue enlargement of 2 or more of 10 selected joints* - Hard tissue enlargement of 2 or more DIP joints - Fewer than 3 swollen MCP joints - Deformity of at least 1 of 10 selected joints*	Upper limb radiculopathy Past or present Hx of neurological disease Infection in the last three months Hx of resistance training for their hands in the last six months Surgery to their hands in the last five years or cortisone injection in the last six months
Radiographic evidence (Kellgren Lawrence > 1)	Uncontrolled cardiovascular disease (e.g. uncontrolled hypertension)
Hand pain for a least three months on consecutive days in the last year	Hx of blood clot in the last 12 months
Hand pain in the week before testing scored at three or higher on an 11-point verbal NRS	Active cancer Hx of upper quadrant lymph node dissection

Note. * = second and third distal interphalangeal (DIP), the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands; ACR = American College of Rheumatology; MCP = Metacarpophalangeal; Hx = History; NRS = numeric rating pain scale

Randomisation

Participants were allocated to either the BFR or HIT group. During the baseline assessment, performed by a blinded assessor, participants' grip and pinch strength were measured across three trials and the highest result was considered as their MVC. Grip strength results were then used to stratify participants into one of three groups (Grip strength below 17.5 kg, between 17.5 and 22.5 kg, greater than 22.5 kg). After stratification, participants were allocated through block randomisation (block sizes of two) to one of the two groups. The block randomisation list was generated through R3.3.3 (Viechtbauer, 2010) using the blockrand package (Snow, 2013).

Grip and pinch strength assessment

Grip and pinch strength were assessed through a digital hand and pinchmeter dynamometer (Biometric Ltd, Newport, UK), which showed signal in real time (See

Figure 20). The hand dynamometer was kept in the second handle position for both strength assessment and training (Trampisch et al., 2012). The pinchmeter was held between the index and thumb (tip to tip pinch) for both assessment and training (Villafañe & Valdes, 2014). For grip and pinch strength testing, the highest of three trials was recorded as the MVC (Gerodimos et al., 2017). Validity and reliability of these measures has been shown by D. Allen and Barnett (2011).

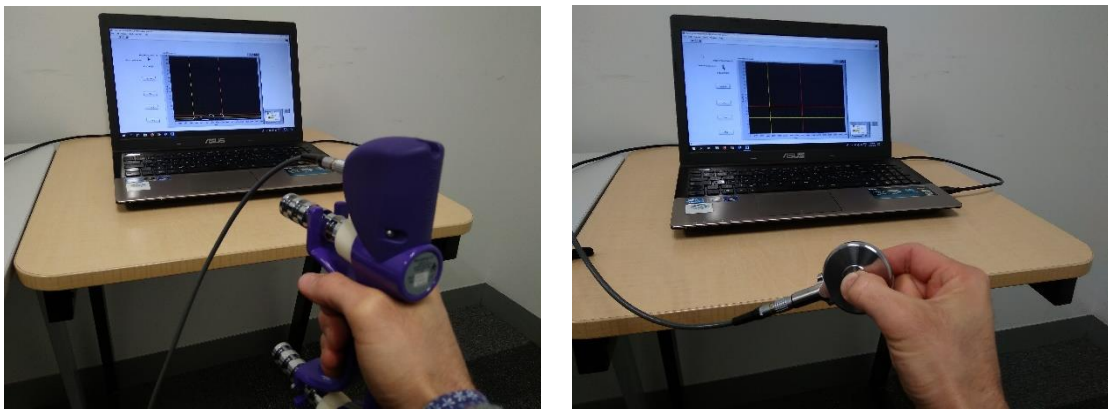


Figure 20. Participant completing a grip (left) and pinch (right) strength task.

Training

Both the BFR and the HIT groups exercised three times a week for six weeks (Grgic et al., 2018). At each session, participants performed a grip and pinch strengthening exercise, which were performed with a digital hand grip and pinchmeter dynamometers (Biometric Ltd, Newport, UK). The dynamometers were connected to a data acquisition board and the signal was transmitted to a customised computer software produced in LabVIEW (LabVIEW software, Version: 2013, Austin, TX, USA), which displayed strength data in real time. Both groups performed two sets of each exercise during the first week, three sets during week two to four, and four sets during week five and six. This progression included both an increase in intensity as well as number of repetitions as suggested by the American College of Sports Medicine (Garber et al., 2011).

Participants in the BFR group performed 30 repetitions during the first set and 15 repetitions in the following sets. This regime was selected based on the findings from our previous literature review (Chapter five). The HIT group performed 10 repetitions in each set. In sitting, positioning was standardised and participants performed all the exercises in 90 degrees of elbow flexion. All the repetitions lasted two seconds, and between repetitions there was one second pause. A tip to tip pinch between index and thumb with the other fingers flexed to touch the palm of the hand was utilised when pinch gripping.

Blood flow restriction training

The BFR group trained at 30% of MVC on week one and two, followed by an increase in intensity to 40% during week three to six. While training, participants wore a blood pressure cuff (width: 13.5 cm, length 53 cm) on their exercising arm, proximally to the forearm muscles, like in the studies by Takarada, Takazawa, Sato, et al. (2000) and Yasuda et al. (2015). The pressure delivered to the arm was individualised and was set to 50% of participants' arterial occlusion. Arterial occlusion (mmHg) was calculated utilising the equation published by Loenneke, Allen, et al. (2015) (Equation 1) based on systolic (SBP) and diastolic blood pressure (DBP) and arm circumference.

Equation 1

$$\text{Arterial occlusion} = 0.514\,(\text{SBP}) + 0.339(\text{DBP}) + 1.461\,(\text{Arm circumference}) + 17.236$$

Arm circumference was measured once at baseline and blood pressure was measured during each session before initiating training. Pressure was maintained during the inter-sets rests, which lasted 30 seconds and was released upon completion of each exercise.

High intensity training

The high intensity exercise group trained at 60% of MVC on week one and two, followed by an increase in intensity to 70% during week three to six (Garber et al., 2011). Participants rested for two minutes between each set of exercise.

Pain, treatment adherence, pain exacerbations and training acceptability

Pain was measured through an 11-point numeric rating scale (NRS), with anchors of 0 = "no pain" and 10 = "worst pain imaginable". All participants reported their current pain intensity in the affected hand before and immediately after training at each session (n = 18). Exercise induced pain (EIP) was calculated by subtracting pre-exercise from post exercise pain for each session.

Treatment adherence was calculated for each group. Percentages were calculated dividing the number of sessions attended by the number of sessions that the participants were supposed to attend. An increase in hand pain for more than 24 hours after treatment was considered as a pain exacerbation and it was recorded at each session. The number of participants who withdrew from each group was recorded. Training acceptability was measured by asking participants to rate "How acceptable was the training?" on a Likert scale (anchors of 1 = "Not at all satisfied" and 6 = "Extremely satisfied") at the end of the six weeks training period. During the last training session, all participants were asked if they had any comments on the training regime and these were recorded.

Data processing and statistical analysis

Data were processed in R 3.3.3 (R Core Team, 2017). Statistical analyses were performed in R 3.3.3 and SPSS software version 22 (SPSS, Chicago, IL, USA). Prior to inferential analyses, data were screened for normality (Shapiro-Wilk test). Non-

normality was observed in some instances including grip and pinch strength for the HIT group, pre-exercise pain and training acceptability. The Wilcoxon signed-rank test was used to test differences between initial and final measurement on grip, pinch strength and pre-exercise pain for the HIT and BFR groups. Paired t-tests were used to assess differences between initial and final grip and pinch strength measures for the BFR group. Effect size estimates were calculated using the formula: Post training mean – pre training mean / pooled standard deviation for parametric tests (J. Cohen, 1992). The strength of this effect can be interpreted as 0.2- 0.49 = small; 0.5-0.79 = medium; ≥ 0.8 = large (J. Cohen, 1992). For non-parametric tests, effect size estimates were calculated utilising the formula: r = z/sqrt(N), where N is twice the number of cases (Pallant, 2010). The strength of this effect can be interpreted as 0.1 = small; 0.3 = medium; 0.5 = large (Pallant, 2010). To test differences on treatment adherence between groups, a chi-squared test was used. Due to the low number of pain exacerbations per group, a Fisher's exact test was utilised to assess differences between groups. A Mann-Whitney U test was utilised to assess differences in training acceptability between BFR and HIT groups. The alpha level was set at 0.05 for all tests. One-tailed tests were used in the analysis.

