RESISTANCE TRAINING, INSULIN SENSITIVITY & METABOLIC HEALTH

by
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Abstract

Skeletal muscle is the largest organ in the human body, comprising 40%-50% of total body weight and more than 600 skeletal muscles in a human body performing common functions such as body movements, maintaining posture, storing protein and glycogen and generating heat. Approximately 0.8% skeletal muscle mass declines per year a process known as sarcopenia. On top of that, ageing also results in a decrease in muscle strength, at a rate of approximately 1-3% per year (Keller & Engelhardt, 2013). Skeletal muscle is the major organ responsible for glucose uptake under insulin stimulated conditions, accounting for ~80% of total glucose disposal and low muscle strength and mass likely contribute to metabolic dysregulation seen in Type 2 diabetes. Research has shown that resistance exercise training can increase strength, muscle size, fat-free mass, connective tissue thickness, decrease body fat, reduce blood pressure and improve insulin sensitivity and VO_{2max} (Croymans et al., 2013; Ozaki et al., 2013; Abdul & Defronzo, 2010). In order to monitor efficacy of such resistance training interventions it is important to be able to accurately quantify skeletal muscle mass and several methods exist for this purpose, although many require expensive equipment making them not always possible to use.

The aim of chapter 2 was to investigate the repeatability and validity of a relatively cheap and portable A-mode ultrasound device. This chapter has found that A mode ultrasound is a repeatable measure of muscle thickness (CV of 4.6%) and that both A and B mode ultrasound provide valid measures of muscle volume, as compared to the gold standard MRI (r=0.96).

Following this, the aim of chapter 3 was to determine if this A-mode ultrasound device is able to detect changes in muscle thickness in response to resistance exercise training and to determine its validity. Findings in this Chapter 3 have shown that the A-mode ultrasound can detect increases in muscle thickness of 6.2 ± 5.4%, alongside a 26 ± 7.3% increase in 1RM after 8 weeks of resistance exercise training. However, it was also shown that both A and B mode measures of ultrasound muscle thickness were not valid measures of the resistance exercise induced changes in muscle volume (r=0.30 A-mode & r=0.04 B-mode)

Resistance exercise is known as the most efficacious method to increase muscle strength and mass. It has been demonstrated recently that if exercise is performed to volitional failure then gains in muscle mass, and to a lesser extent strength, are similar regardless of the load at which exercise is performed. The aims of chapter 4, were to investigate the effects of 6

weeks of resistance exercise training, comprised of 1 set of each exercise to voluntary failure, on insulin sensitivity and the time-course of adaptations in muscle strength/mass, in overweight men. Results of this chapter have demonstrated that six weeks of resistance exercise, volitional failure of nine exercises – taking 15-20 min per session – undertaken three times per week resulted in a 16% improvement in insulin sensitivity (61.6 ± 18.0 to 71.3 ± 22.9 $mg.l^2.mmol^{-2}.mU^{-1}.min^{-1}$ after the intervention ($P<0.05$) in healthy overweight men and increases in muscle strength, size and RTD (rate torque development) 50 and 100 were also observed.

Several studies have demonstrated that people from South Asia are up to 4-6 times more likely to develop type 2 diabetes than White Europeans. Furthermore, in a recent study from the UK Biobank, grip strength in South-Asian men and women was 5–6 kg lower than in the other ethnic groups and a greater contributor to diabetes prevalence. As resistance exercise is the most effective intervention for increasing muscle mass, strength, and can improve insulin sensitivity, the aim of the Chapter 5 was to compare the effect of resistance exercise on muscle and metabolic health between South Asians and White Europeans. This chapter has shown that there were no differences in the effect of 12 weeks of resistance exercise training on the majority of the muscle and metabolic outcomes measured, however the increase muscle thickness, 1.2 (95% CI 0.8 to 1.7) mm in South Asians and 2.3 (95%CI 1.8 to 2.9) mm in White Europeans and decrease in systolic blood pressure, 5.1 (95%CI:-7.5 to -2.7) mmHg in White Europeans and a 0.7 (95%CI:-2.4 to 1.0) mmHg in South Asians were attenuated in South Asians. There was also a trend for an attenuated effect of resistance exercise training on $VO_{2max,}$ decrease of 0.7 (95%CI -2.0 to 0.6) $ml.kg.min^{-1}$ in South Asians.

In summary, this thesis has demonstrated that whilst ultrasound measure of muscle thickness is valid at a single time point, this is not the case when evaluating changes with resistance exercise training. Following this we have demonstrated that resistance exercise training, involving a single set of exercise to muscle failure, is effective in inducing short-term improvements in muscle size and strength and also insulin sensitivity in White Europeans, with broadly similar findings in South Asians.

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Author's Declaration

Unless otherwise stated by acknowledgment or reference to published literature, the presented work in this thesis is the author's own, as approved by the Thesis committee and the Graduate Office and has not been submitted for a degree at another institution.

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AHMAD DZULKARNAIN ISMAIL

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List of Abbreviations

CVD	cardiovascular disease
HR	hazard ratios
RT	resistance training
HOMA-IR	homeostatic model assessment insulin resistance
MPS	muscle protein synthesis
MPB	muscle protein breakdown
1RM	1 repetition maximum
BMI	body mass index
OGTT	oral glucose tolerance test
MTT	mixed meal tolerance test
MET	metabolic equivalent
VO_{2max}	maximum rate of oxygen consumption
BIA	bioelectrical impedance
MRI	magnetic resonance imaging
DEXA	dual energy X-ray absorptiometry
CV	coefficients of variation
SD	standard deviation
VL	vastus lateralis
CSA	cross-sectional area
FFA	fat free mass
WHO	World Health Organization
MVC	maximal voluntary contraction
RTD	rate of torque development
AUC	area-under the curve

CHAPTER 1
INTRODUCTION

1.1 Background

Muscle is the largest organ in the human body, comprising 40%-50% of total body weight. There are more than 600 muscles in the human body which perform common functions such as body movements, maintaining posture, storing protein and glycogen and generating heat (Smith & Goodship, 2004). Starting as early as the 4th decade of life, skeletal muscle mass declines at a rate of approximately 0.8% per year and this is a process called sarcopenia (Tieland, Trouwborst, & Clark, 2018), which can be used to highlight the importance of the maintenance of muscle mass. Sarcopenia, first described over two decades ago, is the age-related loss of skeletal muscle mass and this is associated with a decrease in muscle strength and impaired mobility (Tieland et al., 2018). Estimates of the rate of muscle strength loss during aging are reported to be higher, than the losses in muscle mass, at 1-3% per year (Keller & Engelhardt, 2013). This loss of muscle function and quality increases the likelihood of falls, decreases functional independence and reduces quality of life; highlighting the importance of maintenance of muscle function during ageing. From an economic point of view, recent research has indicated that the excess health and social care costs of muscle weakness are £2.5 billion per year, with £1.3 billion per year for health care alone (PinedoVillanueva et al., 2019). The percentage of older people (>65y) is predicted to rise from 17%, of the total UK population, in 2010 to 23% in 2035. Similarly, it is projected that the world population of people aged 60y and over will rise from 600 million in 2000 to 2 billion by 2050, with the subpopulation of those aged 80y and over the fastest growing subpopulation in the world (World Health Organization, 2007). The consequences and socioeconomic burden of muscle loss with age will therefore become an even greater issue than it currently is.

On top of its association with poor physical function, low skeletal muscle mass also has a key role in metabolism and has been found to be associated with many other health outcomes. For example, skeletal muscle is the primary protein store in the body, and during starvation (Richter, 1983) or conditions such as AIDS, can provide gluconeogenic precursors which are crucial for survival (Kotler, Tierney, Wang, & Pierson, 1989). On top of this, as muscle is the primary site for glucose disposal in the body, it is therefore important in metabolic conditions such as diabetes (S.W. et al., 2006). Extending this further, the

importance of muscle in lifelong health is reflected by data demonstrating the association of muscle mass and function with mortality. This is highlighted by recent work where it was demonstrated, in ~500,000 participants (40-69 years) from the UK Biobank, that each 5 kg lower grip strength was associated with increased risk as shown by hazard ratios (HR) of 1.11 (all-cause mortality), 1.14 (CVD events) and 1.06 (all-cancer events) (Celis-Morales et al., 2018). A primary focus of the current thesis is the role of skeletal muscle in insulin sensitivity and the risk of development of type 2 diabetes.

Diabetes is a disease of chronic hyerglycaemia. When carbohydrate containing food is ingested blood glucose levels rise and insulin, from the pancreas, stimulates the transport of glucose into tissues (muscle, adipose and liver) – where it can be stored or oxidized for energy. Diabetes occurs when the pancreas either doesn't make enough insulin and/or the insulin sensitive tissues don't fully respond to insulin (insulin resistance). Glucose, therefore, cannot be taken up into the tissues and hyperglycaemia ensues (DeFronzo, 2004). Over time, hyperglycemia increases the risk of health problems such as kidney disease, heart disease, high blood pressure and it can affect the reproductive system (Way, 2016). Type 1 diabetes or insulin-dependent diabetes, is an immune system disorder where the body's own immune system attacks the insulin-producing cells in the pancreas, destroying its ability to make insulin. Most people are diagnosed with type 1 diabetes as a child or young adult (Ou, Yang, Wang, Hwang, & Wu, 2016). Type 2 diabetes normally begins with peripheral insulin resistance, with the pancreas required to produce more insulin to maintain euglycaemia. Eventually, however, the β-cells of the pancreas can't sustain this increase in insulin production and fail – resulting in hyperglycaemia. Type 2 diabetes historically used to occur, primarily, in older populations, but now more and more young populations are being diagnosed with type 2 diabetes (Way, 2016). This condition is generally a result of poor lifestyle, dietary, and exercise habits (Asif, 2014). The current thesis will focus primarily on type 2 diabetes.

Insulin resistance is a condition in which there is a decreased ability of insulin to stimulate glucose disposal by muscle, adipose tissue, and liver, due to a decrease in the sensitivity of tissues to the action of insulin (Czech, 2017). Insulin resistance is associated with declining insulin production by the pancreas, the emergence of type 2 diabetes and increased risk of cardiovascular disease (CVD) and it is estimated that 10–25% of the general population presents with some degree of insulin resistance with rates varying in different ethnic groups. Furthermore, the exact cause of this insulin resistance is not known but has been linked to

lipid accumulation (particularly diacylglycerols and ceramides), decreases in fatty acid oxidation, mitochondrial dysfunction and reduced dilation of the microvasculature (Ormazabal et al., 2018). In many cases, although not always, the insulin resistance is due to excess body weight, as demonstrated in Figure 1.1. In this diagram it can be seen that obesity can drive insulin resistance in skeletal muscle, adipose and liver tissue, via a variety of different metabolic mechanisms (adapted from Carl D. L & Olefsky M, 2007).

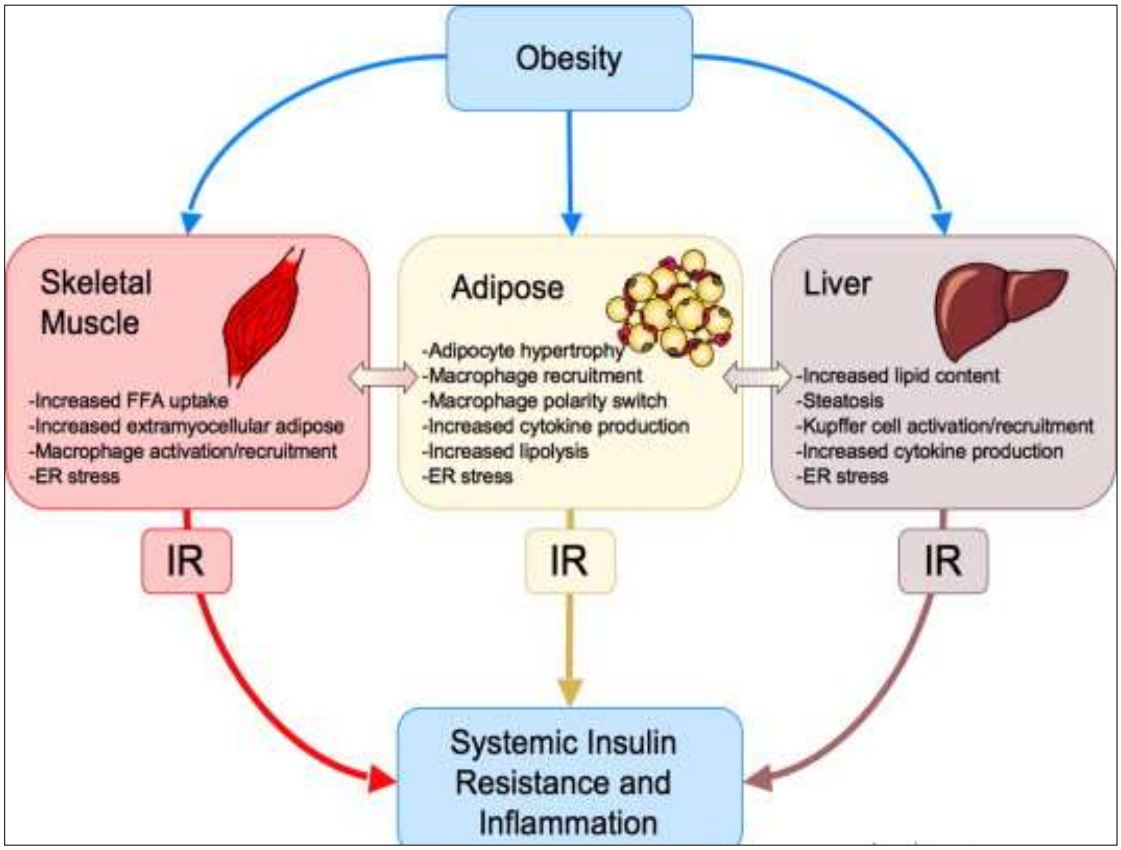

Figure 1.1 Obesity and the development on insulin resistance (adapted from Carl D. L & Olefsky M, 2007).

As mentioned previously, skeletal muscle has received particular attention in diabetes research because it is the major site of glucose disposal, responsible for approximately 80% of glucose clearance in the postprandial state (DeFronzo & Tripathy, 2009). Indeed, for that reason a low muscle mass and strength has frequently been found to be associated with a higher risk of the development of type 2 diabetes (S. Hong et al., 2017). There are indeed several studies which have investigated this association. For example, in an early study Sayer and colleagues have shown that older men, with known and newly diagnosed diabetes, have lower grip strength and a higher risk of impaired physical function (Sayer et al., 2005). Similarly, it has been shown that in older adults with type 2 diabetes not only is muscle

strength and quality (force per unit mass) lower but the declines over time, but interestingly not muscle mass, are more rapid (Seok et al., 2007). So, it is known that people with type 2 diabetes are weaker, that this is associated with poorer functional outcomes, and that their muscle function declines more rapidly over time. But these studies did not investigate the associations between muscle mass, strength and insulin resistance/diabetes status.

Several studies have investigated this. For instance, in 13,644 participants from the NHANES study in the USA it was shown that for each 10% higher skeletal muscle index, the ratio of total skeletal muscle mass to body mass, there was an 11% lower HOMA-IR (Srikanthan & Karlamangla, 2011). Similarly in a study in Korea of 113,913 men and 89,854 women, who were free of type 2 diabetes at baseline, who were followed up for, on average, 2.9 years skeletal muscle mass index was negatively associated with incident type 2 diabetes, with evidence of a dose-response relationship (Hong et al., 2017). In another study of 8,208 Koreans it was shown that hand grip strength was inversely associated with fasting glucose, fasting insulin, HbA1c and HOMA-IR as well as prevalent type 2 diabetes (Kim et al., 2018). Furthermore, in a study of 4,681 adults in the USA moderate, but not high, muscle strength, as assessed during leg and bench press, was associated with a reduced risk of incident type 2 diabetes (Wang et al., 2019). On top of this, in a study of 2,166 older adults, it was found that muscle mass was associated with a lower risk of incident type 2 diabetes in normal, but not overweight women, and not in men. No associations with muscular strength were observed (Larsen et al., 2016). This study may be limited by its relatively low participant numbers. Interestingly, not only are muscle size and strength associated with the risk of diabetes but the quality of skeletal muscle is also associated with risk of diabetes and muscle strength and mass is known to decline in people with type 2 diabetes (Park et al., 2006). These associations highlight the importance of skeletal muscle in insulin resistance and in the development of type 2 diabetes, indeed it has been reported that skeletal muscle insulin resistance is the primary defect in type 2 diabetes (DeFronzo & Tripathy, 2009).

It is clear, therefore, that strategies to increase muscle mass and function may have many favourable effects with regards to functional and metabolic health. Resistance training (RT) is the most effective method for developing muscle strength and increasing muscle mass and possibly insulin sensitivity. It is therefore prudent to now review the evidence supporting the beneficial effects of resistance exercise, beginning with increases in muscle size and strength.

1.2 Effects of resistance training on muscle size and strength

As mentioned above resistance training is the most effective way to increase muscle mass and strength and has been shown to be effective in a wide variety of populations. For example, there are many studies in younger people which have shown that resistance training can increase muscle mass and strength, with gains in strength being greater than muscle mass (Jones, Rutherford, & Parker, 1989; McDonagh & Davies, 1984). On top of this, there is evidence that resistance exercise training can increase muscle mass and function in older adults (Lai, Tu, Wang, Huang, & Chien, 2018). For this, and its many other health benefits, the United Kingdom physical activity guidelines recommend resistance training to work to all the major muscles (legs, hip, back, abdomen, chest, shoulders and arms) on at least 2 days a week for people aged between 19 to 64 (NHS, 2019).

Whilst the current thesis is not focusing on the mechanisms underlying the effects of resistance exercise on muscle mass and function it is prudent to briefly discuss these. The changes in muscle size are driven by changes in muscle protein metabolism, specifically the balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB), with resistance exercise, alongside feeding, known to acutely increase MPS in both absolute terms and relative to MPB (Phillips, Hartman, & Wilkinson, 2005). This results in a positive protein balance and protein accretion in muscle. This increase in muscle size is thought to facilitate increases in the contractile material and this results in an increase in muscular strength. But, as mentioned above, muscle strength is known to increase to a greater extent than muscle mass (Narici et al., 1996), indicating that not all the increase in muscle strength is driven by changes in mass. Indeed, it has been shown that resistance exercise can also alter factors such as muscle architecture (pennation angle) and neural adaptations (firing frequency, synchronisation, cortical adaptations, spinal reflexes and antagonist co-activation) which can contribute to gains in muscle strength (Folland & Williams, 2007).

It is clear, therefore, that resistance exercise can increase muscle mass and function. What is emerging is that resistance exercise training can also be beneficial for health. In order to quantify the efficacy of resistance exercise researchers often rely on imaging devices to quantify changes in muscle size – with common techniques being ultrasound and magnetic resonance imaging (MRI). It is prudent to briefly consider the background of these techniques.

1.2.1 Ultrasound and MRI

Ultrasound in physics applies to all acoustic energy with a frequency above human hearing (20,000 hertz or 20 kilohertz) and typical diagnostic sonographic scanners operate in the frequency range of 2 to 18 megahertz. Ultrasonography is an ultrasound-based diagnostic imaging technique used to visualize subcutaneous body structures including tendons, muscles, joints, vessels and internal organs. The sound waves penetrate human tissue at a speed of 1450–1580 m/s (Sakas and Walter, 1995). The waves are reflected if they hit an interface between two tissue and the reflected waves are recorded by sensors located next to the sound sources. Three different modes of ultrasound are used in medical imaging: A-mode or amplitude mode is the simplest type of ultrasound and a single transducer scans a line through the body with the echoes plotted on screen as a function of depth. A-mode ultrasound is used to judge the depth of an organ or to assess and organ's dimensions. In B-mode ultrasound or brightness mode, a linear array of transducers simultaneously scans a plane through the body that can be viewed as a two-dimensional image on screen. On a grey scale, high reflectivity (bone) is white; low reflectivity (muscle) is grey and no reflection (water) is black. M-mode, M stands for motion. In M-mode a rapid sequence of B-mode scans whose images follow each other in sequence on screen allows range of motion to be visualised, as the organ boundaries that produce reflections move relative to the probe. The M-mode is commonly used for measuring chamber dimensions and calculating fractional shortening and ejection fraction (Carovac et al., 2011). Recently ultrasound has increasingly been used for the measurement of muscle size and architecture and this will be considered in future sections of the thesis.

MRI is known as a gold-standard technique for the measurement of muscle volume/cross-sectional area and is used as a reference for the validation of other imaging techniques such as ultrasound and skinfold (Christelle et al., 2018). MRI provides high contrast images of muscle, fat, and connective tissue, allowing accurate delineation of muscle borders. MRI provides a large field of view relative to ultrasound, which enables visualization of whole muscles and limbs. Previous studies have been carried out where muscle cross-sectional area was measured by MRI in the thigh of a human cadaver and the results compared to photography of corresponding anatomic macroslices. Close correlation was found between MRI and photographic evaluation, differences between the methods ranging from nil to 9.5% dependent on the muscle group. The coefficients of variation for muscle cross-section areas measured by MRI in thigh were ranged from 1.44% to 5.74% (group 1) and 0.69% to 4.73% (group 2) (Ralph et al., 1991).

1.3 Resistance training and health

As mentioned, resistance training has been shown, in a wide variety of populations, to be efficacious in increasing muscle mass and function. On top of this a recent meta-analysis has shown that resistance training exercise can reduce blood pressure, reduce fasting insulin concentrations with more mixed findings when considering blood lipids (Kirwan, Sacks, & Nieuwoudt, 2017). Recent work has also demonstrated, using data from the Scottish and English Health Surveys, that participation in any strength-promoting exercise is associated with a reduced risk of all-cause (HR 0.77) and cancer mortality (HR 0.66) (Williams, Stamatakis, Chandola, & Hamer, 2011). It is not surprising, therefore, that resistance exercise is recommended as part of the physical activity recommendations (WHO, 2011); "Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week". These are, however, increasingly becoming recognised at the "forgotten guidelines" with a recent analysis finding that only 24% of women and 31% of men meet these guidelines, almost half the number of people that meet the guidelines for aerobic activity (Strain, Milton, Dall, Standage, & Mutrie, 2019). The barriers to resistance exercise are similar to those for physical activity in general, such as not having enough time, but with other barriers such as worrying about being too muscular, worries about injury and the equipment being too complex (Schutzer & Graves, 2004). It is clear, therefore, that resistance exercise can have a broad range of health benefits but that few people perform such exercise. As the focus of the current thesis is to look at the effects of resistance exercise on insulin sensitivity.

The purpose of Sojung's study (Lee et al., 2019) was to examine whether 6 months of combined aerobic and resistance exercise training is more effective than either aerobic exercise or resistance exercise alone in improving insulin sensitivity in adolescents. The study involved 118 sedentary adolescents with overweight/obesity who were randomized, with 85 participants (72%) completing the study and 90% exercise attendance. The study found that total adiposity decreased similarly in all groups with improvements in insulin sensitivity (determined during a 3h hyperinsulinaemic/euglycaemic clamp) decreased in all groups, but to the greatest extent in the aerobic exercise group. However, as the focus of the current thesis is adults it is key to look at similar studies in adults.

A meta-analysis (Way, Hackett, Baker, & Johnson, 2016) of studies testing aerobic, resistance and combined exercise interventions and their effects on insulin resistance in

people without diabetes has been carried out. This analyses found that exercise interventions, in people without insulin resistance, can result in a moderate improvement in insulin sensitivity which would translate to a reduction in fasting insulin of around 1.1 mU/L. Differences between aerobic and resistance exercise were explored in moderator analyses and it was found that there was no significant difference between the groups, although the others noted that this analyses was confounded by low power due to few studies. There are more clear findings in people with type 2 diabetes.