Results

Consultations with hand therapists

Several hand therapists from private clinics were involved in consultation meetings. It was their general opinion that strength training would worsen patients' symptoms and was not feasible in this group of people. When challenged with evidence from other joints that strength training was effective in improving pain and function in other types of OA, they argued that hand joints are completely different and symptom "flare ups"

would be very common in hand OA. Thus, clinically they described rarely prescribing resistance exercises and more commonly suggest stretching exercises and splints to immobilise painful thumb joints, which they described as ‘unstable’ and liable to subluxate under loaded pinching activities. Despite these concerns, they agreed to advertise the study in their clinics and refer patients who might be interested in the study.

A different response was obtained when hand therapists working at a public hospital unit were asked the same questions. These therapists were unsure about the benefits of strength training because the evidence in that regard was inconclusive. Similar to private practitioners, the exercises prescribed often aimed at maintaining range of movement and splints were provided to support painful hand joints which required stabilisation/rest. When asked to help with recruitment, they actively assisted by mailing patients on their case-lists who had previously indicated they were happy to take part in research projects.

An additional meeting was held with two hand therapists who teach hand therapy at a postgraduate level within the university system. We were particularly interested in what exercises they thought would be useful to implement, and they agreed that gripping and pinching were particularly appropriate considering that they are functionally important to several daily activities. When asked about strengthening exercises for hand OA they were uncertain about their usefulness as very few research studies have investigated this topic.

Participants

Twenty-nine participants aged between 51 and 87 were recruited. All the participants had evidence of hand OA as indicated in the previously mentioned criteria. Fourteen

participants were randomised to the BFR group and 15 to the high intensity group. The BFR group consisted of 11 females and three males and the high intensity group had 14 females and one male. The mean (SD) age for the BFR and HIT group were 68(7.6) and 70(8.9) respectively. The participants' other characteristics are displayed in Table 12.

Table 12. Participants' characteristics retained at follow-up

	BFR (n = 14)	HIT (n = 14)
Age (years)	68(7.6)	70 (8.9)
Females, n	11	13
Right hand dominant, n	12	11
Height (m)	1.69(0.12)	1.64(0.08)
Mass (kg)	71(16)	64.7(11.3)
BMI (kg/m2)	24.8(5)	24.1(4.8)
Right hand most painful	8	9
Average hand pain in the last week (NRS)*	4.6(2.26)	3.7(2.3)
History of pain (years)	10.6(10.9)	9.4(8.9)
Withdrawn	0	1

Note: All values are mean (SD). n = number of participants; BMI = body mass index; NRS = numerical pain rating scale (0-10, where 0 = "no pain" and 10 = "worst pain imaginable"); * = in most painful hand.

Strength

Grip strength

There was a significant improvement (t_{13} = -2.3, $p < 0.05$) in grip strength between session one and session 16 for the BFR group (session one: *M* = 22.2, *95% CI* = 15.9, 28.4; session 16: *M* = 25.9, *95% CI* = 20.8, 31). However, the HIT group did not improve significantly (Z = -1.32, *p* = 0.19) (session one: *Mdn* = 19.66, *IQR* = 16.95, 23.7; session 16: *Mdn* = 22.7, *IQR* = 18.5, 23.7) (See Figure 21). The within group effect sizes for grip strength were small for both the BFR (*d* = 0.34) and HIT (*r* = 0.27) groups.

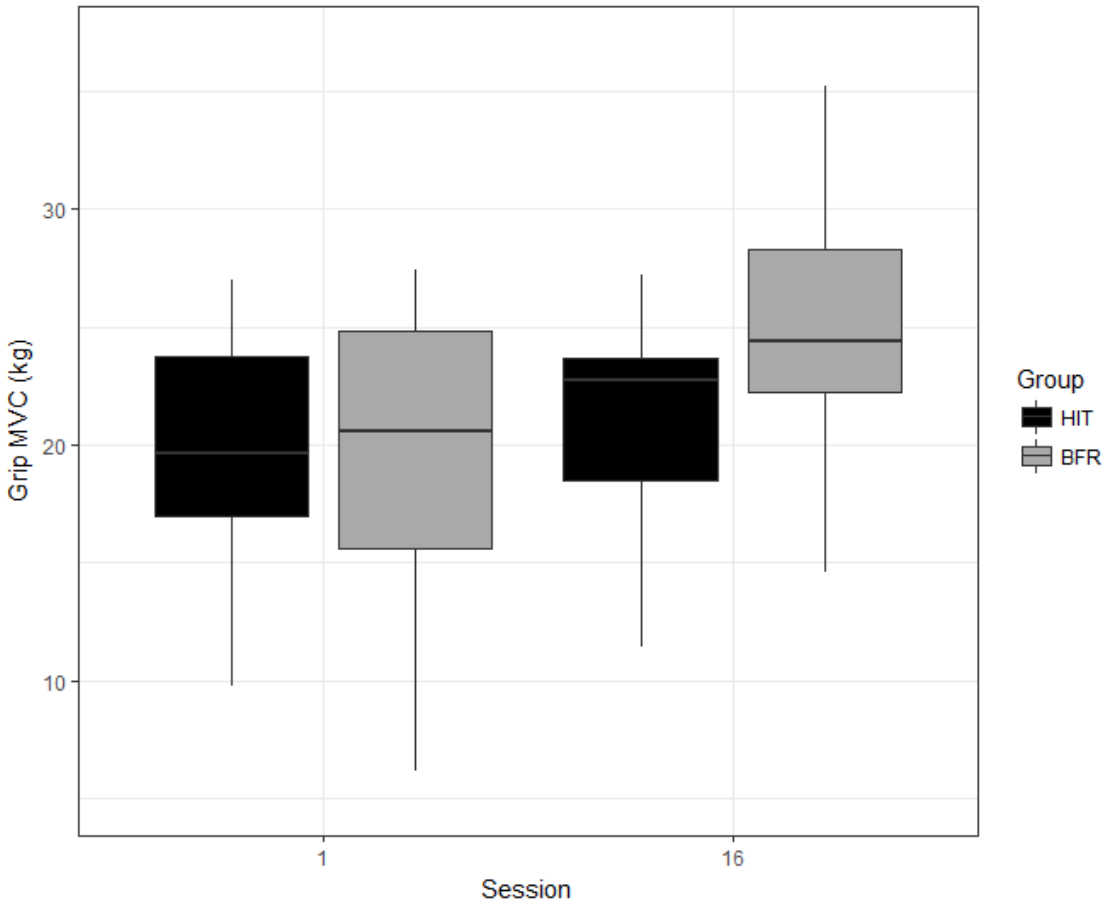


Figure 21. Grip strength results for high intensity training (HIT) and blood flow restriction (BFR) groups at baseline and after 5 weeks of training. Data are displayed as median and interquartile range.

Pinch strength

There was a significant improvement in pinch strength between session one and session 16 for both the BFR (t_{13} = -3.5, p < 0.05) (session one: *M* = 2.91, *95% CI* = 2.36, 3.46; session 16: *M* = 3.62, *95% CI* = 2.9, 4.4) and the HIT group (Z = -3.8, p < 0.001) (session one: *Mdn* = 2.6, *IQR* = 1.9, 3.2; session 16: *Mdn* = 3.3, *IQR* = 2.8, 3.7) (See Figure 22). The within group effect sizes for pinch strength were medium (d = 0.55) and large (r = 0.77) for the BFR and HIT groups respectively.