Bei pan et al (Pan et al., 2018) has conducted a systematic review and meta-analysis on the comparative impact of different methods of exercise training on glycemic control and weight loss in patients with type 2 diabetes. 37 studies with 2208 patients with type 2 diabetes were included in this study and it showed supervised resistance exercise results in a decrease in HbA1c (0.3%) compared to no exercise, a similar reduction to that seen in aerobic exercise. On top of that, resistance exercise training also improved systolic blood pressure (3.90 mmHg lower) and total cholesterol (22.08 mg/dl lower), compared to no exercise group. These findings are similar to a previous meta-analysis, which found that all modes of exercise results in a decrease in HbA1c in people with type 2 diabetes: aerobic (-0.73%), resistance (-0.57%) and combined (-0.51%) (Umpierre, 2011).

It is clear, therefore, that in people with type 2 diabetes that resistance exercise training can result in improvements in HbA1c to a similar extent as aerobic exercise. Data in healthy adults is less clear with fewer studies, but does indicate a similar beneficial effect of resistance training as seen with aerobic exercise on insulin sensitivity. What remain to be established are the optimal frequency, intensity and duration of resistance training to maximise benefits of resistance training. This is a topic which has recently been a focus for many research studies but looking at gains in muscle mass and strength as the outcomes. It may be that these developments can be translated to help optimise improvements in insulin sensitivity.

1.4 Resistance training to voluntary failure

Current American College of Sports Medicine (ACSM) recommendations are that to maximise gains in strength, for a novice, a load of 60-70% 1 repetition maximum (1RM) should be applied and 1-3 sets of 8-12 repetitions should be performed with a rest period of 2-3 min between sets. To maximise gains in muscle mass, for a novice, a load of 70-85% 1RM should be applied and 1-3 sets of 8-12 repetitions should be performed with a rest period of 2-3 min between sets. However, these recommendations have recently came under a deal of criticism and been challenged by several researchers (Fisher, Steele, Bruce-Low, & Smith, 2011). The primary reason for these criticisms is the assumption that relatively heavy loads are required to recruit all motor units and muscle fibres and thus maximise muscle growth.

The size principle dictates that motor units and the fibres which they innervate will be recruited progressively as the requirements to generate force increase. That is, the smaller, lower threshold motor units that innervate type 1 fibres are recruited first followed by higher threshold motor units, that innervate type 2 fibres (Henneman, 1985). For this reason many researchers have hypothesised that to maximise gains in muscle mass and strength heavier loads are required to ensure activation, fatigue and thus hypertrophy of all muscle fibres (Jenkins et al., 2015). However, the data generated from these studies in support of this hypothesis are based on the use of surface electromyography data to show a greater muscle activation when lifting heavier loads (Jenkins et al., 2015; Schoenfeld et al., 2015). Interpretation of such data is not straight forward and it cannot be assumed that higher electromyography (EMG) amplitude, whilst lifting heavier loads, can be attributed to the recruitment of the complete pool of motor units.

Indeed, recent research (Patterson et al., 2019) in both men and women has shown that if resistance exercise is performed to volitional failure then the load at which the exercise is performed does not alter the gains in muscle mass and strength. The theory behind these findings are that by progressing to voluntary failure even at light loads will result in full motor unit recruitment as the small motor units will fatigue and require the recruitment of the larger motor units which in turn will fatigue. There are several studies which have made comparisons of the efficacy of resistance exercise training at different resistance exercise loads when performed to voluntary failure.

One early study (Burd et al., 2010) investigated this, although it did not carry out a long term training study, but in fact looked at the end point of muscle protein synthesis, as an indicator of muscle remodelling and hypertrophy. In this study 15 men were recruited and performed 4 sets of unilateral leg extension exercise with legs performing 2 of the following: 90% 1RM until volitional failure, 30% 1RM work-matched to 90% 1RM to failure or 30% 1RM until volitional failure. When post-exercise MPS was compared between the groups there were no differences between the 90% and 30% 1RM groups to failure, both of which were higher than the 30% 1RM work-matched group. This indicates that the acute remodelling response to resistance exercise to voluntary failure does not differ with different loads. However, it is known that acute post-exercise MPS rates do not predict long term hypertrophy responses to resistance exercise training (Burd et al., 2010).

Long term training studies have thus been performed. In this study (Mitchell et al., 2012) eighteen untrained men had their legs randomly assigned to two of three training conditions that differed in contraction intensity and contraction volume (1 or 3 sets of repetitions): 30% 1RM 3 sets (30%-3), 80% 1RM 1 set (80%-1) and 80% 1RM 3 sets(80%-3), with all sets performed to voluntary failure. Subjects trained each leg with their assigned regimen for a period of 10 weeks, 3 times/week. The researchers made pre- and post-training measures of strength, muscle volume by magnetic resonance (MR) scans, as well as pre- and post-training biopsies of the vastus lateralis. Training-induced increases in muscle volume were not different between groups. Isotonic maximal strength gains were not different between 80%-1 and 80%-3, but were greater in both than in 30%-3, whereas training-induced isometric strength gains were not different between conditions. This data indicates that long term gains in size and strength are not mediated by load, when exercise is performed to voluntary failure. Interestingly as well a single set was just as beneficial as three sets.

Further research (Morton et al., 2016) has used a whole resistance training model, and found that high or low loads, performed to volitional failure, resulted in similar muscle hypertrophy and strength improvements in men with previous resistance training. Forty-nine resistance-trained men performed 12 weeks of whole-body resistance training and were randomly allocated into a higher-repetition group who lifted loads of 30-50% of 1RM for 20–25 repetitions per set or a low repetition group (75–90% 1RM, 8–12 repetitions/set), with all sets being performed to volitional failure. 1RM strength increased for all exercises in both groups, with only the change in bench press being significantly different between groups with a larger increase in the low repetition/high load group. Markers of hypertrophy (fat-free

mass and type I and type II muscle fibre cross-sectional area) increased with training to the same extent in both groups. As with aforementioned studies this study indicates that, in this case, in resistance exercise trained men, hypertrophy and strength gains are not mediated by load when exercise is performed to failure.

Similar findings have been made in other studies of trained men (Schoenfeld et al., 2014). In this study, eighteen experienced young men, in resistance training, were matched to baseline strength and randomly assigned to 1 of 2 experimental groups: a low load resistance training routine where 25–35 repetitions were performed per set per exercise or a high load (sets were performed to the point of momentary concentric muscular failure) resistance training routine where 8–12 repetitions were performed per set per exercise. The study found that the lower load condition produced similar gains in muscle thickness when compared to high load on the elbow flexors (5.3 vs. 8.6%, respectively), elbow extensors (6.0 vs. 5.2%), and quadriceps femoris (9.3 vs. 9.5%). Even lower load had increased maximal muscle strength, high load resulted in greater increases in 1RM testing in the bench press (6.5 vs. 2.0%, respectively).

All of the aforementioned studies have been exclusively in males, but there is one recent study which has been carried out in females. The aim of this study (Stefanaki, Dzul, & Gray, 2019) was to compare the effect of 6 weeks of resistance training to volitional failure at low (30% 1 repetition maximum (RM)) or high (80% 1RM) loads on gains in muscle size and strength in young women. Thirteen women completed 2 training sessions per week for 6 weeks and muscle strength (1RM) and vastus lateralis muscle thickness (ultrasound) were measured before and after training. Training comprised 1 set to volitional failure of unilateral leg extensions and bicep curls with each limb randomly assigned to train at either 80% 1RM or 30% 1RM. Increases in muscle thickness and strength were not different between loads. So similarly, as seen in men, when resistance exercise is performed to volitional failure gains in muscle size and strength are independent of load in young women.

It is clear, therefore, that resistance exercise to failure is one way in which gains in muscle mass and strength can be achieved independently of the load at which exercise is performed. This can make exercise prescription more simple. Interestingly as well when comparing data looking at 1 vs 3 sets of resistance training there was very little further benefit of the extra sets. This leads to the possibility of a simple and time-saving form of resistance exercise which can increase muscle mass and strength, which may also result in improvements in

insulin sensitivity. There are currently no studies which have investigated the effects of resistance training to failure on insulin sensitivity.

What is also true from previous work, although something rarely discussed, is that the majority of studies of resistance exercise have been in populations of White European descent. This is an important observation, as it is known that muscle size and strength differ between different ethnic groups and thus different ethnic groups may benefit to a varying degree from such exercise. One population in particular who may benefit from such exercise are people of South Asians descent who have a lower muscle mass and strength and are, interestingly, at a higher risk of developing type 2 diabetes.

1.5 South Asians

Type 2 diabetes has rapidly developed into a major public health problem in South Asia (defined here as Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka) in recent decades. During this period, major lifestyle changes associated with economic transition, industrialization, urbanization, and globalization have been key determinants in the increasing burden of non-communicable diseases (Hills et al., 2018). Reduced physical activity, and increased sedentary behaviours are also reflected in the increasing prevalence of type 2 diabetes and related risk factors in the region (Hills et al., 2018). Whether living in urban environments in the Indian subcontinent, or amongst the diaspora in high-income countries, South Asians have age-standardised rates of type 2 diabetes ~2-4 fold higher than white people of European descent. Their diabetes risk rises at substantially lower levels of body mass index (BMI): at a BMI of 22-24 $kg.m^{-2}$ it is equivalent to that in white Europeans with a BMI of 30 $kg.m^{-2}$. South Asians typically develop diabetes 5-10 years earlier than white Europeans by the age of 70, 30-40% have diabetes (Wells, Pomeroy, Walimbe, Popkin, & Yajnik, 2016). South Asians transition through the 'pre-diabetes' phase more rapidly than Europeans and once they develop diabetes, disease progression is faster and micro vascular complications develop more rapidly (Ramachandran, 2012). The International Diabetes Federation (2017) estimates that the prevalence of diabetes in adults in the region range from 4·0% in Nepal to 8·8% in India. The prevalence of overweight ranges from 16·7% in Nepal to 26·1% in Sri Lanka, and the prevalence of obesity ranges from 2·9% in Nepal to 6·8% in Sri Lanka. An increasing proportion of children, adolescents, and women are overweight or obese, leading to a heightened risk of type 2 diabetes (Hills et al., 2018). Because of the presence of multiple risk factors and a body composition

conducive to the development of type 2 diabetes, South Asians should be aggressively targeted for type 2 diabetes prevention.

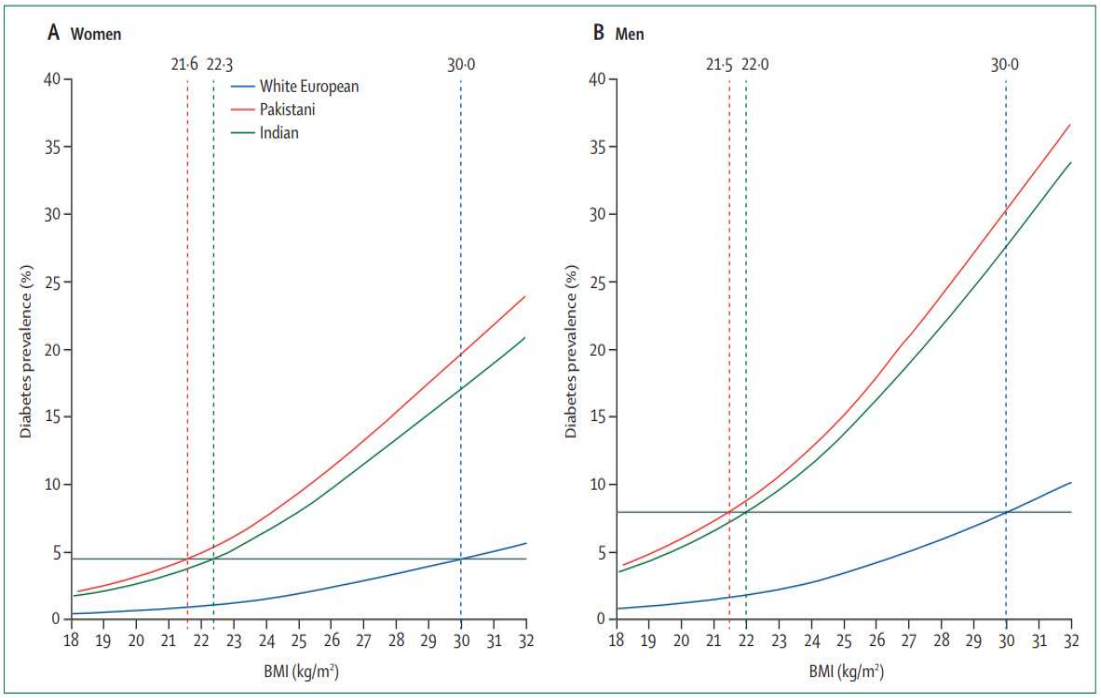

Figure 1.2 Age-adjusted associations between diabetes prevalence and adiposity, derived using data from the UK Biobank study (Uduakobong E. Ntuk, Gill, Mackay, Sattar, & Pell, 2014)**.**

Figure 1.2 shows the relationship between diabetes prevalence and BMI in White European, Pakistani and Indian women (A) and men (B). The horizontal line in figure A is the diabetes prevalence for White European women with BMI 30 kg/m^2 and dotted vertical lines show the BMI values (Pakistani women 21.6 kg/m^2 and Indian women 22.3 kg/m^2) at which the same diabetes prevalence is seen. The horizontal line in figure B is the diabetes prevalence for White European men with BMI 30 kg/m^2 and dotted vertical lines show the BMI values (Pakistani men 21.5 kg/m^2 and Indian women 22 kg/m^2) at which the same diabetes prevalence is seen. This clearly shows that diabetes occurs at lower BMI in South Asians compared to White European.

1.5.1 Consequences of the increase in type 2 diabetes in South Asians

The increasing prevalence of diabetes in South Asians has significant effects on health and also has economic costs. Many studies have confirmed that type 2 diabetes more than doubles the risk of cardiovascular disease. As mentioned, type 2 diabetes is particularly prevalent in South Asians and occurs earlier with progression faster, relative to White

Europeans (Einarson, Acs, Ludwig, & Panton, 2018). It may, therefore, be expected that this will drive higher rates of cardiovascular disease in South Asians.

An early study Mather and colleagues (Mather, Chaturvedi, & Fuller, 1998) compared mortality and morbidity in a cohort of South Asians and European people with diabetes in London, UK, in an 11-year follow-up of a population. With a sample of 730 South Asians (mean age 55 in 1984) and 304 Europeans (mean age 67 in 1984) with diabetes. In 1995, 242 (33 %) of South Asians, and 172 (57 %) of Europeans had died. This study showed that all-cause mortality was in fact lower in South Asians with type 2 diabetes compared to White Europeans. However, 77% of South Asians deaths were caused by circulatory disease, compared with percentage of European deaths. Furthermore, South Asian survivors were 3.8 times more likely to report a history of myocardial infarction than White Europeans. This study, therefore, showed that although the risk of all-cause mortality was lower in South Asians the risk of cardiovascular disease was in fact higher. This finding is not, however, universal.

There are few other studies, to date, that have also investigated mortality risk in South Asians and White Europeans with and without type 2 diabetes. One study showed that years of life lost due to type 2 diabetes is higher among White Europeans than South Asians (Gujral, Pradeepa, Weber, Narayan, & Mohan, 2013). This was substantiated by another study that showed all-cause mortality risk to be lower among South Asians than White Europeans (S. Zaman et al., 2013). In contrast with this, a study by Tillin's study found that all-cause mortality risk is higher in South Asians compared to White Europeans with type 2 diabetes, but the risk is similar between South Asians and White Europeans without type 2 diabetes (Shneiderman & Tillin, 2015). These conflicting results may be due to differences in study design. The study by S. Zaman et al. did not adjust for important variables including smoking and adiposity measures. Furthermore, mortality risk may have changed over time due to improvements in health care; the study by Tillin et al. was published recently, but the follow-up period started twenty years ago. The all-cause mortality risk may be balanced by the lower risk for cancer in South Asians, as cancer is a major contributor to all-cause mortality (Shneiderman & Tillin, 2015). Therefore, the greater mortality risk among South Asians attributed to CVD might be offset by the lower risk for cancer, resulting in no difference in all-cause mortality risk.

It has been demonstrated that South Asians have a higher type 2 diabetes prevalence and also that they have a predisposition to cardiovascular disease. The mechanisms which underlie the increased type 2 diabetes risk in South Asians remains to be determined. The following sections will explore some of the differences with South Asians which may explain their higher diabetes risk.

1.5.2 Genetic predisposition

Available genetic data including 29,618 cases and 40,329 controls from 38 studies, Sohani and colleagues (Sohani et al., 2014) noted 24 single nucleotide polymorphisms (SNPs) from 21 loci to be associated with type 2 diabetes in South Asians. SNPs identified were common to both South Asians and White Europeans and no clear evidence of a difference between these two ethnic groups in the type 2 diabetes risk associated with these SNPs or in their population. However, recent evidence from an epigenome-wide association study in 13,535 South Asians and 7,066 White Europeans in the London Life Sciences Prospective Population study found that a DNA methylation score based on the methylation level of five genes – ABCG1, PHOSPHO1, SOCS3, SREBF1, and TXNIP – was similarly predictive of type 2 diabetes in White Europeans and South Asians, but that South Asians had a DNA methylation score 0.86 standard deviation higher than the White Europeans. This accounted for 32% of the 2.5-fold increased diabetes risk in South Asians that was not accounted for by differences in adiposity, glycaemic measures or physical activity (Arti Shah & Kanaya, 2014).

1.5.3 Fetal programming

A recent meta-analysis showed clearly that low birth weight (a marker of fetal under nutrition) was associated with greater risk of type 2 diabetes with each kg increase in birth weight associated with a ~25% decrease in diabetes risk (Whincup et al., 2008). Whilst South Asians have lower birth weights, a recent analysis which related birth weights to diabetes-related traits in 3,744 9-10 year olds from different ethnicities did not support low birth weight *per se* as an explanation for the emerging ethnic difference in risk markers for diabetes. Moreover, South Asians children have a higher percentage of body fat at birth (based on skin-folds and/or cord leptin levels), accompanied by higher cord insulin concentrations commensurate with insulin resistance (Lawlor et al., 2014; Yajnik et al., 2002). When adjustment was made for maternal fasting glucose levels, which were higher in the (predominantly Pakistani) South Asians women, the ethnic difference in cord leptin halved and became non-significant. Further analyses of 1,415 women and their singleton

live-born infants (629 white British and 786 Pakistani) supported the hypothesis that maternal fasting glucose levels may mediate the relationship of Pakistani ethnicity to greater fat mass at birth (Lawlor et al., 2014). If this hypothesis is correct, future randomised trials investigating the effects of lifestyle intervention in South Asians pregnant women at elevated risk of gestational diabetes would seem worthwhile, with key end-points including rates of gestational diabetes, birth weights and, critically, neonatal body composition. intervention trials in humans are important to translate the research into the fetal programming hypothesis beyond mere observations and elucidation of mechanisms to real-world clinical importance (Sattar & Gill, 2015).

1.5.4 Pancreatic beta-cell capacity

In contrast to clear evidence for greater insulin resistance and related metabolic dysfunction in South Asians, there is less evidence available for inadequate beta-cell capacity. However, some recent data, using indirect measures, has emerged. Data from the Whitehall study in the UK (Ikehara et al., 2015), using HOMA-B% as an estimate of beta-cell function in 230 South Asians and 5,749 White Europeans aged 39-79 at baseline assessed at 5-yearly intervals from 1991-1994 to 2007-2009, suggest that beta-cell function is higher in South Asians at age 50 years, a finding corroborated by data from the Southall study (Mather et al., 1998); however, while HOMA-B% increased in White Europeans with age to compensate for increasing (HOMA-S%) insulin resistance, this did not occur in South Asians, who also experienced a decline in beta cell function from the age of ~60 years onwards (Tabák et al., 2009). Interestingly, cross-sectional data from the MASALA and MESA studies in the US showed slightly lower HOMA-B values in South Asians (mean age 57 years) compared with adults of White European descent (mean age 63 years) (Kanaya et al., 2014). Furthermore, in the Whitehall study, there was clear evidence of a sharper rise in fasting plasma glucose in South Asians compared with White Europeans over time (Ikehara et al., 2015), which suggests that South Asians have higher insulin secretion at younger ages to compensate for their higher insulin resistance, but they are unable to maintain this later in life, leading to a more rapid age-related increase in glycaemia.

Interestingly, in the Whitethall study, whilst adjustment for truncal adiposity and insulin resistance completely attenuated the excess incident diabetes risk in South Asian women, the excess diabetes risk remained in South Asians men, tempting speculation on the importance of inadequate compensatory beta cell function in explaining this excess risk (Ikehara et al., 2015). One limitation of HOMA-B% is that does not account for underlying

insulin resistance and thus provides a relatively crude estimate of beta-cell function. In a study of migrant South Asians in the US, Gujral (Gujral et al., 2013) and co-workers found that the disposition index – a more dynamic estimate of beta cell function, derived from glucose and insulin measures across an oral glucose tolerance test (OGTT) – was more strongly associated with 'pre-diabetes' and type 2 diabetes than whole body insulin sensitivity assessed using the Matsuda index. Given the above findings, further detailed assessment of beta cell function in South Asians across the life-course appears warranted.

In general, whilst South Asians are able to produce more insulin at younger ages to compensate for their peripheral insulin resistance, it appears that an earlier decline in beta cell function accompanies transition to dysglycaemia and ultimately diabetes. Whether these patterns represent earlier beta cell 'exhaustion' secondary to higher levels of insulin production needed throughout the life-course to compensate for insulin resistance; lower inherent beta cell capacity; are reflective of more rapid accumulation of ectopic fat around the pancreas; or are the consequence of some other mechanism such as enhanced hepatic insulin extraction, require further investigation. The clinical implications of these findings are also uncertain, though there has been some speculation that incretin-based therapies may be particularly suitable for South Asians with diabetes (Sattar & Gill, 2015).

1.5.5 Physical activity & fitness

Cardiorespiratory fitness is a strong, independent predictor of health. Indeed in a recent study it was shown that for each metabolic equivalent (MET: VO_2 of 3.5 ml/kg/min) higher cardiorespiratory fitness was associated with a reduced risk of all-cause mortality (hazard ratio: 0.96) and incident cardiovascular disease (hazard ratio: 0.96), respiratory disease (hazard ratio: 0.96), chronic obstructive pulmonary disease (hazard ratio: 0.90) and colorectal cancer (hazard ratio: 0.96) (Steell et al., 2019). Others have also reported similar findings. On top of this a higher cardiorespiratory fitness has also been shown to be associated with a reduction in type 2 diabetes incidence (Lesser et al., 2015).

Cardiorespiratory fitness has been rarely examined in South Asians populations. In a small study of 20 South Asians and 20 age and BMI matched White Europeans it was found that cardiorespiratory fitness (measured as VO_{2max}) was ~20% lower in South Asians (Hall et al., 2010). On top of this, fat oxidation during submaximal exercise was also lower (~40%) in South Asians and both differences in VO_{2max} and submaximal fat oxidation we correlated with differences in the insulin sensitivity index. This indicates that the reduction in

cardiorespiratory fitness and muscles capacity to oxidize fat may contribute to the higher diabetes risk in South Asians. Furthermore in a recent study of 100 South Asians and 100 age and BMI matched European men (no diabetes, aged 40-70 years) it was found that $VO_{2max}$was ~20% lower in South Asians, compared to White Europeans, and it explained 68% of the variance in of the higher insulin resistance ($HOMA_{IR}$) seen in South Asians (Ghouri et al., 2015).

As with cardiorespiratory fitness, many studies have found that a higher level of physical activity is associated with a reduced risk of many health outcomes (e.g. McKinney et al., 2016), including a reduction in risk of type 2 diabetes. As with the majority of these studies the majority of data comes from White Europeans. Interestingly, it has been demonstrated that for the same health benefits of physical activity seen in White Europeans that South Asians may need to participate in 10-15 minutes more moderate physical activity per day on top of the existing recommendations (232 min/week versus 150 min/week) (Iliodromiti et al., 2016). This is on top of the observation that physical activity levels are often lower in South Asians.

For example a systematic review by Fischbacher (Fischbacher, Hunt, & Alexander, 2004), evaluated the evidence that physical activity is lower in South Asians groups relative the general UK population. They identified 12 studies in adults and 5 in children and reported lower levels of physical activity among all South Asians groups. These lower levels of physical activity among UK South Asians ethnic groups may contribute to their increased risk of type 2 diabetes. Similar findings have been made in other studies.

Furthermore, data from the Health Survey for England from 1999 to 2004 on 5421 South Asians and 8974 White European participants aged 18 - 55 years were used to compare physical activity levels (Williams et al., 2011). Analyses of covariance tested the association between ethnicity and self-reported total physical activity metabolic equivalents of task (MET) scores, adjusting for age, sex, self-reported health, adiposity and socioeconomic status. Total MET-min/week was consistently lower in UK South Asians than in white participants (973 vs. 1465 MET-min/week). Differences between South Asians and Caucasians were consistent across sexes, age groups and subgroups and were independent of covariates. Variables such as urbanization and psychological distress were associated with physical activity, but overall data indicated that physical inactivity in South Asians was not attributable to area or individual sociodemographic factors.

These differences are already evident at a young age. Indeed a study which investigated Ethnic differences in physical activity in children in the United Kingdom in 9–10 year old British children of South Asian, African and White Europeans (Owen et al., 2009). It was a cross-sectional study of urban primary school children in 2006 and 2007 and Actigraph-GT1M activity monitors were worn by 2071 children during waking hours on at least 1 full day. In White Europeans children, mean daily counts per minute of registered time (CPM) and mean daily steps were 394, 785, 498 and 10,220, respectively. Compared with White Europeans, South Asians recorded 18,789 fewer counts, 41 fewer CPM and 905 fewer steps per day.

Overall, there are a few studies which have demonstrated that cardiorespiratory fitness and physical activity are lower in South Asians relative to White Europeans. Due to the importance of both cardiorespiratory fitness and physical activity, which are also associated with each other, in the risk of type 2 diabetes it is likely that these will contribute to increase in type 2 diabetes risk in South Asians.

1.5.6 Body composition

As well as differences in cardiorespiratory fitness and physical activity there are also differences in body composition between South Asians and White Europeans which may contribute to their increased diabetes risk. As mentioned previously the risk of type 2 diabetes per unit increase in BMI (or indeed waist circumference) is higher in South Asians compared to White Europeans. This suggests that the adverse health effects of increasing adiposity are worse in South Asians.

Data demonstrate that South Asians have more total body fat that White Europeans and on it is stored more centrally (A. Shah, Hernandez, Mathur, Budoff, & Kanaya, 2012). On top of this even after adjustment for adiposity markers, South Asians remain insulin resistant, relative to White Europeans (Nightingale et al., 2013). As well as overall fat storage being higher in South Asians there is some evidence that South Asians have a lower capacity to store fat safely in the superficial subcutaneous depots. This may be particularly important as fat stored in the superficial subcutaneous depots has been found to be relatively safe, i.e. carrying little in the way of negative health consequences, whereas ectopic and visceral fat storage is associated with negative metabolic effects (Goossens, 2017). With this in mind, several studies have shown that South Asians store a larger proportion of their total fat in

deep subcutaneous and visceral depots (Sattar & Gill, 2015). There is also some indication that South Asians may store more of their fat ectopically in the liver (Bhopal, 2013) .

South Asians have less lean tissue than Caucasians for a given BMI. Skeletal muscle is quantitatively the most important site of glucose disposal (Lambadiari, Triantafyllou, & Dimitriadis, 2015) and it is conceivable that this could contribute to their greater insulin resistance and diabetes risk. Lear and colleagues study has reported that South Asian men and women (n=202) had higher body fat percentages, lower lean mass, a higher fat-to-lean mass ratio and were more insulin resistant than Europeans (n=208) (Lear, Kohli, Bondy, Tchernof, & Sniderman, 2009). Other than that, in a study of 514 South Asians and 669 Europeans aged 56-86 years, Eastwood and colleagues reported that South Asian men and women had lower thigh muscle cross-sectional areas, and that thigh muscle area was significantly negatively associated with HbA1c in South Asians (but not White Europeans) in analyses adjusted for abdominal superficial subcutaneous and visceral adipose tissue, and thigh subcutaneous adipose tissue. Thigh muscle attenuated the excess diabetes prevalence observed in the South Asians independently of visceral adipose tissue (Eastwood et al., 2014).

Interestingly similar findings are seen with muscle strength. In a recent analysis from the UK Biobank data where it was found that 5 kg lower grip strength was associated with a 9% higher prevalence of type 2 diabetes (Lee et al., 2018). To our knowledge, this is the largest study of this nature to highlight the strong association between muscle strength and metabolic health. Interestingly these associations differed between ethnicities. Of primary relevance to the current thesis, it was found that not only was grip strength lower in South Asians but, the attributable risk for diabetes associated with low grip strength was higher in South-Asian people (3.9 and 4.2 cases per 100 men and women) than in people of White Europeans origin (2.0 and 0.6 cases) 12. This highlights that low strength is associated with a disproportionately large number of diabetes cases in South Asians (U. E. Ntuk et al., 2017).

In conclusion, it has been shown that both body fat distribution and muscle mass/strength differ between South Asians and White Europeans, with less safe fat storage and lower muscle mass/strength in South Asians. As these are associated with metabolic health it is likely that these differences contribute to the higher diabetes risk in South Asians. This section also highlights the fact that South Asians, in particular, may benefit from strategies to increase muscle mass and strength. As mentioned previously the main way to increase

muscle mass/strength is via resistance training exercise. There have currently been very few studies of resistance training exercise in South Asians.

1.6 Resistance exercise in South Asians

Misra and colleagues (Misra et al., 2008) investigated the effect of 12 weeks of resistance exercise on glycaemic outcomes and body composition in 30 Indian patients diagnosed with type 2 diabetes. They found a reduction in visceral fat, although no reduction was found in total body fat and no increase in muscle mass was seen. On top of this, they found a 0.33% reduction in glycated haemoglobin (HbA1c) levels, similar to that observed in other ethnicities, although no comparator group was included in the study. Similar results were obtained from untrained South Asian middle-aged 35 males and 13 females with type 2 diabetes investigated by Hameed and colleagues (Hameed, Manzar, Raza, Shareef, & Hussain, 2012). Progressive resistance training for 12 weeks resulted in a reduction in circulating glucose levels and an increase in muscle size and strength in both men and women. However, the investigators in this study did not observe any changes to blood pressure or blood lipids. These studies demonstrate that South Asians can respond to resistance exercise but without a White Europeans comparator group they do not provide information on whether there is any evidence of an anabolic resistance.

In another study by Knox and colleagues, but with healthy males in their mid-twenties, resistance exercise resulted in the improvement of the upper arm size and strength in a similar manner between the 13 South Asians and 15 Caucasians, but the lower body strength improved by an average of 23.5kg less among South Asians (Knox, Sculthorpe, Baker, & Grace, 2017). However, in a later study, Knox and colleagues (Knox, Sculthorpe, & Grace, 2019) did not find a significant difference between ethnicities in terms of muscle mass gain and insulin-glucose response. The exercise regimens for both studies were limited to six weeks period, which is insufficient to get a true response, particularly for muscle mass where changes are slower, especially with small sample sizes as the ones used for these two studies.

As detailed in the introduction section resistance exercise can confer many health benefits and yet very few people carry out such exercise. As with physical activity in general time is cited as a barrier to participation in resistance exercise and current recommendations are complex, making participation for a novice not a simple task. Performing resistance exercise, a single set, which is of relatively short duration, of exercise to failure 2-3 times per week

can increase muscle mass and strength but little is known about is metabolic effects. This could be a useful strategy in many populations but one in particular is South Asians who are at a higher risk of diabetes compared to White Europeans. The mechanisms underlying this heightened risk remain to be established and are multi factorial in nature, but low muscle mass/strength may contribute. Indeed, low muscle strength has been shown to be a stronger risk factor for diabetes in South Asians compared to White Europeans. Resistance exercise training may therefore be particularly effective in this population.

1.7 Aims of thesis

The gold-standard method to measure muscle mass is magnetic resonance imaging (MRI), which requires expensive equipment and facilities. Other methods, such as skin folds, bioelectrical impedance (BIA) and anthropometric measurements involve minimal and easily portable equipment but their accuracy can be poor (Kyle et al., 2004). The use of ultrasound to measure muscle thickness in humans datesbacktothemid-1960s (Pineau, Filliard, & Bocquet, 2009; Wagner, 2013) and systematic reviews have concluded that ultrasound is a valid and reliable measure of muscle size (Nijholt, Scafoglieri, Jager-Wittenaar, Hobbelen, & van der Schans, 2017). Although the use of ultrasound has increased, the cost of equipment, lack of portability and training required has limited its widespread application. Thus, the aim of **Chapter 2** was:

- To investigate the repeatability and validity of a relatively cheap and portable A-mode ultrasound device.

Subsequently,
Following this the aims of this **Chapter 3** were:

- To determine if the A-mode ultrasound device is able to detect changes in muscle thickness in response to resistance exercise training
- To determine the validity of both A- and B-mode ultrasound, compared to MRI, in detecting exercise induced increases in muscle size.

As mentioned it has been demonstrated recently that if exercise is performed to volitional failure then gains in muscle mass, and to a lesser extent strength, are similar regardless of the load at which exercise is performed (Mitchell et al., 2012; Morton et al., 2016). The early time-course of adaptations to such exercise remains to be established, as does whether this

form of exercise can also improve insulin sensitivity. The aims of this **Chapter 4** were, therefore:

- To investigate the effects of 6 weeks of resistance exercise training, compromised of 1 set of each exercise to voluntary failure on, i) insulin sensitivity and ii) the time-course of adaptations in muscle strength and mass, in overweight men.

It is also evident that muscle mass and metabolic function differs between people from different ethnic groups with South Asians having a lower muscle mass and a 4-6 times higher risk of developing type 2 diabetes than White Europeans (Hu, 2011; Arti Shah & Kanaya, 2014; Unnikrishnan, Pradeepa, Joshi, & Mohan, 2017). As resistance exercise is the most effective intervention for increasing muscle mass, strength, and can improve insulin sensitivity (Brooks et al., 2007) the aim of **Chapter 5** was:

- To compare the effect of resistance exercise training on muscle and metabolic health between South Asians and White Europeans.

CHAPTER 2 – REPEATABILITY AND VALIDITY OF AN A-MODE ULTRASOUND DEVICE TO MEASURE MUSCLE SIZE

2.1 Introduction

Skeletal muscle is the largest organ in the human body, comprising 40%-50% of total body weight. There are more than 600 skeletal muscles in a human body performing common functions such as body movements, maintaining posture, storing protein and glycogen and generating heat (Smith & Goodship, 2004). Due to these important functions, skeletal muscle is an important and often underappreciated organ in determining overall health (Wolfe, 2006). Starting as early as the 4th decade of life skeletal muscle mass declines at a rate of approximately 0.8% per year, a process termed sarcopenia (Tieland et al., 2018). Alongside this loss of muscle mass, ageing also results in a decrease in muscle strength, at a rate of approximately 1-3% per year (Keller & Engelhardt, 2013). This loss of muscle mass and strength results in a decrease in mobility, loss of independence, increased risk of falls and a decrease in quality of life (Padilla Colón, Collado, & Cuevas, 2014).

Skeletal muscle is also the major organ responsible for glucose uptake under insulin stimulated conditions, accounting for ~80% of total glucose disposal (DeFronzo & Tripathy, 2009). Defects in muscle likely contribute to metabolic dysregulation seen in type 2 diabetes with peripheral insulin resistance a major contributor. For example, in a study of Japanese Americans, thigh muscle mass area was inversely associated with future insulin resistance (Han et al., 2018). On top of this, researchers have performed a cross-sectional study with 14,807 adult participants aged between 18 and 65 in the fourth and fifth Nutrition Examination Survey, with Dual Energy X-ray Absorptiometry (DEXA) data, to investigate whether muscle mass was associated with insulin resistance and metabolic syndrome, with inverse associations observed (Kim & Park, 2018).

Therefore, that strategies to increase muscle mass may be of benefit to metabolic health. Resistance exercise training is the most efficacious method to increase muscle mass and strength, with other beneficial effects also noted. The physiological adaptations resulting from a well-designed resistance exercise training programme are increased strength, increased muscle mass, increased connective tissue thickness, decreased body fat, decreased blood pressure, improved insulin sensitivity and VO_{2max} (Ashton et al., 2018).

In order to monitor efficacy of such training interventions it is important to be able to accurately quantify skeletal muscle mass and several methods exist for this purpose. Common laboratory methods include dual-energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI), both of which require expensive equipment and expertise. Other methods, such as skin folds, bioelectrical impedance (BIA) and anthropometric measurements involve minimal and easily portable equipment but their accuracy can be poor (Kyle et al., 2004). The use of ultrasound to measure muscle thickness in humans dates back to the mid-1960s (Pineau et al., 2009; Wagner, 2013) and systematic reviews have concluded that ultrasound is a valid and reliable measure of muscle size (Nijholt et al., 2017). The BodyMetrix ultrasound (BX2000) is a 2.5 MHz, A-mode ultrasound with associated Body View Professional software (IntelaMetrix, Inc., Livermore, CA) used for the measurement of fat and muscle layer thickness in the human body. Most other studies have previously employed B-mode ultrasound for the measurement of muscle thickness and no studies, thus far to our knowledge, have employed the cheaper A mode ultrasound for this purpose.

Although the use of ultrasound has increased, the cost of equipment, lack of portability and training required has limited its widespread application. Thus, the aim of this study was to investigate the repeatability and validity of a relatively cheap (~£1,500) and portable ultrasound device.

Hypotheses: Study A – The BodyMetrix (BX2000) ultrasound has good repeatability in measuring muscle thickness.

Study B – Both A- and B-mode ultrasound measures of muscle thickness are valid methods to quantify muscle size.

2.2 Methods

2.2.1 Study A – Ultrasound BodyMetrix BX2000 (IntelaMetrix, Inc., Livermore, CA) device repeatability in the measurement of skeletal muscle thickness.

2.2.2 Experimental design

Exclusion criteria included; current smoking, physician diagnosed diabetes, uncontrolled hypertension (>160/90 mm Hg on anti-hypertensive medication. All participants were in good health at the time of testing and currently did not participate in any resistance exercise or taking any dietary supplements. Participants were asked to avoid strenuous exercise for 48h prior to study visits. On the first study visit participants visited the laboratory, were introduced to the research group, completed a health screen questionnaire and had blood pressure, height and weight recorded. All participants had vastus lateralis muscle thickness measured on four consecutive days at the same time of each day by the same investigator. The study was approved by the Ethics Committee of the College of Medical Veterinary and Life Sciences at the University of Glasgow, and adhered to the declaration of Helsinki (1964). All tests were carried out in the Human Physiology Labs in the West Medical Building.

2.2.3 Muscle thickness

BodyMetrix (BX2000): Conventional ultrasound imaging is B-mode ultrasound, meanwhile the BodyMetrix device is an A-mode single beam ultrasound. When used in its normal mode the BodyMetrix device is similar to traditional A-mode ultrasound. This simply means that the device acquires the tissue structure along a single line. The manufacturer of this device is IntelaMetrix, Inc., Livermore, CA.

Measurements were performed on the dominant side after 20 minutes resting in a supine position. Trochanterion and Tibiale Laterale land marking was employed to determine the midpoint of the thigh across the vastus lateralis. After that, the handheld ultrasound device (BodyMetrix BX2000) was used, after application of ultrasound gel, to measure muscle thickness between 35-65% of the thigh length along the belly of the vastus lateralis. The scan speed was adjusted to ensure the image completely filled the scan panel. When the scan was completed a cross sectional image the fat layer, muscle layer, and if applicable bone, across the length of the scan was produced on screen. Figure 2.1 shows an example of a completed scan. Measurements of muscle thickness were then made by clicking on the

subcutaneous fat layer and the inferior edge of the vastus lateralis muscle. Muscle thickness results are then displayed.

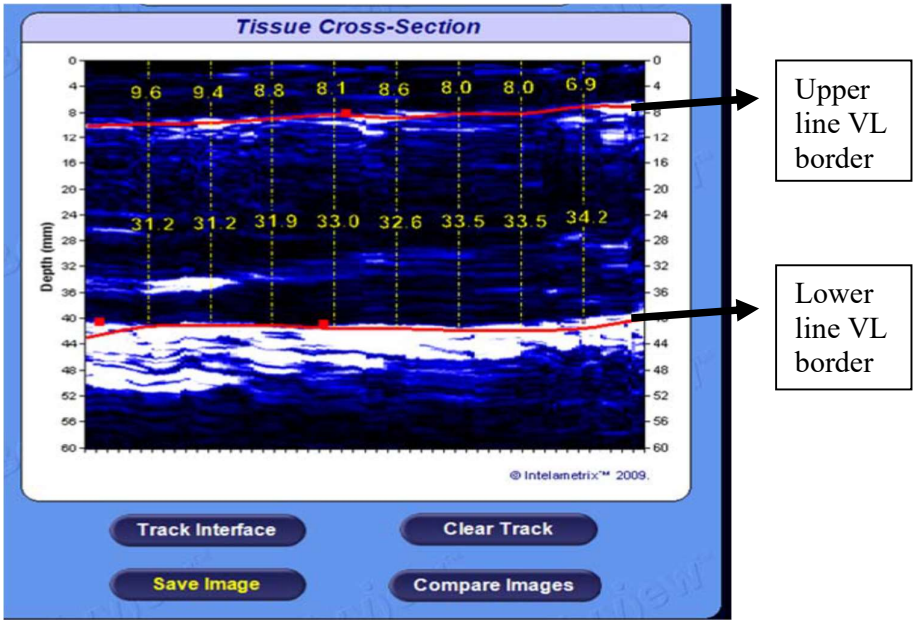

Figure 2.1 Illustration of BodyMetrix track interface

2.2.4 Statistical analysis

Coefficients of Variation (CV) for muscle thickness measurements over four consecutive days were calculated.

2.2.5 Study B –Comparison of BodyMetrix BX2000 Ultrasound to traditional B-mode Ultrasound and MRI.

2.2.6 Experimental design

Exclusion criteria included; current smoking, physician diagnosed diabetes, uncontrolled hypertension (>160/90 mm Hg on anti-hypertensive medication). All participants were in good health at the time of testing and currently did not participate in any resistance exercise or taking any dietary supplements. On the first study visit participants visited the laboratory, were introduced to the research group, completed a health screen questionnaire and had height and weight recorded. All participants were scanned for muscle thickness of their vastus lateralis by A-mode (BodyMetrix) and B-mode (Telemed) ultrasound and for muscle volume (right anterior thigh) and total body lean mass by Magnetic Resonance Imaging (MRI). The study was approved by the Ethics Committee of the College of Medical

Veterinary and Life Sciences at the University of Glasgow, and adhered to the declaration of Helsinki. All tests were carried out in the Human Physiology Labs of the West Medical Building.

2.2.7 Muscle thickness, volume and lean mass:

In each participant the following measurements were made on a single occasion.

BodyMetrix BX2000: Measurements of muscle thickness were performed as in **part A**.

Telemed Ultrasound: B-mode image is a cross-sectional image representing tissues within the body. It is constructed from echoes, which are generated by reflection of ultrasound waves at tissue boundaries, and scattering from small irregularities within tissues. Each echo is displayed at a single point in the image, which corresponds to the relative position of its origin within the body cross section, resulting in a scaled map of echo-producing features. The brightness of the image at each point is related to the strength or amplitude of the echo, giving rise to the term B-mode (brightness mode).

Measurements of muscle thickness were performed on the dominant side after 20 minutes rest in a supine position. To locate the measurement sites of the quadriceps muscles, an anthropometric tape measure was placed along the length of the thigh from the superior tip of the patella to the anterior superior iliac spine. Using the superior pole of the patella as the reference point, a mark was made at 50% of this distance. A second mark was then made on the vastus lateralis at 10% of the thigh circumference in the lateral direction from the original mark. Measurements were made at this point. These locations were based on data from Kawakami, Muraoka, Kubo, Suzuki, and Fukunaga (2000).

With the participant lying supine, a strap was placed around both feet to prevent hip external rotation. Ultrasound measurements (LS128 CEXT-IZ by Telemed, Lithuania) were made by placing linear transducer over the point marked with pen. The depth of the image was adjusted until the femur was visible in the centre of the screen, and the gain was adjusted until muscle boundaries were also visible on screen. Three images were taken of each muscle and saved in a de-identified format for subsequent analysis (Figure 2.2). Sufficient ultrasound gel was used to minimise muscle compression with the transducer head.

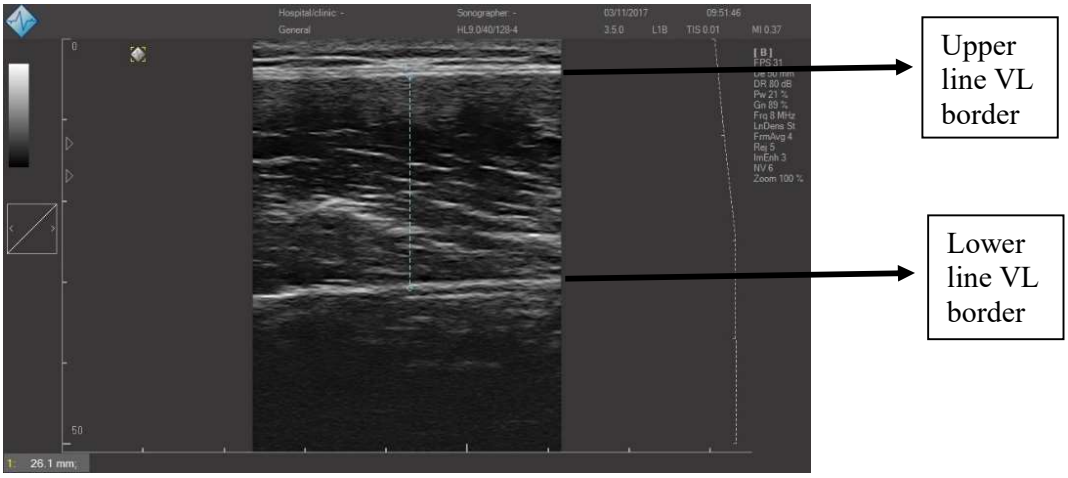

Figure 2.2 Image from Telemed ultrasound

MRI: A whole-body multiple-slice MRI scan was performed to quantify total individual lean mass and right anterior thigh volume. Each volunteer underwent whole body fat and water MR imaging with a modified 2 point Dixon fat and water sequence on a MR750w wide bore 3 T MR platform (GE Healthcare) using the integrated quadrature body coil. MR images were acquired with the volunteers supine and arms by their sides. The pulse sequence was a 3D dual echo spoiled gradient echo sequence within and opposed phase echo times of 1·15 ms and 2·3 ms, respectively. The repetition time was 3·7 ms and the flip angle was 10 ° with an acquired resolution of 2·6 x 4·3 x 3.0 mm^3 reconstructed to 2·0 x 2·0 x 3·0 mm^3 The image protocol was applied repeatedly, starting from the head, with a 30 mm image stack overlap until whole body coverage was achieved. In the abdominal region expiratory breath hold acquisition was used to minimize respiratory artefacts. For post processing, all the images scanned were analysed by using segmentation software by AMRA™ (Advanced MR Analytics AB, Linkoping, Sweden). AMRA is an international digital health company and the first in the world to transform images from a rapid, 6-minute whole body MRI scan into precise, 3D-volumetric fat and muscle measurements (Karlsson et al., 2015).