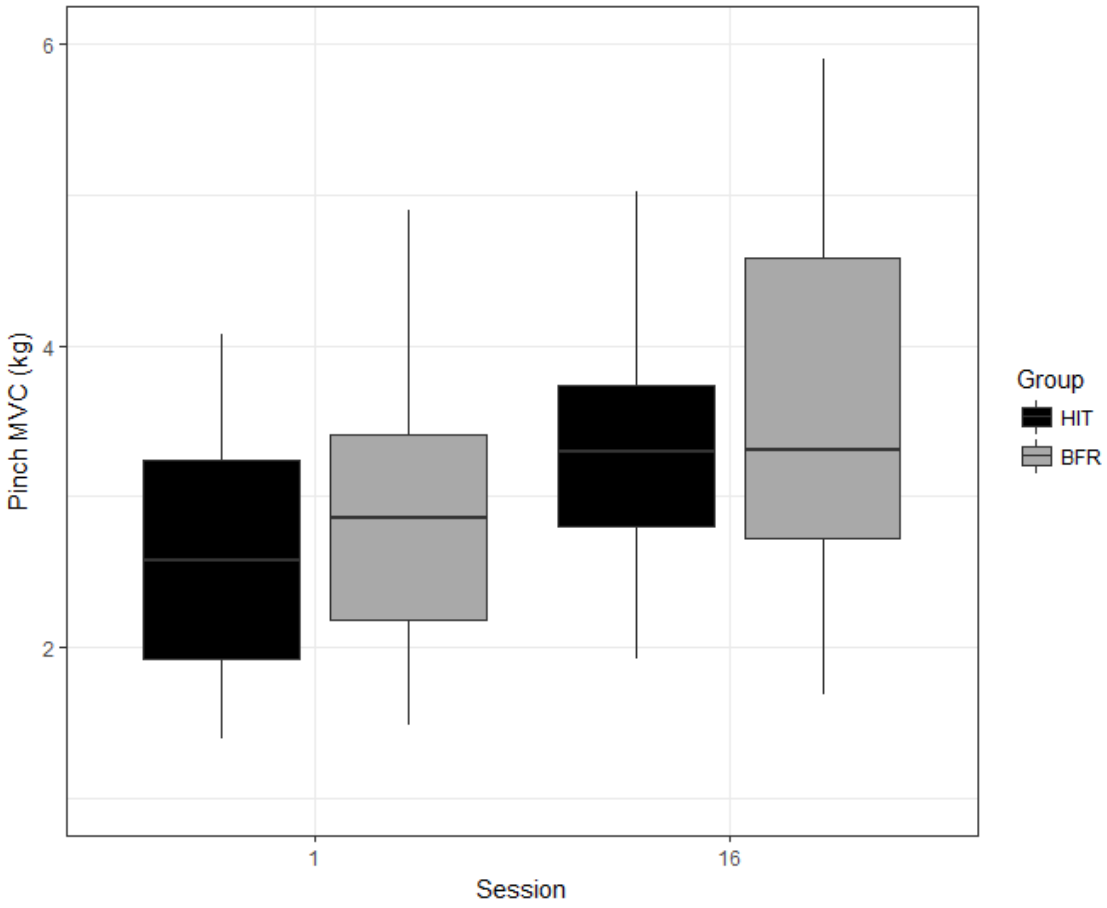


Figure 22. Pinch strength results for high intensity training (HIT) and blood flow restriction (BFR) groups at baseline and after 5 weeks of training. Data are displayed as median and interquartile range.

Pain

Pre-exercise pain did not increase across eighteen sessions as shown in Figure 23 for either the BFR or the HIT group.

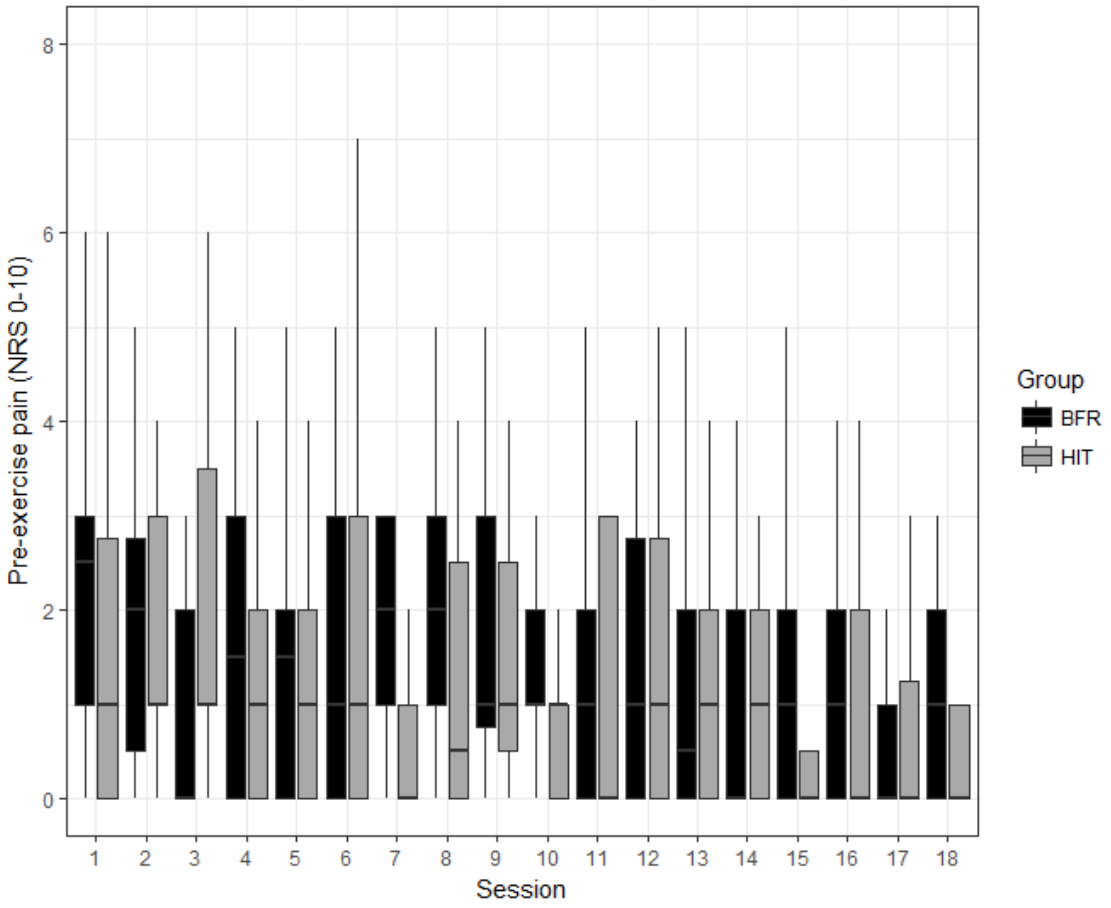


Figure 23. Pre-exercise pain scores (NRS, 0 = "no pain", 10 = "worst pain imaginable") for the high intensity training (HIT) and blood flow restriction (BFR) groups across 18 training sessions. Data are displayed as median and interquartile range.

Rather, in agreement with our hypothesis, pre-exercise pain decreased significantly (p < 0.05) for both the BFR (Z = -2.4, p < 0.05) (Session one: *Mdn* = 2.5, *IQR* = 1, 3; Session 18: *Mdn* = 1, *IQR* = 0, 2) and HIT groups (Z = -2.14, p < 0.05) (Session one: *Mdn* = 1, *IQR* = 0, 2.8; Session 18: *Mdn* = 0, *IQR* = 0, 1) from week one to six. Figure 24 shows changes in pre-exercise pain for both groups on session one and 18. The within group effect sizes for pain were medium for both the BFR (r = 0.49) and the HIT (r = 0.44) group.

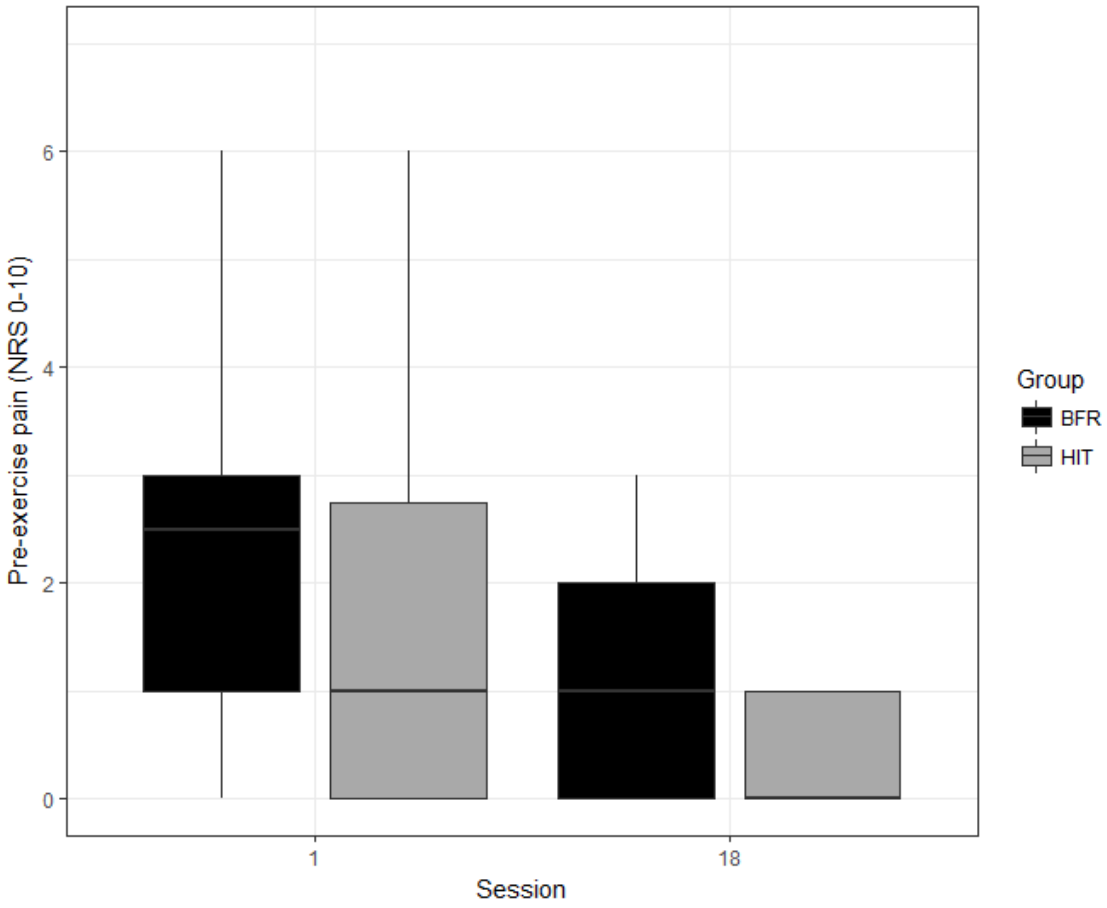


Figure 24. Pre-exercise pain scores (NRS, 0 = “no pain”, 10 = “worst pain imaginable”) for the high intensity training (HIT) and blood flow restriction (BFR) groups across session one and 18. Data are displayed as median and interquartile range.

Exercise induced pain was similar across the 18 training sessions even though, exercise volume doubled by the end of the training period (See Figure 25).

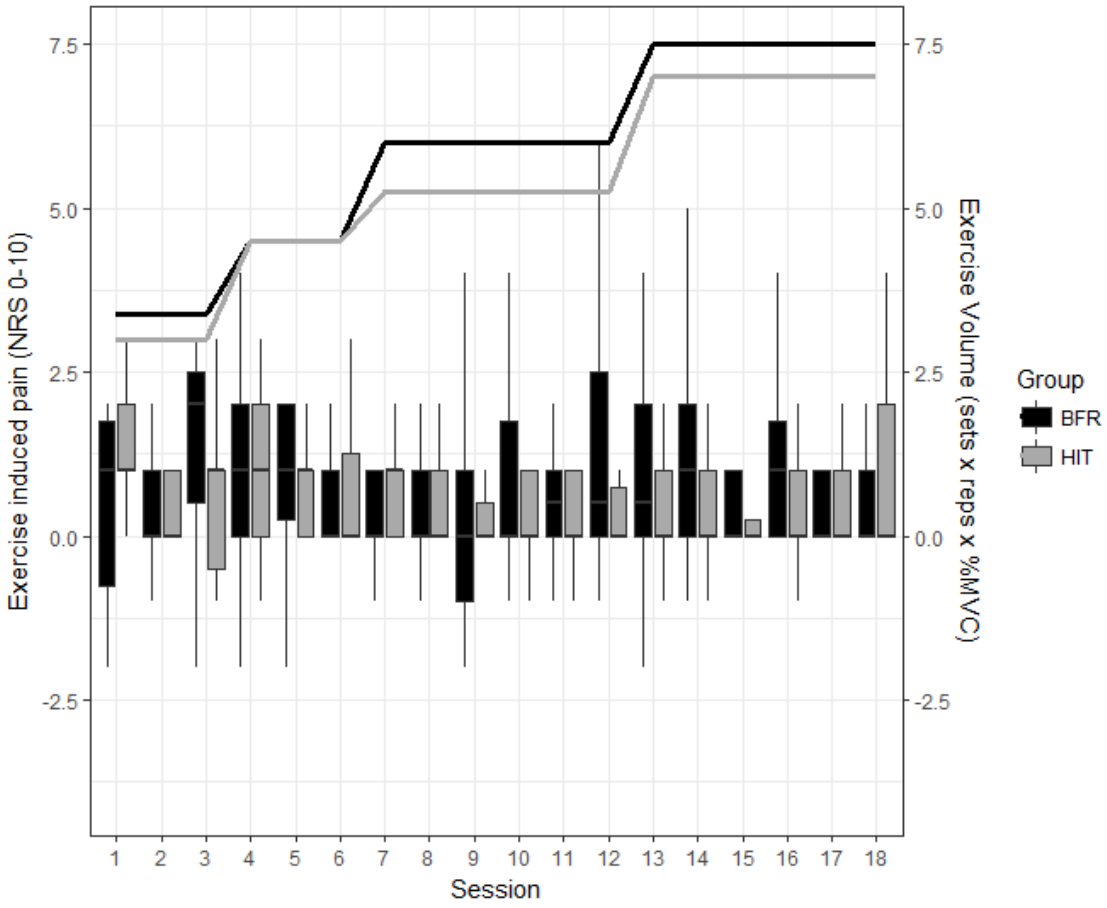


Figure 25. Exercise induced pain (box plots) (left axis) and exercise volume (continuous lines) (right axis) for high intensity training (HIT) and blood flow restriction (BFR) groups across 18 training sessions. Data for the EIP on are displayed as median and interquartile range.

Completion rate, treatment adherence, pain exacerbations and training acceptability

Twenty-eight participants completed the study. One participant from the HIT group withdrew after one training session because the exercises were too painful. As predicted, there was not a significant association between the type of training and treatment adherence (X^2 = 2.6, p = 0.11). The BFR group missed 6% of the training sessions while the HIT group missed 11%. However, in contrast to our hypotheses, the number of pain exacerbations (BFR: 1.7%; HIT: 4%) was not significantly different between the two groups (p = 0.17, *Fisher's exact test*) and training acceptability did not differ (W = 99, p = 0.63) between the BFR (*Mdn* = 6, *IQR* = 6, 6) and HIT groups (*Mdn*

= 6, *IQR* = 5.3, 6). Only one of the participants from the HIT group had comments on the training regime. Specifically, they reported that the exercise intensity for the pinching exercise was a bit excessive. No other comments were made from the participants completing either regime.

Recruitment rate

Recruitment took place in the North Shore and Manukau, which are two suburban areas of Auckland. A total of 159 potential participants were approached, of which 97 and 62 were from the North Shore and Manukau respectively. Most of the participants from Manukau were identified through the public hospital system hand therapy unit (n = 52) and 10 responded to a local paper advertisement. In the North Shore, 21 potential participants were identified from an existing AUT database associated with previous research, 27 by word of mouth of existing participants, 15 through presentations to local retirement villages, 13 responded to a local journal advertisement, 11 were recruited through the Never2old program (AUT gym), seven through advertisement at North Shore Hospital (WDHB), three through Arthritis New Zealand advertisement. Of these, 27 people from the North Shore and two people from Manukau were included in the study. Details of the selection and randomisation process are reported in Figure 26.