2.2.8 Statistical analysis

Bivariate correlations were used to compare muscle thickness (BodyMetrix and Telemed), lean mass and right anterior thigh volume, measured by MRI, between devices. Bland Altman plots were used to compare muscle thickness measures between the two ultrasound devices. Data are reported as mean ± standard deviation (SD) and statistical significance was set a priori at $p \leq 0.05$. Statistical Package for the Social Sciences (SPSS) was used for all statistical analyses.

2.3 Results

2.3.1 Study A

2.3.2 Participants

Five female (18-55 years) and eight male (28-61 years) participants were recruited to take part in this study.

2.3.3 Baseline Characteristics (Study A)

Table 2-1 Baseline participant characteristics.

	(n = 13)
Age (y)	35.2 ± 12.6
Height (cm)	174 ± 7
Weight (kg)	75.4 ± 7.05
BMI (kg m^{-2})	24.2 ± 3
Data are mean ± SD	

Baseline descriptive characteristics of the participants are presented in Table 2-1.

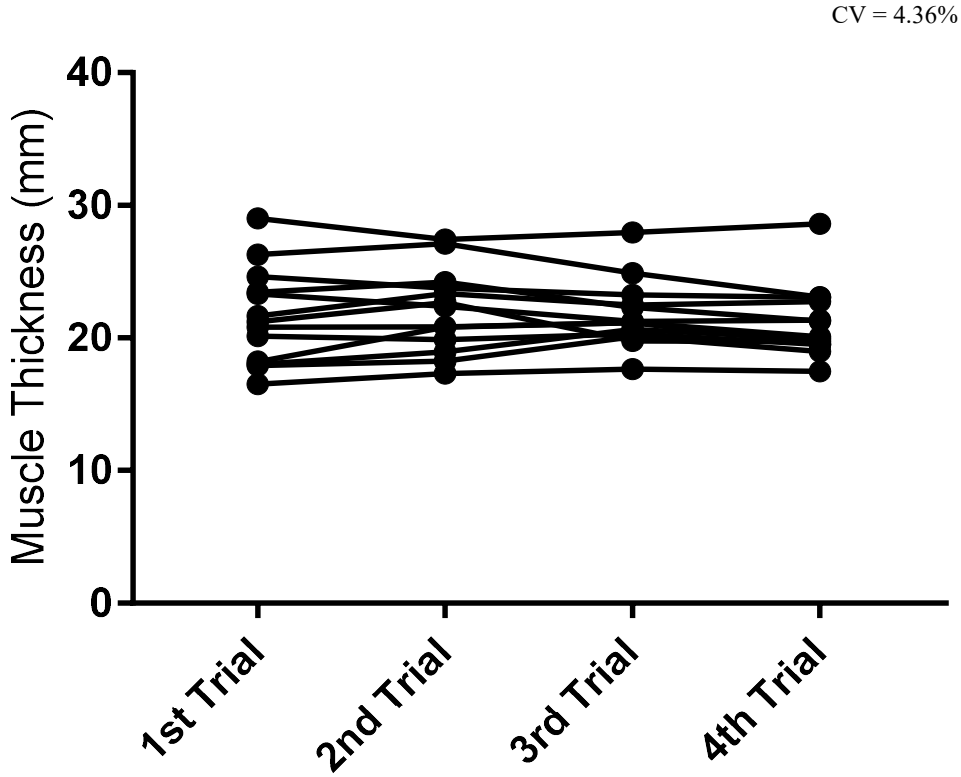

Figure 2.3 Vastus lateralis muscle thickness on 4 consecutive days for all participants.

The data are displayed in Figure 2.3. It can be seen that when vastus lateralis muscle thickness was measured over 4 consecutive days with the BodyMetrix BX2000 a CV of 4.36% was found.

2.3.4 Study B

2.3.5 Participants

We recruited 20 men (age 27 ± 6years, height 178cm ± 8.64, weight 78.83kg ± 11.31, and BMI 24.83 kg m^{-2} ± 3.4) were recruited in Glasgow, United Kingdom from March 2016 to August 2017.

2.3.6 Baseline Characteristics (Study B)

Table 2-2 Baseline participant characteristics.

	Male (n = 20)
Age (y)	26 ± 6
Height (cm)	177 ± 8.3
Weight (kg)	78.4 ± 12.9
BMI (kg m^{-2})	25.1 ± 3.7
Data are mean ± SD	

Baseline descriptive characteristics of the participants are presented in Table 2-2.

2.3.7 Correlations

Table 2-3 Correlations of muscle thickness (BodyMetrix and Telemed) with lean mass and muscle volume

		BodyMetrix	Telemed	Lean mass	Muscle volume
Body Metrix	Pearson Correlation Coefficient	-	.962**	.487*	.738**
Telemed	Pearson Correlation Coefficient	.962**	-	.453*	.697**

**. Correlation is significant at p < 0.01 level (2-tailed).
*. Correlation is significant at p < 0.05 level (2-tailed).

As shown in Table 2-3 and Figure 2.4, there was a positive relationship between the BodyMetrix and Telemed measures of muscle thickness. Furthermore, there were positive relationships between both BodyMetrix and Telemed muscle thickness measurements and muscle volume (Figure 2.6 & 2.8) and lean mass (Figure 2.5 & 2.7), although these associations were weaker.

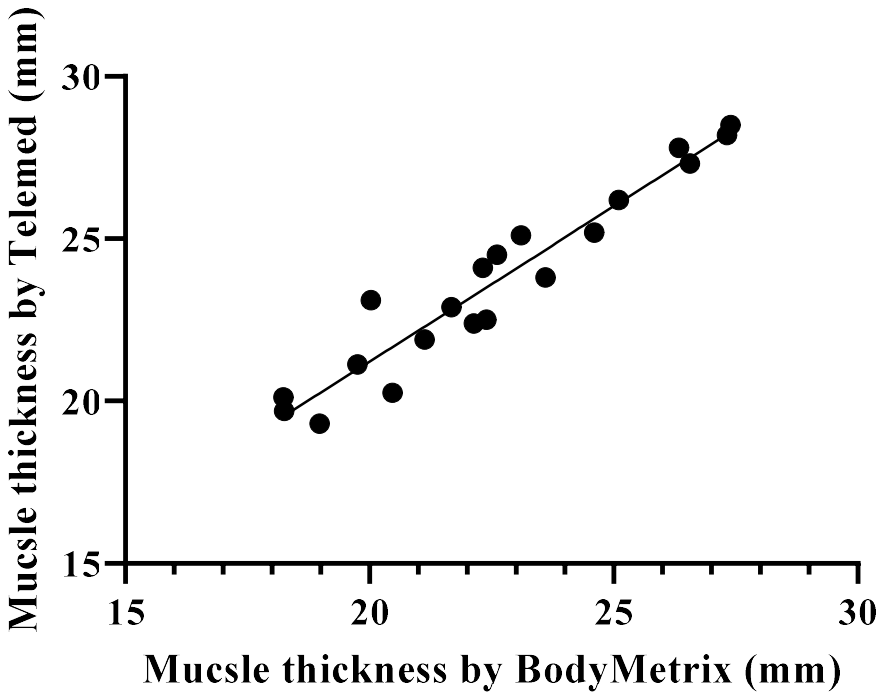

Figure 2.4 Correlation between measures of muscle thickness, acquired via BodyMetrix and Telemed ultrasound devices

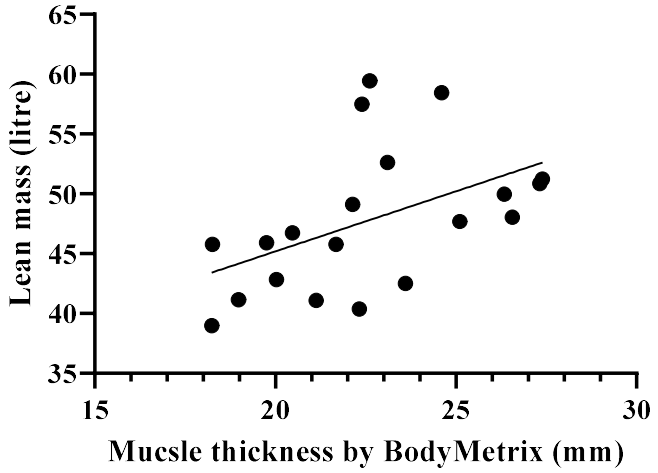

Figure 2.5 **Correlation between muscle thickness, acquired via BodyMetrix, and lean mass**

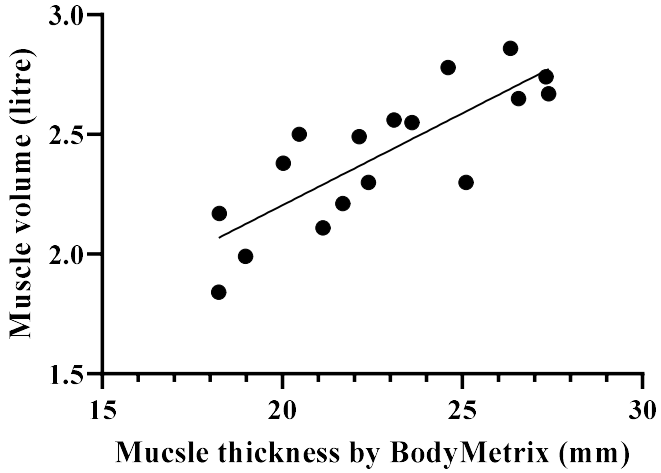

Figure 2.6 **Correlation between muscle thickness, acquired via BodyMetrix, and muscle volume**

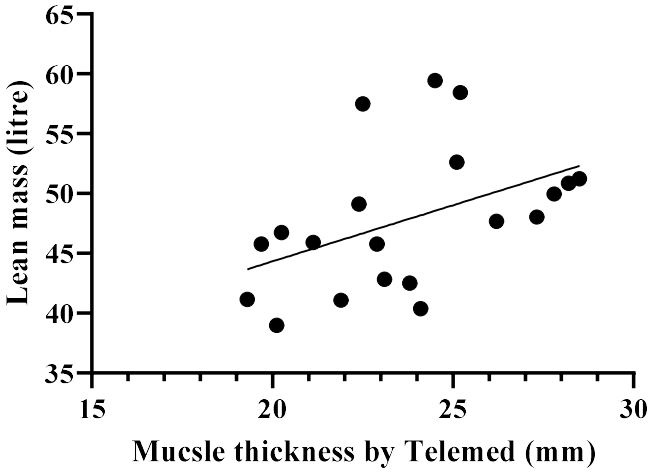

Figure 2.7 **Correlation between muscle thickness, acquired via Telemed, and lean mass**

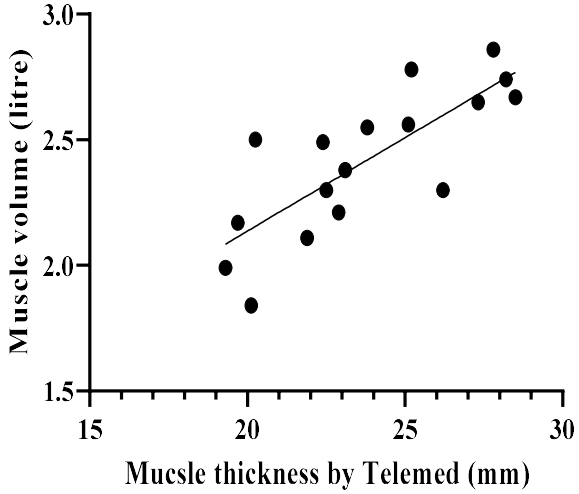

Figure 2.8 **Correlation between muscle thickness, acquired via Telemed, and muscle volume**

2.3.8 Bland-Altman Plots

As shown in Figure 2.9 the mean difference between ultrasound devices in the measurement of vastus lateralis muscle thickness was 1.10 ± 1.96mm (mean difference and limits of agreement). There was no obvious variance in the difference across the muscle thickness measurement range. A one-sample t-test was run to determine whether the difference in muscle thickness between the devices was different from 0, and a significant difference was noted ($p < 0.01$).

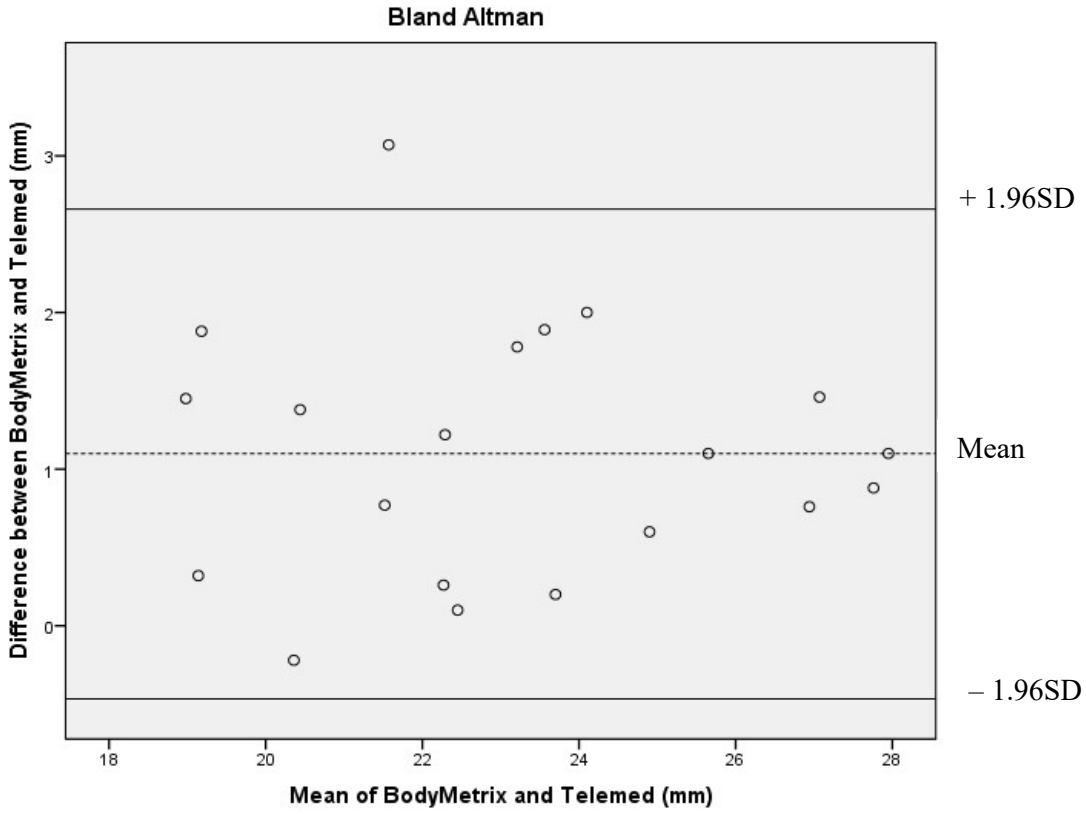

Figure 2.9 Bland Altman plots comparing BodyMetrix and Telemed measurements of VL muscle thickness. The mean difference between ultrasound and Telemed measurements are provided, and the 95% confidence intervals.

2.4 Discussion

The aims of this chapter were: i) to determine the repeatability of the BodyMetrix ultrasound in the measurement of skeletal muscle thickness and ii) to compare it with B-mode (Telemed) ultrasound measures of muscle thickness and MRI measures of right anterior thigh muscle volume and total body lean mass. The present study found a CV of 4.6% for repeated measurements of vastus lateralis muscle thickness using the BodyMetrix ultrasound device. Furthermore, we found positive correlations and good agreement between the A and B mode ultrasound devices, although the bodymetrix did underestimate muscle thickness by 1.1mm, and also positive correlations of muscle thickness (both A and B mode devices) with MRI measures of thigh muscle volume and total lean mass. Together this indicates that the BodyMetrix A mode ultrasound device is a repeatable and valid measure of muscle size.

The hypotheses of the current study were, therefore, confirmed. Whilst this is the first study, to our knowledge, to investigate the repeatability and the validity of the BodyMetrix ultrasound device other studies have investigated this using more traditional B-mode ultrasound devices. Indeed, a previous study compared muscle thickness, measured by B-mode ultrasound, and to vastus lateralis muscle cross-sectional area (measured by CT and MRI) and muscle volume (Franchi et al., 2018). As in the current study positive correlations were found between muscle thickness and both cross sectional area ($r=0.82$, $p<0.001$), and muscle volume ($r=0.76$, $p<0.001$). Similar findings were reported by Takai et al. (Takai et al., 2013) in healthy Japanese middle-aged and older people. In this study muscle thickness at four sites of the lower limb and the bone-free lean tissue mass of the right leg were determined using B-mode ultrasound and dual-energy x-ray absorptiometry (DEXA). The data demonstrated that B-mode ultrasound muscle thickness measurements have a high potential for estimating leg skeletal muscle mass in healthy Japanese middle-aged and older, as strong positive correlations ($r=0.86$, $p<0.001$) were observed between ultrasound and DEXA derived measures of muscle mass.

On top of this Miyatani, Kanehisa, Ito, Kawakami, & Eukunaga, (2004) compared muscle thickness, measured with B-mode ultrasound, at multiple sites with muscle volume, measured with MRI, at the same site. The authors found that ultrasound derived muscle thickness measures were a good predictor (accounting for 42-70% of the variability) of muscle volume. In a subsequent study, by the same group, Miyatani et al. (Miyatani, Kanehisa, Kuno, Nishijima, & Fukunaga, 2002) recruited 46 men aged from 20 to 70 years

who were randomly assigned to either a validation or a cross-validation group. In the multiple regression equation, B-mode ultrasound measures of muscle thickness explained 75% of the variation in the muscle volume, measured by MRI, and the present results indicate that B-mode ultrasound measurements at mid-thigh are useful for estimating the muscle volume of knee extensors.

Furthermore, Abe et al (Abe, Loenneke, & Thiebaud, 2016) have compared B–mode ultrasound measures of muscle thickness (at 9 sites) before, during and after 20 days bed rest and compared these to muscle cross-sectional area (CSA), measured with MRI, at the same sites. Muscle thickness of the anterior thigh was positively correlated with muscle CSA ($r=0.91$) measured at the same site. Along with the current work, therefore, ultrasound (both A and B mode) are valid measures of muscle size. This is of benefit to the field as such devices are considerably cheaper than DEXA and MRI measures of muscle size.

On top of measures of muscle mass, other work has compared muscle thickness measures to whole-body measures of lean tissue mass (Takai et al., 2013). Muscle thickness at nine sites of the body was determined using B-mode ultrasound and dual-energy x-ray (DEXA) was used to measure lean tissue mass. The estimated fat free mass (FFM) (44.4 ± 9.0 kg) did not significantly differ from that of the DEXA-based FFM (44.4 ± 9.2 kg), without systematic error. From this data it was concluded that B-mode ultrasound muscle thickness measurement is useful to predict FFM in the elderly, and its accuracy is improved by using the product of muscle thickness and limb length as an independent variable. We have extended this work to show that muscle thickness measured at a single point (vastus lateralis) is also correlated with whole body lean mass, although as expected the correlations were not as strong as they were with muscle volume.

In conclusion this chapter has found that A mode ultrasound is a repeatable measure of muscle thickness and that both A and B mode ultrasound provide valid measures of muscle mass, as compared to the gold standard MRI. These measurements were all made basally with no intervention applied to the participants and whether ultrasound measures of muscle thickness are able to detect exercise training induced changes in muscle mass remains to be established.

CHAPTER 3 – VALIDITY OF ULTRASOUND DEVICES TO MEASURE CHANGES IN MUSCLE SIZE WITH RESISTANCE EXERCISE TRAINING

3.1 Introduction

As discussed previously, skeletal muscle mass has an important role in health, and resistance exercise training is the most effective method to increase muscle mass and strength (A. R. Hong, Hong, & Shin, 2014). Indeed, research has shown that resistance exercise training can increase strength, muscle size, fat-free mass, connective tissue thickness, decrease body fat, reduce blood pressure and improve insulin sensitivity and VO_{2max} (Croymans et al., 2013; Ozaki, Loenneke, Thiebaud, & Abe, 2013). Measuring the increases in muscle mass after a period of resistance exercise training can be challenging, as many of the methods are expensive and complicated (such as the gold standard MRI). In Chapter 2, it was demonstrated that the BodyMetrix BX2000 A-mode ultrasound device was repeatable and valid (as was the TELEMED B-mode ultrasound) when looking at cross-sectional baseline measures of muscle size. However, it remains to be established whether it is a valid method in being able to measure the small changes in muscle mass that occur with an anabolic stimuli, such as resistance exercise training.

During the course of the current thesis studies being carried out a similar research study was published. In this study (Franchi et al., 2018) it was demonstrated that % changes in vastus lateralis muscle thickness, measured by conventional B-mode ultrasound, in response to 12 weeks of resistance exercise training were positively correlated with % changes in vastus lateralis cross sectional area (r=0.69) but not muscle volume (r=0.33), both measured by MRI. This is in spite of positive correlations between muscle thickness and both cross sectional area and muscle volume at baseline. This latter data agrees with the findings of chapter 2 that ultrasound is a valid measure of muscle mass at a single time point but indicates that it may not be a valid measure of the resistance exercise induced changes in muscle mass. Whether similar findings are observed with the more accessible A-mode ultrasound device also remains to be established.

The aims of this chapter, therefore, were to determine if the A-mode Ultrasound BodyMetrix BX2000 is able to detect changes in muscle thickness in response to resistance exercise training (Part A) and ii) to determine the validity of the A-mode Ultrasound BodyMetrix

BX2000 device and B-mode ultrasound, compared to MRI, in detecting exercise induced increases in muscle size (Part B).

Hypotheses: Study A – The BodyMetrix (BX2000) ultrasound can detect increases in muscle thickness in response to resistance training.

Study B – Both A- and B-mode ultrasound measures of muscle thickness are valid methods to quantify increases in muscle size with resistance training.

3.2 Methods

3.2.1 Study A

3.2.2 Study protocol:

Exclusion criteria included; current smoking, physician diagnosed diabetes, uncontrolled hypertension (>160/90 mm Hg on anti-hypertensive medication), previous history of established coronary heart disease (e.g. myocardial infarction, coronary artery bypass graft surgery, coronary angioplasty), body mass index >35kg.m^2, family history of early cardiac death (<40 years) and lactose intolerance. All participants were in good health at the time of testing and did not participate in any resistance exercise or take any dietary supplements. The study was approved by the Ethics Committee of the College of Medical Veterinary and Life Sciences at the University of Glasgow, and adhered to the declaration of Helsinki. All tests were carried out in the Human Physiology Labs in the West Medical Building. On the first study visit participants visited the laboratory, were introduced to the research group, completed a health screen questionnaire and had resting blood pressure, height and weight recorded. Before and two days after an 8-week resistance exercise training programme participants attended the laboratory after an overnight fast and having avoided exercise for 2 days. In each of these visits' height, body weight, body composition, muscle strength, vastus lateralis muscle thickness and blood pressure were measured.

3.2.3 Resistance exercise training:

Participants attended the laboratory 3 times a week for an 8-week period. After training and familiarisation to the exercises the 1 repetition maximum (1RM) for the following exercises was determined: leg extension, leg flexion, lateral pull down, chest press, biceps and triceps curls. In each training session participants performed one set of 9 repetitions at 85% of their 1RM. This built up over the first six sessions; session 1:60%1RM, session 2:65%1RM, session 3:70%1RM, session 4:75%1RM, session 5:80%1RM, session 6:85%1RM. All sessions were supervised and attendance was 100%.

3.2.4 Measurements

Vastus lateralis muscle thickness:

Measurements were performed as in Chapter 2 using the BodyMetrix BX2000 device.

Body composition measurements:

Height and body mass were recorded using standard procedures, and fat free mass was assessed by BOD POD (COSMED) – an air displacement plethysmograph.

One-repetition maximum measurements:

For each of the aforementioned exercises carried out during training, 1RM was measured at 0, 4, and 8 weeks. After a warm up with a few light repetitions, the weight applied for each exercise was progressively increased, with 2 minutes rest between contractions, until the participant could not perform a full single repetition of the exercise.

3.2.5 Statistical analyses:

Muscle thickness and 1RM were compared (baseline vs. post-training) via paired t-tests. Data are reported as mean ± standard deviation (SD) unless otherwise stated and statistical significance was set *a priori* at $p \leq 0.05$. GraphPad Prism software (Version 5) was used for all statistical analyses.

3.2.6 Study B

3.2.7 Study protocol

Baseline measurements:

Participants were free from injury, metabolic, cardiovascular disease, or coagulopathic conditions, normotensive (blood pressure <150/90mmHg) and did not participate in any moderate to high intensity aerobic exercise or resistance exercise. The study was approved by the Ethics Committee of the College of Medical Veterinary and Life Sciences at the University of Glasgow, and adhered to the declaration of Helsinki. All tests were carried out in the Human Physiology Labs in the West Medical Building. On the first study visit participants visited the laboratory, were introduced to the research group, completed a health screen questionnaire and had blood pressure, height and weight recorded. Before a 12 week resistance exercise training programme participants attended the laboratory having avoided exercise for 2 days. In each of these visits 1RM, vastus lateralis muscle thickness, total lean body mass and right thigh muscle volume were measured.

Resistance exercise training:

Participants completed 12 weeks of resistance exercise training with 2 sessions per week. Each exercise session involved participants carrying out 1 set to failure at 80% of 1RM of the following exercises: bench press, leg extension, leg flexion, seated row, calf press, latissimus pulldown, triceps curl and biceps curl. For each of the aforementioned exercises 1RM was measured at 0, 4, 8 and 12 weeks with the training load adjusted accordingly. All sessions were supervised and attendance was 100%.

Post-training measurements:

Three days after the final exercise session one repetition maximum (1RM), vastus lateralis muscle thickness, total body lean mass and right thigh muscle volumes were measured.

3.2.8 Measurements

Vastus lateralis muscle thickness:

Measurements were performed as in Chapter 2 using the BodyMetrix BX2000 device and the Telemed B-mode ultrasound device.

Lean mass and right anterior thigh volume (MRI):

Measurements were performed as in Chapter 2

3.2.9 Statistical analyses:

Muscle thickness, right anterior thigh muscle volume and total body lean mass were compared (baseline vs. post-training) via paired t-tests. Bivariate correlations were used to compare changes in muscle thickness (BodyMetrix and Telemed) measurements between devices and to lean mass and right anterior thigh volume, measured by MRI. Bland Altman plots were used to compare muscle thickness measures between the two ultrasound devices. Data are reported as mean ± standard deviation (SD) unless otherwise stated and statistical significance was set *a priori* at $p \leq 0.05$. GraphPad Prism software (Version 5) was used for all statistical analyses.

3.4 Results

3.4.1 Study A

3.4.2 Participants:

Twelve male (age 32 ± 16 years, height 179 ± 6 cm, weight 73.4 ± 10.6 kg, BMI 23.0 ± 3.9kg.m²) and nine female (age 40 ± 20 years, height (cm) 168 ± 5 weight (kg) 62.4 ± 6.9, BMI (kg.m²) 22.2 ± 1.6) participants were recruited to take part in this study.

Baseline characteristics and the repeated measurements upon completion of the resistance exercise training are shown in Table 3-1.

Table 3-1 Baseline characteristics of participants

	Pre	Post
Age (y)	36 ± 18	-
Height (cm)	174 ± 8	-
Body mass(kg)	68.7 ± 10.0	69.2 ± 10.3
Systolic blood pressure (mm Hg)	130 ± 14	124 ± 12
Diastolic Blood pressure (mm Hg)	75 ± 10	72 ± 9
BMI (kg m^{-2})	22.6 ± 3.1	22.8 ± 3.2
Fat free mass (kg)	55.7 ± 10.2	56.0 ± 10.1

Data are mean ± SD (n=21)

As shown in Table 3-2, there were increases ($p < 0.05$) in 1RM for all the exercises with 8 weeks of resistance training exercise. For the sum of the individual 1RMs, there was a 26 ± 7% increase after 8 weeks of resistance training exercise. For vastus lateralis muscle thickness, there was an increase ($p < 0.05$) of 6.2 ± 5.4% after 8 weeks of resistance exercise training (Table 3.2).

Table 3-2 Vastus Lateralis muscle thickness and participants' 1RM before and after 8 weeks of resistance exercise training

	Pre	Post
Muscle thickness (mm)	18.9 ± 3.3	19.8 ± 3.2*
Leg extension (kg)	54 ± 22.3	72.8 ± 22.9*
Leg flexion (kg)	46.7 ± 17.8	66.5 ± 20.6*
Latt pulldown (kg)	46.9 ± 17.1	60.9 ± 18.8*
Chest press (kg)	44.1 ± 20.7	59.2 ± 22.5*
Seated row (kg)	53.4 ± 17.6	71.1 ± 19.4*
Biceps curl (kg)	41.7 ± 14.6	52.9 ± 19.1*
Triceps curl (kg)	23.8 ±7.3	28.3 ± 9.3*
Sum of individual 1RMs (kg)	310.4 ± 111.2	412.9 ± 124.7*

Data are mean ± SD (n=21)

*denotes a significant difference from baseline $p < 0.05$

3.4.3 Study B

3.4.4 Participants:

We recruited 20 men residing in the Glasgow area. Inclusion criteria were aged between 18-45 years and BMI<35kg/m².

Baseline characteristics and the repeated measurements upon completion of the resistance exercise training are shown in Table 3-4.

Table 3-3 Participant characteristics before and after 12 weeks of resistance training

	Pre	Post
Age (y)	26 ± 6	-
Height (cm)	176 ± 8	-
Body mass (kg)	78.4 ± 13	78.9 ± 8.3
BMI (kg.m²)	25.1 ± 3.8	25.2 ± 3.9

Data are mean ± SD (n=20)

As shown in table 3-4, 12 weeks of resistance exercise training resulted in increases ($p<0.05$) in vastus lateralis muscle thickness, total lean body mass and right thigh muscle volume. Vastus lateralis muscle thickness was increased by 6.8 ± 3.3% (BodyMetrix) and 6.2 ± 2.9 % (Telemed), and total lean body mass increased by 8.4 ± 8.8% and right thigh muscle volume by 2.5 ± 3.2%.

Table 3-4 Measures of vastus lateralis muscle thickness, lean mass and muscle volume at baseline and after 12 weeks of resistance training

	Pre	Post	Percentage change
BodyMetrix ultrasound (mm)	22.6 ± 2.9	24.26 ± 3*	6.85 ± 3.3%
Telemed ultrasound (mm)	23.7 ± 2.9	25.24 ± 2.8*	6.17 ± 2.9%
Lean mass (L)	47.8 ± 5.98	52.87 ± 9.9*	8.43 ± 8.7%
Muscle volume(L)	2.39 ± 0.29	2.45 ± 0.27*	2.52 ± 3.1%

Data are mean ± SD (n=20)

*denotes a significant difference from baseline< 0.05

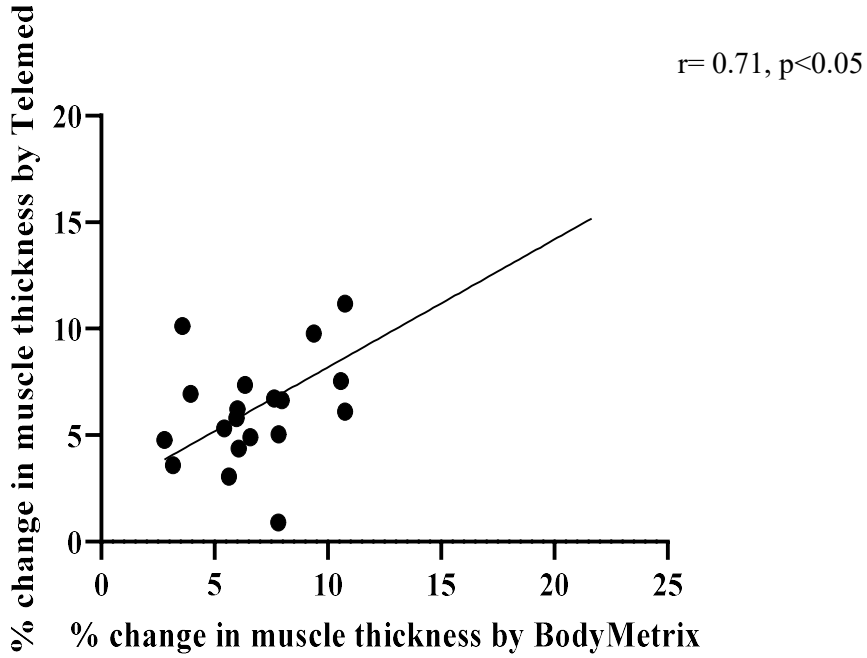

Figure 3.1 **Correlation between percentage (%) change in VL muscle thickness acquired via BodyMetrix and Telemed Ultrasound devices after 12 weeks of resistance training**

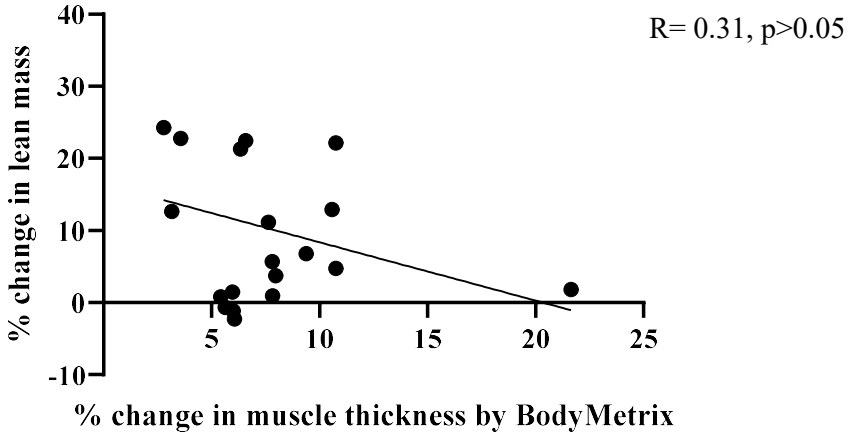

Figure 3.2 **Correlation between percentage (%) change in VL muscle thickness acquired via BodyMetrix and lean mass after 12 weeks of resistance training**

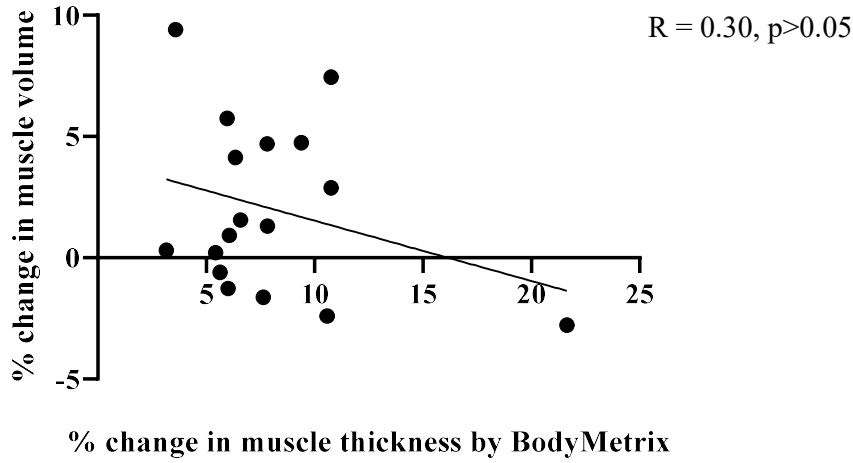

Figure 3.3 **Correlations between percentage (%) change in VL muscle thickness acquired via BodyMetrix and muscle volume after 12 weeks of resistance training**

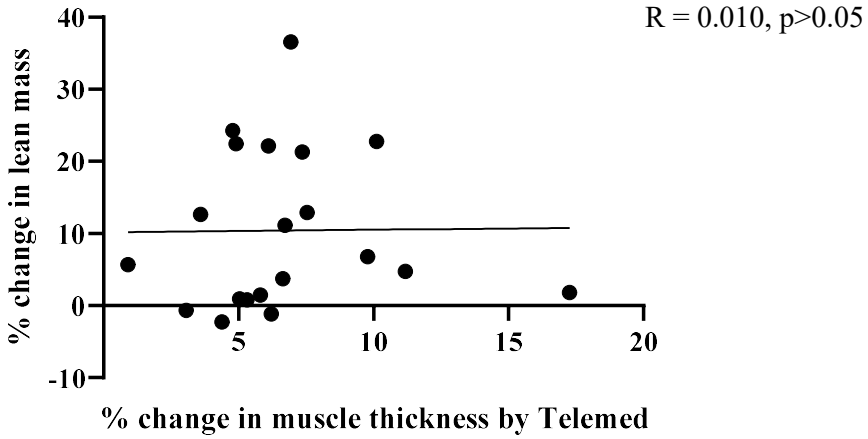

Figure 3.4 **Correlations between percentage (%) change in VL muscle thickness acquired via Telemed ultrasound and lean mass after 12 weeks of resistance training**

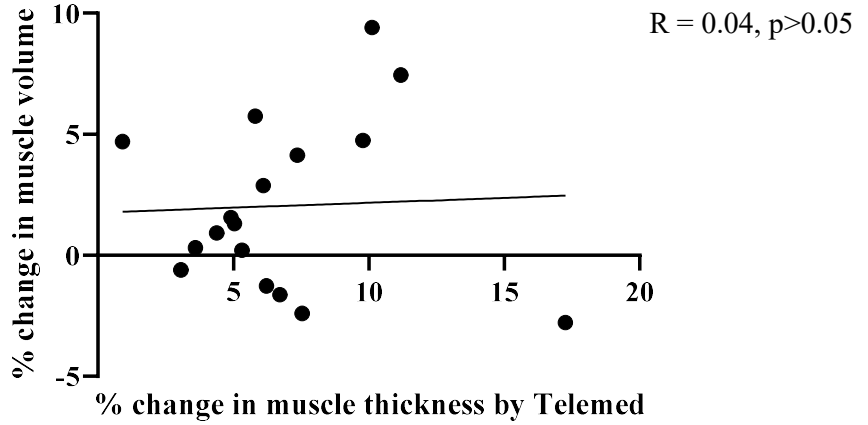

Figure 3.5 **Correlations between percentage (%) change in VL muscle thickness acquired via Telemed ultrasound and muscle volume after 12 weeks of resistance training**

As seen in figure 3.1, there is a positive correlation (r = 0.71) between percentage change in vastus lateralis muscle thickness between BodyMetrix ultrasound and Telemed ultrasound measurements. However, no correlation was observed between BodyMetrix muscle thickness and lean mass and muscle volume (r = 0.31 & r = 0.30 respectively). Similarly, no correlation was seen between Telemed muscle thickness and lean mass and muscle volume (r = 0.01 & r = 0.04 respectively).

3.4.5 Bland-Altman Plot

As shown in Figure 3.6 the mean difference between ultrasound devices in the measurement of vastus lateralis muscle thickness was 1.25 ± 1.96mm (mean difference and limits of agreement). There was no obvious variance in the difference across the muscle thickness measurement range. A one-sample t-test was run to determine differences between the two devices differed from 0, with no difference noted ($p = 0.40$).

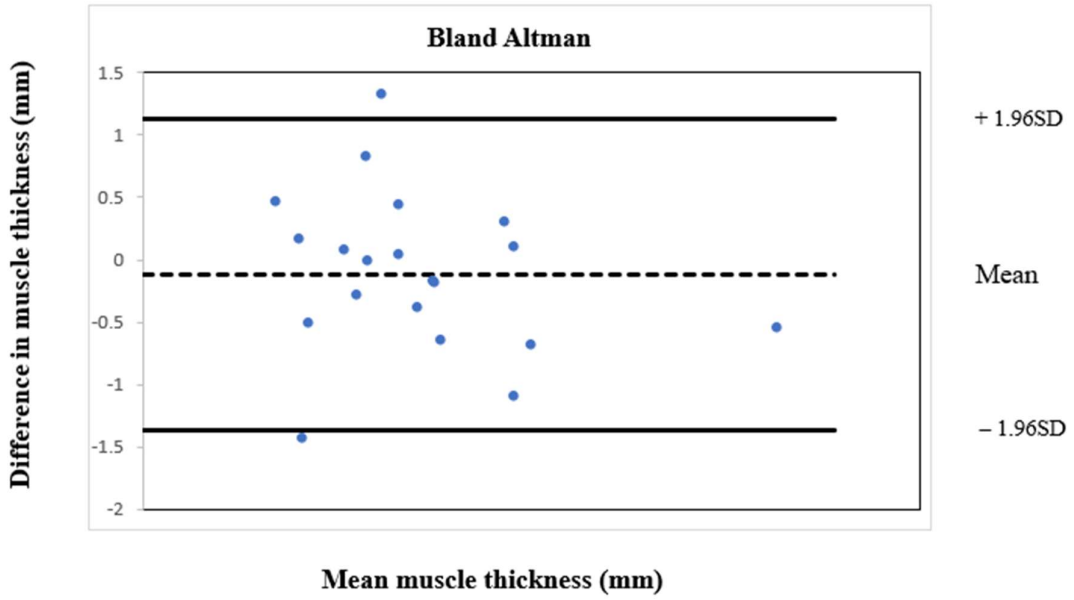

Figure 3.6 Bland Altman plots comparing BodyMetrix and Telemed measurements of VL muscle thickness. The mean difference between BodyMetrix ultrasound and Telemed measurements are provided, and the 95% confidence intervals.

3.5 Discussion

In agreement with our hypothesis, the current chapter (part A) has shown that significant increases in muscle thickness, with a resistance exercise training program, can be detected using an A mode BodyMetrix ultrasound device. Indeed, vastus lateralis muscle thickness increased by 6.2 ± 5.4% alongside a 26 ± 7.3% increase in 1RM after 8 weeks of resistance exercise training. This is the first study investigating the effects of resistance training on muscle thickness vastus lateralis using A mode BodyMetrix ultrasound. However, it was also shown that both A and B mode measures of ultrasound muscle thickness were not valid measures of the resistance exercise induced changes in muscle volume or lean mass, in opposition to our hypotheses.

The use of ultrasound to detect resistance exercise induced changes in muscle thickness has been investigated previously, but primarily using B-mode ultrasound. For example, Schoenfeld et al (2014) evaluated muscle thickness using B mode ultrasound imaging comparing low, moderate, and high-volume resistance training protocols in resistance trained men. Thirty four healthy resistance trained men were randomly assigned to one of three experimental groups: a low-volume group performing one set per exercise per training session (n = 11), a moderate-volume group performing three sets per exercise per training session (n = 12), or a high-volume group performing five sets per exercise per training session (n = 11). Training for all routines consisted of three weekly sessions performed on non-consecutive days for 8 weeks. Results showed all groups increased muscle thickness in most of the measured sites (elbow flexors, mid-thigh, and lateral thigh) from baseline to post intervention. For vastus lateralis thickness specifically, the low volume group had increases of 2.9% ± 1.9, the moderate volume group increases of 4.6 ± 2.3% and the high-volume group increases of 7.2 ± 3%. Another study (Starkey et al., 1996) has shown one set of high-intensity resistance training was as effective as three sets for muscle thickness in previously untrained adults and the muscle thickness was measured by B-mode ultrasound. A further study investigated the effects of 15-week resistance exercise training program on muscle thickness in several parts of the quadriceps femoris using B-mode ultrasound and results have shown an increase of muscle thickness at all muscles and sites except the vastus medialis (Santos, Valamatos, Mil-Homens, & Armada-da-Silva, 2018) .

To my knowledge there has only been one previous study which as used A-mode ultrasound to detect changes in muscle thickness with resistance exercise training Evangelista et al

(2019) measured vastus lateralis muscle thickness using A-mode ultrasound (BodyMetrix BX2000) before and after 8 weeks of resistance exercise training. Participants performed 4 sets of 8–12 repetition maximum (RM) with a 90 second rest between sets of bench press, elbow extension, seated rows, biceps curl, knee extension, and knee flexion. Training was twice a week for 8 weeks and an increase in vastus lateralis muscle thickness of 7.3% were found. This is similar to what we have found in the current study.

Our data regarding the validity of ultrasound measures of muscle thickness (part B) are similar to those of Franchi et al (2018). In their study after 12 weeks of resistance exercise training vastus lateralis muscle thickness, measured using B-mode ultrasound, increased by 7.5 ± 6.1%, with increases in cross-sectional area mid of 5.2 ±5 % and muscle volume of 5.0 ± 6.9%, both measured by MRI, also noted. However, whilst positive correlations between these measures of muscle size were observed at baseline the change of percentage in muscle thickness with training was correlated with % change in cross-sectional area mid (r=0.69) but not the change of percentage in muscle volume (r= 0.33). This may be due to observations that hypertrophy does not occur homogenously both within and between muscle groups. For example, Narici et al. (1989) demonstrated in his study that relative increases in cross sectional area of quadriceps femoris muscle were greater in the proximal than in the distal regions after knee extension training. Two possible reasons for these regional differences in muscle hypertrophy may be due to differences in muscle activation during exercise and differences in contractile protein synthesis. Furthermore, Wakahara et al. (2011) investigated regional differences in muscle hypertrophy in response to 12 weeks resistance training of the elbow extensors in 12 subjects. This study has shown, similarly to the study of Narici, that increases in muscle cross sectional area after the training intervention were smaller in distal regions compared to the middle and proximal regions. This may explain why ultrasound, where muscle thickness was measured at a single point, is a valid measure of muscle size basally but in response to resistance exercise this regional hypertrophy is picked up by the MRI measures of muscle volume (whole muscle measure) but not by the ultrasound measure of muscle thickness (single point).

These findings are similar to those in the current thesis. Indeed, in the current chapter the data demonstrates that whilst muscle thickness, using both A and B mode ultrasound, increases after resistance exercise training these increases do not correlate with MRI measures of right anterior thigh muscle volume or whole body lean mass. This means that whilst ultrasound measured muscle thickness can be a valid measure of muscle size cross-

sectionally at baseline (as shown in chapter 2 and the study of Franchi et al (Franchi et al., 2018)) it is not a valid technique to measure changes in muscle size with resistance exercise training (current chapter and Franchi study (Franchi et al., 2018)).

Conclusion

The main conclusion of the current chapter is that whilst ultrasound measures of muscle thickness are increase with resistance exercise training caution must be employed if considering using this technique to monitor changes in muscle size with exercise training.