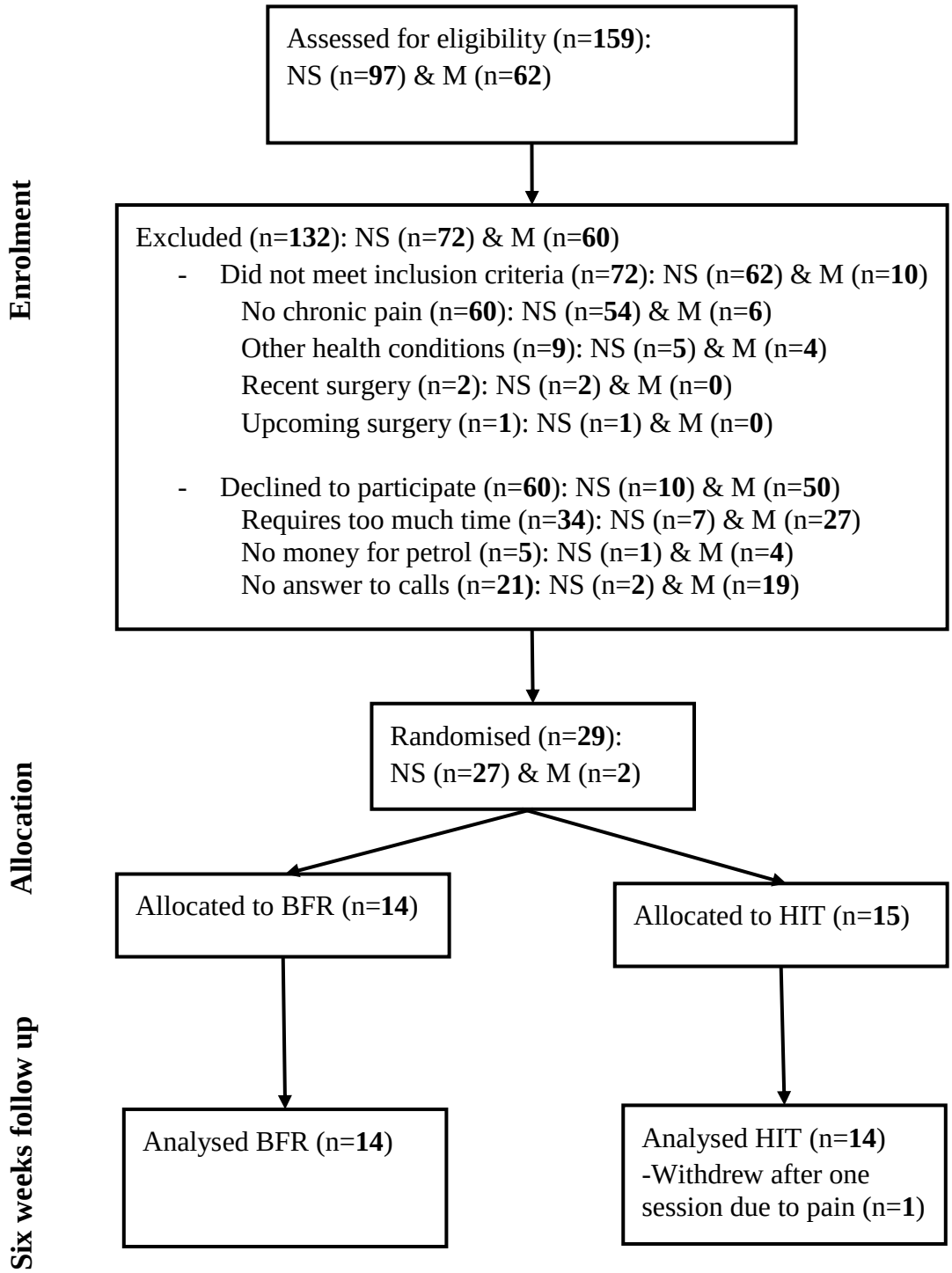


Figure 26. Participants' recruitment process in the North Shore (NS) and Manukau (M).

Discussion

In this feasibility study we compared HIT and BFR training in people with hand OA and quantified the potential gains in strength after six weeks training. In addition, pre-exercise hand pain was measured and showed a significant decrease over the treatment period. Furthermore, exercise induced pain remained stable and did not appear to worsen with increased training volume in either training group. Finally, the feasibility of BFR and HIT for people with hand OA was demonstrated by showing an acceptable drop-out rate, a low number of pain exacerbations, good treatment adherence and excellent training acceptability.

Our findings showed that pinch strength increased significantly after six weeks training, demonstrating a 28% and 16% improvement in the HIT and BFR groups respectively. However, grip strength increased significantly only in the BFR group, with a 19% and 15% increase in the BFR and HIT groups respectively. The lack of statistically significant improvements in grip strength for the HIT group might be due to the small sample size of our study. In the time frame allowed, we did not manage to recruit 22 participants per group as we were planning to. In this regard, our recruitment potential was lower compared to previous studies, with only 18% of all the people contacted consenting to be included in the present study. This figure is lower than other studies that were able to recruit 30-50% of participants approached. This discrepancy might be due to different recruitment strategies. In the studies by Hennig et al. (2015) and Østerås et al. (2014), who implemented similar programs for OA hands, participants were recruited through hand surgeons or from existing databases of patients who were actively seeking treatment for hand OA. In contrast, our recruitment strategy was broader and was not specifically targeted to people actively seeking treatment for their hand OA. In the future, we might try to establish stronger relationships with medical

specialists to successfully recruit people with hand OA (e.g. hand surgeons and rheumatologists). Due to local ethics committee rulings, only hospital clinicians could contact patients to invite them to participate. Given the very limited non-clinical time available to clinicians, their enthusiasm to engage with us was limited in some locations. Furthermore, recruitment differed across regions. It was very notable that although 62 people were approached in the Manukau region, only two took part. Not having enough time was the main reason why participants could not take part in the study (See Figure 26). It is possible that longer hours of work, associated with the lower socioeconomic status in this region, led to participants declining the invitation. Interestingly, several studies have shown that inadequate income affects patients access to health care and is often associated with higher disability in the long term (Langley, Davie, et al., 2013; Langley, Lilley, et al., 2013; Wyeth, Samaranayaka, Davie, & Derrett, 2017). It might be therefore necessary to provide more funding when training regimes are delivered in Manukau or deliver the intervention outside of normal work hours. The inability to contact participants ourselves was an additional factor, which limited our recruitment potential in South Auckland. It has also been demonstrated that the higher the number of alternative contact details the greater the chances of recruiting participants (Langley, Lilley, et al., 2013). Unfortunately, for privacy reasons, patients' information provided by the Manukau DHB was restricted and often limited to one contact number.

Even though we did not reach the target number of participants for our feasibility study, the strength gains obtained were notable. When compared to previous resistance training regimes in a hand OA population (Chapter four), improvements in strength were typically greater. Grip strength improved by 15-19% in our study, approximately double the pooled mean of our meta-analysis, which showed an 8% improvement. In the study by Hennig et al. (2015), which showed the greatest strength gains in our meta-

analysis, grip strength increased between 22% and 27% in their HIT group, which in comparison to our study was slightly greater. The longer duration of the exercise regime in the study by Hennig et al. (2015), which lasted for three months, probably contributed to this. Furthermore, the baseline grip strength in the study by Hennig et al. (2015) was lower (M = 15 kg, SD = 7 kg), providing a greater margin for improvement. Our strength gains are similar to those in knee OA, where six weeks of progressive resistance training has been shown to improve quadriceps strength between 13% and 22% (Foley, Halbert, Hewitt, & Crotty, 2003), with similar results obtained after 12 weeks (17% and 22%) of training (Lim, Hinman, Wrigley, Sharma, & Bennell, 2008). The strength improvements that we noted in our study were most likely due to both neural changes and muscle morphological changes (Moritani & deVries, 1979). In healthy young subjects, it appears that 80% of the strength improvements after two weeks of training are due to increased muscle activation with only 20% due to muscle morphological changes (Moritani & deVries, 1979). However, at six weeks the trend is reversed with hypertrophy being the main driver of muscle strength gains (Moritani & deVries, 1979). During the first few weeks of resistance training, increases in corticomotor and spinal motor neuron excitability, as well as increases in size and number of neuromuscular junctions have all been shown to contribute to increases in muscle strength (Deschenes, Sherman, Roby, Glass, & Harris, 2015). It is also possible that a reduction in pain associated with resistance training may contribute to improvements in muscle strength by increasing voluntary muscle recruitment potential (Cantero-Téllez, Martín-Valero, et al., 2015; G. Jones et al., 2001). We are unable to assess the relative contribution of neural and muscle morphological changes in strength gains shown in our study because we did not measure such outcomes. The mechanisms involved in strength gains with BFR may be similar to HIT even though they would be driven by local muscle hypoxic conditions. While a number of factors are involved,

BFR induces muscle hypoxia, which causes fatigue of type I fibres, followed by an increase in type II fibre recruitment to maintain the same level of muscle contraction (Scott et al., 2014). Corticomotor excitability has also been shown to increase following a session of BFR compared to a matched volume exercise without BFR (Brandner et al., 2015), suggesting that neural adaptations may play an important role in strength changes associated with BFR in the short term (See Figure 19 for all the possible mechanisms associated with BFR).