CHAPTER 4 – THE EFFECT OF SHORT DURATION RESISTANCE TRAINING ON INSULIN SENSITIVITY AND MUSCLE ADAPTATIONS IN OVERWEIGHT MEN

The current chapter has been published as follows:
Ismail AS, Alkhayl FFA, Wilson J, Johnston L, Gill JMR, Gray SR. The effect of short-duration resistance training on insulin sensitivity and muscle adaptations in overweight men. *Exp Phsiology* (2019) 104(4):540-545

4.1 Introduction

Skeletal muscle has an often-underappreciated role in health (Wolfe, 2006) with low muscle strength being linked with an increased risk of a range of poor health outcomes, including all-cause, CVD, cancer and respiratory disease mortality (Celis-Morales et al., 2018). Similarly, low muscle strength has been shown to be associated with higher type 2 diabetes incidence, with findings more equivocal for low muscle mass (See Hong et al., 2017; Li et al., 2016). Furthermore, the increased risk of CVD mortality that is seen in people with type 2 diabetes is attenuated in those with high grip strength (Celis-Morales et al., 2018). This suggests that the maintenance of muscle strength/mass is important for metabolic health. This is likely because, as mentioned previously, skeletal muscle is the main site of glucose disposal postprandially (Abdul-Ghani & Defronzo, 2010). Resistance exercise – the most efficacious method to increase muscle strength and mass – has been found to consistently improve insulin sensitivity in people with type 2 diabetes (Umpierre, 2011) and, although there are fewer studies, the available data indicates a similar effect in healthy adults (Conn et al., 2014; Flack et al., 2011). This is alongside the many other health benefits associated with resistance exercise (Winett & Carpinelli, 2001).

It is, therefore, not surprising that the current physical activity recommendations include advice for adults to perform muscle strengthening activities on two days per week (Who, 2010). When recommending resistance exercise training there are many variables to be taken into consideration, including the number of sets, repetitions and load. The American College of Sports Medicine (ACSM) recommend that for novice lifters resistance training 2-3 days per week with 1-3 sets of 8-12 repetitions with a training load of 60-85% one-repetition maximum (1RM) promotes muscular hypertrophy and can maximize strength (Ratamess et

al., 2013). The strength of the evidence in support of these recommendations has, however, been challenged by several researchers (Fisher et al., 2011).

Indeed, it has been demonstrated recently that if exercise is performed to volitional failure then gains in muscle mass, and to a lesser extent strength, are similar regardless of the load at which exercise is performed (Mitchell et al., 2012; Morton et al., 2016). The early time-course of adaptations to such exercise remains to be established. Interestingly it was also found, in one study, that there was little difference in changes in muscle mass & strength comparing one and three sets to failure of each exercise (Mitchell et al., 2012). This may have important public health implications as the time commitment of exercise can be reduced, and it is well established that time is a major barrier to exercise participation (Trost, Owen, Bauman, Sallis, & Brown, 2002), but the exercise remain efficacious. However, it remains to be established if this shorter duration form of exercise can also improve insulin sensitivity.

The aims of the current chapter, therefore, were to investigate the effects of 6 weeks of resistance exercise training, compromised of 1 set of each exercise to voluntary failure, on i) insulin sensitivity and ii) the time-course of adaptations in muscle strength and mass, in overweight men.

Hypotheses: i) Six weeks of resistance training to voluntary failure will enhance insulin sensitivity.

ii) Six weeks of resistance training to voluntary failure will increase muscle strength and mass.

4.2 Materials and methods

4.2.1 Study protocol

All participants had BMI >25 kg.m^2, participated in less than 2h per week of moderate/high intensity aerobic exercise, undertook no resistance training, and were normotensive, free from injury, metabolic or cardiovascular disease. The study was approved by the Ethics Committee of the College of Medical Veterinary and Life Sciences at the University of Glasgow, and adhered to the declaration of Helsinki. During a baseline visit, after an overnight fast, participants' body composition (BOD-POD), vastus lateralis muscle thickness (Telemed: B-mode ultrasound) and knee extensor maximal isometric torque (during a maximal voluntary contraction (MVC)) were measured and an oral glucose tolerance test (OGTT) undertaken. A 7-day food diary was then used to measure habitual dietary intake. Participants' 1RM was then determined for the following exercises: leg press, bench press, leg extension, shoulder press, leg flexion, seated row, calf raise, lat pulldown and biceps curl (M2 machine, Inspire Fitness ®, Corona, CA, USA). Following the baseline assessment, participants began the 6-week resistance training programme. Sessions were carried out on a Monday, Wednesday and Friday with each session lasting approximately 15-20 minutes. Prior to each Friday session, vastus lateralis muscle thickness and knee extensor maximal isometric torque were measured. Three days after the final training session, after an overnight fast, a second OGTT was performed and body composition, vastus lateralis muscle thickness, knee extensor maximal isometric torque measured. Measurements were taken at the same time of the day by the same investigator. The participants were asked to refrain from any other resistance exercise training for the duration of the study and to maintain their usual physical activity and dietary habits.

4.2.2 Resistance exercise training

The resistance training intervention comprised three sessions per week, with each session consisting of one set of each of the aforementioned nine exercises at 80%1RM to volitional failure. Participants 1RM for each exercise were re-measured at week 3 and the load adjusted accordingly.

4.2.3 Procedures

Vastus Lateralis Muscle thickness: Measurements were performed as in Chapter 2 using the B – mode Telemed ultrasound.

*1RM measurements***:** For each of the aforementioned exercises carried out during training 1RM was measured at baseline, 3 week and three days after the last session – as described in chapter 3.

Knee extensor maximal isometric torque and rate of torque development (RTD): Maximal isometric torque of the right knee extensor muscles was measured during an MVC with the participants seated securely with the use of seatbelts and a knee angle of 90°. Participants were asked to contract maximally with contractions repeated ≥3 times with the highest values used for subsequent analysis. Force was recorded throughout the contraction with a load cell (Biometrics, Newport, UK). The rate of torque development (RTD) was calculated from the MVC data. The torque at time instants 0, 50, 100, 200 and 300ms was determined and the RTD for each time interval calculated by subtracting from the torque at each time point from the torque at 0 and dividing by the time interval.

Oral glucose tolerance test: A cannula was inserted into an antecubital vein and a baseline blood sample was collected. Participants then consumed 75g of glucose and further blood samples were collected after 30, 60, 90 and 120 min. Blood samples were analysed for glucose and insulin using a clinically validated analyser.

Body composition: Body fat mass and lean mass were measured via an air-displacement plethysomograph (BOD-POD, Cosmed, Shepperton, UK) according to the manufacturer's guidelines.

Statistical analyses: Time-averaged area-under the curve (AUC) was calculated, using the trapezium rule, for glucose and insulin responses during the OGTT. Glucose and insulin data were also used to estimate insulin sensitivity via the Cederholm index.

$$\text{Cederholm index} = \frac{75000 + (G_0 - G_{120}) \times 180 \times 0.19 \times BM}{120 \times G_{mean} \times \log (I_{mean})}$$

Where BM is body mass (kg), G_0 and G_{120} are plasma glucose concentrations at 0 and 120 min (mmol.L^{-1}), and I_{mean} and G_{mean} are the mean insulin (mU.L^{-1}) and glucose (mmol.L^{-1}) concentrations during the OGTT.

Glucose AUC, insulin AUC, Cederholm Index, body composition and 1RM were compared (baseline vs. post-training) via paired t-tests. Time-course data (weekly vastus lateralis muscle thickness and knee extensor maximal isometric torque) were compared over time via analysis of variance (ANOVA). Where a main effect was observed in the ANOVA weekly values were compared to baseline values via post-hoc Tukey tests. Data are reported as mean ± standard deviation (SD) unless otherwise stated and statistical significance was set *a priori* at $p \leq 0.05$. GraphPad Prism software (Version 5) was used for all statistical analyses.

4.3 Results

4.3.1 Participants

Ten men (age: 36 ± 8years; height 175 ± 9 cm; weight 89 ± 14kg; BMI 29±3 kg.m^2) volunteered to participate in the current study.

The habitual energy intake of participants was 2130 ± 410 kcal/day, comprising 82 ± 11 g/day protein, 260 ± 69 g/day carbohydrate and 86 ± 19 g/day fat. Body fat mass was lower (Baseline: 26 ± 13 kg, post-intervention: 24 ± 13 kg, P<0.05) and lean mass higher (63 ± 8 vs 65 ± 7 kg, P<0.05) post-intervention compared to baseline. The 1RM for all nine exercises was higher (P<0.05) post-intervention compared to baseline measures (Table 4-1). Overall the sum of individual 1RMs was 18.3 ± 4.5% higher after the intervention, when compared with baseline.

Table 4-1 One-repetition maximum for training exercises before and after 6 weeks of resistance exercise training. Data are mean (SD)* denotes a significant difference from baseline values.

	Baseline (kg)	Post-intervention (kg)	Percentage increase (%)
Leg press 1RM	89 ± 18	104 ± 23*	16 ± 5
Leg extension 1RM	72 ± 14	85 ± 13*	19 ± 9
Calf press 1RM	89 ± 24	101 ± 25*	16 ± 8
Leg flexion 1RM	50 ± 14	63 ± 12*	26 ± 13
Chest press 1RM	57 ± 209	69 ± 10*	22 ± 8
Seated row 1RM	65 ± 8	76 ± 7*	17 ± 5
Lat pulldown 1RM	51 ± 6	61 ± 8*	19 ± 9
Biceps curl 1RM	51 ± 5	60± 5*	17 ± 8
Triceps curl 1RM (	26 ± 6	33 ± 6*	28 ± 17
Sum of individual 1RMs	551 ± 76	651 ± 91*	18 ± 4

Data are mean ± SD (n=10)
*denotes a significant difference P<0.05

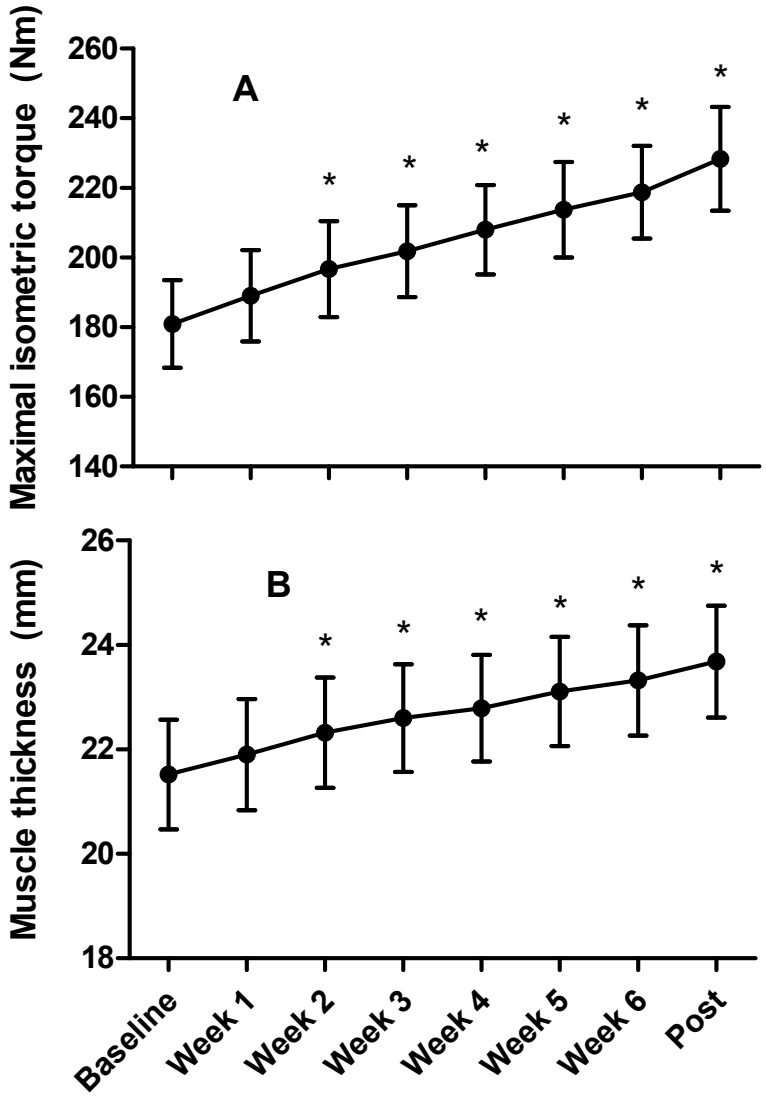

Figure 4.1 **Knee extensor maximal isometric torque (A) and vastus lateralis (B) thickness time-course of adaptations in response to six weeks of resistance exercise training.** Data are presented as mean ± SD * denotes a significant difference from baseline values.

The time-course analysis revealed main effects ($P<0.05$) of time for knee extensor maximal isometric torque and vastus lateralis muscle thickness (Figure 4.1). Knee extensor maximal isometric torque was 26.9 ± 8.3% higher and vastus lateralis muscle thickness 10.3 ± 2.5 % higher after the intervention compared with baseline. Post-hoc analysis revealed that knee extensor maximal isometric torque and vastus lateralis muscle thickness were higher, compared to baseline at weeks 2, 3, 4, 5, 6 and post-intervention.

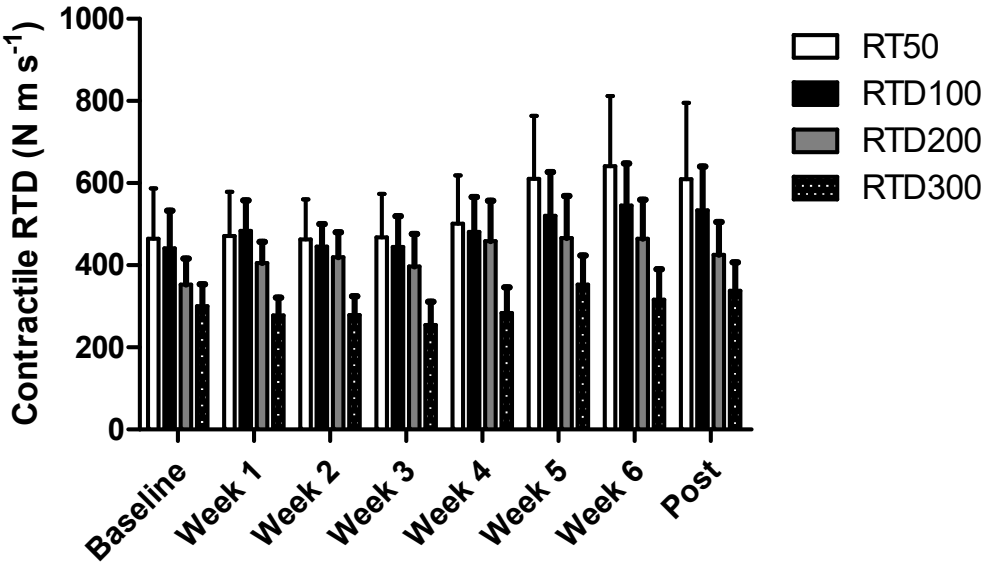

Figure 4.2 Knee extensor RTD time-course of adaptations in response to six weeks of resistance exercise training. Data are presented as mean ±SD.

Main effects of time ($P<0.05$) were seen for RTD50 and 100, but not RTD200 and 300, with post-hoc analysis finding no significant differences between the time points (Figure 4.2).

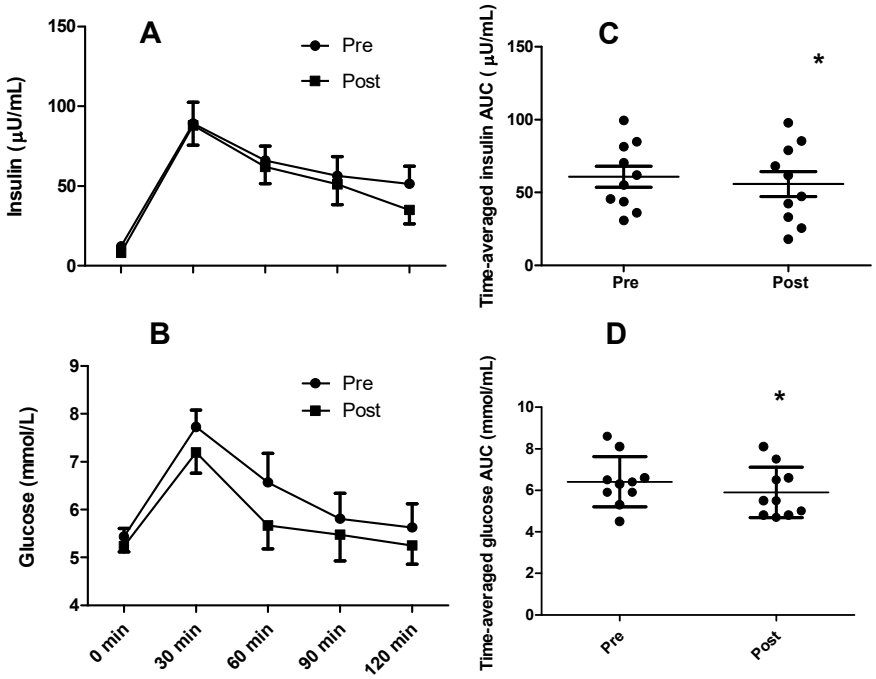

Figure 4.3 Plasma insulin (A) and glucose (B) concentrations and time-averaged insulin (C) and glucose (D) responses during an oral glucose tolerance test, before and after six weeks of resistance exercise training.

Data are presented as mean ±SD * denotes a significant difference from baseline values

After the intervention the time-averaged glucose and insulin AUC were lower (7.4 ± 12.8% and 12.0 ± 17.0% respectively, both $P<0.05$) relative to at baseline (Figure 4.3). At baseline the Cederholm index was 61.6 ± 18.0 $mg.l^2.mmol^{-2}.mU^{-1}.min^{-1}$ and this increased to 71.3 ± 22.9 $mg.l^2.mmol^{-2}.mU^{-1}.min^{-1}$after the intervention ($P<0.05$), an increase of 16.3 ± 18.7%.

4.4 Discussion

The present study has demonstrated that six weeks of resistance exercise, comprising one set to volitional failure of nine exercises – taking 15-20 min per session – undertaken three times per week resulted in a 16% improvement in insulin sensitivity in healthy overweight men. On top of this, increases in muscle strength, size and RTD50 and 100 were also observed. Whilst previous work has shown that single set resistance exercise to failure can increase muscle strength (Mitchell et al., 2012), and the present study is the first study to demonstrate that such simple exercise, with a weekly time commitment of less than one hour, can increase insulin sensitivity in overweight men and is also the first to demonstrate the time course of adaptations in muscle strength and size.

Previous work has demonstrated that resistance exercise can improve insulin sensitivity in people with type 2 diabetes (Umpierre, 2011) and, although there are fewer studies, the available data indicates a similar effect in healthy adults (Conn et al., 2014; Flack et al., 2011). The present study agrees with these findings and has added to the body of evidence in healthy adults by showing that insulin sensitivity increases by ~16%. Importantly, the exercise protocol in present study where participants performed a single set to volitional failure for each exercise, with the sessions lasting 15-20 minutes, involved a much smaller time-commitment than the majority of previous resistance training interventions which generally involved multiple (2-4) sets of exercise for each muscle group (Conn et al., 2014; Flack et al., 2011; Umpierre, 2011). Thus, the present resistance training intervention may be pragmatically more appealing to many.

The present data adds to the evidence base for the health benefits of resistance exercise, which includes a reduction in blood pressure, improvements in blood lipids and an association with lower mortality (Cornelissen, Fagard, Coeckelberghs, & Vanhees, 2011; Stamatakis et al., 2018). Thus, it is clear why the physical activity recommendations include muscle strengthening activities (Who, 2010). It is surprising, however, that participation in muscle strengthening activities is so low. Indeed analysis in Scotland has shown that only 31% of men and 24% of women met the muscle strengthening guideline, which is around half the numbers of those that meet the guidelines for aerobic physical activity (Strain, Fitzsimons, Kelly, & Mutrie, 2016). Although the reasons for this are not clear, the reported barriers to participation in resistance exercise training are broadly similar to those reported for general physical activity (Burton et al., 2017; Trost et al., 2002), although there are some

specific barriers to resistance exercise (e.g. fear of looking too muscular and perceived risk of a heart attack, stroke or death and the equipment is too bulky). Time, as with for general physical activity, is cited as a major barrier to resistance exercise training participation and the current study, by employing a single set of exercise, has shown that a relatively time-efficient form of resistance exercise training remains effective at improving insulin sensitivity and increasing muscle size and function. Together with previous work (Burd et al., 2010; Fisher et al., 2011; Mitchell et al., 2012; Morton et al., 2016)this data indicates that the current, and somewhat complex, recommendations (Ramachandran, 2012) for resistance exercise could be changed to provide clear and simple advice that people should perform a single set to failure at a load acceptable to them.

Another novel aspect of the present study is that we have investigated the early time-course of adaptations in muscle size and strength, with measures made on a weekly basis, during resistance exercise training. Similar work in young healthy men and using a different resistance exercise protocol (6 weeks of training (6 x 8 repetitions at 75%1RM) 3 times per week) measured muscle strength every 10-11 days, and vastus lateralis muscle thickness and muscle protein synthesis every 3 weeks (Brook et al., 2015). Although this study found that strength increases progressively over the 6 weeks, muscle thickness and muscle protein synthesis were only increased during the first, but not the second, half of the intervention. The authors, therefore, concluded that hypertrophy predominates in the early part of resistance exercise training and then after ~3 weeks this response wanes. The present study disagrees with this assertion with muscle size and strength increasing progressively during the 6-week training period. This is more in line with the findings of Damas and colleagues (Damas et al., 2016) who found hypertrophy from 3-10 weeks of resistance exercise training (3 sets, 9-12 repetitions per set with load adjusted to maintain this repetition range and each set to failure) in young healthy men, although no hypertrophy was evident in the first 3 weeks of training. The differences between these studies may relate to the participants studied, methods and/or the resistance exercise training intervention employed but we are currently unable to uncover the precise mechanisms. This is also the first study to measured RTD after such exercise and we found that RTD50 and 100, but not RTD200 and 300, increased over the exercise intervention. Previous work has found that longer term more (14 weeks) traditional resistance exercise can increase RTD 50, 100, 200 and 300 (Aagaard, Simonsen, Andersen, Magnusson, & Dyhre-Poulsen, 2002). It may be that a longer duration of resistance training to failure would be required to see such increases.

Our study was not without limitations. Our selection of the subjects was from overweight people and the main reason for this because probably there were more likely a population that would get benefit from this kind of exercise. A key limitation of the present study is that we have only included men and whilst we have no reason to think responses would differ in women, this remains to be established. Furthermore, another limitation is that the current chapter does not have a control arm maintaining habitual physical activity/diet, and therefore the true magnitude of the effect of such exercise on insulin sensitivity might differ from that reported here. Although we recruited overweight men, most of them were insulin sensitive and whether these results are significantly true to the people or population at risk such as people with type 2 diabetes or different ethnic groups such as South Asians still remains to determine.

In conclusion, the current chapter has shown that 6 weeks of single set resistance exercise to failure results in improvements in insulin sensitivity and progressive increases in muscle size and strength in young overweight men. Such exercise, which is of shorter duration to the more traditional and recommended multiple set resistance exercise training, may be a useful tool to improve muscle and metabolic health.

CHAPTER 5 – A COMPARISON OF THE MUSCLE AND METABOLIC ADAPTATIONS TO RESISTANCE EXERCISE TRAINING BETWEEN SOUTH ASIANS AND WHITE EUROPEANS

5.1 Introduction

The maintenance of skeletal muscle mass is of major importance in everyday life and also in many clinical conditions. The main role of skeletal muscle is its ability to contract and allow activities of daily living to take place and its importance here is highlighted by the condition sarcopenia, the age-related loss of skeletal muscle mass. In sarcopenia the loss of muscle mass reduces older people abilities to carry out everyday tasks (i.e. standing from a seated position), reduces quality of life and increases risk of falls, often leading to hospitalisation (Cruz-Jentoft et al., 2010). However as mentioned skeletal muscle plays a wider role in determining health. Indeed, evidence has shown that muscle mass is important in recovery from critical illness, obesity prevention, the prevention of osteoporosis and ultimately mortality rates (Tieland et al., 2018).

The maintenance of muscle mass is also of clear importance metabolically as it is both the primary site for glucose disposal and also a major protein store. It has long been known that protein stored in muscle can be used to replenish circulating blood amino acid levels in times of crisis, such as starvation or disease (Cruzat, Rogero, Keane, Curi, & Newsholme, 2018). This is important in health, as not only are circulating amino acids needed for the synthesis of new proteins but they also serve as precursors for hepatic gluconeogenesis (Hanson & Owen, 2013). Muscle also plays a crucial role in the development of type 2 diabetes, as insulin resistance of the muscle requires greater insulin secretion from the pancreas to maintain euglycaemia, however, often a point is reached at which insulin secretion cannot counteract the insulin resistance in muscle and hyperglycaemia ensues (Cerf, 2013). Skeletal muscle insulin resistance is considered to be the initiating or primary defect in type 2 diabetes, that is evident decades before B-cell failure and overt hyperglycemia develops (DeFronzo & Tripathy, 2009). Insulin resistance is defined as a reduced response of target tissues (compared to people with normal glucose tolerance without a family history of diabetes), such as the skeletal muscle, liver, and adipocytes, to insulin (DeFronzo & Tripathy, 2009). As muscle mass is of clear importance, although not the only factor, for good control of blood glucose levels it is therefore not surprising that muscle mass has been

shown to be closely linked with insulin resistance and type 2 diabetes (DeFronzo & Tripathy, 2009; Tian et al., 2017).

It is also becoming evident that muscle mass and metabolic function differs between people from different ethnic groups. For the current chapter we will focus on South Asians. This is because several studies have demonstrated that people from South Asia are also up to 4-6 times more likely to develop type 2 diabetes than White Europeans (Hu, 2011; Arti Shah & Kanaya, 2014; Unnikrishnan et al., 2017). This is becoming a major worldwide problem with, for example, 67 million people in India currently having type 2 diabetes - a figure projected to rise to 79.4 million by 2030 (Kaveeshwar & Cornwall, 2014). Whilst the mechanisms underlying these observations remain to be established, low skeletal muscle mass has been implicated (Kanaya et al., 2014). Indeed, people from South Asia have 7-25% less lean mass than White Europeans people, across the lifecourse, from infants up to 80 year olds (Sattar & Gill, 2015; Unnikrishnan et al., 2017; Williams et al., 2011). Furthermore, in a recent study from the UK Biobank, grip strength in South-Asian men and women was 5–6 kg lower than in the other ethnic groups. On top of this, the risk for diabetes associated with low grip strength was substantially higher in South-Asian participants (3.9 and 4.2 cases per 100 men and women, respectively) than in white participants (2.0 and 0.6 cases per 100 men and women, respectively) (Ntuk et al., 2017). It appears, therefore, that strategies to increase muscle mass in South Asians may be of particular benefit for metabolic health. As resistance exercise is the most effective intervention for increasing muscle mass, strength, and can improve insulin sensitivity (Brooks et al., 2007), the aim of the current chapter was to compare the effect of resistance exercise on muscle and metabolic health between South Asians and White Europeans.

Hypothesis: Improvements in muscle and metabolic health in response to resistance exercise training will be attenuated in South Asians relative to White Europeans.

5.2 Methods

This study was carried out in collaboration with another PhD student (Faris Alkahyl) and the responsibilities for recruitment and exercise training of participants was shared. All the outcome measurements in the current thesis were made entirely by myself.

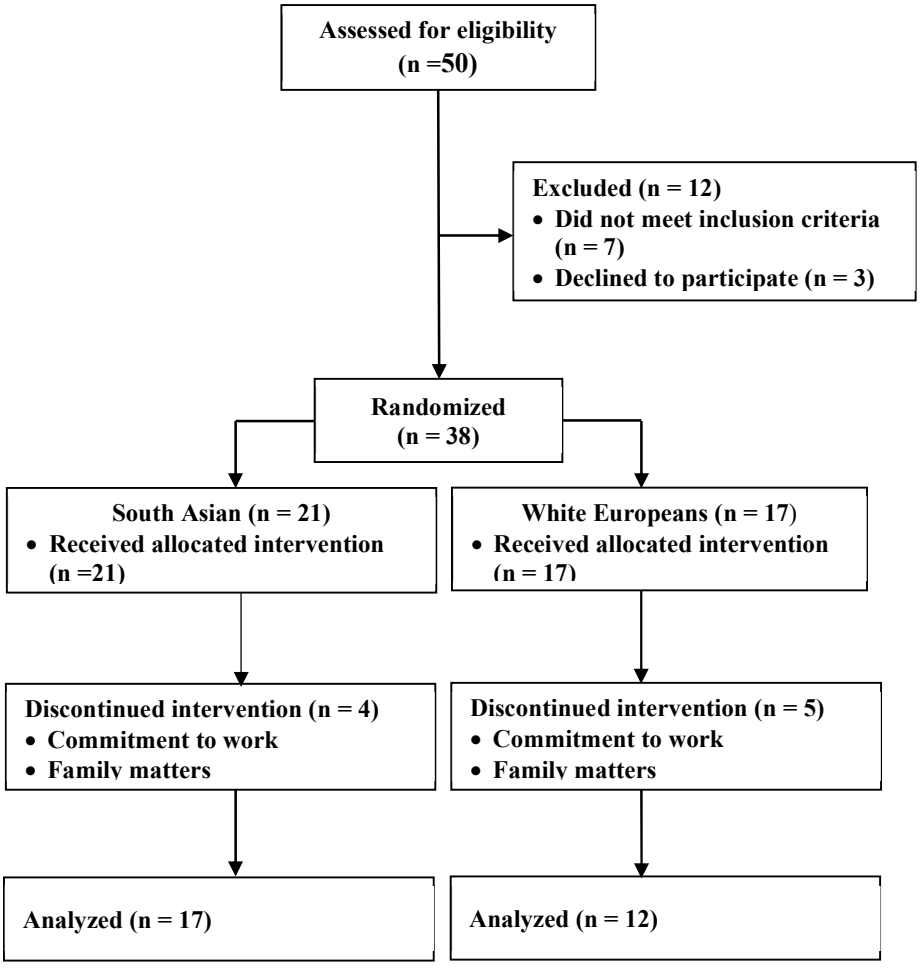

Figure 5.1 Consort diagram of study process for the South Asians and Muscle Mass study.

5.2.1 Study protocol:

Baseline measurements

Exclusion criteria included; current smoking, physician diagnosed diabetes, uncontrolled hypertension (>160/90 mm Hg on anti-hypertensive medication), previous history of established coronary heart disease (e.g. myocardial infarction, coronary artery bypass graft surgery, coronary angioplasty), body mass index >35kg.m^2, family history of early cardiac death (<40 years) and lactose intolerance. All participants were in good health at the time of testing and did not participate in any resistance exercise training or take any dietary

supplements. On the first study visit participants visited the laboratory, were introduced to the research group, completed a health screen questionnaire and had resting blood pressure, height and weight recorded. On a subsequent visit the participants attended the laboratory after an overnight fast and having avoided exercise for 2 days. During this visit baseline measures of fitness (VO_{2max}), vastus lateralis muscle thickness via A- and B-mode ultrasound, nutritional intake via a 7-day food diary, physical activity levels via an accelerometer for a 7 day period, knee extensor muscle strength, rate of torque development (RTD*)*, mixed meal tolerance test and blood pressure were made.

Resistance exercise training

Following these baseline assessments participants completed 12 weeks of resistance exercise training with 2 sessions (4 sessions in the first week) per week. Each exercise session involved participants carrying out 1 set to failure at 80% of 1RM of the following exercises: bench press, leg extension, leg flexion, seated row, calf press, latissimus pulldown, triceps curl and biceps curl. For each of the aforementioned exercises 1RM was measured at 0, 4 and 8 weeks and the load re-adjusted accordingly. After a warm up with a few light repetitions, the weight applied for each exercise was progressively increased, with 2 minutes rest between contractions, until the participant could not perform a full single repetition of the exercise. All sessions were supervised and attendance was 100%.

Post-training measurements:

Three days after the final exercise session measures of fitness (VO_{2max}), body composition (muscle and fat mass) via MRI, vastus lateralis muscle thickness via ultrasound, knee extensor muscle strength and rate of torque development (RTD*)*, mixed meal tolerance test and blood pressure were made.

5.2.2 Outcome measures:

Vastus lateralis muscle thickness

Measurements were performed as in Chapter 2 using the BodyMetrix BX2000 device and the Telemed B-mode ultrasound device.

Maximal oxygen uptake

Participants performed a 5-minute warm up at 30 watts on cycle ergometer followed by an incremental cycle ergometer tests, with 30watts increased in work rate every 1 minute, until

they could no longer sustain the required work rate. Expired air, heart rate and RPE were measured at each stage. Measured at week 0 and 12.

Mixed meal tolerance test (MTT)

A cannula was inserted into an antecubital or forearm vein and a resting blood sample taken after a 10 min rest period. Subjects then consumed a standard test meal (containing 800 kcal, 37% fat, 47% carbohydrate, 17% protein). Further blood samples were taken over the next 5 hours to assess glucose, insulin, c-peptide and triglycerides. Blood samples were collected 30, 45, 60, 90, 120, 180, 240 and 300 minutes after the consumption of the meal. Samples were analysed in the University of Glasgow clinical biochemistry laboratory using automated analysers and commercially available assays.

Knee extensor maximal isometric torque and rate of torque development (RTD)

Maximal isometric torque of the right knee extensor muscles was measured during an MVC with the participants seated securely, with the use of seatbelts, and a knee angle of 90°. Participants were asked to contract maximally, with contractions repeated ≥3 times and the highest value used for subsequent analysis. Force was recorded throughout the contraction with a load cell (Biometrics, Newport, UK). The rate of torque development (RTD) was calculated from the MVC data. The torque at time instants 0, 50, 100, 200 and 300ms was determined and the RTD for each time interval calculated by subtracting from the torque at each time point the torque at 0 and dividing by the time interval.

Statistical analyses

Baseline measures were compared between the ethnic groups by two-sample t-tests. The change in variables was compared between the ethnic groups via linear regression analysis with adjustment for age and the baseline values of the outcome being compared. Data are reported as mean ± standard deviation (SD) unless otherwise stated, with the change with resistance exercise training data reported as age baseline adjust mean (95%CI). Statistical significance was set *a priori* at $p \leq 0.05$. GraphPad Prism and STAT software (Version 5) were used for all statistical analyses.

5.4 Results

5.4.1 Participants:

17 South Asians and 12 White Europeans were recruited in Glasgow, United Kingdom to take part in this study. As shown in tables 5-1 and 5-2 there were no differences (P>0.05) in fasting blood data, height, body mass, BMI, blood pressure, dietary intake, physical activity, muscle thickness and RTD data. There were however differences (P<0.05) in age and MVC, with South Asians being younger and having a lower MVC.

Table 5-1 Pre & post participant characteristics of South Asians and White Europeans participants

	Pre South Asians (n=17)	Post South Asians (n=17)	Pre White Europeans (n=12)	Post White Europeans (n=12)
Age (y)	24 ± 4*		31 ± 7*	
Height (cm)	178 ± 9.4	178 ± 9.4	178 ± 7.3	178 ± 7.3
Body mass (kg)	77.9 ± 13.9	79.1 ± 14.2	81.9 ± 7.7	82.2 ± 6.6
Systolic blood pressure (mm Hg)	129 ± 11	127 ± 10	125 ± 6	120 ± 4*
Diastolic Blood pressure (mm Hg)	75 ± 9	73 ± 6	72 ± 6	71 ± 5
BMI (kg m^{-2})	25 ± 4	25 ± 4	26 ± 3	26 ± 3

Data are mean ± SD
* Denotes a significant difference between ethnicities (P<0.05)

There were no differences between South Asians' and White Europeans' body mass, diastolic blood pressure and BMI in their response to 12 weeks of resistance training. However, for systolic blood pressure, a significance difference (p=0.05) was noted with a 5.1 (95%CI: -7.5 to -2.7) mmHg decrease in White Europeans and a 0.7 (95%CI:-2.4 to 1.0) mmHg decrease in South Asians.

Table 5-2 Baseline muscle and metabolic health data of South Asians and White Europeans participants

	South Asians (n=17)	White Europeans (n=12)
Muscle thickness (mm)	21.6 ± 2.9	22.5 ± 3.7
MVC (Nm)	183.3 ± 35.6*	207.7 ± 22.9*
RTD 50($Nm.s^{-1}$)	320.6 ± 261	299.2 ± 118.2
RTD 100 ($Nm.s^{-1}$)	350.2 ± 278.4	265.9 ± 103.6
RTD 200 ($Nm.s^{-1}$)	341.5 ± 217.3	235.3 ± 90.5
RTD 300 ($Nm.s^{-1}$)	285.3 ± 164.8	234.4 ± 81.3
VO_{2max} ($ml.kg.min^{-1}$)	34.1 ± 5.6	38.5 ± 7.9
Fasting C-peptide (ng/ml)	5.07 ± 1.63	5.87 ± 1.68
Fasting glucose (mmol/L)	5.08 ± 0.69	5.18 ± 0.76
Fasting insulin (µU/ml)	48.5 ± 25.6	52.9 ± 25.6
Fasting triglycerides (mmol/L)	1.42 ± 0.94	1.12 ± 0.43
Total energy intake (kcal/day)	2229 ± 490	2112 ± 582
Protein intake (g/day)	88.2 ± 15.9	85.0 ± 22.4
Carbohydrate intake (g/day)	389.9 ± 438.7	250.9 ± 90.6
Fat intake (g/day)	98.2 ± 21.1	93.6 ± 27.7
Sedentary time (min/day)	419.2 ± 201.4	519.2 ± 290.5
Light physical activity (min/day)	64.3 ± 26.9	61.1 ± 26.5
Moderate physical activity (min/day)	47.8 ± 27.5	41.8 ± 18.6
Vigorous physical activity (min/day)	6.3 ± 7.7	4.9 ± 6.7
Moderate to vigorous physical activity(min/day)	60.4 ± 33.0	51.9 ± 19.0

Data are mean ± SD
* Denotes a significant difference between ethnicities ($P<0.05$)

As shown in figure 5.2, in response to 12 weeks of resistance training exercise the increase in muscle thickness (A) was 1.2 (95%CI 0.8 to 1.7) mm in South Asians and 2.3 (95%CI 1.8 to 2.9) mm in White Europeans. There was a significant difference in the change in muscle thickness between the ethnic groups in their responses to training (p=0.032). For VO_{2max} (B), there was a decrease of 0.7 (95%CI -2.0 to 0.6) ml.kg.min^{-1}in South Asians and an increase of 1.6 (95%CI -0.1 to 3.3) ml.kg.min^{-1}in White Europeans over the 12 week intervention period. There was a trend for a difference between the ethnic groups in their VO_{2max} responses to training (p=0.055). MVC increased by 44 (95%CI 34 to 53) Nm in South Asians and by 54 (95%CI 42 to 67) Nm in White Europeans after 12 weeks of resistance training. There was no difference between the ethnic groups in their responses to training (p>0.05).

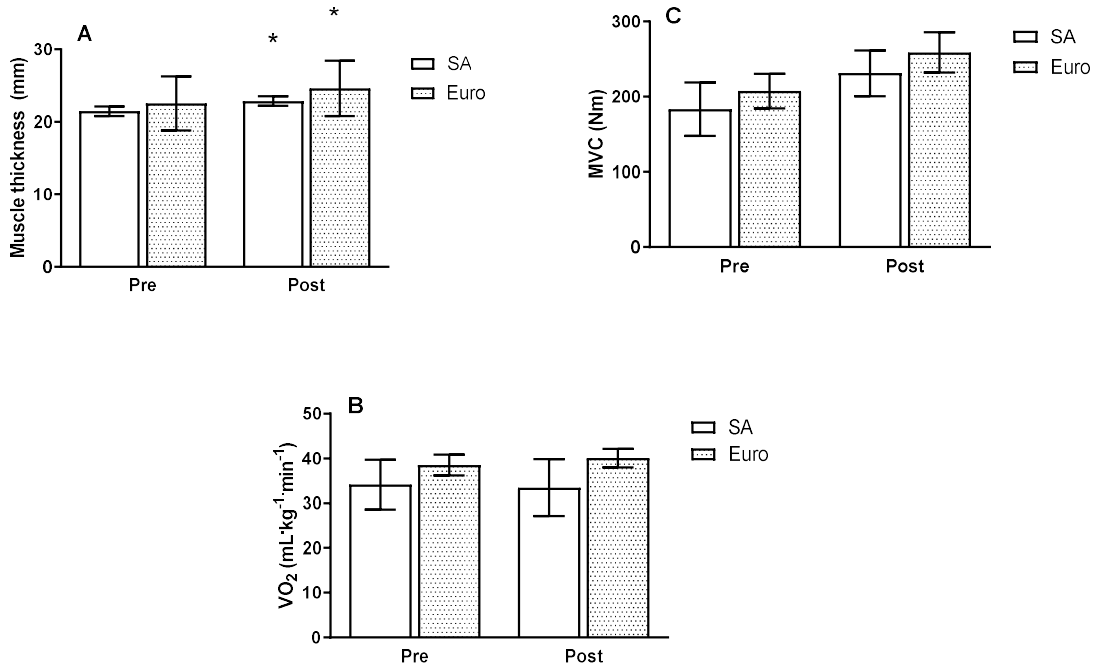

Figure 5.2 **Muscle thickness (A), VO_{2max} (B) and MVC (C) before and after 12 weeks of resistance exercise training in South Asians and White Europeans participants.** Data are presented as mean (SD).

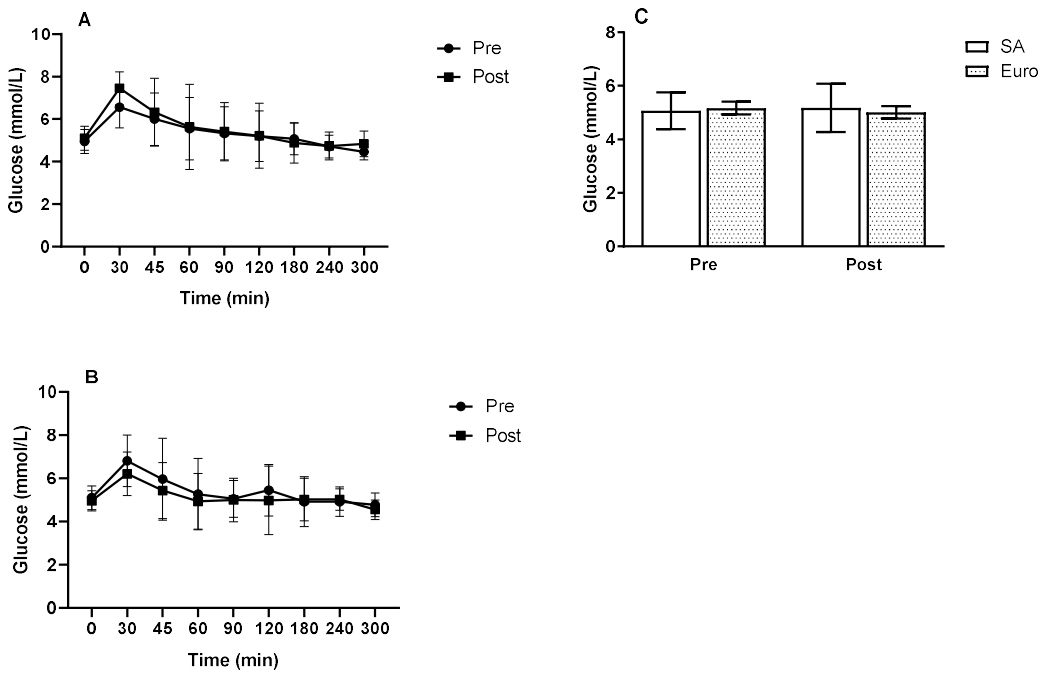

Figure 5.3 Baseline and post-intervention blood glucose responses to a mixed meal tolerance test in South Asians (A) and for White Europeans (B) and time-averaged AUC (C). Data are presented as mean (SD).

After 12 weeks of resistance exercise training, the time-averaged glucose AUC for South Asians was 0.04 (95%CI -0.5 to 0.6) mmol/L higher, whilst for White Europeans, the time-averaged glucose AUC was 0.17 (95%CI -.74 to 0.40) mmol/L lower. There were no differences between ethnicities in their responses to training ($p>0.05$) (Figure 5.3).

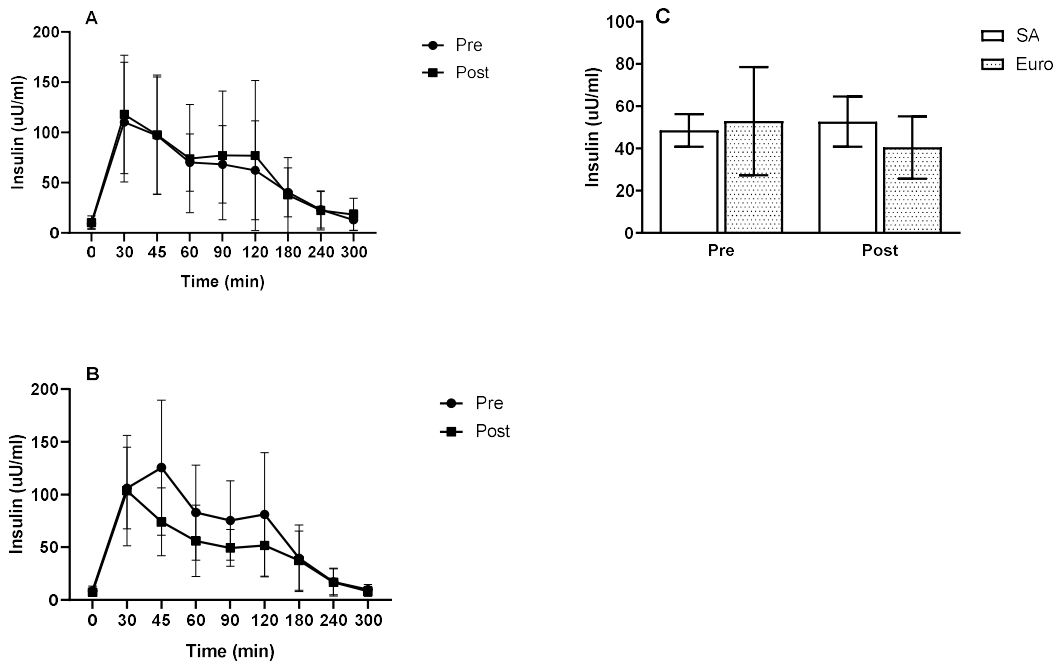

Figure 5.4 Baseline and post-intervention insulin responses to a mixed meal tolerance test in South Asians (A) and for White Europeans (B) and time-averaged AUC (C). Data are presented as mean (SD).

After 12 weeks of resistance exercise training, the time-averaged insulin AUC for South Asians was increased by 0.1 (95%CI -13 to 14) uU/ml. For White Europeans, the time-averaged insulin AUC was decreased by 8.4 (95%CI -23 to 6) uU/ml (Figure 5.4). There were no differences between ethnicities in their responses to training ($p>0.05$).