In our study, improvements in strength were accompanied by a reduction in pre-exercise pain over six weeks training for both the BFR and HIT groups. This decrease in pre-exercise pain occurred in spite of a progressive increase in exercise volume, which doubled from baseline to the end of the six weeks training for both the HIT and BFR groups. The mean change in pre-exercise pain intensity was 1.4 and 0.6 points in the BFR and HIT groups respectively. These results are consistent with the pain reduction after six weeks of training reported by Hennig et al. (2015), which showed a mean change of 0.9 points on NRS scale. In OA, several mechanisms associated with exercise have been suggested to contribute to pain relief (Susko & Fitzgerald, 2013). At the articular level, exercise may modulate cartilage homeostasis and inflammation. Thus, cartilage compression favourably influences chondrocyte's gene expression and therefore the production of proteoglycans and extracellular matrix (Chowdhury, Bader, & Lee, 2006). The adequate amount of therapeutic load has not been identified yet, and it most likely depends on the initial degree of cartilage degeneration and individual difference in phenotypic response to environmental stimuli (Roddy et al., 2005). It also appears that submaximal muscle contractions and cyclic exercise have positive effects on aggrecan and proteoglycan synthesis (Xu, Buckley, Evans, & Agarwal, 2000). Joint inflammation has an important role in OA pain (Sokolove & Lepus, 2013). Modulation of systemic inflammatory markers and reduction of joint cytokines through exercise has

been suggested and is related to a decrease of upregulation of cyclooxygenase-2 and prostaglandins which in turn leads to pain relief by increasing the depolarisation thresholds of peripheral nociceptors (Knapik et al., 2013). A reduction in joint inflammation also has positive effects on chondrocytes, whose activity is impaired by chemicals involved in the inflammatory process. Another mechanism that exercises may reduce pain is through modulation of central pain inhibitory pathways. Thus, in healthy people, unilateral isometric gripping exercises have been shown to increase pressure pain thresholds and reduce pain ratings during a temporal summation test in both the exercised and contralateral hand (Koltyn & Umeda, 2007). Furthermore, in a group of participants with knee OA, stationary bike and resistance exercises increased pressure pain thresholds in the knee (Fingleton, Smart, & Doody, 2017). Interestingly, only the participants presenting with normal condition pain modulation, presented with exercise induced analgesia, suggesting that functional descending inhibitory pathways are required to obtain symptom relief with exercise (Fingleton et al., 2017). Behavioural and psychological factors may also improve symptoms and modulate the pain experience (Somers et al., 2012) contributing to the effect observed in this and other studies (Bennell & Hinman, 2011; Golightly et al., 2012; Li et al., 2015).

Interestingly, exercise induced pain (i.e. the immediate change in pain from pre to post exercise) did not increase over six weeks of training. No formal statistical analysis was performed on this set of data, however, it is clear from the graph (Figure 25) that exercise induced pain did not progressively increase, despite a doubling of exercise volume during the training period. No study has previously assessed exercise induced pain at the session level in people with hand OA. However, similar findings have been shown in people with knee OA where pain increased immediately after exercise by between 0.5 and two points from pre-exercise levels (Beckwée et al., 2015). Furthermore, Beckwée et al. (2015) and Hall et al. (2018) showed that in knee OA the

number of participants withdrawing from exercise interventions is increased in people who experience higher exercise induced pain. Beckwée et al. (2015) also observed that exercise adherence was negatively correlated with exercise induced pain and that the average exercise induced pain in the participants who decided to withdraw was a mean of 1.6 points greater than in the individuals who continued with the program. In our study, only one participant in the HIT group dropped out because of a significant increase in symptoms after the first exercise session. Interestingly, this participant also indicated that they did not really have time to continue. Clinically, it is possible that utilising BFR rather than HIT in people who report high levels of pain during exercise may reduce dropout rates. While Bryk et al. (2016) showed that BFR training was associated with lower pain during exercise when compared to traditional HIT in people with knee OA, exercise induced pain appeared similar in the BFR and HIT groups in our study.

Treatment satisfaction has been shown to affect training adherence (Krogh, Lorentzen, Subhi, & Nordentoft, 2014). In our study, no differences in treatment satisfaction or adherence were observed between the exercise groups. A recent review by Minshull and Gleeson (2017) reported an exercise adherence in people with knee OA similar to ours, with participants attending more than 90% of the sessions. While being aware of the possibility of pain exacerbations with HIT, only one of the participants in our HIT group commented saying that the intensity was excessive for their liking. No such comments were made from people in the BFR group. Our findings were in contrast to the anecdotal opinion of private hand therapists who suggested that resistance exercises would worsen symptoms over time and that pain exacerbations would occur very frequently. Furthermore, our approach was different from other authors (Dziedzic et al., 2015; Lefler & Armstrong, 2004; Rogers & Wilder, 2009) who advocated adapting exercise intensity based on pain and yet the results were not as deleterious as suggested.

Conclusion

Both HIT and BFR are feasible resistance training interventions for people with hand OA. They both induced significant strength gains and were associated with a reduction in joint pain intensity over six weeks of training. Training adherence, pain exacerbations and participant retention rate were acceptable in both BFR and HIT and despite exercise volume doubling over the training period, exercise induced pain remained stable in both groups. Participant recruitment was challenging, particularly in Manukau. Potential strategies to improve recruitment may include increased financial incentives, alternative training times and greater involvement of hand surgeons and rheumatologists.

Chapter Seven: Summary and Conclusions

Symptomatic hand osteoarthritis is a condition affecting millions of people worldwide and an estimated 134,000 people in New Zealand (Y. Zhang et al., 2002). A limited number of evidence informed conservative treatments are available for this condition even though it has severe repercussions on functional ability and quality of life (Poole et al., 2013). Furthermore, there is still an incomplete understanding of the impairments suffered by people with hand OA and how these relate to hand function. This thesis aimed to provide a more comprehensive assessment of potential impairments in hand OA, explore their relationships with different measures of hand function and systematically review the existing literature, in order to inform the development of novel and/or improved conservative treatment(s) for this condition.

Key findings

In Chapter three, a case-control study was undertaken comparing selected sensorimotor and muscle performance parameters between people with hand OA and age and gender matched controls. Furthermore, the relationships between these measures and hand function were explored. The results of our study showed that hand OA was associated with impairments in working body schema, with hand OA participants slower and less accurate in the hand left/right discrimination task (egocentric task) compared to controls. A methodological advancement implemented in this study was the use of an allocentric left/right discrimination task, which required rotation around an object centred reference frame rather than a body centred reference frame. This allowed us to control for factors that might otherwise explain the impaired performance in the

egocentric task, including general cognitive impairment and delayed reaction times (De Simone et al., 2013). Furthermore, this was the first study to assess the presence of neglect-like symptoms in people with hand OA with higher scores reported compared to healthy controls, providing further evidence for a disturbance in working body schema and suggesting a possible attentional bias away from the most painful hand (Moseley, Gallagher, et al., 2012; Reid et al., 2016). No differences were identified when two-point discrimination (TPD) threshold were assessed in the hand OA and control group. This was unexpected considering the presence of tactile acuity deficits in several other chronic pain conditions (Catley et al., 2013), including knee OA (Stanton et al., 2013). It is possible that assessment of TPD in the most painful area of the hand may reveal significant deficits in people with hand OA (Catley et al., 2014). An additional novel finding of this study was the correlation between TPD threshold and objective measures of hand function, which had not been previously assessed in hand OA. Furthermore, no previous research had assessed grip endurance in people with hand OA and, despite the use of absolute rather than relative force matching targets, we found no differences in endurance between healthy controls and hand OA participants. On the other hand, grip strength was shown to be significantly reduced by approximately 15% in people with hand OA and moderately correlated with the disability of the arm, shoulder and hand questionnaire (DASH) score. This suggested that targeting muscle weakness may be an appropriate strategy to improve muscle performance and hand function. However, when conducting a systematic review and meta-analysis on the effectiveness of resistance training interventions for hand OA (Chapter four), only a small number of studies were identified, which showed no overall benefit when compared to a no exercising control group. Our findings were confirmed by a recent review by Østerås et al. (2017), who suggested that further studies on resistance training for hand OA were necessary. Upon closer examination of the studies included in our review, several exercise prescription

limitations were identified that may explain the overall lack of efficacy of these interventions. Furthermore, several authors (Dziedzic et al., 2015; Lefler & Armstrong, 2004; Rogers & Wilder, 2009) indicated that high intensity resistance training (HIT) was considered inadvisable in people with hand OA due to the increased chance of inducing pain exacerbations in this group of people. An alternative form of resistance training, which utilises low loads such as blood flow restriction (BFR) was therefore considered as a potential alternative to HIT for people with hand OA. Our systematic review and meta-analysis on BFR (Chapter five) expanded our understanding of the most effective training regimes as well as the safety precautions required when applying this intervention in adults 50 years and older and people undergoing a period of disuse, populations with some relevance to hand OA. Before embarking in a full scale RCT assessing the effectiveness of BFR and HIT training in people with hand OA, a feasibility study was planned and completed (Chapter six). This was the first study in hand OA which implemented HIT with sufficient intensity, frequency and progression to conform to established guidelines (Garber et al., 2011). Furthermore, no previous study has utilised BFR training in people with hand OA. Our results showed that both HIT and BFR training interventions were acceptable for participants with hand OA and that they induced significant strength gains, with a reduction in pre-exercise pain over time and no change in exercise induced pain despite the training volume almost doubling over the course of the intervention.