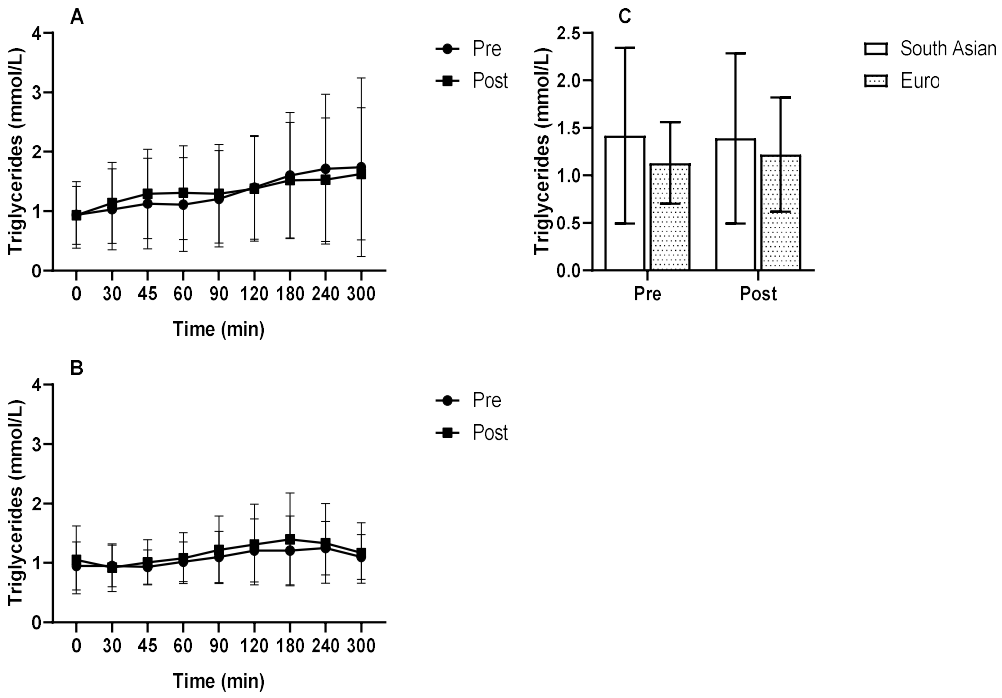

Figure 5.5 Baseline and post-intervention triglycerides responses to a mixed meal tolerance test in South Asians (A) and for White Europeans (B) and time-averaged AUC (C). Data are presented as mean (SD).

After 12 weeks of resistance exercise training, there was little change in the time-averaged triglycerides AUC for South Asians (+0.004 (95%CI -0.2 to 0.2) mmol/L or White Europeans (+0.1 (95%CI -0.1 to 0.3) mmol/L, with no differences between ethnicities in their responses to training ($p>0.05$).

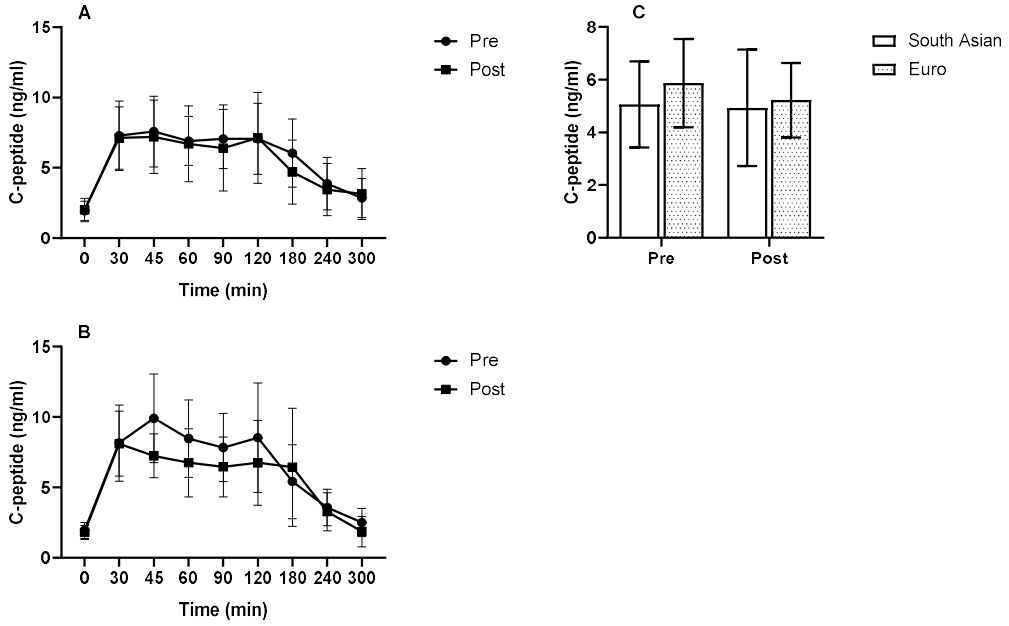

Figure 5.6 Baseline and post-intervention C-peptide responses to a mixed meal tolerance test in South Asians (A) and for White Europeans (B) and time-averaged AUC C-peptide (C). Data are presented as mean (SD).

After 12 weeks of resistance exercise training, the time-averaged C-peptide AUC for South Asians was decreased by 0.4 (95%CI -1.2 to 0.4) ng/mL, and for White Europeans, the time-averaged C-peptide AUC was decreased by 0.6 (95%CI -1.3 to 0.1) ng/mL. There were no differences between ethnicities in their responses to training ($p>0.05$).

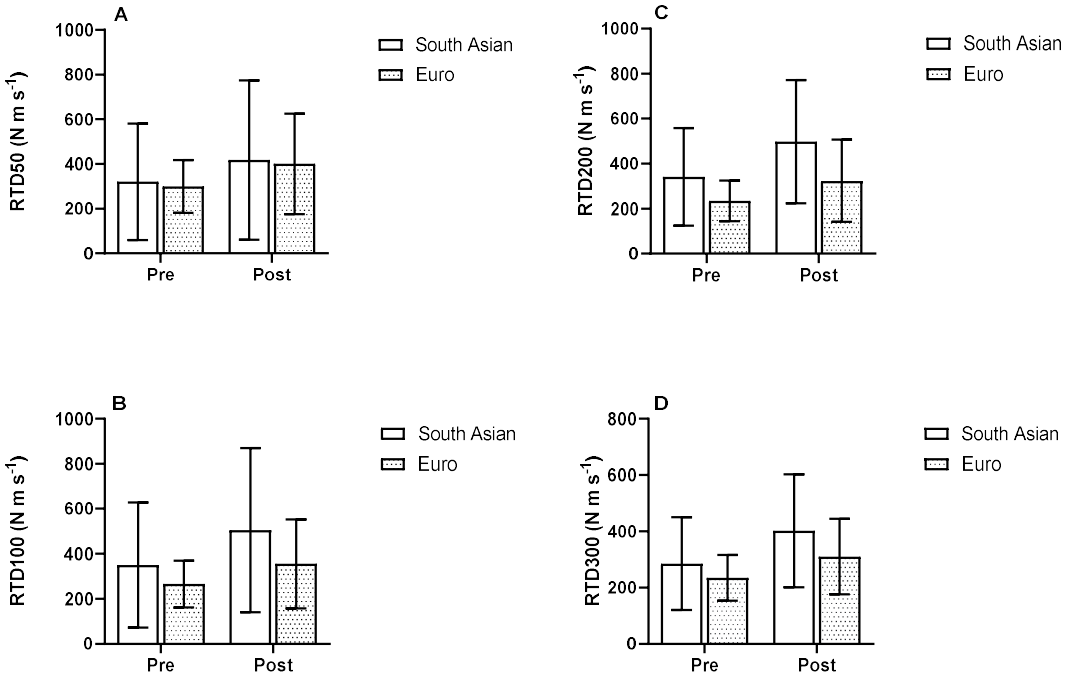

Figure 5.7 Baseline and post-intervention knee extensor rate of torque development (RTD) responses to 12 weeks of resistance training in South Asians and White Europeans, RTD50 (A) RTD100 (B) RTD200 (C) and RTD300 (D). Data are presented as mean (SD).

As shown in figure 5.7, RTD50 in South Asians increased by 90.2 (95%CI -67.1 to 247.6) $Nm.s^{-1}$ with an increase of 76.7 (95%CI -52.7 to 206) $Nm.s^{-1}$ for White Europeans. RTD100 in South Asians increased by 101.7 (95%CI -35 to 239.4) $Nm.s^{-1}$with an increase of 70.3 (95%CI -42.7 to 183.4) $Nm.s^{-1}$ for White Europeans. RTD200 in South Asians increased by 103.1 (95%CI -8.3 to 214.4) $Nm.s^{-1}$with an increase of 71.2 (95%CI -20.3 to 162.7) $Nm.s^{-1}$ for White Europeans. RTD300 in South Asians increased by 84.3 (95%CI -5.1 to 173.7) $Nm.s^{-1}$ with an increase of 67.1 (95%CI -6.1 to 140) $Nm.s^{-1}$ for White Europeans. There was no difference ($p>0.05$) between the ethnicities in the change for any RTDs with 12 weeks of resistance training.

5.5 Discussion

The current chapter has shown that there were no differences in the effect of 12 weeks of resistance exercise training on the majority of the muscle and metabolic outcomes measured, however the increase muscle thickness and decrease in systolic blood pressure were attenuated in South Asians. There was also a trend for an attenuated effect of resistance exercise training on VO_{2max} in South Asians.

This current chapter's findings on muscular strength, in this case MVC, are not the same as a previous study from Knox et al (Knox et al., 2019) . In their study the strength adaptation between age matched White Europeans and South Asians men was compared during six-weeks of resistance exercise training. Muscle strength adaptations were measured by measurement of 1RM and it was found that whilst upper body strength gains did not differ between the ethnic groups there was a smaller increase in lower body strength in South Asians. It is hard to make direct comparisons between these studies, as the study of Knox et al only had a 6 week intervention, where increases in strength are at an early stage, and used a 3 repetition maximum protocol of only 2 exercises (squat and bench press) to measure strength. Furthermore, different strength measurement protocols were employed and whilst it is known that 1RM measures correlate with maximal isometric torque measurements (Verdijk, Van Loon, Meijer, & Savelberg, 2009), and whether 1RM represents a valid measure of changes in strength with resistance exercise training remains to be established. It is, therefore, not clear whether the gains in muscle strength in response to resistance exercise training do differ between south Asians and white Europeans, although the data of the current study (which we would argue is the most robust available) indicates that no differences occur. Thus, resistance exercise should still be recommended to south Asians as the primary method to increase muscle strength. One of the main, but not the only, driver of gains in muscle strength is hypertrophy, ie increase in muscle size (Folland et al, 2007). Besides that, a study on the effects of resistance training were obtained in untrained South Asian middle-aged 35 males and 13 females with type 2 diabetes in a study by Hameed and colleagues (Hameed, Manzar, Raza, Shareef, & Hussain, 2012). Progressive resistance training for 12 weeks resulted in an increase in upper body muscle strength of 11.36% and lower body muscle strength of 11.23% in both men and women.

Looking at the current chapters muscle size data it was found that the increase in muscle thickness was attenuated in South Asians. It is important at this point to re-iterate, however,

that caution must be applied when interpreting this data as ultrasound measures of muscle thickness are not a valid marker of changes in muscle volume with resistance exercise training (chapter 3 and (Franchi et al., 2018)). Others have, however, made similar findings possibly indicating an anabolic resistance to resistance exercise in South Asians. Indeed, in the study of Knox et al (Knox et al., 2019) it was shown fat-free mass (measured by bioelectrical impedance) did not increase in South Asians with resistance exercise, although it is key to note that it did not increase in White Europeans either – likely due to the aforementioned short duration of training employed. In another study of South Asians with type 2 diabetes (Misra et al., 2008), with no White Europeans comparator group, it was shown that in response to 12 weeks of progressive resistance exercise training no increase in lean body mass or leg mid-thigh muscle cross sectional area were observed.. Whilst in the current chapter, increases in muscle thickness were observed in South Asians the magnitude of this increase as less than seen in White Europeans. Alongside the previous literature this indicates that there may be a partial anabolic resistance to resistance exercise in South Asians, although further work is needed to confirm this. It is possible that this anabolic resistance, is reflected in an attenuation in the resistance exercise induced increases in muscle protein synthesis and this would be worthy of further investigation.

As it has been shown that muscle mass is important for glycaemic control it may be hypothesised, based on the current muscle thickness findings, that there is an attenuation in the beneficial effect of resistance exercise training in insulin sensitivity. However, the current study found that there was no difference in the glucose, insulin, triglyceride or c-peptide responses, after a mixed-meal tolerance test, to resistance exercise training between South Asians and White Europeans. Whilst this is, at first glance, not what may be expected it is worth remembering that resistance exercise can promote changes in insulin sensitivity independently of changes in muscle mass. For example, it is known that resistance exercise training can result in, for example, decreases in body fat (Willis et al., 2012) and improvements in mitochondrial function (Porter et al., 2015) both of which may contribute to improvements in insulin sensitivity.

Of interest looking at the magnitude of the change in insulin AUC was dramatically lower in South Asians compared to White Europeans and this may be worth investigating in a larger study cohort to determine if there are any real differences seen. Other studies have looked at markers of glycaemic control in response to resistance exercise training in South Asians. Indeed, Knox et al. also compared markers of cardio-metabolic health between South

Asians and White Europeans in response to 6 weeks of resistance exercise training. Whilst they found a decrease in fasting blood glucose this was similar between ethnicities, and no change in HOMA-IR was seen in either group. Again, this likely stems from the short protocol employed in this study. On the other hand, the study of Misra et al, found an increase in insulin sensitivity and a decline in HbA1c and fasting blood glucose after 12 weeks of resistance exercise training in South Asians with type 2 diabetes. It would appear, therefore, that resistance exercise can be of benefit for glycaemic control and insulin sensitivity in South Asians with type 2 diabetes, but whether it has any beneficial effect in younger healthy populations remains to be established.

Interestingly, and unexpectedly, we also found that the improvement in systolic blood pressure with resistance exercise (Cornelissen et al., 2011) was blunted in South Asians, relative to White Europeans. Whilst it is known that vascular function is lower in South Asians relative to White Europeans (Murphy et al., 2007) this is the first study, we are aware of, to show that there is an attenuation in blood pressure responses to resistance exercise training in South Asians. The mechanisms underlying these findings remain to be investigated. It is also well established that South Asians have lower VO_{2max} than White Europeans (Hall et al., 2010), and further work is needed to establish whether the trend observed in the current chapter, that the increase in VO_{2max} with resistance exercise training is absent in South Asians, is verified in a larger study cohort.

This study does come with several limitations. The major limitation is the relatively small sample size of both ethnicities which may not provide sufficient statistical power to determine differences in all of the outcome's measures. On top of this, although the current study was of longer duration than many previous studies 12 weeks remains a relatively short duration. Furthermore, we did not employ the gold standard (MRI) measure of muscle mass and so further work is needed to verify the current findings using muscle thickness data.

The current chapter found that some of the beneficial effects of resistance exercise may be attenuated in South Asians, compared to White Europeans. Often the primary reason to carry out muscle strengthening activities is to maintain muscle function over the lifecourse, to prevent/delay some of the deleterious effects of muscle weakness, and there was a robust increase in muscle strength in South Asians. Resistance exercise should, therefore, continue to be recommended for South Asians with further work needed to investigate the metabolic effects of such exercise in this population.

CHAPTER 6 – GENERAL DISCUSSION

6.1 Discussion

The aim of the first chapter of this thesis was to investigate the repeatability and validity of a cheap A-mode ultrasound device (BodyMetrix) in the measurement of muscle size. The data revealed that this device had a good repeatability (CV of 4.6%) in measuring vastus lateralis muscle thickness and that there was good agreement between A and B mode ultrasound devices, and also positive correlations of muscle thickness (both A and B mode devices) with MRI measures of thigh muscle volume and total lean mass. Together this indicates that this A mode ultrasound device is repeatable and, as with the B-mode ultrasound, is a valid measure of muscle size. It also gave confidence in applying this technique in further studies in this thesis.

This is the first study to our knowledge that has investigate the repeatability and validity of A-mode ultrasound and the findings indicate that this could be a useful and relatively cheap tool to measure muscle size. The findings are in agreement with other findings in the literature, using B-mode ultrasound, which has shown it to be a valid measure of muscle size when compared to DEXA and MRI based measures of muscle size (Abe et al., 2016). However, whilst these findings are encouraging, often people will want to not just measure muscle size on a single occasion but will instead want to track changes in muscle mass during an intervention, most likely resistance exercise training. It, therefore, remained necessary to investigate the validity of A- and B-mode ultrasound in detecting changes in muscle size with resistance exercise training.

The second aim of this thesis, therefore, was to firstly investigate whether the A-mode ultrasound device was able to detect exercise induced changes in muscle size and then to determine its validity, along with more traditional B-mode ultrasound, compared to MRI measures of muscle size. During the course of this study being carried out a similar study by Franchi and colleagues (Franchi et al., 2018) was published and the findings in the current thesis are similar to this other published work.

Firstly, the current data found that the A-mode ultrasound was able to detect increases in muscle size with resistance exercise training, with increases of 6.2 ± 5.4 % in vastus lateralis muscle thickness found. However, whilst in chapter 2 the data revealed that both A- and B-

mode ultrasound were valid measures of muscle size during a single measurement the data of chapter 3 showed that neither were valid measures of the increase in muscle size in response to resistance exercise training. As mentioned previously the findings of chapters 2 and 3 are similar to those of Franchi et al (Franchi et al., 2018) who also reported that whilst positive correlations between these measures of muscle size (B-mode ultrasound and MRI) were observed at baseline the increase in vastus lateralis muscle thickness with resistance exercise training was correlated with increases in thigh anatomical cross-sectional area but not with the increases in muscle volume. This means that whilst ultrasound measured muscle thickness is a valid measure of muscle size cross-sectionally at baseline it is not a valid technique to measure changes in muscle size with resistance exercise training.

This finding, unfortunately, casts some doubt on some of the findings of chapters 4 and 5 which began, due to time constraints, before the findings of chapter 3 were known. In chapters 4 and 5, we applied the relatively novel and time-efficient resistance training technique of a single set of resistance exercises to volitional failure to investigate the effects of such training on muscle size and insulin sensitivity. In these studies, the aim was to investigate the effects of this training in two relatively “high risk” populations: chapter 4 – overweight men and chapter 5 – South Asians.

In chapter 4, we investigated the short-term efficacy of such training with six weeks of resistance exercise, comprising one set to volitional failure of nine exercises – taking 15-20 min per session – undertaken three times per week. It was shown that muscle strength and muscle size increased rapidly and linearly during the 6 weeks of training, although due to the findings of chapter 3 caution must be applied when interpreting the muscle thickness data. Furthermore, another major limitation of the study was that no control group was included. On top of the aforementioned changes in muscle we also found that only 6 weeks of this training resulted in a 16% improvement in insulin sensitivity, measured during an oral glucose tolerance test. This study is the first study to demonstrate that such simple exercise, with a weekly time commitment of less than one hour, can increase insulin sensitivity in overweight men and is also the first to demonstrate the time course of adaptations in muscle strength and size. This could help to pave the way, along with other work, for a simplification of the resistance exercise training guidelines and help to facilitate the uptake of resistance exercise for the general public. As time is one of the most frequently cited barrier to any exercise (Trost et al., 2002) then short duration resistance exercise may be appealing as an option to help achieve resistance exercise recommendations. Other

barriers, such as a dislike of gyms and the equipment needed, do still need to be overcome and so much work is needed to help increase uptake of resistance exercise in the general population.

This improvement in insulin sensitivity made studying such exercise in a population known to be at increased risk of type 2 diabetes, such as South Asians (Hu, 2011; Arti Shah & Kanaya, 2014; Unnikrishnan et al., 2017) of interest, particularly as there had been very few studies of resistance exercise in this population. In this study we found that no differences in the effect of 12 weeks of resistance exercise training on the majority of the muscle and metabolic outcomes measured, however the increase muscle thickness and decrease in systolic blood pressure were attenuated in South Asians. There was also a trend for an attenuated effect of resistance exercise training on VO_{2max} in South Asians. However, caution must be applied when interpreting this data as ultrasound measures of muscle thickness are not a valid marker of changes in muscle volume with resistance exercise training (chapter 3). But, Knox et al (Knox et al., 2019) made similar findings possibly indicating an anabolic resistance to resistance exercise in South Asians. They found that fat-free mass (measured by bioelectrical impedance) did not increase in South Asians with resistance exercise, although it is key to note that it did not increase in White Europeans either – likely due to the aforementioned short duration of training employed. In another study of South Asians with type 2 diabetes, it was shown that in response to 12 weeks of progressive resistance exercise training no increase in lean body mass or leg mid-thigh muscle cross sectional area were observed. In this chapter, increases in muscle thickness were observed in South Asians, but the magnitude of the increase was less than seen in White Europeans. Again, this indicates a potential blunting of the anabolic response to resistance exercise in South Asians.

Another importance finding from this chapter was the improvement in systolic blood pressure with resistance exercise was blunted in South Asians, relative to White Europeans. Even though, it is known that vascular function is lower in South Asians relative to White Europeans this is the first study, to show that there is an attenuation in blood pressure responses to resistance exercise training in South Asians. The mechanisms underlying these findings remain to be investigated in the large number of populations. Our finding also had confirmed and agreed on few previous studies that South Asians have lower VO_{2max} than White Europeans. Based on the previous literature this indicates probably may be a partial anabolic resistance to resistance exercise in South Asians, further work is needed to confirm

this statement and further work also needed to establish whether the trend observed in the Chapter 5, that the increase in VO_{2max} with resistance exercise training is absent in South Asians, is verified in a larger study cohort.

So overall this thesis has shown that resistance exercise can be of clear benefit in increasing muscle size/function and insulin sensitivity, although further work is to investigate this in South Asians. Thus, it is clear why the physical activity recommendations include muscle strengthening activities (Who, 2010). However, analysis in Scotland has shown that only 31% of men and 24% of women met the muscle strengthening guideline, which is around half the numbers of those that meet the guidelines for aerobic physical activity (Strain et al., 2019). Time, as with for general physical activity, is cited as a major barrier to resistance exercise training participation and the current study, by employing a single set of exercise, has shown that a relatively time-efficient form of resistance exercise training remains effective at improving insulin sensitivity and increasing muscle size and function. Together with previous work (J. H. Lee, Kim, & Kim, 2017; Verdijk et al., 2009; Yamamoto et al., 2016) this data indicates that the current, and somewhat complex, recommendations (Who, 2010) for resistance exercise could be changed to provide clear and simple advice that people should perform a single set to failure at a load acceptable to them.

6.2 Future work

In a larger cohort investigate whether South Asians do not improve insulin sensitivity, as White Europeans do, in response to resistance exercise training. If this is confirmed investigate why this is the case. As resistance exercise training is of benefit in many ways, even in South Asians who still show improvements in muscle size and strength, then we need to look at ways to increase uptake. We have shown a time-efficient way but other barriers (don't like gyms, travel to gyms, complicated equipment, scared of injury, don't want to look too muscular), need to still be overcome.

6.3 Conclusion

In summary, the current thesis has demonstrated that whilst ultrasound measure of muscle thickness are valid at a single time point, this is not the case when evaluating changes with resistance exercise training. Following this we have demonstrated that resistance exercise training, involving a single set of exercise to muscle failure, is effective in inducing short-

term improvements in muscle size and strength and also insulin sensitivity in White Europeans, with broadly similar findings in South Asians.

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