Recommendations for future research

The results from this thesis highlighted a series of topics that could be examined further in future research:

1. Our feasibility study showed that HIT and BFR training are two viable interventions that may increase strength, reduce pain and improve function in people with hand OA. It would be of interest assessing the efficacy of these two exercise regimes in a full-scale RCT, including a usual care control group.
2. It would be of interest to explore which hand OA patients respond best to BFR training. It may be that those with more pain during resisted contractions achieve better strength gains with BFR training compared to HIT, as has been found in patellofemoral pain (Giles et al., 2017).
3. Grip strength has been found to be impaired in people with hand OA. Determining which factors contribute to this impairment would be of interest, including muscle atrophy and potential neural activation deficits. For example, preliminary evidence of an activation deficit may be found by comparing the ratio between grip strength and muscle volume in healthy controls and people with hand OA (Konishi et al., 2007).
4. Neglect like symptoms suggest the possibility of an attentional processing bias away from the most painful side in people with hand OA (Moseley, Gallagher, et al., 2012; Reid et al., 2016). It would be of interest to explore this further through objective measurements such as the temporal order judgement protocol utilised by Moseley, Gallagher, et al. (2012), comparing people with hand OA to healthy controls.
5. Assessing TPD threshold at the most painful site of the hand may reveal significant difference between people with hand OA and healthy controls. If such changes were

identified, and given the significant association between TPD and measures of hand function identified in Chapter three, it is possible that tactile discrimination training may improve function and, perhaps, reduce pain in people with hand OA (Moseley & Wiech, 2009).

6. In Chapter three we observed correlations between pain intensity and hand left/right discrimination accuracy and reaction time. While our cross-sectional design does not allow us to determine the direction of this relationship, targeted interventions like graded motor imagery (which incorporates the left/right discrimination task) have been shown to relieve pain in other chronic pain conditions (Bowering et al., 2013; Moseley, 2006). It would be of interest to determine whether a similar intervention also alleviates symptoms in people with hand OA.

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Appendix A: Neurobehavioral questionnaire

I. CHECK ALL of the following statements that are TRUE and rate them:

1. _____If I don't focus my attention on my painful limb it would lie still, like dead weight.

Never 1 2 3 4 5 6 Always

2. _____My painful limb feels as though it is *not* part of the rest of my body.

Never 1 2 3 4 5 6 Always

3. _____I need to focus all of my attention on my painful limb to make it move the way I want it to.

Never 1 2 3 4 5 6 Always

4. _____My painful limb sometimes moves involuntarily, without my control.

Never 1 2 3 4 5 6 Always

5. _____My painful limb feels dead to me.

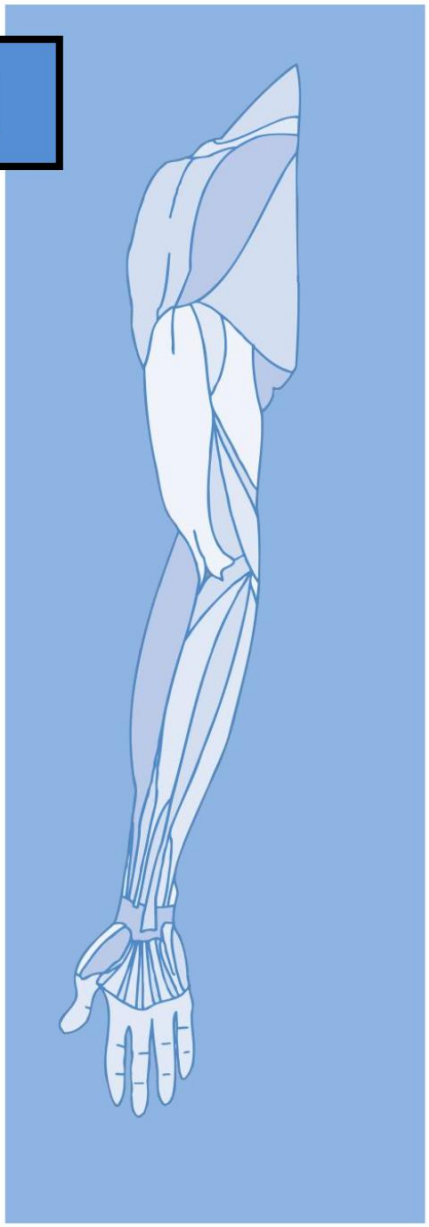
Never 1 2 3 4 5 6 Always

II. If you have further comments with regard to these questions, please comment:

Appendix B: DASH

DISABILITIES OF THE ARM, SHOULDER AND HAND – British English

THE DASH



INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to do certain activities.

Please answer every question, based on your condition in the last week, by circling the appropriate number.

If you did not do an activity in the last week, please give your best guess which response would be most accurate.

It doesn't matter which hand or arm you use to do the activity; please answer based on your ability regardless of how you do the task.

British English translation courtesy of: Prof Alison Hammond[1], Dr Yeliz Prior[1], Prof Sarah Tyson[2]
[1] Centre for Health Sciences Research, University of Salford;
[2] Centre for Long term Conditions Research, University of Manchester, UK.

1

DISABILITIES OF THE ARM, SHOULDER AND HAND – British English

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	*MILD DIFFICULTY*	*MODERATE DIFFICULTY*	*SEVERE DIFFICULTY*	*UNABLE*
1 Open a tight or new jar	1	2	3	4	5
2 Write	1	2	3	4	5
3 Turn a key	1	2	3	4	5
4 Prepare a meal.	1	2	3	4	5
5 Push open a heavy door	1	2	3	4	5
6 Place an object on a shelf above your head	1	2	3	4	5
7 Do heavy household jobs (e.g. wash windows, clean floors)	1	2	3	4	5
8 Garden or outdoor property work	1	2	3	4	5
9 Make a bed	1	2	3	4	5
10 Cary a shopping bag or briefcase	1	2	3	4	5
11 Carry a heavy object (over 10 lbs/ 5kgs)	1	2	3	4	5
12 Change a lightbulb overhead	1	2	3	4	5
13 Wash or blow dry your hair	1	2	3	4	5
14 Wash your back	1	2	3	4	5
15 Put on a jumper	1	2	3	4	5
16 Use a knife to cut food	1	2	3	4	5
17 Recreational activities which require little effort (e.g. card playing, knitting, etc)	1	2	3	4	5
17 Recreational activities which require you to take some force or impact through your arm, shoulder or hand (e.g. golf, hammering, tennis etc)	1	2	3	4	5
18 Recreational activities in which you move your arm freely (e.g. playing Frisbee, badminton etc)	1	2	3	4	5
20 Manage transport needs (getting from one place to another)	1	2	3	4	5
21 Sexual activities	1	2	3	4	5

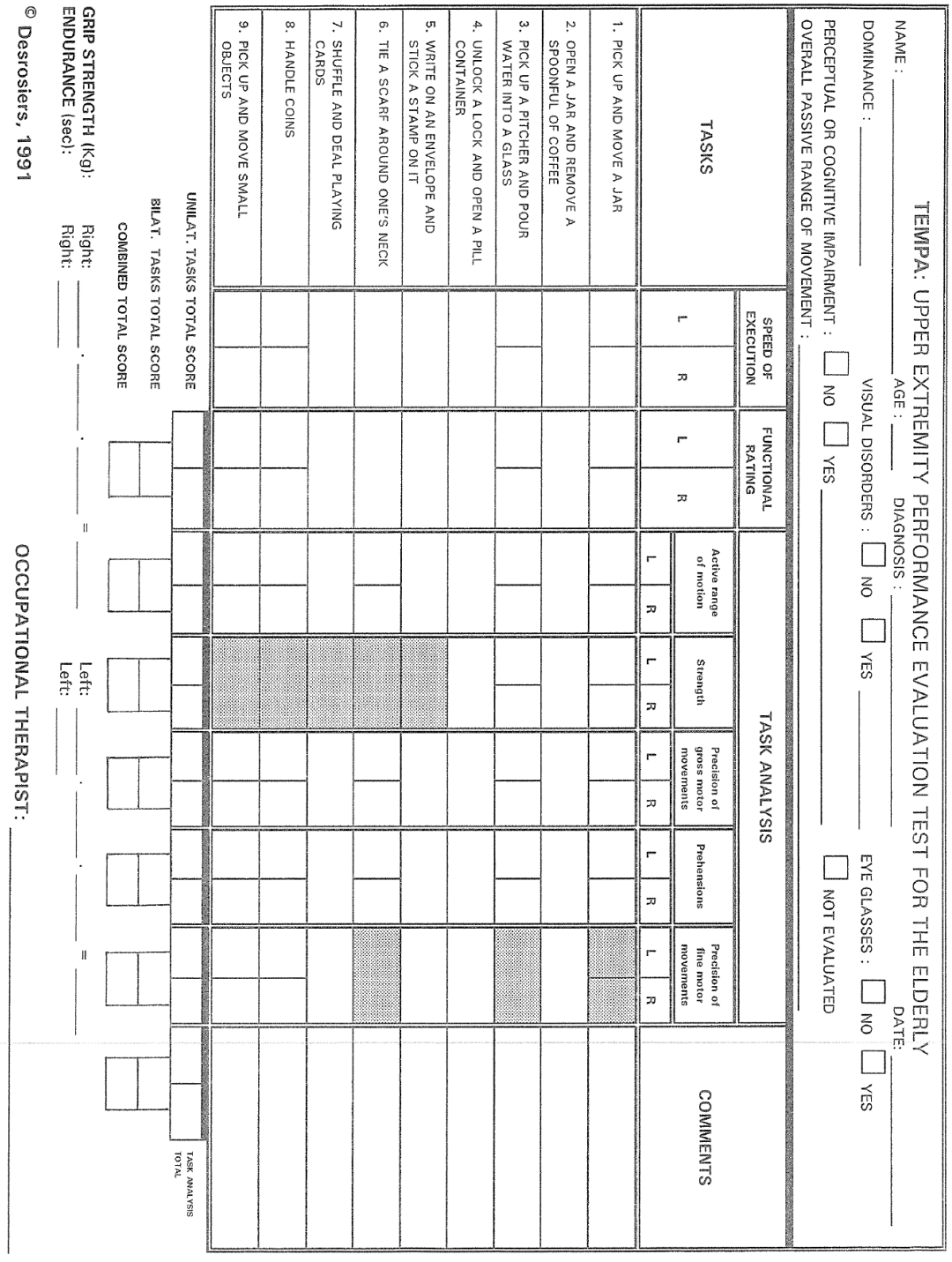
	NOT AT ALL	SLIGHTLY	MODERATELY	Quite a bit	Extremely
22 During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family. friends, neighbours or groups? *(circle number)*	1	2	3	4	5
	NOT LIMITED AT ALL	**SLIGHTLY LIMITED**	**MODERATELY LIMITED**	**VERY LIMITED**	**UNABLE**
23 During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? *(circle number)*	1	2	3	4	5
Please rate the severity of the following symptoms in the last week *(circle number)*	**NONE**	**MILD**	**MODERATE**	**SEVERE**	**EXTREME**
24 Arm, shoulder or hand pain	1	2	3	4	5
25 Arm, shoulder or hand pain when you do any specific activity	1	2	3	4	5
26 Tingling (pins and needles) in your arm, shoulder or hand	1	2	3	4	5
27. Weakness in your arm, shoulder or hand	1	2	3	4	5
28 Stiffness in your arm, shoulder or hand	1	2	3	4	5
	NO DIFFICULTY	**MILD DIFFICULTY**	**MODERATE DIFFCULTY**	**SEVERE DIFFCULTY**	**SO MUCH DIFFICULTY THAT I CAN'T SLEEP**
29 During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5
	STRONGLY DISAGREE	**DISAGREE**	**NEITHER AGREE OR DISAGREE**	**AGREE**	**STRONGLY AGREE**
30 I feel less capable, less confident or less useful because of my arm, shoulder or hand problem *(circle number)*	1	2	3	4	5

DASH DISABILITY/SYMPTOM SCORE = [(sum of n responses)/n – 1] x 25 (where n is the number of completed responses)

A DASH score may not be calculated if there are greater than 3 missing items.

3

Appendix C: TEMPA



TEMPA: UPPER EXTREMITY PERFORMANCE EVALUATION TEST FOR THE ELDERLY

NAME : _____ AGE : ____ DIAGNOSIS : _____ DATE: _____

DOMINANCE : _____ VISUAL DISORDERS : ☐ NO ☐ YES _____ EYE GLASSES : ☐ NO ☐ YES

PERCEPTUAL OR COGNITIVE IMPAIRMENT : ☐ NO ☐ YES _____ ☐ NOT EVALUATED

OVERALL PASSIVE RANGE OF MOVEMENT : _____

TASKS	SPEED OF EXECUTION		FUNCTIONAL RATING		TASK ANALYSIS								COMMENTS
					Active range of motion		Strength		Precision of gross motor movements		Prehensions		Precision of fine motor movements		
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	
1. PICK UP AND MOVE A JAR															
2. OPEN A JAR AND REMOVE A SPOONFUL OF COFFEE															
3. PICK UP A PITCHER AND POUR WATER INTO A GLASS															
4. UNLOCK A LOCK AND OPEN A PILL CONTAINER															
5. WRITE ON AN ENVELOPE AND STICK A STAMP ON IT															
6. TIE A SCARF AROUND ONE'S NECK															
7. SHUFFLE AND DEAL PLAYING CARDS															
8. HANDLE COINS															
9. PICK UP AND MOVE SMALL OBJECTS															
UNILAT. TASKS TOTAL SCORE															TASK ANALYSIS TOTAL
BILAT. TASKS TOTAL SCORE															
COMBINED TOTAL SCORE															

GRIP STRENGTH (Kg): Right: _____ . _____ . _____ = _____ Left: _____ . _____ . _____ = _____

ENDURANCE (sec): Right: _____ Left: _____

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OCCUPATIONAL THERAPIST: _____

Appendix D: Purdue pegboard test

Purdue Pegboard Score Sheet Model 32107

For Purdue Pegboard Model 32020

Quick Reference Means (normative population averages) in Parts

Occupational Area	Right Hand	Left Hand	Both Hands	Right + Left + Both	Assembly
Male & Female Applicants for Assembly Jobs*	17.86	16.60	14.38	48.81	43.58
Male & Female Applicants for Gen. Factory Work*	17.15	16.01	13.79	46.76	39.30
Male & Female Applicants for Production Work*	17.94	16.81	14.10	48.85	40.67
Female Applicants for Electronic Prod. Work*	18.47	16.77	14.53	49.84	43.76
Female Hourly Production Workers*	18.02	16.81	14.34	49.14	38.08
Male Hourly Production Workers*	16.45	16.31	13.37	46.11	36.89
Male Maintenance and Service Employees*	15.49	15.25	12.31	43.04	38.71
Female Applicants for Sewing Machine Operator: Three Trial Sum*	55.20	51.78	44.03	151.09	133.41

* Data taken from the Appendix A (Tables 8-15) in the original Purdue Pegboard Manual

Subject Record

Name: _____ Dominant Hand: Right / Left

Reason for Administering: _____

_____

Test Administrator Name: _____ Test Date: _____

Scoring Grid Based on Number of Parts

	Trial One	Trial Two	Trial Three	Trial Average
Right Hand				
Left Hand				
Both Hands				
Right + Left + Both				
Assembly				

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Appendix E: Study one ethical approval

AUTEC SECRETARIAT

2 October 2014

Peter McNair
Faculty of Health and Environmental Sciences

Dear Peter

Re Ethics Application: **14/277 Cortical remodelling and functional deficits in symptomatic hand osteoarthritis: A case-control study,**

Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC).

Your ethics application has been approved for three years until 2 October 2017.

As part of the ethics approval process, you are required to submit the following to AUTEC:

- A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 2 October 2017;
- A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 2 October 2017 or on completion of the project.

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this.

To enable us to provide you with efficient service, please use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz.

All the very best with your research,

Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Nicolo Edoardo Magni fisioterapistamagni@gmail.com

Auckland University of Technology Ethics Committee
WA505F Level 5 WA Building City Campus
Private Bag 92006 Auckland 1142 Ph: +64-9-921-9999 ext 8316 email ethics@aut.ac.nz

Appendix F: Study four ethical approval

AUTEC Secretariat

Auckland University of Technology
D-88, WU406 Level 4 WU Building City Campus
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

2 March 2017

Peter McNair
Faculty of Health and Environmental Sciences

Dear Peter

Ethics Application: 17/50 **Blood flow restriction training for hand osteoarthritis: A randomised controlled trial.**

Thank you for submitting your application for ethical review to the Auckland University of Technology Ethics Committee (AUTEC). I am pleased to confirm that your ethics application has been approved for three years until 2 March 2020.

As part of the ethics approval process, you are required to submit the following to AUTEC:

- A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 2 March 2020;
- A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 2 March 2020 or on completion of the project;

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this.

To enable us to provide you with efficient service, we ask that you use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz.

All the very best with your research,

Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: fisioterapistamagni@gmail.com; david.rice@aut.ac.nz